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KIDNEY WEEK 2020 REIMAGINED

OCTOBER

Abstract Supplement

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Abstract Supplement

Abstract Publication
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- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
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TH-OR01

Global Phase 3 Clinical Trials of Vadadustat vs. Darbepoetin Alfa for Treatment of Anemia in Patients with Dialysis-Dependent CKD

Kai-Uwe Eckardt, INNO2VATE Author Group *Charite Universitatsmedizin Berlin, Berlin, Germany*.

Background: Vadadustat (VADA) is an investigational, oral, hypoxia-inducible factor prolyl hydroxylase inhibitor that has advanced to phase 3 development for treatment of anemia of CKD. In phase 2 trials, VADA raised and maintained Hb concentrations.

Methods: Two randomized, phase 3, global, open-label, sponsor-blind, parallel-group active-controlled noninferiority (NI) trials comparing VADA vs darbepoetin alfa (DA) were conducted in patients with anemia of DD-CKD ($INNO_2VATE$ trials). The trials included 1) Correction/Conversion trial of patients new to dialysis (incident trial, NCT02865850) and 2) Conversion trial of patients on maintenance dialysis (prevalent trial, NCT02892149). The primary safety endpoint was time to first major adverse cardiovascular event (MACE: all-cause mortality, nonfatal MI, nonfatal stroke) prespecified as a pooled analysis of both trials. Primary and key secondary efficacy endpoints, prespecified as separate analyses for each trial, were mean difference in change in Hb from baseline between VADA vs DA to wks 24-36 and wks 40-52, respectively.

Results: 3923 patients were randomized 1:1 to VADA or DA (incident, N=369; prevalent, N=3554). Median (Q1, Q3) duration of follow-up was 1.2 (0.8, 1.7) and 1.7 (1.2, 2.2) years in the incident and prevalent trials, respectively. VADA was noninferior to DA for time to first MACE (HR 0.96; 95% CI: 0.83, 1.11) and met a prespecified NI margin of 1.25. Among incident dialysis patients, the least squares (LS) mean difference in change in Hb between VADA vs DA from baseline to wks 24-36 was -0.31 g/dL (95% CI: -0.53, -0.10) and from wks 40-52 was -0.07 g/dL (95% CI: -0.34, 0.19). In the prevalent trial, the LS mean difference in change in Hb from baseline to wks 24-36 was -0.17 g/dL (95% CI: -0.23, -0.10), and wks 40-52 was -0.18 g/dL (95% CI: -0.25, -0.12). Primary and key secondary efficacy endpoints met the prespecified NI margin of -0.75 g/dL in both trials. Incidence of treatment-emergent adverse events (TEAEs) in VADA vs DA was 83.8% vs 85.5% in the incident trial and 88.3% vs. 89.3% in the prevalent trial, respectively.

Conclusions: VADA was noninferior to DA in time to first MACE and correction/maintenance of Hb in DD-CKD patients with anemia. The incidence of TEAEs was comparable between VADA and DA.

Funding: Commercial Support - Akebia Therapeutics, Inc.

TH-OR02

Roxadustat for the Treatment of Anemia in CKD Patients Not on Dialysis (NDD): A Phase 3, Randomized, Open-Label, Active-Controlled Study

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Background: Roxadustat is an orally administered hypoxia-inducible factor prolyl hydroxylase inhibitor to treat anemia in adult CKD patients (pts). Efficacy and safety of roxadustat versus darbepoetin alfa (DA) were assessed in NDD CKD pts in a randomized, open-label, active-controlled phase 3 study.

Methods: NDD CKD pts with anemia were randomized to roxadustat or DA for up to 2 years. Dose adjustments were permitted to correct and maintain hemoglobin (Hb) within 10–12 g/dL. The primary endpoint was Hb response, defined as Hb ≥11.0 g/dL and Hb increase from baseline (BL) of ≥1.0 g/dL in pts with BL Hb >8.0 g/dL, or an increase of ≥2.0 g/dL in pts with BL Hb ≤8.0 g/dL, during the first 24 weeks of treatment without rescue therapy. Noninferiority of roxadustat to DA was declared if the lower bound of the two-sided 95% confidence interval (CI) for the difference (roxadustat – DA) in proportion of responders was >-0.15. Key secondary endpoints included change in low-density lipoprotein (LDL) cholesterol, time to first IV iron use, change in mean arterial pressure (MAP), and occurrence of hypertension. Treatment-emergent adverse events (TEAEs) were assessed.

Results: Of 616 randomized pts (roxadustat, 323; DA, 293), 424 completed 2 years of treatment (roxadustat, 215; DA, 209). Mean BL Hb was 9.55 g/dL in both groups. In the per protocol set, the proportion of pts who achieved Hb response during the first 24 weeks was 89.5% (roxadustat; n=256/286) and 78.0% (DA; n=213/273), with a difference of 11.51% (95% CI: 5.66%, 17.36%), thereby establishing roxadustat's noninferiority to DA. Noninferiority of roxadustat to DA was demonstrated for MAP and time to occurrence of hypertension. Superiority of roxadustat to DA was demonstrated for decreasing LDL cholesterol ($p<0.001$) and increasing time to first IV iron use ($p=0.004$). The incidence of TEAEs was comparable between roxadustat (91.6%) and DA (92.5%). Common TEAEs in both groups were end-stage renal disease, hypertension, decreased eGFR, and peripheral edema.

Conclusions: Roxadustat was noninferior to DA for Hb response during the first 24 weeks of treatment in NDD CKD pts. Safety profiles were comparable between groups.

Funding: Commercial Support - Astellas Pharma, Inc.

TH-OR03

Roxadustat Treatment of Anemia in Non-Dialysis-Dependent CKD Is Not Influenced by Iron Status

Robert Provenzano,[1] Steven Fishbane,[2] Daniel W. Coyne,[3] Carol A. Pollock,[4] Maksym Pola,[5] Willis Chou,[6] Khalil G. Saikali,[6] Kin-Hung P. Yu.[6] *[1]Wayne State University, Detroit, MI; [2]Northwell Health, Great Neck, NY; [3]Washington University in Saint Louis, Saint Louis, MO; [4]Royal North Shore Hospital, St Leonards, NSW, Australia; [5]AstraZeneca, Warsaw, Poland; [6]FibroGen Inc, San Francisco, CA.*

Background: Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor for anemia in CKD, improves iron absorption and bioavailability. This analysis of Phase 3 studies explored the efficacy of roxadustat in pts with non-dialysis-dependent (NDD) CKD with iron repletion or depletion at baseline.

Methods: Data from 3 completed randomized Phase 3 studies in NDD-CKD pts were analyzed individually and in the pooled population by iron status. Pts were randomized to roxadustat or placebo for up to 4 years. Baseline (BL) hemoglobin (Hb) and change from BL (CFB) were summarized overall and in pts with iron repletion or iron depletion. Iron repletion was defined as ferritin ≥100 µg/L and transferrin saturation (TSAT) ≥20%; the remainder were defined as iron depleted. Oral iron was allowed on study and IV iron was allowed as rescue.

Results: Across studies, 2391 and 1886 pts with NDD-CKD were treated with roxadustat and placebo, respectively. Mean (SD) BL Hb was 9.10 (0.74) g/dL (roxadustat) and 9.10 (0.73) g/dL (placebo). At BL, 1433 (60%) pts were iron replete for roxadustat and 1127 (60%) pts were iron replete for placebo. Mean CFB in Hb with roxadustat was summarized by study and iron status (Table 1). Hb CFB was similar in iron-replete and -depleted patients receiving roxadustat. Roxadustat dose and iron use in subgroups will be explored.

Conclusions: Roxadustat corrected and maintained Hb in patients with NDD-CKD and anemia regardless of iron status at baseline.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Change from baseline in Hb overall and by iron status with roxadustat treatment across NDD studies over Weeks 28 to 52 regardless of rescue therapy

Study	N in analysis	Mean (SD) baseline Hb for study (g/dL)	Adjusted LS mean Change from baseline in Hb
001 (OLYMPUS)	Overall = 1384	9.11 (0.73)	1.75 (0.03)†
	Iron-replete = 782		1.71 (0.04)†
	Iron-depleted = 552		1.76 (0.05)†
060 (ANDES)	Overall = 616	9.10 (0.75)	2.02 (0.04)†
	Iron-replete = 366		1.98 (0.05)†
	Iron-depleted = 241		2.10 (0.07)†
608 (ALPS)	Overall = 391	9.08 (0.76)	1.99 (1.82, 2.16)§
	Iron-replete = 204		1.97 (1.74, 2.20)§
	Iron-depleted = 187		1.99 (1.69, 2.29)§
Pooled	Overall = 2391	9.10 (0.74)	1.94 (0.02)†
	Iron-replete = 1433		1.94 (0.03)†
	Iron-depleted = 956		1.94 (0.03)†

†Least squares mean change from baseline to average during Weeks 28–52 (± standard error) in the intention to treat population for overall results; least squares mean change from baseline to average during Weeks 28–36 (± standard error) in the FAS population for baseline iron subgroup results.
§Least squares mean change from baseline to average Hb during Weeks 28-52 (95% confidence interval) in the all randomized population.
Least squares mean was derived using the multiple imputation strategy by combining the results of the ANCOVA model with other covariates.
For 001, iron replete was defined as ferritin >100 µg/L and transferrin saturation >20%.
For 001, iron depleted was defined as ferritin <100 µg/L and <20%.
Hb, hemoglobin; LS, least squares; NDD, non-dialysis dependent; standard deviation, SD.

TH-OR04

Roxadustat Is Not Associated with an Increased Risk of Neoplasm in Patients with CKD and Anemia

Daniel W. Coyne,[1] Steven Fishbane,[2] Pablo E. Pergola,[3] Robert Leong,[4] Ming Zhong,[4] Dustin J. Little,[5] Kin-Hung P. Yu.[4] *[1]Washington University in Saint Louis School of Medicine, Saint Louis, MO; [2]Northwell Health, Great Neck, NY; [3]Renal Associates PA, San Antonio, TX; [4]FibroGen Inc, San Francisco, CA; [5]AstraZeneca, Gaithersburg, MD*.

Background: Roxadustat is a novel, orally bioavailable, small molecule that reversibly inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase enzymes and activates HIF and transcription of HIF-responsive genes, including for erythropoietin. Preclinical studies of roxadustat in multiple animal species did not demonstrate a carcinogenic signal. We report neoplasm-related adverse events (AEs) and serious adverse events (SAEs) from the roxadustat global phase 3 program.

Methods: Data from six pivotal studies were pooled: 3 compared roxadustat to placebo in patients with non–dialysis-dependent (NDD) CKD, and 3 compared roxadustat to epoetin alfa in patients with dialysis-dependent (DD) CKD. Patients were excluded from the studies if they had a history of malignancy, except for those determined to be cured or in remission for ≥5 years, curatively resected basal/squamous cell cancers, cervical cancer in situ, or resected colon polyps. AEs/SAEs reported during the treatment period +28 days and +7 days after the last dose of study drug in the NDD- and DD-CKD populations, respectively, were compared. Events were coded using the Medical Dictionary for Regulatory Activities, System Organ Class "Neoplasms benign, malignant and unspecified (incl cysts and polyps)."

Results: In the NDD population, 4270 patients were randomized (roxadustat=2386, placebo=1884), corresponding to 3870.7 and 2323.2 patient-exposure years (PEY), respectively. Neoplasm-related AE rates were 2.5/100 PEY in both the roxadustat and placebo groups. Neoplasm-related SAE rates were 1.1/100 PEY and 1.3/100 PEY in the roxadustat and placebo groups. In the DD population, 3880 patients were randomized (roxadustat=1940, epoetin alfa=1940), corresponding to 3315.3 and 3743.6 PEY, respectively. Neoplasm-related AE rates were 2.7/100 PEY and 2.3/100 PEY in the roxadustat and epoetin alfa groups. Neoplasm-related SAE rates were 1.1/100 PEY and 1.2/100 PEY. In both the NDD- and DD-CKD populations, there were no between–treatment-group differences in the organ types of neoplasms.

Conclusions: There were no clinically meaningful between–treatment-group differences in neoplasm-related AE and SAE rates in the roxadustat phase 3 clinical trials.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

TH-OR05

Roxadustat Treatment Results in Consistent Improvements in Hemoglobin (Hb) vs. Placebo: An Analysis of Three Multinational Randomized Clinical Trials in Patients with Non-Dialysis-Dependent CKD (NDD-CKD)

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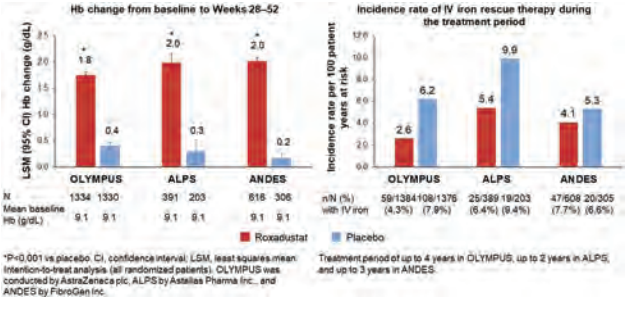
Background: Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor that increases endogenous erythropoietin and enhances iron utilization. To evaluate the consistency of Hb increases across studies and global geographic regions, we analyzed data from three pivotal Phase 3 trials of roxadustat in patients with anemia and NDD-CKD.

Methods: While based on the same trial design, the studies were performed by different investigators and companies in differing global regions. Patients with baseline Hb <10 g/dL and eGFR <60 ml/min/1.73 m^2 not on dialysis were randomized to roxadustat or placebo (pbo) in the OLYMPUS (North and South America, Asia-Pacific and Europe; N=2781, 1:1 ratio to pbo), ALPS (South America, Europe and South Africa; N=597, 2:1 ratio to pbo), and ANDES (North and South America, Asia-Pacific and Australasia; N=922; 2:1 ratio to pbo) double-blind randomized controlled trials (RCTs). Oral iron was administered unrestricted; intravenous (IV) iron was limited to rescue therapy in those with low iron stores and poor treatment response. The primary endpoint was the mean change in Hb from baseline to the average over Weeks 28–52.

Results: Significant (P<0.001) and consistent improvements in Hb were observed with roxadustat vs pbo across all studies (Figure) and were maintained over time. IV iron rescue therapy use was lower with roxadustat vs pbo (Figure). Overall safety of roxadustat was comparable with pbo and consistent with the CKD patient population.

Conclusions: Roxadustat consistently improved anemia in patients with NDD-CKD across the global roxadustat clinical program, in studies performed by different investigators and companies and in varying global locations.

Funding: Commercial Support - AstraZeneca



TH-OR06

Hemoglobin (Hb) Correction with Roxadustat Is Associated with Improved Iron Homeostasis in Patients with Dialysis-Dependent CKD (DD-CKD)

Pablo E. Pergola,[1] Chaim Charytan,[2] Dustin J. Little,[3] Stefan Tham,[4] Lynda Szczech,[5] Steven Fishbane.[6] *[1]Renal Associates PA, San Antonio, TX; [2]New York Hospital Queens, Division of Nephrology, Flushing, NY; [3]Clinical Research, AstraZeneca, Gaithersburg, MD; [4]Clinical Research, AstraZeneca, Gothenburg, Sweden; [5]FibroGen Inc., San Francisco, CA; [6]Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

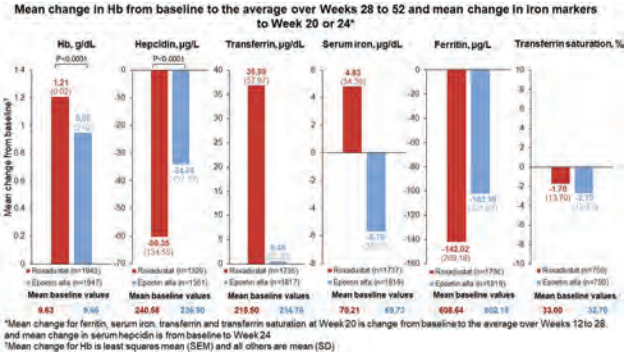
Background: Anemia in CKD is multifactorial, with contributions from reduced erythropoietin production and hepcidin-induced functional iron deficiency. Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, treats anemia by enhancing erythropoietin synthesis and increasing iron availability via reducing hepcidin and increasing iron transport. We assessed the effect of roxadustat on iron parameters in patients with DD-CKD.

Methods: Patients were randomized to open label roxadustat or epoetin alfa in 3 pivotal DD-CKD trials. Intravenous (IV) iron was administered per usual care with epoetin alfa and was limited to rescue therapy with roxadustat. Mean changes from baseline in Hb, hepcidin, and iron parameters were evaluated. Pooled results are reported.

Results: Overall, 3890 patients were evaluated (roxadustat N=1943; epoetin alfa N=1947; mean baseline Hb 9.7 g/dL for both groups), including 1515 incident dialysis patients (roxadustat N=756; epoetin alfa N=759; overall mean baseline Hb values ~8.8 g/dL). Mean Hb increased more from baseline averaged over Weeks 28–52 with roxadustat vs epoetin alfa (1.21 vs 0.95 g/dL; P<0.0001). Roxadustat-treated patients used less IV iron, with mean monthly IV iron use over Weeks 28–52 of 80.3 mg for roxadustat and 108.2 mg for epoetin alfa (P<0.0001). Roxadustat reduced hepcidin and increased transferrin and serum iron; transferrin saturation did not change vs epoetin alfa (Figure). Reduction in ferritin occurred predominantly in patients with the highest baseline values when assessed by quartile (>800 μg/L).

Conclusions: Roxadustat facilitated iron transport and utilization by increasing both iron-carrying capacity (transferrin) and serum iron, in contrast to the effects on these parameters seen with epoetin alfa. Overall, these changes contributed to decreased need for IV iron use while achieving greater Hb increase from baseline with roxadustat vs epoetin alfa.

Funding: Commercial Support - AstraZeneca



TH-OR07

Renoprotective Effects of Ferric Citrate in a Mouse Model of CKD

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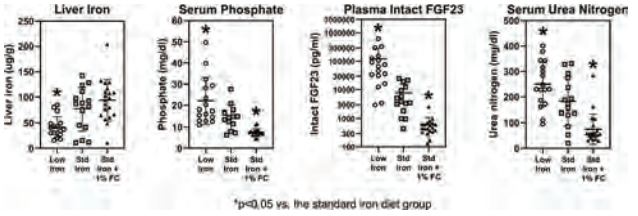
Background: Ferric citrate (FC) is an effective phosphate binder and iron replacement product. In the setting of chronic kidney disease (CKD), both decreasing enteral phosphate absorption and improving iron status could lower pathologically elevated FGF23 levels and indirectly improve kidney function. In a murine model of CKD, we assessed how FC (and iron status in general) affects FGF23 levels and kidney function.

Methods: Five-week-old *Col4α3* knockout mice were placed on five-week diets containing low iron (4 ppm), standard iron (48 ppm), or standard iron supplemented with FC (48 ppm + 1% FC) (n = 15-20 mice per group). Mice were euthanized at ten weeks of age.

Results: Compared to the standard iron diet group, the mice on low iron diets developed iron deficiency anemia (lower liver iron, lower hemoglobin, lower mean corpuscular volume, and higher red cell distribution width); markedly worsened kidney function (higher serum urea nitrogen, creatinine, and phosphate); and markedly higher FGF23 levels (increased bone and marrow *Fgf23* mRNA expression, and approximately ten-fold higher plasma intact FGF23 concentrations) (**Figure**). Conversely, compared to the standard iron diet group, the mice treated with FC had similar hemoglobin (with increases in liver and serum iron not reaching statistical significance), but decreased serum phosphate; decreased marrow *Fgf23* mRNA expression; approximately ten-fold lower plasma intact FGF23 concentrations; decreased systemic inflammation; and markedly improved kidney function (decreased serum urea nitrogen, serum creatinine, urine albumin-to-creatinine ratio, and expression of renal fibrosis markers, along with increased kidney *Klotho* mRNA expression) (**Figure**).

Conclusions: In the setting of CKD, iron deficiency anemia is associated with markedly increased intact FGF23 levels and worsened kidney function. In this CKD model, compared to either iron-deficient or standard iron conditions, FC decreased serum phosphate, markedly decreased intact FGF23, and dramatically improved kidney function. These data support further human studies of how FC affects CKD progression.

Funding: Commercial Support - Akebia Therapeutics, Inc.



*p<0.05 vs. the standard iron diet group

TH-OR08

Regional Variation of Erythropoietin-Stimulating Agent Hyporesponsiveness in the Global Daprodustat Dialysis Study (ASCEND-D)

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Background: Hyporesponsiveness to erythropoiesis-stimulating agents (ESA) is present in 10%–15% of the prevalent dialysis population. We explored baseline characteristics and predictors of ESA hyporesponsiveness in a global randomized cardiovascular outcomes study comparing an investigational hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), daprodustat, with conventional ESA treatment.

Methods: ASCEND-D (NCT02879305) recruited 2964 prevalent dialysis patients receiving ESA treatment (standardized to weekly intravenous [IV] epoetin) who were iron replete at baseline. Primary ESA hyporesponsiveness definition: ESA Resistance Index (ERI, ESA Units/kg/week/hemoglobin g/L) ≥2 or IV ESA equivalent dose ≥450 Units/kg/week. Predictors of ESA hyporesponsiveness were determined using a multivariable regression model. Alternate hyporesponder definitions were explored.

Results: Using the primary definition, 354 (12%) patients were ESA hyporesponsive. Selected baseline characteristics in the overall population and by ESA responsiveness, along with the results from the multivariable analysis, are shown below. Additional predictors of ESA hyporesponsiveness include a history of heart failure (0.013), dialysis vintage (0.033), smoking status (0.046), aspirin use (0.039), and ACEi/ARB use (0.081).

Conclusions: This is the first global HIF-PHI study to report pre-specified definitions and predictors of ESA hyporesponsiveness. While most of the strong predictors identified in our study have been previously reported, geographic region stands out as an unexpected finding that requires further investigation.

Funding: Commercial Support - GlaxoSmithKline

Baseline Characteristics	Overall (N=2964)	ESA Hyporesponsive (n=354)	ESA Responsive (n=2560)	Multivariable Analysis p-value
Age, years	58 (47–68)	55 (42–64)	59 (48–68)	<0.0001
Women, %	43	50	42	0.0085
Body Mass Index, kg/m^2	26.8 (23.1–31.3)	24.5 (21.4–28.7)	27.0 (23.3–31.6)	<0.0001
White/ Black/ Asian/ Other, %	67/ 16/ 12 / 5	54/ 19/ 17/ 10	69/ 15/ 11/ 5	NS
NAm/LA/EMEA/APAC, %	29/14/44/13	32/29/21/18	29/11/47/12	<0.0001
Hemoglobin, g/dL	10.4 (9.7–11.1)	10.0 (9.3–10.8)	10.5 (9.8–11.10)	NA
ERI, U/kg/week/g/L	0.74 (0.41–1.31)	2.68 (2.28–3.52)	0.65 (0.38–1.02)	NA
ESA dose, Units/week	5751 (3155–9694)	17730 (15714–24199)	5181 (3000–7990)	NA
IV iron dose, mg/month	97 (0–217)	109 (0–237)	93 (0–217)	0.0003
hsCRP, mg/L	4.0 (1.5–10.4)	6.0 (2–14.4)	3.8 (1.5–9.9)	NS
Albumin, g/dL	3.9 (3.6–4.1)	3.8 (3.5–4.0)	3.9 (3.7–4.1)	<0.0001
Ferritin, µg/L	595 (344–962)	592 (303–972)	597 (347–956)	NS
TSAT, %	33 (26–41)	29 (24–39)	33 (26–42)	<0.0001

Data presented as median (interquartile range) unless stated
APAC, Asia Pacific; EMEA, Europe Middle East Africa; hsCRP, high sensitivity C reactive protein; LA, Latin America; NAm, North America; NA, variable not included in modeling analysis; NS, not statistically significant for inclusion in the final model; TSAT, transferrin saturation.

TH-OR09

Adverse Event Rates Are Higher Post-Transfusion vs. Overall Follow-up and Independent of Background Anemia Treatment in Patients with CKD

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Background: The use of transfusion can treat anemia in the short term but may increase the risk of adverse events. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Roxadustat has been shown to decrease the need for transfusions in patients with chronic kidney disease (CKD).

Methods: Data were pooled from three pivotal, phase 3 studies of roxadustat vs. placebo in patients with non-dialysis-dependent (NDD) CKD and three pivotal phase 3 studies of roxadustat vs. epoetin alfa in patients with dialysis-dependent (DD) CKD. We evaluated rates of intravascular volume-related adverse events (AEs; reported from a predefined list [heart failure, pulmonary edema, respiratory failure] as a direct cause of excess intravascular volume or as a potential symptom) and treatment-emergent adverse events (TEAEs) during the 14-day post-transfusion period and the overall follow-up period (last dose + 28 days) in patients who had ≥1 transfusion.

Results: Intravascular volume-related AE and TEAE rates were at least 9-fold higher during the 14-day post-transfusion period vs. the overall follow-up period across all subgroups (Table). Trends in overall TEAE rates were similar across treatment groups.

Conclusions: Intravascular volume-related AEs occurred at higher rates post-transfusion across all populations. The reduction in transfusions for patients taking roxadustat could lower patient risk and healthcare resource use in managing CKD-related anemia.

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Table: Rates* of intravascular volume-related AEs and TEAEs

Intravascular volume-related AEs	NDD (n=4270) Rate (n/PEY)	ID (n=1526) Rate (n/PEY)	DD (n=3880) Rate (n/PEY)
During 14-day post-transfusion period	130.0 (62/47.7)	158.1 (11/7.0)	146.2 (45/30.8)
During total follow-up period	13.2 (134/1012.5)	12.8 (22/172.4)	13.8 (131/951.8)
Rate ratio	9.82	12.39	10.62
TEAEs			
During 14-day post-transfusion period	859.6 (410/47.7)	862.1 (60/7.0)	919.6 (283/30.8)
During total follow-up period	66.4 (672/1012.5)	57.4 (99/172.4)	47.2 (449/951.8)
Rate ratio	12.95	15.02	19.49

*Defined as the number of patients per 100 PEY
AEs, adverse events; DD, dialysis dependent; ID, incident dialysis; NDD, non-dialysis dependent; PEY, patient-exposure years; TEAEs, treatment-emergent adverse events

TH-OR10

A Real-World Longitudinal Analysis of Anemia Treatment Prescriptions in Non-Dialysis-Dependent CKD Patients, a CKDopps Study

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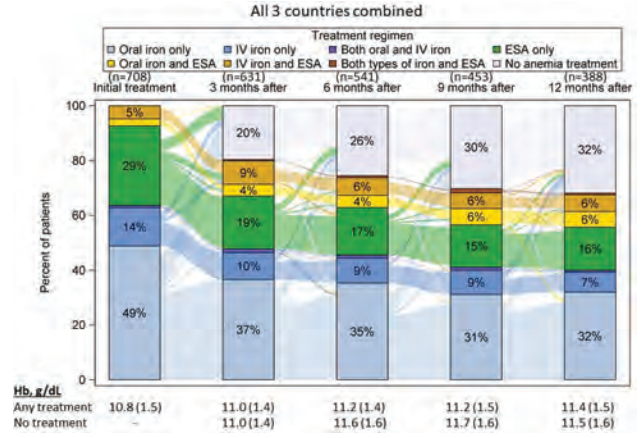
Background: Previously lacking in the literature, this analysis aims to comprehensively describe longitudinal patterns of anemia management, including prescriptions of ESA and iron replacement, for non-dialysis dependent chronic kidney disease (NDD-CKD) stage 3 to 5 patients under nephrologist care.

Methods: We analyzed data from a prospective cohort of 2455 NDD-CKD patients from Brazil, Germany and the US, who were not using anemia medications (oral iron, intravenous [IV] iron, or erythropoiesis stimulating agent [ESA]) at enrollment in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDOPPS). We reported the cumulative incidence function (CIF) [HK1] of anemia treatment initiation, stratified by patient characteristics. For patients that started therapy, we report the frequency of medication type at the moment of initiation, as well as switches and discontinuation over 12 months.

Results: The CIF of any anemia treatment initiation at 12 months was 54% for patients with Hb <10 g/dL. For oral iron therapy, the CIF at 12 months was 26% (19%, 32%) for TSAT<20%, and 22% (17%, 28%) for ferritin <100. For IV iron use, CIF at 12 months was 6% (3%, 11%) for patients with TSAT<20% and 4% (2%, 7%) for patients with ferritin <100ng/mL. For ESA use, the CIF at 12 months was 38% (29%, 47%) for patients with Hb <10 g/dL, and 11% (8%, 14%) for Hb 10 to <12 g/dL. Medication types at initiation and longitudinal treatment patterns (switches and discontinuation) are shown in the figure.

Conclusions: In a period of 12 months, anemia medication is initiated in a limited number of NDD-CKD patients with clinical signs that would indicate to do so. This longitudinal analysis using data from the real-world setting, call attention to a sub-optimally management of anemia in the NDD CKD setting.



Anemia medication starts and switches within a year of follow-up.

TH-OR11

Heparin Aggravates Cardiac Injury in Animal Models with High FGF-23

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Background: It has been assumed that fibroblast growth factor (FGF) 23 as an endocrine FGF family member has low affinity for heparin, and instead requires klotho, a transmembrane protein, as a co-receptor on specific target cells. However, we and others have shown that elevated FGF23 levels can specifically activate FGFR4 in cardiac myocytes lacking klotho and thereby induce cardiac hypertrophy in animal models of chronic kidney disease (CKD). We have recently found that heparin does act as a FGF23 co-receptor by mediating FGF23 binding mainly to FGFR4 and thereby increases the pathologic actions of FGF23 on cultured cardiac myocytes. Here, we determine the *in vivo* relevance of these findings by studying the cardiac effects of heparin injections in three different mouse models with elevated serum FGF23 levels.

Methods: First, 12-week old, male BALB/cJ mice received serial i.v. injections of isotonic saline, heparin, FGF23, or FGF23 and heparin combined twice daily for 5 consecutive days. Second, 4-week old Alport mice (Col4a3^{tm1Dec}), received serial i.v. injections of saline or heparin 3 times per week for 6 weeks. Third, 5-week old BALB/cJ mice on either 0.2% adenine diet or control chow were injected with either saline or heparin 3 times per week for 10 weeks. At the end of the experiment, echocardiographic analysis was performed, and tissue and serum were isolated for further analysis.

Results: Administration of heparin worsened cardiac outcomes in all three animal models. Compared with saline and FGF23 injections, BALB/cJ mice receiving FGF23 and heparin in combination developed a significant increase in heart weight / tibia length ratio, as well as in left ventricular (LV) mass and epicardial area. Alport mice receiving heparin injections showed increased heart weight / body weight ratios, LV mass and cardiac myocyte area, compared to wildtype littermates and Alport mice receiving saline. In addition, BALB/cJ mice on the adenine diet showed increased heart weight / body weight ratios and cardiac myocyte area when heparin was administered.

Conclusions: Our animal studies suggest that frequent heparin injections in individuals with elevated serum FGF23 levels, as the case in end-stage renal disease patients receiving hemodialysis, might contribute to adverse cardiac outcomes and high mortality.

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TH-OR12

Hypoxia-Inducible Factor 1 Alpha Regulates FGF-23 Production and Bone Metabolism in CKD

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Background: Renal osteodystrophy (ROD) is a complex bone disorder associated with chronic kidney disease (CKD) which affects over one in ten Americans. CKD also leads to increased bone production of the phosphate regulating hormone, fibroblast growth factor 23 (FGF23). ROD and FGF23 are associated with adverse clinical outcomes, including cardiovascular events and death. Hypoxia-inducible factor 1 alpha (HIF1α) regulates FGF23 expression in osteoblasts and osteocytes, and we hypothesized that osseous HIF1α plays an important role in ROD and FGF23 excess in CKD.

Methods: We generated mice harboring a conditional deletion of *Hif1α* in osteocytes (Hif1α$^{Dmp1\text{-}cKO}$) and crossed them to Col4a3^{KO} mice, a mouse model of progressive CKD. We studied bone and mineral metabolism alterations of wild-type (WT), Hif1α$^{Dmp1\text{-}cKO}$, Col4a3^{KO} and compound Col4a3^{KO} Hif1α$^{Dmp1\text{-}cKO}$ (CPD) mice. In parallel, we also treated 6 week-old WT and Col4a3^{KO} mice with a HIF inhibitor (BAY 87-2243) for 4 weeks. Finally, we compared the differentiation and mineralization potential of newly generated MC3T3-E1 osteoblast cell lines overexpressing *Hif1α* (Hif1α^{Tg}) or *Hif1α* shRNA (Hif1α^{KO}) to MC3T3-E1 transfected with an empty vector (Ctr).

Results: Deletion of Hif1α delayed progression of CKD, as CPD mice showed reduced levels of BUN compared to age-matched Col4a3^{KO} mice (-25%). CPD mice also showed lower FGF23 levels (-80% vs. Col4a3^{KO}) and we obtained similar results in Col4a3^{KO} mice administered with a HIF inhibitor (-80% FGF23, -30% BUN, vs. Ctr-Col4a3^{KO}). CPD mice also showed improved trabecular and cortical bone parameters (+50% trabecular bone volume, -20% cortical porosity vs. Col4a3^{KO}). Finally, deletion of *Hif1α* increased alkaline phosphatase (ALP) positive colonies and mineral deposits in Hif1α^{KO} cultures compared to Ctr cells, and led to a 30% reduction in *Fgf23* expression. In contrast, Hif1α^{Tg} cells showed reduced osteogenic potential, with fewer ALP colonies and mineral deposits, and a 2-fold increase in *Fgf23* expression.

Conclusions: Our data suggest that osseous HIF1α stimulates FGF23 production in CKD and is a negative regulator of osteoblast differentiation and function. Thus, inhibition of HIF1α in bone might represent a novel therapeutic strategy to improve bone and mineral outcomes in CKD.

Funding: NIDDK Support

TH-OR13

Deletion of the Sodium/Hydrogen Exchanger Isoform 6 in Mice Is Associated with an Age-Dependent Loss of Bone Volume

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Background: The sodium/hydrogen exchanger isoform 6 (NHE6) localizes to recycling endosomes, where it mediates endosomal alkalinization through K+/H+ exchange. NHE6 function in the endosome is essential for clathrin-mediated endocytosis, receptor recycling and endosomal signaling. Mutations in the SLC9A6 gene encoding the NHE6 isoform cause severe X-linked mental retardation, epilepsy, autism and corticobasal degeneration in humans. Patients with SLC9A6 mutations exhibit skeletal malformations, and a previous study suggested a role of NHE6 in osteoblast-mediated mineralization. The goal of this study was to explore the role of NHE6 in bone homeostasis

Methods: NHE6 expression, osteoclast differentiation and cell-mediated resorption were assessed in osteoclast precursor cells isolated from wild-type and NHE6 knock-out mice. In a next series of experiments, we used primary osteoblasts, extracted from calvaria of new-born mice, to study NHE6 expression, proliferation, and cell-mediated mineralization in vitro. To determine the impact of the in vitro findings on structural bone parameters, we performed high-resolution microcomputed tomography (μCT) studies on lumbar vertebrae of wild-type and NHE6 knock-out mice

Results: NHE6 transcript and protein are expressed in both primary osteoclasts and mineralizing osteoblasts. In vitro studies with osteoclasts and osteoblasts derived from NHE6 knock-out mice demonstrated normal osteoclast differentiation and osteoblast proliferation. However, NHE6-deficient osteoclasts exhibited a resorptive deficit, and the mineralization capacity was increased in osteoblasts lacking NHE6. Microcomputed tomography studies revealed a reduced bone volume at a single lumbar vertebral site (L4) but otherwise unaltered structural bone parameters in NHE6 knock-out mice compared to wild-type mice at 3 months of age. At 6 months of age, however, NHE6 knock-out mice displayed a significantly reduced bone volume and trabecular number as well as an increased trabecular space at all lumbar vertebrae studied (L3-L5) compared to wild-type mice

Conclusions: Thus, loss of NHE6 results in an age-dependent loss of bone volume in mice. The results of our in vitro studies argue against a direct bone cell-autonomous cause of the bone phenotype observed in NHE6 knock-out mice and suggest extraosseus factors as likely mediators

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TH-OR14

Circadian PTH Secretion Is Entrained by Feeding, While the Internal Circadian Parathyroid Clock Is Independent but Affected by CKD

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Background: We have previously shown that an internal molecular circadian clock operates in the parathyroids. Whether this circadian clock regulates the 24h rhythm of PTH secretion and whether it is impacted by feeding or CKD is unknown.

Methods: Rats were kept in 12h:12h light:dark cycle and fed *ad libitum*. Blood samples and parathyroid glands were harvested at 4h interval (N=38). Then feeding was restricted to the inactive light phase at ZT2-ZT12 (ZT: *zeitgebertime*, time since lights on) for 4 weeks and blood and glands obtained again (N=39). CKD was induced by 5/6 nephrectomy and high phosphate (P) diet for 8 weeks and parathyroid glands were harvested every 4th-hour (N=44). Plasma PTH, P, total calcium, FGF23, and urea were measured. Parathyroid expression of core circadian clock genes was examined by qPCR.

Results: Circadian rhythmicity was found for PTH ($p<0.0002$), P ($p<0.0001$), FGF23 ($p<0.02$), and urea ($p<0.0001$). Restricted feeding to the habitual inactive period inverted the acrophase timing of PTH (ZT9.6 → ZT23.6), P (ZT8.7 → ZT21), FGF23 (ZT7.4 → ZT22.9) and urea (ZT21.2 → ZT8.4). Restricted feeding did not significantly affect the period, acrophase timing, MESOR or amplitude of circadian clock genes: *Bmal1, Per1-3, Cry1-2* and *Rev-erbα*. The rhythmicity of parathyroid circadian clock genes was severely deregulated in CKD with significant upregulated MESOR of *Per1* ($p<0.0002$), *Per2* ($p<0.03$), and *Rev-erbα* ($p<0.004$) and downregulation of *Npas2* ($p<0.05$). The

significant rhythmicity of *Per1* ($p<0.02$) was abolished. In CKD the best fitting period of rhythmicity was reduced to 20h as opposed to the normal 24h for *Per1, Per2, Per3* and *Cry2*. Significant shifts in acrophase were found for *Npas2, Per3* and *Cry1,* while amplitude of *Rev-erbα* increased.

Conclusions: Feeding restricted to the inactive period inverted the acrophase of plasma PTH, P and FGF23 and revealed a clear dissociation between the phase of PTH secretion rhythm and the phase of the circadian clock in the parathyroid glands. In CKD the circadian rhythm of core clock genes were significantly interfered, affecting MESOR, phase, period, amplitude as well as rhythmicity.

TH-OR15

A Single-Cell Transcriptome Atlas of Adult Parathyroids in Secondary Parathyroidism

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Background: Secondary hyperparathyroidism (SHPT) is one of the common complications in patients with chronic kidney disease. The development of SHPT is accompanied by the change of cell composition, while the exact cell type changes and mechanism are yet to be defined. Therefore, single cell sequencing was conducted to analysis the cell composition of parathyroid gland.

Methods: In current study, parathyroids from 3 SHPT patients were digested to obtain single cell suspension. A total of 21519 cells were obtained and the mRNA expression profiles were analyzed by single cell sequencing and bioinformatics. Furthermore, the development separation track of cell subpopulations was constructed by pseudotime analysis (Figure 1A).

Results: There may be 21 cell subpopulations in parathyroid, among which 6 subpopulations (clusters 0, 1, 2, 5, 11, 17) are high function subpopulations of parathyroid, which were indicated by high expression of gcm2 (glial cells missing homolog 2), PTH (parathyroid hormone), CaSR (calcium sensing receptor) and KL (Klotho) genes (Figure 1B-D). The results of pseudotime analysis in the 6 high function subpopulations show that cluster 0 is at the beginning of the main group separation track, cluster 1, 2, 5 are in the middle, while cluster11 and 17 are at the end (Figure 1E). Multiple genes may play major role in the differentiation of cluster 0, including tspan1, park7, atp6v0b, rpl11, rps8 and etc (Figure 1F).

Conclusions: There are 6 subpopulations out of total 21 cell subpopulations of parathyroid cells with higher parathyroid hormone secretion and regulation function in SHPT patients. Among which, cluster 0 may be the initiation differentiation cell of high functional cells, because it may be a subpopulation with high proliferation and differentiation potential.

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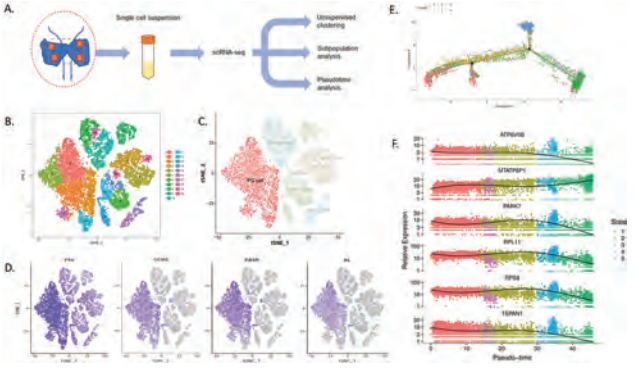

Identification and analysis of subpopulations of uremic hyperparathyroidism glands.

TH-OR16

Calcium Isotopes: A Novel Biomarker of Bone Mineralization in CKD

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Background: Serum Ca, bone biomarkers and radiological imaging do not allow accurate evaluation of bone mineral balance (BMB), a key determinant of bone mineral density (BMD) and fracture risk. Naturally occuring stable (non-radioactive) Ca isotopes, ^{42}Ca and ^{44}Ca, are absorbed from our diet and sequestered into different body compartments following kinetic principles of isotope fractionation. Isotopically light ^{42}Ca is preferentially incorporated into bone, and heavier ^{44}Ca excreted in urine and feces. Their ratio ($\delta^{44/42}Ca$) in serum and urine gives a direct measure of BMB; $\delta^{44/42}Ca$ is higher during bone formation than bone resorption.

Methods: Ca isotopes were measured by plasma-ionization mass-spectrometry in blood, urine, feces and dialysate. The relationship between bone Ca gain and loss was calculated using a compartment model, and expressed as $\delta^{44/42}Ca$ 128 children in CKD4-5 and on dialysis (CKD4-5D) and 117 healthy participants (age <30) underwent Ca isotope measurement, bone biomarkers, DXA and tibial peripheral quantitative CT (pQCT), an accurate measure of cortical BMD.

Results: In healthy children the $\delta^{44/42}Ca_{Blood}$ and $\delta^{44/42}Ca_{Urine}$ were higher than in adults ($p<0.0001$), reflecting avid Ca uptake during bone formation. Since urinary Ca excretion is impaired in CKD, $\delta^{44/42}Ca_{Blood}$ was higher and $\delta^{44/42}Ca_{Urine}$ lower in CKD4-5D compared to controls ($p<0.0001$ for both). In CKD2-5D $\delta^{44/42}Ca_{Blood}$ positively correlated with cholecalciferol ($p=0.01$) and alfacalcidol ($p=0.002$) doses, implying increased bone Ca uptake when Ca bioavailability is increased. $\delta^{44/42}Ca_{Blood}$ positively correlated with biomarkers of bone formation (ALK, $p=0.05$) and inversely with resorption markers (PTH, $p=0.013$; TRAP5b, $p<0.001$ and CTX, $p=0.006$). $\delta^{44/42}Ca_{Blood}$ correlated positively with tibial cortical BMD-Z-score ($p=0.006$, $R^2=0.39$), and DXA hip BMD-Z-score ($p=0.02$). Significant and independent predictors of tibial cortical BMD-Z-score were $\delta^{44/42}Ca_{Blood}$ ($\beta=0.68$, $p=0.006$) and PTH (β-0.39, $p=0.04$), together predicting 67% of the variability in BMD.

Conclusions: Ca isotope ratios provide a novel, non-invasive method of assessing bone mineralization. Defining an accurate biomarker of BMB forms the basis of future studies investigating Ca dynamics in disease states and the impact of treatments that affect bone homeostasis.

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TH-OR17

Secondary Hyperparathyroidism Is Associated with Weight Loss and Longer-Term Mortality Among Patients Undergoing Hemodialysis: Results from the Dialysis Outcomes and Practice Patterns Study

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Background: Wasting is a common complication of kidney failure that leads to weight loss and poor outcomes. Recent experimental data identified parathyroid hormone (PTH) as a driver of adipose tissue browning and wasting, but little is known about the relations among secondary hyperparathyroidism (SHPT), weight loss, and risk of mortality in patients undergoing hemodialysis.

Methods: We included 42,319 participants receiving hemodialysis for at least one year in the DOPPS phases 2-6 (2002-2018). Linear mixed models were used to estimate the association between baseline PTH and percent weight change over 12 months, adjusting for country, demographics, comorbidities, and labs. Accelerated failure time models were used to assess 12-month weight loss as a mediator between baseline high PTH and mortality after 12 months.

Results: At baseline, mean (SD) body weight was 74 (22) kg and the median PTH level was 251 pg/mL (interquartile range [IQR], 131-444 pg/mL). Baseline PTH was inversely associated with 12-month weight change: 12-month weight loss >5% was observed in 21%, 18%, 18%, 17%, 16%, and 14% of patients for PTH ≥600 pg/mL, 450-600, 300-450, 150-300, 50-150, and <50 pg/mL, respectively. In adjusted analysis, 12-month weight change compared to PTH 150-299 pg/mL was -0.60%, -0.12%, -0.10%, +0.15%, and +0.35% for PTH ≥600, 450-600, 300-450, 50-150, and <50 pg/mL, respectively ($P<0.01$). Interacting baseline PTH*appetite, high PTH was associated with weight loss only in persons with preserved appetite ($P<0.01$). During follow-up after the 12-month weight measure (median, 1.0 [IQR, 0.6-1.7] years; 6125 deaths), patients with baseline PTH ≥600 pg/mL had 11% (95% CI, 9-13%) shorter lifespan, and 18% (95% CI,14-23%) of this effect was mediated through weight loss ≥2.5%.

Conclusions: Our findings indicate that SHPT may be a novel mechanism of wasting in dialysis patients, corroborating experimental data, and that this pathway may be a mediator between elevated PTH levels and mortality. Future research should determine whether PTH-lowering therapy can limit or prevent weight loss and improve longer-term dialysis outcomes.

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TH-OR18

SNF472 Consistently Slows Progression of Coronary Artery Calcification Across Subgroups of Patients on Hemodialysis

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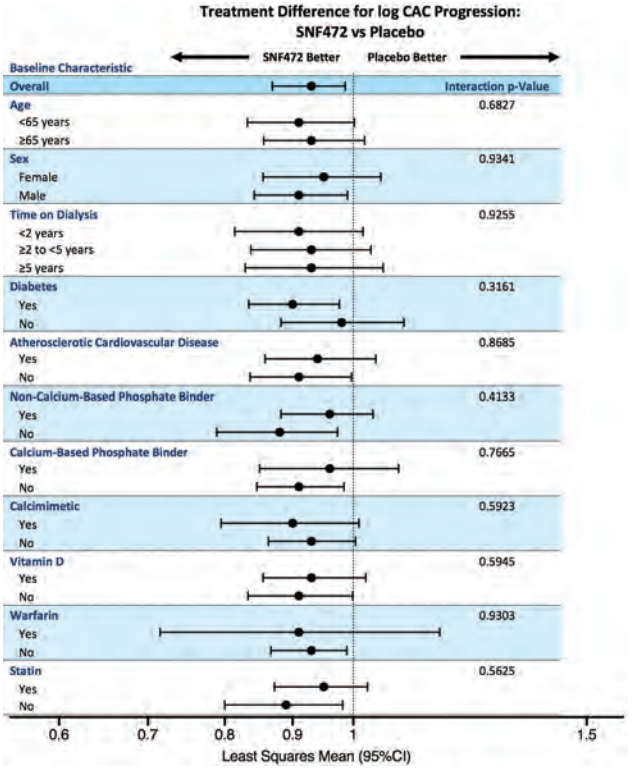
Background: In the CaLIPSO study, SNF472 significantly attenuated progression of coronary artery calcium (CAC) volume score compared with placebo. This pre-specified analysis examined CAC progression in key subgroups.

Methods: Patients were randomized to SNF472 300 mg (n=92), SNF472 600 mg (n=91) or placebo (n=91) infused 3x/week during hemodialysis (HD) for 52 weeks on top of standard care therapy determined by each investigator. We examined change in log CAC volume score from baseline to week 52 in the combined SNF472 dose groups vs placebo for subgroups of age, sex, diabetes, dialysis vintage, arteriosclerotic cardiovascular disease (ASCVD), use of non-Ca phosphate binders, Ca-based phosphate binders, calcimimetics, activated vitamin D, warfarin, or statins in the modified ITT population (mITT, defined as subjects who received at least one dose of study drug and had an evaluable post-baseline CT scan).

Results: Baseline characteristics were similar across treatment groups: mean age was 64 y, 39% were female; 62% had diabetes, and 41% had prior ASCVD. Median HD vintage was 42 mo; 33% received HD for ≥5 years. Concomitant medications at baseline were: 62% non-Ca phosphate binders, 28% Ca-based phosphate binders, 31% calcimimetics, 51% activated vit D, 8% warfarin, and 64% statins. In the overall mITT, CAC volume progression was 11% in the combined SNF472 groups vs 20% in placebo (p=0.016). Treatment differences for CAC volume progression were similar across subgroups (Figure). All interaction p-values were non-significant and comparisons favored SNF472 vs placebo in each subgroup.

Conclusions: SNF472 treatment for 52 weeks attenuated CAC progression compared with placebo in all subgroups.

Funding: Commercial Support - Sanifit



TH-OR19

Pharmacodynamic (PD) Profiling of Reloxaliase in Patients with Severe Hyperoxaluria

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Background: Hyperoxaluria is a major risk factor for kidney stones and can lead to chronic kidney disease (CKD). With decreasing kidney function, plasma oxalate (POx) rises and oxalate may deposit in the kidneys and other tissues (systemic oxalosis) leading to ESRD. Reloxaliase (REL), a non-absorbed, oxalate specific oral enzyme therapy designed to degrade oxalate along the GI tract, may potentially reduce the systemic and renal oxalate burden in patients with enteric and primary hyperoxaluria (EH and PH). This study tested the PD of REL, and addressed questions regarding potential formate accumulation (by-product of oxalate degradation) and systemic absorption of oxalate decarboxilase (OxDc, the active component of REL).

Methods: This 12-week, open label study enrolled subjects with EH, CKD and hyperoxalemia (UOx ≥40mg/d, eGFR <45mL/min and POx>5µmol/L, n=10) and PH (UOx ≥40 mg/d, n=5) who received 7,500u of REL 5x/day with meals/snacks. Parameters assessed at baseline, and weeks 4, 8 and 12 included POx and UOx (only if eGFR >15mL/min), plasma formic acid (pre- and post-prandial/post-dose; Q² Solutions) and OxDc (specific ELISA, Absorption Systems).

Results: Reported adverse events (AEs) were mostly GI related; there were no related serious AEs. In EH, both POx and UOx decreased substantially; in PH, UOx did not change, and POx stayed normal at baseline and during treatment (Table). There was no formate accumulation, as all samples were below or within normal range (1-9mg/L). Similarly, there was no detectable absorption of REL, as all samples were below the limit of detection of the assay for OxDc (<0.0001% of the administered dose of 37,500 u/day).

Conclusions: Reloxaliase was well tolerated; the absence of formate accumulation further supports its safety. The lack of REL absorption, in addition to supporting low potential for systemic toxicity, confirms its site of action within the GI tract. This best aligns with the pathophysiology of EH as evidenced by the substantial reduction in both POx and UOx in EH subjects with CKD/ESRD.

Funding: Commercial Support - Allena Pharmaceuticals

Change from Baseline to Weeks 4-12[1]		All EH		PH2 & PH3
		eGFR 15-45[2] n=3	eGFR<15 n=7	eGFR>60 n=5
POx (umol/L)	Mean (SD)	-28.7% (18.6)	-29.2% (30.2)	NA[3]
UOx/UCr (mg/g)	Mean (SD)	-35.4% (8.8)	NA	4.4% (19.6)

[1] Mean was calculated if at least 2/3 values during treatment were available
[2] eGFR (mL/min/1.73 m²)
[3] In PH subjects POx was normal, or below detection limit of the assay

TH-OR20

Efficacy and Safety of Upacicalcet in Hemodialysis Patients with Secondary Hyperparathyroidism: A Phase 3 Study

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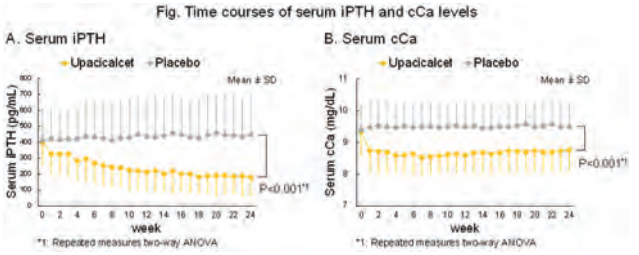
Background: Secondary hyperparathyroidism (SHPT) is a major complication of hemodialysis (HD) patients. Calcimimetics suppress the hyperfunction of parathyroid and reduce serum calcium and phosphorus levels, and are currently used for the treatment of SHPT. Upacicalcet (UPA) is a novel intravenous small molecule calcimimetic in late-stage development in Japan to treat SHPT of HD patients. We report the efficacy and safety of UPA in HD patients.

Methods: This study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. UPA or placebo (PBO) was administered t.i.w. at the end of HD at an initial dose of 50 mcg or 25 mcg. The doses were subsequently adjusted to maintain serum intact PTH (iPTH) levels between 60-240pg/ml (recommended level of Japanese guideline) every 3 weeks between 25 and 300 mcg during 24 weeks of treatment. The primary endpoint was the percentage of patients who achieved a mean iPTH level of 60–240 pg/ml in weeks 22 to 24.

Results: A total of 154 SHPT patients were enrolled, and randomly allocated to UPA group (n: 103) or PBO group (n: 51). The primary endpoint, percentage of patients achieving the target iPTH range was greater for UPA (67.0%) than for PBO (8.0%) (P<0.001). UPA significantly reduced iPTH and cCa levels compared with PBO (Fig.). Concerning phosphorus, no statistically significant difference between the groups was observed while it tended to decrease in the UPA group. In the safety assessment, treatment emergent adverse events (AE) occurred in 88 patients (85.4%) and 36 patients (72.0%) in the UPA and the PBO groups. The incidences of upper-gastrointestinal-related AE were 20.4% in the UPA and 18.0% in the PBO groups (P=0.8298). As an AE, hypocalcemia did not occur in either group.

Conclusions: This study demonstrates that UPA significantly decreases iPTH without increasing the incidence of upper-gastrointestinal symptoms as compared to PBO. It is suggested that UPA will be a promising calcimimetic agent capable of safe and appropriate management of SHPT.

Funding: Commercial Support - Sanwa Kagaku Kenkyusho Co., Ltd.



TH-OR21

Primary Cilia and the Glycocalyx Are Flow Sensors for Nitric Oxide Production by Thick Ascending Limbs

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Background: The primary cilium is an organelle found on essentially all epithelial cells. Similarly, the glycocalyx is a matrix-like layer of proteoglycans, glycosaminoglycans (GAGs) and plasma proteins covering the surface of all cells. In vascular endothelial cells, primary cilia and GAGs such as heparan sulfate and chondroitin sulfate mediate responses to the mechanical forces exerted by blood flow. In thick ascending limbs, increases in luminal flow enhance nitric oxide (NO) production, an important regulator of kidney function including sodium reabsorption; however, the role of primary cilia and the glycocalyx in NO production by thick ascending limbs is unknown. We hypothesized that primary cilia and the glycocalyx act as flow sensors and thus mediate flow-induced NO production by thick ascending limbs.

Methods: We measured flow-induced NO in isolated rat thick ascending limbs using DAF-FM. Intracelllular NO was first measured during the control period without and with luminal flow. NO was measured again during the experimental period after treating tubules for 15 min to deciliate cells or to degrade major glycocalyx GAGs. Dibucaine (0.1 mM) was used to remove cilia from cells. Heparinase III (0.2 or 0.4 U/ml) and chondroitinase ABC (0.2 U/ml) were used to degrade heparin sulfate and chondroitin sulfate, respectively.

Results: In untreated control tubules, flow-induced NO did not differ between the two periods, 4.33 ± 1.03 vs 4.68 ± 0.84 arbitrary units (AU)/min. Dibucaine decreased flow-induced NO from 4.25 ± 0.62 to 1.19 ± 0.65 AU/min ($p < 0.002$). Heparinase (0.2 U/ml) attenuated flow-induced NO from 4.02 ± 0.84 to 1.80 ± 0.74 AU/min ($p < 0.04$); a higher concentration (0.4 U/ml) caused a greater decrease from 4.24 ± 0.86 to 1.56 ± 0.41 AU/min ($p < 0.006$). Heat inactivation of heparinase (0.2 U/ml) abolished its effect (3.01 ± 0.34 to 2.83 ± 0.22 AU/min). Chondroitinase (0.2 U/ml) decreased flow-induced NO from 4.17 ± 0.96 to 2.45 ± 0.49 AU/min ($p < 0.038$).

Conclusions: We conclude that both primary cilia and the glycocalyx act as flow sensors in thick ascending limbs and transduce mechanical stimuli into chemical signals that ultimately result in NO production by this segment.

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TH-OR22

Cell-Autonomous Expression of Membrane Transport Proteins in Mammalian Distal Nephron

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Background: Reabsorption of NaCl in kidney thick ascending limb (TAL) via NKCC2 involves the action of luminal (ROMK) and basolateral (Kir4.1/Kir5.1 multimers) potassium channels, a basolateral calcium sensing receptor (CaSR), and the claudin (Cldn) family of proteins. Morphological heterogeneity of TAL cells has been reported, as well as mosaic expression of ROMK and Kir4.1. We hypothesized that this variability between TAL cells extends to other aspects of their function.

Methods: We studied TAL EM morphology, zonal and cell-autonomous heterogeneity of the transport proteins at steady state in mice, rats and humans, and under stimulation by vasopressin (AVP; V2R agonist dDAVP for 72 h) using AVP-deficient Brattleboro rats. NKCC2, phosphorylated (p) NKCC2, ROMK, Kir4.1, CaSR, Cld-10 and Cld-16 signals were analyzed by immunofluorescence, in situ hybridization (ISH), EM and Western blot (WB).

Results: Between cortex and medullary kidney zones, TAL morphological cell heterogeneity was observed, but not at a cell-to-cell level within each zone. NKCC2 was continuously expressed in all TAL cells, while pNKCC2 signals were heterogeneous, increasing from inner stripe of outer medulla to cortex and varying between cells of each zone. ROMK and Kir4.1 protein expression showed conspicuous heterogeneity in a mutually exclusive pattern, with stronger pNKCC2 expression in the ROMK-negative, Kir4.1-positive cell type. CaSR and Cldn-16 signals were moderate to absent in ROMK-positive cells, but intensified in ROMK-negative cells, while Cld-10 was strongly expressed only in ROMK-positive cells. ISH revealed no cell heterogeneity of ROMK mRNA. In Brattleboro rats, 72h dDAVP increased the number of ROMK- and Kir4.1-positive cells and the overlap of both signals in mTAL, and stimulated NKCC2 phosphorylation. Cldn-10 expression was induced in the outer stripe of outer medulla. Morphological alterations in the TAL included proliferation of microvilli. WB showed 2.2-fold increase of ROMK and 1.3-fold increase of Kir4.1 abundance, but down-regulation of CaSR to 60%.

Conclusions: These results demonstrate mosaic expression of ROMK, Kir4.1, CaSR, Cld-10, and Cld-16 in TAL, which correlate with cell-heterogeneous levels of NKCC2 activation.

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TH-OR23

Optical Clearing and 3D Imaging Reveal a Sexual Dimorphism in the Structure and Remodeling Response of the Distal Convoluted Tubule

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Background: The abundance of the distal convoluted tubule (DCT) thiazide-sensitive sodium chloride cotransporter (NCC) is greater in females than males. Because structural remodeling of the DCT is dependent on NCC activity, it has been generally assumed that there is a corresponding sexual dimorphism in DCT morphology. Until now, this has never been directly examined. Here, combining new optical clearing techniques with staining for markers of DCT segments, volumetric imaging we quantitatively assess DCT morphology in male and female mice and study DCT remodeling response to furosemide.

Methods: Male and Female (3-month-old) mice were treated with vehicle or Furosemide administered in the food (100 mg/kg per day) for seven days. Total NCC and phospho-active NCC abundance (pNCC) was evaluated by Western Blot in one kidney, the other kidney was perfused and fixed for imaging. Kidneys were cleared using the Clear, Unobstructed Brain/Body Imaging Cocktails and Computational Analysis (CUBIC) pipeline, co-stained with antibodies that label the early DCT (DCT1, parvalbumin) and the entire DCT (DCT1 & 2; NCC), imaged using a high-speed spinning disc confocal microscope, and processed with 3D rendering and analysis software (IMARIS).

Results: We confirmed previous studies that females have greater NCC abundance in the basal state. Surprisingly, the length of the DCT was longer in males (~620 μm) than female mice (~560 μm). Furosemide treatment significantly increased the abundance of NCC and pNCC in both sexes, and this was paralleled by an expansion of the DCT length and volume. The remodeling response to furosemide was more profound in females (~20% increase in DCT length and 50% in DCT1 volume) than males (~8% and 30%, respectively). The DCT elongation effect of furosemide treatment in females stemmed largely from an increase in DCT1 length. Furosemide expanded the DCT2 significantly in males but not females.

Conclusions: Our study reveals a surprising sexual dimorphism of the DCT. The greater NCC density in a shorter structure may provide a means for females to protect sodium balance in face of greater basal distal sodium delivery, yet have larger reserve and remodeling capacity to adapt to unique physiological stresses.

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TH-OR24

Positive Allosteric Modulation of the Calcium-Sensing Receptor (CaSR) by Glucose or Fructose Induces Activation of the Sodium-Chloride Cotransporter (NCC)

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Background: NCC is activated via the CaSR-WNK4-SPAK pathway. Glucose and other sugars act as positive allosteric modulators of the CaSR. This might be relevant in the distal convoluted tubule (DCT), since most glucose is reabsorbed proximally and fructose delivery to the DCT depends largely on dietary intake. Here we studied if positive allosteric modulation of the CaSR by glucose/fructose induces NCC activation via CaSR-WNK4-SPAK.

Methods: We used 1) HEK-293 cells cotransfected with SPAK, WNK4 and/or CaSR and exposed to 0.5 mM extracellular Ca^{2+} with 0, 5.5 or 25mM of glucose/fructose. 2) C57BL/6 wild-type mice treated with vehicle, 20% fructose or dapagliflozin (3 mg/kg ip), +/- calcilytic NPS2143 (30 mg/kg oral gavage). Renal proteins for western blot were extracted 3 h latter. 3) Urinary exosomes from male healthy volunteers to assess NCC activity after exposure to placebo, cinacalcet 30mg at time 0 (n=4) or 5% fructose with water intake (n=3).

Results: Stimulation of HEK293 cells with glucose or fructose increased SPAK phosphorylation, but only if both WNK4 and CaSR were present ($p<0.01$). In mice, we observed increased pNCC in kidneys, together with increased activation of WNK4-SPAK ($p<0.01$), after exposure to 20% fructose. Dapagliflozin also induced activation of SPAK and NCC. These effects of fructose and dapagliflozin were abrogated by co-administration of NPS2143 ($p<0.01$). Preliminary data on human subjects show that when compared to baseline (urinary exoxome pNCC/NCC ratio = 1.0), cinacalcet induced a 77% increase in pNCC/NCC ratio (1.77, $p=0.018$) and fructose induced a a near two-fold increase in pNCC/NCC ratio (2.69, $p=0.006$).

Conclusions: *In vitro* glucose or fructose increases SPAK phosphorylation in a CaSR-WNK4-dependent manner. *In vivo* glucose (dapagliflozin) or fructose increases NCC activity via WNK4-SPAK and data suggest a calcimimetic-like behavior for glucose or fructose in the DCT; this effect appears to be reproduced in humans and represents the

first evidence of NCC activation via CaSR with cinacalcet in humans. Our results suggest that the presence of glucose or fructose in DCT could increase the activity of NCC via CaSR-WNK4-SPAK pathway.

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TH-OR25

Cross-Talk Between Epithelial Sodium Channel and Basolateral $K_{ir}4.1$/$K_{ir}5.1$ Channels in the Cortical Collecting Duct

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Background: The growing body of evidence suggest that inwardly rectifying K^+ (K_{ir}) channels located on the basolateral membrane of epithelial cells in the distal nephron play a crucial role in K^+ handling and blood pressure control, making these channels attractive targets for the treatment of hypertension. The purpose of the present study was to determine how the inhibition of basolateral $K_{ir}4.1$ homomeric or $K_{ir}4.1$/$K_{ir}5.1$ heteromeric K^+ channels affects ENaC-mediated Na^+ transport in the cortical collecting duct (CCD) principal cells.

Methods: Electrophysiological approaches were used to test the effect of fluoxetine, amitriptyline, and recently developed $K_{ir}4.1$ inhibitor, VU0134992, on the activity of $K_{ir}4.1$, $K_{ir}4.1$/$K_{ir}5.1$, and ENaC. Channel activity was recorded in CHO cells transfected with respective channel subunits, cultured polarized epithelial $mCCD_{c11}$ cells, and native freshly isolated rat and human CCD tubules. To test the effect of pharmacological $K_{ir}4.1$/$K_{ir}5.1$ inhibition on electrolyte homeostasis *in vivo*, Dahl salt-sensitive rats were injected with amitriptyline (15 mg/kg/day).

Results: We found that inhibition of $K_{ir}4.1$/$K_{ir}5.1$, but not $K_{ir}4.1$ channel, substantially suppresses both amiloride-sensitive I_{SC} in $mCCD_{c11}$ cells and single-channel ENaC activity in principal cells of rat and human CCD tubules. Furthermore, we demonstrate that i.p. injection of $K_{ir}4.1$/$K_{ir}5.1$ antagonist for three days leads to a significant drop in plasma K^+ level, triggering sodium excretion, and diuresis.

Conclusions: These data uncover a putative mechanism underlying a renal control of blood electrolytes mediated by $K_{ir}4.1$/$K_{ir}5.1$ and introduce a new molecular target for the treatment of salt-sensitive hypertension.

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TH-OR26

ClC-K2 Chloride Channel Determines Acid-Base Transport and Chloride Reabsorption in Intercalated Cells of the Collecting Duct

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Background: Intercalated cells (ICs) of the collecting duct (CD) play a critical role in regulation of systemic acid-base homeostasis. In addition, ICs are capable of performing trans-cellular Cl^- reabsorption particularly during volume depletion. While the major apical membrane transport systems are well characterized, little is known about mechanisms and contribution of the basolateral membrane in both processes. Kidney specific ClC-K2 is expressed in the basolateral membrane of the distal nephron segments, including the CD.

Methods: We generated ClC-K2 deficient mice using cre-loxP strategy to investigate the role of the channel in acid-base and Cl^- transport. We combined BCECF-sensitive intracellular pH (pH_i) measurements with fluorescent AQP2-based identification of principal cells (PCs) and ICs to assess ClC-K2-dependent pH_i changes in different cell types.

Results: ClC-K2 inhibition with NPPB (100 μM) had no effect in PCs of WT mice, whereas it induced rapid intracellular acidification in B-type and alkalization in A-type of ICs. NPPB failed to significantly affect pH_i in CDs from ClC-K2 deficient mice. Extracellular Cl^- removal to drive basolateral Cl^- exit via ClC-K2 had no effect on pH_i in PCs, but caused alkalization in B-type and acidification in A-type of ICs. Importantly, Cl^- removal did not induce pH_i changes in both A- and B-type of ICs from ClC-K2 deficient mice. This suggests that ClC-K2 mediates trans-cellular Cl^- reabsorption and determines apical acid-base transport by controlling intracellular Cl^- concentration. Moreover, application of Angiotensin II (Ang II, 500 nM) increased ClC-K2 single channel activity and augmented respective ClC-K2-dependent pHi changes in B- but not A-type of ICs to favor apical Cl^-/HCO_3^- exchange. In addition, induction of metabolic acidosis with NH_4Cl supplementation in water, increases H^+ secretion from ICs of WT but not ClC-K2 deficient mice. Furthermore, ClC-K2 activity (measured as NPPB-dependent pH_i changes) was increased in A-type but decreased in B-type of ICs, overall favoring urinary acidification in WT mice.

Conclusions: Altogether, our results show that ClC-K2 is central for acid-base transport in the CD. ClC-K2 activity can be independently regulated in A- and B-type of ICs during different physiological conditions to allow fine tuning of renal acid-base handling.

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TH-OR27

Evolutionary Conserved TLDc Domain Defines a New Class of V-ATPase Interacting Proteins

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Background: Kidney-specific V-ATPase regulates acid-base homeostasis, and its disfunction causes distal renal tubular acidosis (dRTA). We recently found that nuclear receptor coactivator 7 (Ncoa7) interacts with kidney V-ATPase, and its deletion in mice resulted in dRTA. Ncoa7 belongs to a group of proteins playing a role in the oxidative stress response, that contain the evolutionarily conserved TLDc domain. We found that another of these proteins, Oxr1, also interacts with the V-ATPase. Here we asked if other proteins from this family, i.e. Tbc1d24, Tldc1 and Tldc2 interact with V-ATPase in kidney and if their TLDc domains mediate this interaction.

Methods: Interaction between endogenous Tbc1d24, Tldc1 and Tldc2 and V-ATPase was assessed by co-immunoprecipitation (co-IP) and western blotting of mouse kidney lysates. Interaction with the V-ATPase was also studied by GST pull-downs from kidney lysates using purified GST-tagged wild-type TLDc domains of Ncoa7, Oxr1, Tbc1d24, Tldc1 and Tldc2, or mutant TLDc domains of Ncoa7 (G802A, G815A, S817A, G845A, G896A, L926A, E938A) followed by western blotting for B1.

Results: In Co-IP studies of mouse kidney lysates we found that endogenous Tbc1d24 interacted with the B1 subunit isoform of V-ATPase, but not with the more ubiquitous B2 subunit isoform. However, we did not detect any interaction between V-ATPase and endogenous Tldc1 or Tldc2 in Co-IPs, possibly due to low sensitivity of the anti-Tldc1 and anti-Tldc2 antibodies. Additionally, we found that the purified TLDc domains of Ncoa7, Oxr1 and Tldc2, but not Tbc1d24 or Tldc1, interacted with V-ATPase in GST pull-downs. Finally, the G815A, G845A and G896A mutants in evolutionarily conserved regions of the Ncoa7 TLDc domain did not interact with V-ATPase, L926A and E938A mutations resulted in a decreased interaction, while S817A or the non-conserved G802A mutation (used as a positive control), did not decrease interaction at all.

Conclusions: In the kidney, Tbc1d24 and possibly Tldc2, as well as Ncoa7 and Oxr1, interacted with V-ATPase and may play a role in the V-ATPase-dependent regulation of renal acid-base homeostasis. We conclude, that the TLDc motif is a protein-protein interaction domain that defines a new class of V-ATPase interacting regulatory proteins. The evolutionary conserved amino acids within the TLDc domain of Ncoa7 are critical for its interaction with the V-ATPase.

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TH-OR28

Lysine Acetylation of Aquaporin 3 Affects Water Permeability of the Collecting Duct

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Background: We recently reported that there are > 400 proteins in the inner medullary collecting duct (IMCD) that are post-translationally lysine acetylated (ac), including the basolateral water channel, aquaporin-3 (AQP3). The purpose of this study was to determine if lysine acetylated AQP3 (acAQP3) affects water permeability.

Methods: We developed an antibody to detect acAQP3 and found acAQP3 localized to the basolateral membrane of the cortical and outer medullary CD in mice and human kidney biopsies. In mice, following 24 h of water deprivation, acAQP3 was also found in the IMCD. Next, we developed AQP3 K point mutation plasmids; an acetylated mimetic K282Q ($AQP3^{Q/Q}$), and a deacetylated mimetic K282R ($AQP3^{R/R}$). These were stably expressed in vasopressin-responsive mouse cortical CD cells and loaded with a volume sensitive dye. Finally, using CRISPR/CAS we engineered whole body point mutation mice. The $AQP3^{Q/Q}$, $AQP3^{R/R}$ and littermate controls $AQP3^{WT/WT}$ were placed on standard chow and: 1) ad lib water, 2) 5% sucrose water for hydration, or 3) 24 h water deprivation and urine flow measured.

Results: Following osmotic stimulus, we found $AQP3^{Q/Q}$ cells had the highest water permeability followed by the $AQP3^{WT/WT}$ cells and the $AQP3^{R/R}$ cells. From our mutant mice, as adults, control and $AQP3^{Q/Q}$ mice had similar urine flow on all protocols. However, the $AQP3^{R/R}$ mice produced double the urine on protocols 1 and 2. Thus, maintenance of deacetylated AQP3 enhances fluid excretion under normal and hydrated conditions. To further determine whether the increased urine flow was due to impaired water permeability, we immunolocalized AQP2 and AQP3 under ad lib conditions. $AQP3^{Q/Q}$ mice had enhanced expression of AQP3 in the basolateral membrane, and reduced AQP2 expression in the apical membrane. In contrast, the $AQP3^{R/R}$ mice had diffuse AQP3 localization in the CD, with no obvious change in AQP2.

Conclusions: Together, these preliminary data suggest that acAQP3 promotes localization to the basolateral membrane of the CD and supports the hypothesis that acAQP3 could serve as an important regulator of CD function in fluid homeostasis.

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TH-OR29

Role of TRPC3 in the Control of Osmosensitivity and Renal Water Handling in the Mouse Collecting Duct

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Background: Kidney is central in the control of systemic water balance of the organism. AVP facilitates aquaporin 2 (AQP2) translocation to the apical plasma membrane to augment water permeability of the collecting duct (CD). Inability of CD to respond to AVP signal causes NDI leading to polyuria, dehydration and thirst. Stimulation of CD water reabsorption by AVP can only occur in the presence of positive osmotic difference between the cytosol and luminal fluid. Extracellular hypotonicity increases $[Ca^{2+}]_i$ and causes cell swelling due to AQP2-driven water influx. The role of the osmosensitive $[Ca^{2+}]_i$ signaling in renal water transport and urinary concentration remains unknown.

Methods: The employed techniques include simultaneous measurement of $[Ca^{2+}]_i$ dynamics with Fura 2 and the rate of cell swelling as a readout of the AQP2-dependent water reabsorption in freshly isolated split-opened CD of wild type and TRPC3 -/- mice; immunofluorescent detection of AVP-induced AQP2 trafficking to the apical membrane and metabolic cage balance studies.

Results: TRPC3 is a Ca^{2+} permeable mechano-activated channel abundantly expressed in the CD. We found that TRPC3 deletion or pharmacological inhibition precluded $[Ca^{2+}]_i$ elevations induced hypotonicity and severely slowed the rate of cell swelling indicative of diminished water transport in the CD. TRPC3 -/- and WT mice had comparable serum and urine osmolarity in control conditions, but exhibited a significantly greater bodyweight loss, and urinary volume excretion after 24 h of water deprivation (WD) despite higher AVP levels when compared to WT. Furthermore, osmosensitive $[Ca^{2+}]_i$ elevations were greatly increased in CDs from WT but not TRPC3 -/- animals after 24 h WD. Greatly accelerated rate of cell swelling was observed in WT, while it was only modestly increased in TRPC3 -/- mice under the same condition. Using immunofluorescent microscopy, we found that AQP2 translocated to the apical plasma membrane in WT, while maintaining mostly cytosolic localization in TRPC3 -/- after 24 h WD.

Conclusions: Our studies show a significant role of TRPC3 in osmosensitivity and regulation of AVP-dependent AQP2 trafficking in the CD. TRPC3 deletion compromises systemic water balance producing an NDI-like phenotype.

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TH-OR30

Distinct Cellular Osmoregulatory Response in the Skin of Patients with Disturbed Glycosaminoglycan Biosynthesis

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Background: Several studies have shown that during high Na^+ diet (HSD) sodium content of the skin increases. Nuclear factor of activated T cells 5 (NFAT5) is a hypertonicity driven transcription factor responsive to environmental osmotic changes. Sulfated glycosaminoglycans (GAGs) have been suggested to neutralize Na^+-induced hypertonic effects by facilitating a dynamic non-osmotic Na^+ storage compartment. Patients with diabetes mellitus type 1 (DM1) and hereditary multiple exostoses (HME) display decreased GAG sulfation. We questioned whether these patients show distinct cellular osmoregulatory responses to a HSD.

Methods: We performed an experimental randomized cross-over study in 8 DM1, 7 HME, and 12 healthy males with similar age, BMI and eGFR. All subjects followed both an 8-day low Na^+ diet (<50mmol/d) and a HSD (>200mmol/d) in randomized order, separated by a 7-to-10-day washout period. After each diet, blood samples and skin biopsies were obtained. With immunohistochemistry, skin NFAT5 expression and GAG sulfation patterns were semi-quantitatively analyzed by researchers blinded for diet status.

Results: HSD increased dermal NFAT5 expression in controls, whereas in DM1 and HME no changes were observed (Fig1A). In controls, HSD also increased averagely sulfated heparan sulfate in the dermis (Fig1B). During HSD, dermal NFAT5 expression and plasma osmolality were negatively correlated in controls (Fig1C).

Conclusions: In response to HSD, controls showed a hypertonicity-driven response in skin tissue. No hypertonicity-driven changes could be observed in the skin of patients with disturbed GAGs. In controls during HSD, dermal NFAT5 was associated with lower plasma osmolality, suggesting interstitial hypertonicity. Our study implicates that intact GAGs might be important for the skin interstitium to increase hypertonicity and respond to HSD with remodeling the sodium buffering compartment. This underlines the importance of intact GAGs in non-osmotic sodium buffering in humans.

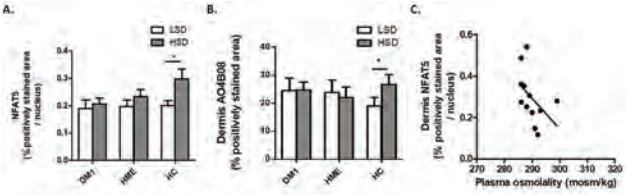

Fig 1 A. High salt diet (HSD) increased expression of NFAT5 in dermal skin (median % positively stained area (IQR) 0.19 (0.09) vs. 0.28 (0.13), p=0.02) of healthy controls. **B.** HSD increased dermis averagely sulfated heparan sulfate (AO4B08) (median % positively stained area (IQR) 15.3 (14.5) vs. 29.9 (20.9), p=0.019) in healthy controls. **C.** Significant negative correlation between dermis NFAT5 expression and plasma osmolality in healthy controls (r=-0.62, p=0.032).

TH-OR31

Risk Factors for AKI During Autologous Stem Cell Transplantation in AL Amyloidosis

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Background: Acute kidney injury (AKI) is a common complication after high dose melphalan and autologous stem cell transplantation (HDM/SCT) in AL amyloidosis patients. However, its incidence, outcome and risk factors are not well known.

Methods: This observational study included 173 AL amyloidosis patients who underwent HDM/SCT in the Amyloidosis Center at Boston University School of Medicine. Demographic, laboratory and clinical data were prospectively collected and analyzed retrospectively. AKI was defined as an increase in serum creatinine to ≥ 1.5 times the baseline value and occurring within the first 30 days after HDM/SCT.

Results: The median age was 57 years (range 32-77). Fifty-nine percent of patients were male. Renal and cardiac involvement were present in 65.3% and 19.7% of patients, respectively. Median eGFR was 83 mL/min/1.73m^2 (range 9-213) and median proteinuria was 2,503 mg/24h (range 0-19,996). The median time from diagnosis to SCT was 4 months (range 1-100). AKI occurred in 28.3% of patients. The causes of AKI were: ATN (27.9%), pre-renal injury (26.4%), melphalan-induced AKI (12.0%), cardiorenal physiology (5.8%), AIN (2.9%), contrast-induced AKI (1.5%), obstructive nephropathy (1.5%), and no clear etiology (22.0%). AKI was associated with increased overall mortality with a hazard ratio of 4.78 (95% CI, 1.9-11.9, p<0.001). The 10-year overall survival was 87.5% for patients who did not have AKI versus 56.2% who had AKI. Baseline characteristics significantly associated with AKI development were: amyloid renal involvement, renal function, proteinuria, hypoalbuminemia, IVSD, atrial fibrillation, use of midodrine or diuretics. Sepsis in the post-transplant period, IV vancomycin use, and *C. difficile* infection were significantly associated with AKI. In terms of hematologic factors, anemia severity, and the need for red blood cell transfusion were significantly associated with AKI. Prolonged thrombocytopenia was associated with AKI; however, delayed WBC engraftment was not associated with AKI.

Conclusions: AKI occurs frequently after HDM/SCT in AL amyloidosis patients and is associated with several risk factors and an increased overall mortality. Prophylactic measures addressing some of these risk factors may reduce this risk.

TH-OR32

Associations Between the Immunoglobulin Germline Gene Usage and the Tropism of Organ Involvement and Renal Amyloid Deposition Patterns in Immunoglobulin Light-Chain Amyloidosis by Mass Spectrometry

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Background: The goal of this study was to characterize the associations between the immunoglobulin light chain variable region (IGVL) germline gene usage and organ tropism, renal amyloid deposition patterns in Chinese patients with AL amyloidosis.

Methods: 105 patients were selected randomly from an overall database of 310 patients with AL amyloidosis diagnosed by renal biopsies during 2000 to 2018. The clinical manifestation and organ involvement were assessed. The renal amyloid deposits on different compartments were evaluated and classified into three patterns: (1) glomerular dominant amyloid deposition pattern (G-AL, n=27); (2) vascular dominant deposition pattern (V-AL, n=32); (3) diffuse amyloid deposition pattern (D-AL, n=46). IGVL germline gene usage was identified based on proteomic analysis of renal amyloidotic tissue by mass spectrometry using a reference database supplemented with sequences of IGVL of AL amyloidosis. The associations of IGVL genes with organ involvement, renal amyloid deposition patterns and survival were assessed.

Results: IGVL genes were successfully identified in 84.8% patients (89/105). LV 6-57 (31.2%) was the most common λ IGVL gene identified among patients with AL amyloidosis, and KV 1-33 (50.0%) was predominant in κ IGVL patients. When compared with patients with renal involvement, the frequency of LV 1-44 (12.1% vs 4.3%, P=0.639)

and LV 1-47 (9.1% vs 4.3%, P=0.636) were high among patients with combined renal and cardiac involvement. Among the specific compartment of kidney with amyloid deposits, LV 6-57 was more likely to have G-AL (42.9% vs 26.9% vs 26.7%, P=0.399), and LV 1-51 was associated with V-AL (19.2% vs 3.3% vs 0, P=0.019). Patients with LV 2 family had a tendency at increased risk of developing into ESRD compared with other IGVL families (P=0.027).

Conclusions: IGVL germline gene usage was associated with organ tropism, renal amyloid deposition patterns and renal survival in Chinese patients with AL amyloidosis. Whereas, the results were preliminary and exploratory, and should be proved in a large cohort of AL amyloidosis patients.

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TH-OR33

Treatment of AL Amyloidosis with Daratumumab Monotherapy

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Background: Immunoglobulin light chain amyloidosis (AL) is characterized by poor outcome. Daratumumab (D) is a first in class anti CD38 human antibody (IgG1κ) which proved to be effective in combination with bortezomib in MM refractory to conventional bortezomib-based regimens. Its effectiveness and safety in the treatment of AL amyloidosis is under study. This study reports the experience with D monotherapy in a series of severe patients (pts) with AL amyloidosis and multiorgan and biopsy-proven renal involvement.

Methods: Five pts, mean age 64 years were treated with D following antibody testing and extended RBC antigen phenotyping. Treatment protocol was as follows: 16 mg/kg D i.v. administered weekly for 8 weeks, then every 2 weeks (8 doses), and then monthly for 1 year.

Results: In pt #1, in dialysis, who was refractory to conventional therapies D administration resulted in normalization of the FLC ratio with disappearance of serum M-component and Bence-Jones (BJ) proteinuria. In pt #2 who had a relapsing disease, D treatment resulted in a rapid decrease of proteinuria and N-terminal propeptide (NT-pro-BNP) levels with disappearance of serum M-component and BJ proteinuria and normalization of the FLC ratio. Pt #3 was treated front-line. He had an impressive decrease of proteinuria and NT-proBNP levels with normalization of FLC ratio and disappearance of serum M-component. In pt #4, who was intolerant to conventional regimens, D therapy resulted in decrease in proteinuria, disappearance of serum M-component and improvement in the FLC ratio, which were paralleled by a reduction of NT-proBNP levels. Pt #5 had a relapsing disease. D achieved a decrease of proteinuria, a decrease of serum M-component with increase of FLC ratio. This was the only patient who experienced an infusion reaction during the first dose. The 4 pt with still preserved renal function also showed renal response with sCr improvement or stabilization and a decrease in proteinuria levels These data were paralleled by the reduction of NT-proBNP values in the 3 pts with cardiac involvement.

Conclusions: Daratumumab monotherapy resulted in the disappearance of M-proteins in every pt with FLC ratio normalization in 4 out of 5 subjects and impressive decrease of proteinuria and pro-BNP values proving to be an effective therapeutic option for pretreated/naïve patients with severe AL with renal involvement.

TH-OR34

Immune Checkpoint Inhibitor Use in Kidney Transplant Recipients: A Multicenter Study

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Background: Immune checkpoint inhibitors (ICIs) significantly improved the survival in many cancers, but the data on survival benefit in KTx recipients are lacking. ICIs are reported to be associated with higher acute rejection rate in KTx recipients, but the risk factors of ICI-associated rejection are not fully understood.

Methods: We conducted a multicenter observational study to investigate the clinical characteristics of ICI-associated rejection and the survival outcomes of KTx recipients treated with ICI. 66 KTx patients with a functioning allograft at the time of ICI initiation were collected from 18 institutions. In addition, historical control groups of KTx recipients with advanced stage melanoma (AJCC stage III-IV, n=17) and cutaneous squamous cell carcinoma (cSCC, AJCC stage III (unresectable)-IV), n=23), who could be considered as potential ICI candidates, were collected to compare the overall survival (OS).

Results: In ICI cohort, median age was 64, male dominant (83%) and transplant to ICI initiation was median 11 years. cSCC was the most frequent malignancy (n=22), followed by melanoma (n=21). 28 patients (42.4%) experienced rejection, of which 18 (64.2%) lost allograft and returned to dialysis. Median time from ICI initiation to rejection was 26 days. In biopsy-proven rejection (n=13), both mixed acute cell and antibody-mediated rejection (n=7, 53%) and acute cell-medicated rejection (n=6, 47%) were seen. By Chi square test, mTOR inhibitor use (*p=0.012) and the use of higher number of immunosuppression drugs (*p=0.049) were associated with lower risk of rejection. For both melanoma and cSCC cohort, ICI groups experienced higher rejection rate (57% and 40%, for melanoma and cSCC, respectively), compared to non-ICI control groups (12% and 4.3%), suggesting the higher rejection rate in ICI groups was not solely explained by reduction in immunosuppression. OS didn't show statistical difference in melanoma cohort (log rank test p=0.22), but OS was significantly longer in cSCC cohort (log rank test *p=0.015), when compared ICI vs non-ICI control groups.

Conclusions: Our multi-center study provides a novel data on the survival benefit and the risk factors of rejection in KTx recipients with ICI use compared to non-ICI control groups.

Funding: NIDDK Support, Private Foundation Support

TH-OR35

Daily Caffeine Consumption and Risk of AKI Related to Platinum-Salt Chemotherapy: A Prospective Cohort Study

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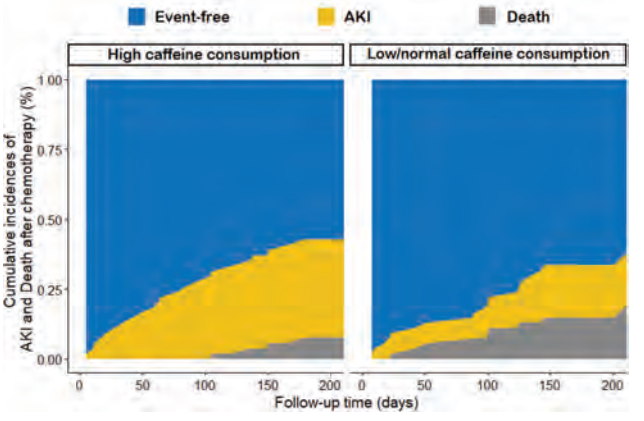
Background: Although their efficacy has been well-established in Oncology, the use of platinum salts remains limited due to the occurrence of acute kidney injury (AKI). Caffeine has been suggested as a potential pathophysiological actor of platinum salt-induced AKI, through its hemodynamic effects. This work aims to study the association between caffeine consumption and the risk of platinum salt-induced AKI.

Methods: We conducted a single-center prospective cohort study that has included 108 consecutive thoracic cancer patients receiving a first-line platinum-salt chemotherapy between January 2017 and December 2018. Before the first course of chemotherapy, they were all invited to fill in a previously validated auto-questionnaire, designed for a detailed evaluation of their daily caffeine consumption (mg/day). The association of daily caffeine consumption with the risk of platinum-salt induced AKI was estimated by cause-specific Cox proportional hazard model adjusted for several known confounders (baseline renal function and serum albumin level, nature and dose of platinum-salt, tobacco exposure, and Performans status).

Results: Overall, 34 patients (31.5%) (mean age 61.7 years, 65% men, 80% tobacco users) experienced a platinum salt-induced AKI (67% grade 1) and 47 (43.5%) died during follow-up (6.2 months [3.4; 8.4]). The group of high-caffeine consumption (≥ 386mg/day) had a twice higher risk of AKI (HR=2.12 [1.01; 4.45]) in the fully adjusted model. The cumulative incidence of AKI (considering the competing risk of death) was also significantly increased in the high-caffeine consumption group (p=0.03, see figure 1).

Conclusions: In a population of thoracic cancer patients, the group of high-caffeine consumption was exposed to a significantly higher risk of platinum salt-induced AKI.



TH-OR36

Kidney and Cancer Outcomes with Standard vs. Kidney Protective Chemotherapy Regimens for First-Line Treatment of Metastatic Urothelial Carcinoma

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Background: Cisplatin-based combination chemotherapy regimen is the optimal initial treatment for metastatic urothelial carcinoma, but kidney function eligibility and nephrotoxicity are treatment-limiting for many patients. For patients unfit to receive cisplatin, other options include alternative administration schedules (e.g. split dose cisplatin), carboplatin-based regimens and non-platinum regimens. The aims of this study were to compare cancer outcomes and incidence of acute kidney injury (AKI) during treatment among 3 regimens of chemotherapy.

Methods: We conducted a single-center retrospective study of patients receiving first-line chemotherapy for metastatic urothelial carcinoma (2005-2019). We compared standard gemcitabine-cisplatin (gem-cis) to: 1) gemcitabine-cisplatin split dose regimen (split) with cisplatin divided over day 1 and 8; and 2) combination of gemcitabine-carboplatin or single-agent gemcitabine (gem/gem-carbo). We used Fine and Gray hazard models accounting for baseline covariates and competing risk of death.

Results: We identified 183 patients (98 gem-cis, 32 split and 53 gem/gem-carbo). Median age was 67 years-old (IQR: 61-73) and 76% were male. Median baseline eGFR was 78 mL/min/1.73m^2 (IQR: 66-91) in gem-cis, 64 (48-77) in split, and 45 (33-57) in gem/gem-carbo. Patients receiving split and gem/gem-carbo were older, had worse performance status, and hypertension was more frequent. Split and gem/gem-carbo regimens were associated with higher mortality and progressive disease relative to gem-cis when adjusted for age, baseline eGFR, ECOG, hypertension and diabetes with hazard ratio (HR) of 1.56 (95%CI: 1.04-2.34; p=0.03) and 2.02 (95%CI: 1.36-3.01; p<0.01) respectively. Median time to progressive disease was 242 (IQR: 137-444), 182 (122-279) and 131 (68-257) days in gem-cis, split and gem/gem-carbo groups. There was no significant association between regimen type and AKI with HR of 1.32 (95%CI: 0.62-2.81; p=0.47) and 0.98 (95%CI:0.46-2.09; p=0.96) for split and gem/gem-carbo groups versus gem-cis.

Conclusions: Kidney protective chemotherapy regimens were associated with increased disease progression and mortality, without a significant difference in AKI. Alternative kidney protective strategies are needed for patients with CKD and urothelial cancer.

TH-OR37

Risk Factors for Nephrotoxicity with High-Dose Methotrexate (HDMTX) in Haematological Malignancies

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Background: HDMTX is a key component for treatment of haematological malignancy. Nephrotoxicity remains a significant risk factor for HDMTX and therefore, hyper-hydration and urinary alkalinisation are employed to optimise excretion but despite these measures, nephrotoxicity remains 2-12%. Determination of risk factors is key in order to further stratify and ameliorate the risk of acute kidney injury.

Methods: A retrospective review of the electronic medical record was conducted to identify patients with leukaemia or lymphoma who received HDMTX from 1/1/2002 to 12/31/18. We characterised the incidence of AKI, using the acute kidney injury network criteria, and the time to AKI. We assessed key baseline demographics, underlying malignancy, delivered MTX dose, and previous nephrotoxicity. Significant factors on univariate analysis were further assessed on Multivariate analysis. Analysis was performed on Minitab.

Results: We identified 3091 cycles of HDMTX with lymphoma accounting for 90.7% of cases. The incidence of AKI was 19.1% in the lymphoma cohort and 13.6% in the leukaemia cohort (p=0.023). The median time to AKI grade shortened with higher severity of AKI (p<0.001). In those with AKI N3, creatinine increased to this level in a median time of 1 day. All patients requiring dialysis (n=7) developed an AKI at day 1 post HDMTX. Univariate analysis revealed age (p=0.022), Gender (p<0.001), higher BSA (p<0.001), type of malignancy (p=0.023), nephrotoxicity on previous dose (p<0.001), cycle number (p<0.001), GFR by Cockcroft-Gault (p=0.016) and 48-hour MTX level (p<0.001). There was no association between AKI and MTX dose (p=0.225), or GFR by MDRD (p=0.497). Multivariate analysis revealed increased age (p<0.001), male Gender (p<0.001), Lymphoma (p=0.002), previous AKI (p<0.001), cycle number (p=0.032), and 48-hour MTX level (p<0.001) to be significant risk factors for nephrotoxicity.

Conclusions: Nephrotoxicity remains a significant complication with HDMTX despite current prevention measures. High grade AKI occurs early post HDMTX and therefore, risk stratification is vital. Our study identified key risk factors as older, male, AKI on previous dose, diagnosis of lymphoma, elevated 48-hour MTX level and earlier cycle.

TH-OR38

Characterizing the Risk of Development of Proteinuria with Bevacizumab Therapy

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Background: Bevacizumab is a well-known cause of proteinuria. There are multiple hypotheses regarding mechanism that involve the VEGF receptor, nitric oxide metabolism and increased arteriolar glomerular pressure. The most accepted explanation is that Bevacizumab induces thrombomicroangiopathy. However, there is no current model or description of potential risk factors to identify at-risk patients who may need closer monitoring, although a dose dependent relationship has been described previously. There also exists no proven therapy for mitigating or reversing the proteinuria. Current guidelines advise that therapy be either discontinued or completely stopped depending on the level or proteinuria that develops. Some authors have proposed RAAS inhibition, but no data is available to support that theory.

Methods: 1224 patients on Bevacizumab were sampled, with 714 having at least one P/Cr value needed for analysis. The time frame in which data was collected was 600 days. Data sampled included, age, baseline P/Cr, status of type 2 diabetes, chronic kidney disease stage 3, hypertension, use of Angiotensin Converting Enzyme inhibition, and sequential P/Cr values. Cox proportional hazard models were used to assess differences in the instantaneous risk of the event by categories, no violations of proportional hazard models were observed. The primary endpoint was defined as a P/Cr of 1.0 g/g, indicative of progression of proteinuria.

Results: A baseline P/Cr above 0.25 (HR 5.83, p=<0.001), Type 2 Diabetes (HR 1.68, p=0.074), and CKD III (HR 3.25. p=0.007) were associated with an increased risk of developing proteinuria, while age, hypertension (HR 1.11, p = 0.86), a baseline P/Cr < 0.25 (HR 1.04, CI 0.53,2.04, p<0.001) were not. ACE inhibitors had the following association: (Lisinopril; {10 mg, 20 mg, > 20mg}, HR {1.47, 1.76, 1.67}, p=0.67). Treatment duration was also shown to increase risk of the primary endpoint. The cumulative incidence was 23% after 600 days of treatment.

Conclusions: A presence of a baseline P/Cr greater than 0.25 g/g, type 2 diabetes, and CKD III, all showed a significant increase in risk of progressing to proteinuria of greater than 1.0 g/g. Age and hypertension were not associated with increased risk. Due to lack of randomization and incomplete data, further analysis is needed.

TH-OR39

CKD Prevalence, Patterns of Treatment, and Outcomes in Patients with Cancer: A Population-Based Cohort Study

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Background: Chronic kidney disease (CKD) may impede optimal cancer treatment and result in worse outcomes. There are limited data to assess receipt of systemic therapy, radiation therapy, and palliative care in patients with cancer and CKD.

Methods: We conducted a population-based cohort study of all patients (≥18 years old) with a new cancer diagnosis in Ontario, Canada (2007-2015). We categorized patients according to CKD status at cancer diagnosis [estimated glomerular filtration rate (eGFR) ≥60 (referent group), 45-59, 30-44, 15-29, <15 mL/min/1.73m^2, dialysis and transplant recipients]. We used multivariable Fine and Gray proportional hazards models to assess overall survival, receipt of systemic therapy, radiation and palliative care (6-months prior to death) in the 5 most common solid cancers (bladder, breast, colon, prostate, lung) and kidney cancer.

Results: We identified 128,489 patients with a new cancer diagnosis, of whom 16% had pre-existing CKD (eGFR <60 mL/min/1.73m^2). Patients with the 6 cancers of interest accounted for 73% (93,751). Kidney function at cancer diagnosis was associated with (progressively) worse overall survival in CKD stages 3a-5, dialysis, and transplant recipients (Figure a). Increasing CKD stage was associated with significantly reduced receipt of all treatment modalities [systemic therapy, radiation and palliative care (Figure b-d)]. Patients receiving dialysis had 2-fold increased mortality in bladder, breast and colon cancers, and 3-fold mortality in kidney cancers.

Conclusions: In patients with cancer, CKD is associated with reduced exposure to systemic, radiation and palliative treatments and worse overall survival. Strategies to improve cancer care in the CKD population are needed.

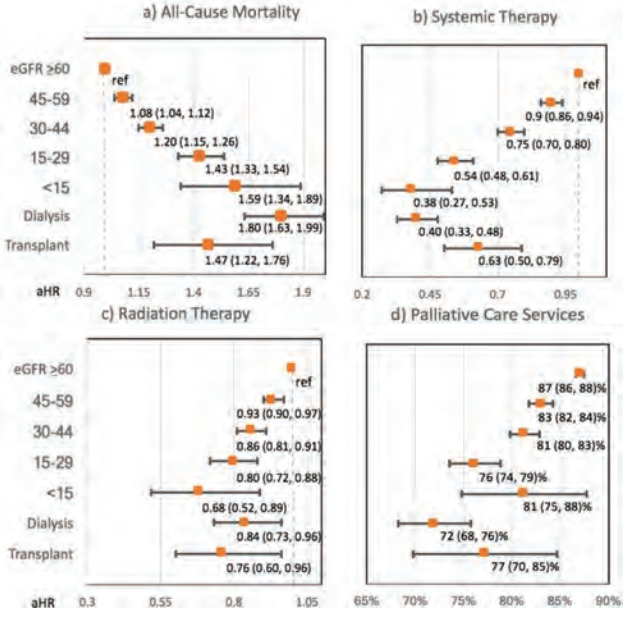

Figure - Adjusted HR by CKD Status

TH-OR40

Assessment of Estimated Glomerular Filtration Rate in a Cohort of 1200 Cancer Patients Using Serum Creatinine and Cystatin C

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Background: eGFR using creatinine (eGFRcr) with the CKD-EPI equation is recommended as the first test for GFR evaluation in clinical practice, but CG equation is commonly used for the prescription of chemotherapy, despite increasing evidence of its inaccuracy compared to measured GFR (mGFR). eGFR using cystatin C (eGFRcys)

is less influenced by muscle mass or nutritional status, and eGFR using both markers (eGFRcr-cys) is more accurate than either eGFRcr or eGFRcys, but neither has been widely assessed in cancer patients. Our aim is to compare the performance of eGFR equations (Table) in cancer patients compared to mGFR.

Methods: This analysis is a cross-sectional evaluation of a prospective cohort of cancer patients in treatment at the ICESP. mGFR was determined by plasma clearance of ^{51}Cr-EDTA indexed for body surface area.

Results: A group of 1,200 patients recruited between April 2015 and September 2017. Patients were 60 (51 – 68) y, 50.8% male. The most common cancer sites were breast (22.6%), prostate (19.8%) and gastrointestinal (13.4%). All eGFRcr equations overestimated mGFR with varying bias. CG had the lowest precision and was least accurate. eGFRcys underestimated mGFR and eGFRcr-cys had minimal bias and was the most accurate of all equations (Table).

Conclusions: All eGFRcr equations overestimated mGFR in our study. CG was the least accurate and should not be preferred over CKD-EPI. eGFRcr-cys is more accurate and can be used as a confirmatory test.

eGFR filtration marker	eGFR equation (year)	Bias (median) (ml/min/1.73 m2)	Precision (IQR) (ml/min/1.73 m2)	Accuracy (1-P30) (%)	Accuracy (RMSE)
eGFRcr	CG (1976)	-8.12 (-9.34 to -6.74)	24.1 (22.4 – 25.7)	24.9 (22.3 – 27.2)	0.23 (0.22 – 0.25)
eGFRcr	MDRD (2006)	-4.83 (-5.98 to -3.63)	20 (18.5 – 21.4)	18.1 (15.9 – 20.3)	0.21 (0.22 – 0.22)
eGFRcr	CKD-EPI (2009)	-8.0 (-8.82 to -7.06)	18.3 (17 – 19.5)	19 (16.8 - 21.2)	0.20 (0.19-0.21)
eGFRcr	Janowitz-Williams (2017)	-5.68 (-6.66 to – 4.93)	20.2 (18.8 – 21.8)	19.6 (17.3 – 21.7)	0.21 (0.20 – 0.22)
eGFRcys	CKD-EPI (2012)	4.57 (3.71 to 5.5)	17.5 (16.3 – 19.3)	12.3 (10.4 - 14)	0.21 (0.20 – 0.22)
eGFRcr-cys	CKD-EPI (2012)	-1.97 (-2.57 to -1.11)	15.9 (14.7 – 16.8)	7.83 (6.25 – 9.26)	0.16 (0.15 – 0.17)

SCr and SCys were measured through certified reference materials. CG (Cockcroft Gault); MDRD (Modification of Diet in Renal Disease), CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), IQR, interquartile range; RMSE, squared root of mean squared error, P30: percentage of estimates that are 30% over or below mGFR. Non-overlapping confidence intervals indicates statistical significance

TH-OR41

Hematopoietic-Specific Melanocortin 1 Receptor Signaling Protects Against Crescentic Glomerulonephritis and Mediates the Beneficial Effect of Melanocortin Therapy

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Background: Emerging evidence suggests that melanocortin 1 receptor (MC1R) signaling may contribute to the beneficial action of melanocortins in glomerular diseases. However, whether hematopoietic MC1R signaling is implicated is unknown.

Methods: MC1R mutant (e/e) or wild-type (WT) mice were injured with rabbit nephrotoxic serum (NTS) and treated with melanocortins, including the Repository Corticotropin Injection (RCI, Acthar® Gel, Mallinckrodt ARD, LLC), NDP-MSH, and the MC1R selective agonist MS05. Some mice received adoptive transfer of syngeneic bone marrow-derived cells (BMDC) beforehand. Kidney function and injuries were evaluated.

Results: Upon NTS injury, e/e mice developed more severe crescentic glomerulonephritis than WT mice, featured by heavier proteinuria, higher serum creatinine levels and exacerbated renal lesions, including crescent formation, renal inflammatory infiltration and fibrosis as well as podocyte damage, marked by loss of expression of podocyte homeostatic markers in glomeruli. Melanocortin therapy substantially improved renal injury in WT mice and this protective effect was blunted in e/e mice. In contrast, adoptive transfer of BMDC derived from WT mice to e/e mice markedly ameliorated NTS nephritis and reinstated the therapeutic efficacy of melanocortins in e/e mice. Mechanistically, the beneficial action of WT BMDC in e/e mice was associated with diminished glomerular deposition of autologous anti-rabbit IgG and reduced fixation of C5b-9 along glomerular capillary loops, entailing a regulatory effect of BMDC-specific MC1R signaling on humoral immune response to NTS antigens. In addition, melanocortin therapy prominently tilted macrophage polarization towards the anti- inflammatory M2 phenotypes in NTS-injured kidneys in WT mice. MC1R signaling is likely involved in this modulation of macrophage behavior, because MC1R was evidently expressed in bone marrow-derived macrophage (BMM) prepared from WT mice but absent from e/e BMM. Furthermore, MS05 diminished M1 phenotypes and promoted M2 polarization in M1-primed WT BMM but not e/e BMM, thus denoting a pro-M2 skewing effect of MC1R signaling.

Conclusions: Hematopoietic MC1R signaling attenuates NTS nephritis *via*, at least in part, regulation of humoral immune response and a pro-M2 skewing effect on macrophage polarization.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

TH-OR42

Spatial Transcriptomics (ST): Integrating Molecular Profiles with Histomorphology in Kidney Tissue Sections

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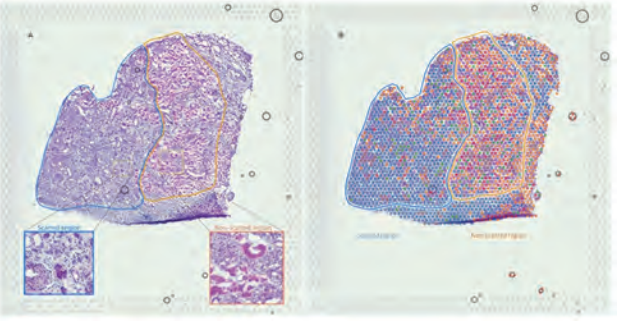
Background: Advances in sequencing methods have increased available molecular information on dissociated cells and tissues. Spatially linking this molecular information with histomorphology is needed to understand a complex organ like the kidney, in both health and disease.

Methods: Here we used the commercially available 10x Genomics ST platform to investigate the spatially resolved transcriptome expressions in fetal (n=2), adult male (n=3) and female (n=3) mouse frozen kidney and a healthy human cortical frozen kidney tissue sections. We utilised Space Ranger (10x Genomics), Seurat and stLearn analysis pipelines to explore the spatial transcriptome expression within the kidney tissue sections. Furthermore, we confirmed the robustness of our ST data against matched publicly available mouse and human kidney scRNA-seq data.

Results: We identified a unique transcriptome plasticity in fetal and adult mouse kidneys, and healthy human cortical kidney tissue. Further dimensional reduction identified transcriptome clusters which correlated with distinct developing kidney structures in fetal mouse kidney tissue, functional cortical and medulla regions in adult mouse kidney tissue, and scarred and non-scarred regions in human cortical kidney tissue.

Conclusions: ST is a non-dissociative sequencing and imaging method which allows molecular profiles to be integrated with histomorphology of frozen kidney tissue sections. This provides a novel opportunity to inform physiological and non-physiological conditions at the cell-cell, nephron and tissue levels.

Funding: Government Support - Non-U.S.



ST provides transcriptome expression within intact kideny tissue sections. **(A)** H&E stained human cortical kidney tissue with scarred and non-scarred regions. **(B)** The same human cortical kidney tissue with the transcript capture spots coloured by clustering using t-SNE projection demonstrates distinct transcriptome expression in scarred and non-scarred regions.

TH-OR43

Automated Atubular Glomeruli Detection Using 3D Glomerular Quantification Algorithms

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Background: Atubular glomeruli are associated with decreased glomerular filtration rate and kidney disease progression. To identify atubular glomerulus requires serial section analysis, tracking individual glomeruli, and then determining whether each glomerulus has or does not have connection to the proximal tubule. This process is labor intensive and very time-consuming, limiting its use. We aimed to test feasibility of automatically detecting atubular glomeruli by using Multi-Object Association for Pathology in 3D (Map3D).

Methods: The Map3D was created including a glomerular detection algorithm, dual-path multi-object tracking algorithm, and pixel-wise large-scale glomerular association algorithm across routine serial sectioning with whole slide imaging (WSI). Atubular glomerular counting was done on 6 normal mouse kidneys, and 3 mice with diphtheria toxin (DT)-mediated proximal tubule-specific injury in mice with tubular cell expression of the DT receptor, and 4 mice with patchy tubulointerstitial fibrosis induced by folic acid (FA). Data from this automated approach was compared with standard manual assessment detailed above and correlated with functional and structural parameters.

Results: The Map3D substantially reduced the time needed for average atubular glomerular counting per sample (30 min Map3D vs. 30 hours human). Atubular glomerular size were smaller than normal glomeruli. The number of complete (i.e. from pole to pole) glomeruli assessed increased by 25.6% using GQuant-3D (86±8.8 per mouse) vs human counting (72±2.7 per mouse). GQuant-3D recognized 14.3±5.5 atubular glomeruli per mouse sample, slightly less (83%) than the 16.7±3.0 atubular glomeruli per mouse sample

recognized by manual human assessment. The percentage of atubular glomeruli by GQuant-3D was increased in DT mice (9.7±2.15%) and FA mice (36.5±7.44%) compared with normal mice (6.0±0.91%). The percentage of atubular glomeruli, counted by either GQuant-3D or human, correlated with interstitial fibrosis (R^2=0.49 or 0.61 respectively), but not with tubular injury marker, KIM-1 and N-GAL.

Conclusions: The Map-3D algorithms reduced time required for atubular glomeruli assessment, provided data correlating well with human manual-based assessment, and correlated well with relevant morphology data. This methodology can be extended to 3D glomerular phenotype analysis.

Funding: NIDDK Support

TH-OR44

A Deep-Learning Approach to Kidney Donor Biopsy Frozen Sections

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Background: Pre-implant assessment of donor kidney biopsies to determine allograft viability is often performed by non-renal pathologists, and carries limited accuracy and reproducibility. The purpose of this work is to develop a deep learning (DL) method for the classification of relevant histologic primitives from donor biopsies as an aid tool to pathologists. Non-sclerotic and sclerotic glomeruli were selected to test this approach.

Methods: A total of 268 frozen sections stained with hematoxylin and eosin (H&E) from cadaveric donor kidney biopsies (128 performed at Duke and 140 at outside institutions) were scanned into whole slide images (WSI) at 40x (Leica Biosystems AT2). Duke WSIs were divided at the patient level into training and validation cohorts (0.8:0.2) and non-Duke WSIs were used as testing dataset. QuPath was employed to manually annotate non-sclerotic (22767) and sclerotic glomeruli (1366). A 9-layer convolutional neural network (CNN), based on the common U-NET architecture, was developed in Python, using randomly selected 256x256 patches from WSI, and image augmentation to boost generalization performance. CNN hyper-parameters were tuned via cross-validation. The CNN's performance was quantified based on the Dice Similarity Coefficient (DSC) between the predicted and ground-truth annotations.

Results: For non-sclerotic glomeruli, the average DSC for train, validation and testing was 0.93, 0.91, 0.90 respectively. The F1, Recall, and Precision for testing was 0.93, 0.96, 0.90 respectively. For sclerotic glomeruli, the average DSC for train, validation and testing was 0.89, 0.87, 0.83 respectively. The F1, Recall, and Precision for testing was 0.87, 0.93, 0.81 respectively. The CNN had higher performance in the regions of high glomerular density and occasionally, outperformed the pathologists in glomerular detection. Lower model performance was observed in the presence of image artifacts and in regions of low glomerular density.

Conclusions: DL applied to image analysis may help standardize and improve accuracy and reproducibility of quantification of histologic primitives in kidney frozen sections, enabling the establishment of synergistic machine-human protocols that can be deployed in clinical practice. The development of DL-segmentation of other relevant histologic primitives is in process.

Funding: Private Foundation Support

TH-OR45

Evaluation of a Direct-to-Digital Histology Method for Rapid Evaluation of Kidney Biopsies

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Background: Digitization of clinical renal biopsy histology is motivated by the importance of early intervention in acute kidney conditions, assessment by remotely-based experienced nephropathologists, and application of emerging computerized quantitative evaluation tools. Despite the interest, image quality and workflow impact are concerns for digital renal pathology. A newly developed tool for rapid, slide-free microscopic image preparation called Clearing Histology with MultiPhoton Microscopy (CHiMP) has demonstrated high efficiency and high quality morphology for diagnostic review in renal disease in a research environment. We sought to commence clinical validation of CHiMP for renal biopsies, including assessing effects on downstream traditional special stains and ability to detect a broad range of clinically relevant pathologic lesions in renal biopsies.

Methods: Kidney core biopsies were procured from 50 consented individuals undergoing renal biopsy for any reason and CHiMP processing was integrated into the routine clinical workflow, using previously-described methods. Images were obtained through entire core biopsies with a prototype fast, high resolution, multiphoton microscope system (Applikate Technologies, Washington, DC) and visualized with web-based software. Samples were subsequently processed using standard methods for clinical interpretation under transmitted-light microscopy, including special stains. A subset of 20 core biopsies underwent detailed morphologic feature detection analysis and quantitative lesion comparison.

Results: Diagnostic quality remotely-reviewable renal images of 10-16 digital slices were available within < 3 hours of receipt. H&E detected morphologic findings were equally detectable in digital images compared to physical, paraffin-embedded sections including cases showing tubular injury, proliferative glomerulonephritis, glomerular deposition disease, and interstitial nephritis. No significant negative effects on downstream processing were identified.

Conclusions: CHiMP can be used in rapid morphologic evaluation of kidney biopsies integrated into clinical work enabling rapid rendering of preliminary diagnoses while simultaneously making digital images available for remote expert evaluation and digital analysis. Continuing validation will test ability to augment detection of rare lesions and quantitative precision.

Funding: NIDDK Support

TH-OR46

Kidney Biopsy Transcript Patterns Offer a Novel Approach to Distinguishing Etiologies of Acute Interstitial Nephritis

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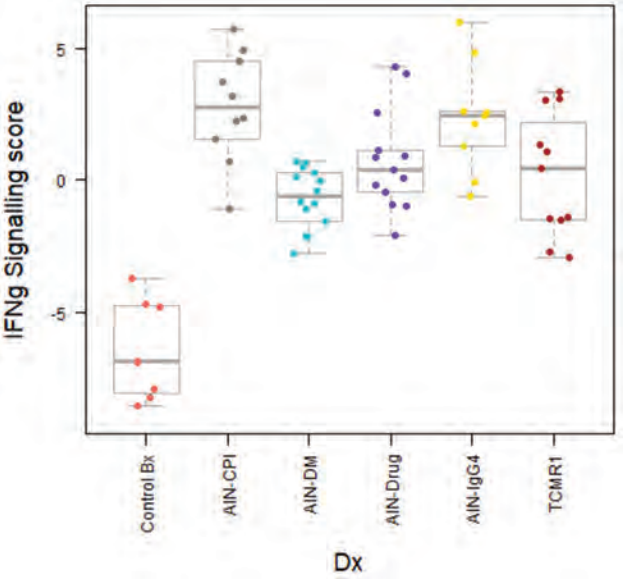
Background: One of the challenges in renal pathology is distinguishing causes of acute interstitial nephritis (AIN). Based on encouraging results from renal allografts, we sought mRNA transcript profiles of checkpoint inhibitor associated AIN (CPI), drug induced AIN (Drug), AIN in diabetes (DM), IgG4-related renal disease (IgG4) and T cell rejection type I (TCMR1).

Methods: Three 20 um sections were obtained from 65 FFPE blocks: 9 controls, 46 AIN types (10 CPI, 13 DM, 14 Drug, 9 IgG4) and 10 TCMR1. RNA was extracted and hybridized with NanoString HOT Panel of 770 probes and analyzed on an nCounter Max instrument. The gene list is available at nanostring.com. Pathway analysis, differential expression and cell type scores were analyzed from normalized mRNA counts using nSolver.

Results: Similarities were found across AIN however each had one or more distinct patterns of transcripts. **CPI AIN** was distinguished from the other causes of AIN by higher IFNγ signaling pathway scores (Fig 1). CPI AIN had more exhausted CD8 cells ($p<0.05$) and NK cells ($p<0.001$) than drug induced AIN. **DM AIN** differed from histologically indistinguishable **Drug AIN** by several genes (e.g. higher *TGFβ2*, p=0.007). **IgG4 AIN** showed the highest levels of B cell receptor signaling, MAPK and mTOR pathways, and highest Th17 and Treg differentiation scores. **TCMR1** had lower scores for TGFβ and TNF pathways and lower Treg scores compared with the other causes of AIN. TCMR1 had the most favorable scores for AKI and pathways related to outcome (eGFR later, GoCAR progression).

Conclusions: Our initial findings suggest that once extended to customized algorithms and validated, this approach may prove fruitful in distinguishing the underlying diagnosis and pathogenesis of diverse causes of AIN.



TH-OR47

Identification of Novel Biomarkers of Kidney Disease Histopathology and Prognosis: Results from the Boston Kidney Biopsy Cohort

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Background: Biomarkers for non-invasive assessments of histopathology and prognosis are needed in patients with kidney disease.

Methods: Using a novel proteomics assay, we measured a multi-marker panel of 225 circulating plasma proteins in a prospective cohort study of 557 individuals with biopsy-confirmed kidney diseases and adjudicated semi-quantitative assessments

of histopathologic lesions. We tested the associations of each biomarker with clinicopathologic diagnoses, histopathologic lesions, and the risks of kidney disease progression (≥40% decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease) and death.

Results: After multivariable adjustment and correction for multiple testing, 39 proteins were independently associated with clinicopathologic diagnoses and 53 with different histopathologic lesions. Kidney-injury molecule-1 (KIM-1) associated with diabetic nephropathy and glomerular and tubulointerstitial diseases. The top performing markers for acute tubular injury and interstitial fibrosis and tubular atrophy were KIM-1 and tumor necrosis factor receptor superfamily member-9 (TNFRSF-9), respectively. Thirty proteins were significantly associated with kidney disease progression and 35 with death (Figure 1 A, B). The top performing markers for kidney disease progression were placental growth factor (PGF; HR 5.4, 95% CI 3.4 to 8.7) and BMP and Activin Membrane Bound Inhibitor (BAMBI; HR 3.0, 95% CI 2.1 to 4.2); the top performing markers for death were TRAIL-receptor-2 (TRAIL-R2; HR 2.9, 95% CI 2.0 to 4.0) and CUB Domain Containing Protein-1 (CDCP1; HR 2.4, 95% CI 1.8, 3.3). Five proteins were significantly associated with decreased risks of death (Figure 1 B).

Conclusions: We identified several biomarkers of kidney disease histology, pathology, and prognosis – many of which have not been reported previously and may represent important avenues for future research.

Funding: NIDDK Support, Private Foundation Support

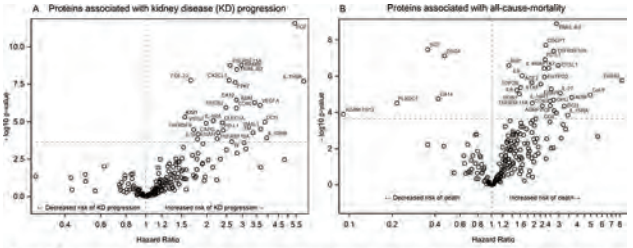

Figure 1. Proteomic discovery of circulating biomarkers associated with kidney disease progression (A) and all-cause-mortality (B). Proportional hazards models are adjusted for age, sex, race, clinicopathologic diagnoses, proteinuria, and eGFR. Dotted lines show Bonferroni-adjusted significance thresholds.

TH-OR48

Complement Activation Assay in an Ex Vivo Microfluidic Cell-Culture System

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Background: Discrimination between different diseases in patients suffering from thrombotic microangiopathies is often challenging. Measuring C5b9 deposit on endothelial cells using confocal microscopy have been shown to be convenient in diagnostic and therapy monitoring of Atypical hemolytic uremic syndrome (aHUS) but methods are complex and costly.

Methods: We developed a cell-based C5b9-ELISA to measure C5b9-deposits on activated endothelial cells. Patients with suspected aHUS and other thrombotic microangiopathies were identified in early disease stage. Serum was drawn and tested versus healthy controls. After confirmation of the diagnosis aHUS therapy efficiency was monitored using the assay.

Results: In patients with the clinical diagnosis of aHUS we were able to show up to six-fold higher C5b9-deposits in contrast to normalized human serum (NHS) (p-value < 0,0001). In comparison to healthy controls, patients suffering from either Shiga-Toxin-HUS or Thrombotic Thrombocytopenic Purpura (TTP) we could demonstrate a two- to three-fold higher deposit (p-value=0.0103 and below). After onset of eculizumab treatment, the amount of C5b9-deposits becomes lower than in healthy controls, proving the efficiency of the therapy. One-Way-ANOVA shows significant differences between aHUS-groups and controls, but not between aHUS patients using Tukeys-multiple comparisons test.

Conclusions: We described a novel, fast and reproducible ELISA to identify aHUS-patients by measuring C5b9-deposits and monitor disease activity. This can give a rise to diagnostic speed and therapy decisions. Further investigation and validation are needed to show interactions with other complement diseases like systemic lupus erythematosus.

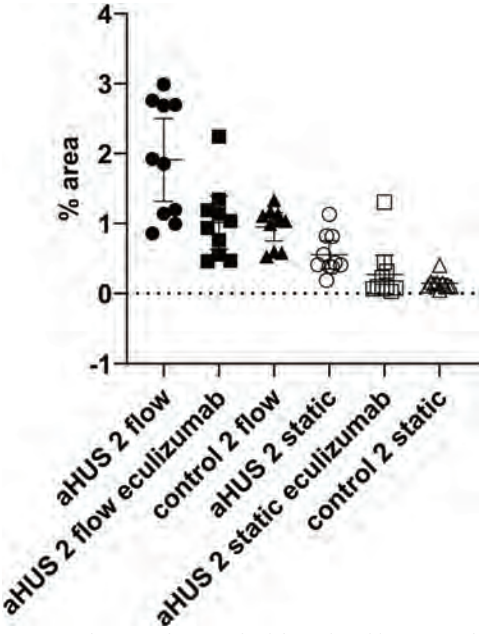

Figure 1: Percentage of area per image stained for C5b9 with 95% CI after treatment with patient serum.

TH-OR49

Barriers and Opportunities to Improve Variability in CKD Laboratory Methodology and Reporting: Results from the College of American Pathologists (CAP) 2019 Survey

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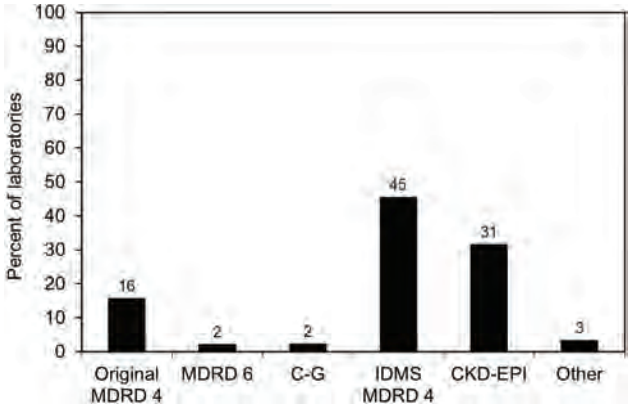
Background: Variability in laboratory practices for estimated GFR (eGFR) and urine albumin-creatinine ratio (uACR) is a barrier to optimal CKD testing and interpretation by clinicians. The CAP serial surveys assess CKD laboratory methodology and reporting.

Methods: The CAP 2019 General Chemistry Survey conducted in December, included 9 questions regarding CKD tests.

Results: Respondents included 7,105 laboratories (83.8% U.S. and 16.2% international) with a response rate of 87.5%. Laboratory reporting of eGFR based on serum creatinine has increased overall from 3% to 92% in CAP surveys between 2003 and 2019. The Figure shows 76% of laboratories were using an isotope dilution mass spectrometry (IDMS) traceable version of the MDRD 4-variable equation (45%) or the CKD-EPI equation (31%), but an incorrect equation was used for IDMS creatinine by 23% of the respondents, resulting in systematic over estimation of kidney function. Barriers for the pediatric population less than 18 years include only 10% of laboratories report the correct bedside Schwartz equation and 20% of laboratories applied an incorrect adult eGFR equation for children. The microalbumin term that KDIGO and KDOQI recommend be eliminated continues to be used by 64.5% of U.S. and 42.2% of international labs, see Table. Lastly, 12.6% of U.S., and 9.4% of international laboratories report only the urine albumin concentration without uACR, which is uniformly not recommended.

Conclusions: Laboratory variability is a call to action for nephrologists to collaborate with clinical laboratorians to improve appropriate CKD testing.



eGFR Equation Reporting

Test order name	U.S. labs	International labs
uACR	911	379
Microalbumin	3537	466
Total responding	5462	1104
Test reporting	**U.S. labs**	**International labs**
Any uACR	3673	744
Urine albumin only	563	81
Total responding	4463	860

Albuminuria Reproting

TH-OR50

Immunotactoid Glomerulopathy: A Rare Entity with Monoclonal and Polyclonal Variants

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Background: Immunotactoid glomerulopathy (ITG) is a rare disease currently classified as an MGRS lesion for which our understanding is limited.

Methods: 73 patients with ITG were identified by retrospective review of all native renal biopsies received at two large renal pathology laboratories from 1993-2019.

Results: ITG biopsy incidence was 0.04%. Median age at diagnosis was 61 years, 86% were Caucasian, and there was no gender predilection. Patients presented with proteinuria (median 6.6 g/day, 58% with full nephrotic syndrome), hematuria (86%), and renal insufficiency (median creatinine 1.6 mg/dl). Hematologic disorders were present in 66%, including lymphoma in 41% (mainly CLL) and plasma cell dyscrasia in 26% (most commonly MGRS). 14% had underlying autoimmune disease and 33% had hypocomplementemia. Light microscopy revealed endocapillary proliferative (35%), membranoproliferative (29%) and membranous (29%) patterns. Immunohistochemical staining for DNAJB9 was negative on all cases tested. Electron microscopy showed microtubular deposits with diameter of 14-60 nm, hollow cores, frequent parallel alignment, and a predominant distribution outside of the lamina densa of the GBM. Immunofluorescence revealed IgG-dominant staining which was light chain restricted and IgG subclass restricted in 67% of cases (most commonly IgG-κ), indicating monoclonal composition. This finding was used to distinguish monoclonal ITG from polyclonal ITG. As compared to polyclonal ITG, monoclonal ITG had a higher incidence of lymphoma (53% vs. 11%), multiple myeloma (8% vs. 0), and MGRS (22% vs. 0). On follow up (median 47 months), 31% had complete remission, 11% partial remission, 35% persistent renal dysfunction, and 24% progressed to ESRD. The median survival (not reaching ESRD or death) was 123 months. Monoclonal ITG was more commonly treated with clone-directed therapy, which was associated with more frequent remission and less frequent ESRD compared to polyclonal ITG. ITG recurred within 10 months in 3 of 5 patients who received kidney transplants.

Conclusions: ITG is an extremely rare disease. Based on our observations, we propose that ITG should be subclassified as two overlapping but distinct entities – monoclonal ITG and polyclonal ITG. Prognosis is good if the underlying hematologic condition is treated.

FR-OR01

Terlipressin Improves Renal Replacement Therapy–Free Survival in Hepatorenal Syndrome Type 1

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Background: Hepatorenal syndrome type 1 (HRS-1) is an ominous form of acute kidney injury in patients with cirrhosis. Recently, the results of the randomized placebo (PBO)-controlled trial (RCT) CONFIRM demonstrated that terlipressin (TERLI) is effective in reversing HRS-1 and in reducing the cumulative need for renal replacement therapy (RRT). However, whether TERLI reduces the need for RRT among survivors has not been determined.

Methods: CONFIRM (NCT02770716) was a North American RCT (n=300) that compared HRS-1 reversal rates between patients treated with albumin plus TERLI (n=199) or albumin plus PBO (n=101) (2:1). We conducted a post hoc intention-to-treat analysis to assess the incidence of RRT among CONFIRM survivors. We also conducted a pooled analysis of the 3 TERLI RCTs in HRS-1 (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to examine 90-day RRT-free survival rates.

Results: In CONFIRM, the cumulative incidences of need for RRT for TERLI at day 14, 30, and 90 were 23%, 26%, and 29% compared with 35%, 36%, and 39% for patients assigned to PBO (P=0.03, 0.07, and 0.1, respectively). Among survivors, significantly fewer TERLI-treated patients remained dependent on RRT at day 14, 30, and 90 (22%, 26%, and 30%, respectively) compared with PBO (39%, 43%, and 46%; P<0.01, P=0.03, and P=0.05, respectively). The 90-day RRT-free survival rate was 35% in the TERLI group vs 30% in the PBO group (P=0.08), with a numerically longer median number of days in the TERLI group (20 vs 11). Pooled analysis of the 3 RCTs revealed a greater 90-day RRT-free survival rate for TERLI-treated (n=352) compared with PBO-treated (n=256) patients (37% vs 29%, P=0.03; OR [95% CI], 1.47 [1.04, 2.07]).

Conclusions: Treatment with TERLI added to albumin decreased the rate of RRT and improved RRT-free survival in patients with HRS-1. This is the first pharmacological intervention proven to reduce the need for RRT in patients with HRS-1. Because of the significant impact of RRT on quality of life, this observation expands the clinical benefit of TERLI and enhances the reported efficacy of TERLI in inducing HRS-1 reversal.

FR-OR02

A Parsimonious Model for Diagnosis of Biopsy-Proven Acute Interstitial Nephritis Using Electronic Health Record Data

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Background: Due to its atypical clinical features and difficulty in establishing diagnosis without a biopsy, acute interstitial nephritis (AIN) diagnosis is delayed or missed. We developed a predictive model for AIN using clinical data from all patients who underwent a kidney biopsy available through the electronic health record.

Methods: We obtained data on all patients who underwent a native kidney biopsy at two centers between 2013-18 and obtained corresponding information of demographics, comorbidities, and all laboratory tests collected up to one year before biopsy. We used least absolute shrinkage and selection operator (LASSO) method to select features associated with AIN and performed area under received operating characteristics curve (AUC) analysis in temporally-split training (70%) and test (30%) sets. We also applied this model to a separate cohort of kidney biopsies with AIN diagnosis adjudicated by 3 pathologists and compared it to the clinician's prebiopsy impression of AIN obtained through chart review.

Results: Among 551 patients who underwent native kidney biopsies, 60 (11%) had AIN on clinical pathology diagnosis. We evaluated 163 potential features for their association with AIN. The five features with the highest AUC were last creatinine at the time of biopsy (AUC, 0.73), BUN to creatinine ratio (0.70), urine specific gravity before biopsy (0.67), serum bicarbonate (0.62), and urine protein (0.62). The top 4 variables picked using LASSO had an AUC of 0.76 in the test set (table). Applying this model to a separate cohort of participants with adjudicated AIN, we noted an AUC of 0.80 (0.73, 0.87), which was higher than the clinician's pre-biopsy impression of AIN (0.61 (0.52, 0.70), P<0.001).

Conclusions: We noted four variables associated with AIN and the model containing these showed a modest AUC but was an improvement on clinician's pre-biopsy impression of AIN.

Funding: NIDDK Support

Features associated with AIN

Risk factor for AIN	OR (95% CI)
Higher creatinine before biopsy (per 1 mg/dl increase)	1.2 (1.0, 1.3)
Lower BUN: Cr ratio (per unit increase)	1.1 (1.0, 1.2)
Lower proteinuria (0 and 1+ vs. 2+ or higher)	2.5 (1.4, 4.4)
Lower specific gravity (per 0.001 increase)	1.1 (1.0, 1.1)
AUC test	0.76 (0.70, 0.82)

AUC, area under receiver operating characteristic curve; OR, odds ratio; CI, confidence interval

AUC training set=0.79

FR-OR03

Development and Validation of a Convolutional Neural Network Model for Intensive Care Unit AKI Prediction

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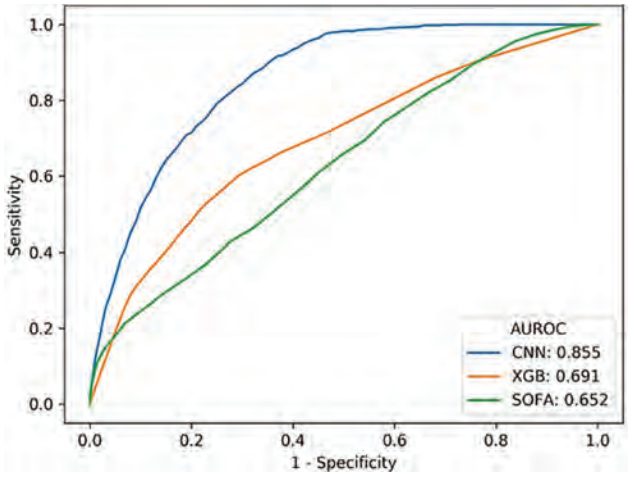
Background: Acute kidney injury (AKI) is common among hospitalized patients and has a significant impact on morbidity and mortality. While early prediction of AKI has the potential to reduce adverse patient outcomes, it remains a difficult condition to predict and diagnose. The purpose of this study was to evaluate the ability of a machine learning algorithm to predict for AKI KDIGO Stage 2 or 3 up to 72 hours in advance of onset using convolutional recurrent neural nets (CNN) and patient Electronic Health Record (EHR) data.

Methods: A CNN prediction system was developed to continuously and automatically monitor for incipient AKI. 7122 patient encounters were retrospectively analyzed from the Medical Information Mart for Intensive Care III (MIMIC-III) database. The CNN machine learning-based AKI prediction model was compared to an established XGBoost AKI prediction model and the Sequential Organ Failure Assessment (SOFA) scoring system. AKI onset was used for the outcome. The model was trained on routinely-collected patient EHR data.

Results: On a hold-out test set, the algorithm attained an Area Under the Receiver Operating Characteristic (AUROC) of 0.85 and PPV of 0.25, relative to a cohort AKI prevalence of 5.21%, for long-horizon AKI prediction at a 72-hour window prior to onset. The ROC curve comparison of 72-hour prediction on the 10% hold-out test set is shown in **Figure 1**. The CNN model, which was provided text data through Doc2Vec input, outperformed the XGBoost model and the SOFA score.

Conclusions: A CNN machine learning-based AKI prediction model outperforms XGBoost and the SOFA scoring system, demonstrating superior performance in predicting acute kidney injury 72 hours prior to onset, without reliance on changes in serum creatinine.

Funding: Other NIH Support - This work was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) [grant ID: 1R43AA02767401]



ROC curve comparison of prediction performance using a CNN classifier, an XGB classifier, and the SOFA score, 72 hours prior to AKI onset on the MIMIC III ICU hold out data set.

FR-OR04

Outcomes from the Use of the Selective Cytopheretic Device (SCD) in Critically Ill Children Receiving CRRT: A Report of the Multicenter Pediatric SCD (pSCD) Study

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Background: Critically ill children who develop acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) are at increased risk of death. The SCD promotes an immunomodulatory effect in a hypocalcemic environment (ionized Ca (ionCa) < 0.4 mmol/L) in animal models of inflammation. In a randomized trial, adult ICU patients on CRRT treated with the SCD, who maintained CRRT ionCa < 0.4 mmol/L, had improved survival/dialysis independence. We conducted an FDA grant sponsored safety evaluation (adverse and serious adverse events) of the SCD in 16 critically ill children.

Methods: 4 center US study of the SCD in children (>15 kg, ≤22 years) with AKI and multiorgan failure receiving CRRT. The SCD was integrated post CRRT membrane, changed daily, and circuit ionCa maintained <0.4 mmol/L. Pts received SCD treatment for up to 7 days or CRRT discontinuation.

Results: 16 pts (8F/8M) completed the study from 12/2016 thru 2/2020. Mean pt age was 12 yr (range 4-21 yr), weight was 53 kg (range 19-111 kg) and PRISM 2 score was 7 (range 2-19). Two pts received ECMO. The most common ICU diagnosis was shock. Circuit ionCa were maintained at <0.4 mmol/L for 90.2% of assessments. Median SCD duration was 6 days (range 1 to 7). 15/16 pts survived SCD therapy, 12/16 patients survived to ICU discharge. All 12 ICU survivors were dialysis independent at 60 days. No SCD related adverse events were noted.

Conclusions: Our data suggest the SCD is safe in critically ill children who require CRRT. While we cannot make efficacy claims, the 75% survival rate and 100% renal recovery rate in surviving children suggest a favorable benefit to risk ratio.

Funding: Other U.S. Government Support

FR-OR05

Nicotinamide Riboside with Pterostilbene Increases NAD^+ in Patients with AKI: A Randomized, Double-Blind, Placebo-Controlled, Stepwise Safety Study of NRPT in Patients with AKI

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Background: Preclinical studies have identified both NAD^+ and sirtuin augmentation as potential strategies for the prevention and treatment of AKI. Nicotinamide riboside (NR) is a NAD^+ precursor vitamin and pterostilbene (PT) is potent sirtuin activator found in blueberries. Here, we tested the effect of combined NR and PT (NRPT) on whole blood NAD^+ levels and safety parameters in patients with AKI.

Methods: We conducted a randomized, double-blind, placebo-controlled study of escalating doses of NRPT in 24 hospitalized patients with AKI. The study was comprised of four Steps during which NRPT (5 subjects) or placebo (1 subject) was given twice a day for two days. NRPT dosing was increased in each Step: Step 1 250/50mg, Step 2 500/100mg, Step 3 750/150mg and Step 4 1000/200mg. Blood NAD^+ levels were measured by liquid chromatography-mass spectrometry and safety was assessed by history, physical exam, and clinical laboratory testing.

Results: AKI resulted in a 50% reduction in whole blood NAD^+ levels at 48 hr compared to 0 hr in patients receiving placebo (p=0.05). There was a trend for increase in NAD^+ levels in all NRPT Steps individually at 48 hr compared to 0 hr, but only the change in Step 2 reached statistical significance (47%, p=0.04), and there was considerable interindividual variability in the NAD^+ response to treatment. Considering all Steps together, NRPT treatment increased NAD^+ levels by 37% at 48hr compared to 0hr (p=0.002). All safety laboratory tests were unchanged by NRPT treatment, including creatinine, estimated glomerular filtration rate (eGFR), electrolytes, liver function tests, and blood counts. Three of 20 patients receiving NRPT reported minor gastrointestinal side effects.

Conclusions: NRPT increases whole blood NAD^+ levels in hospitalized patients with AKI. In addition, NRPT up to a dose of 1000mg/200mg twice a day for two days is safe and well tolerated in these patients. Further studies to assess the potential therapeutic benefit of NRPT in AKI are warranted.

Funding: Commercial Support - Elysium Inc

FR-OR06

Role of Angiopoietins in CKD Progression After Hospitalization

Sherry Mansour,[1] Steven G. Coca,[2] Yaqi Jia,[3] Vernon M. Chinchilli,[4] Wassim Obeid,[3] Francis P. Wilson,[1] Samir M. Parikh,[5] Edward D. Siew,[8] Talat Alp Ikizler,[8] Jonathan Himmelfarb,[6] Paul L. Kimmel,[7] Chirag R. Parikh.[3] ASSESS-AKI Consortium *[1]Yale University School of Medicine, New Haven, CT; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Johns Hopkins University, Baltimore, MD; [4]Pennsylvania State University, University Park, PA; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]University of Washington, Seattle, WA; [7]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [8]Vanderbilt University Medical Center, Nashville, TN.*

Background: The factors determining chronic kidney disease (CKD) progression after an episode of acute kidney injury (AKI) are poorly understood. Angiopoietins play a role in vessel remodeling after AKI, where Angiopoietin-1 (Angpt-1) maintains vessel stability and Angiopoietin-2 (Angpt-2) destabilizes quiescent vessels. We investigated whether the balance of Angpt-1 and -2 was prognostic of CKD and mortality after hospitalization in patients with and without AKI.

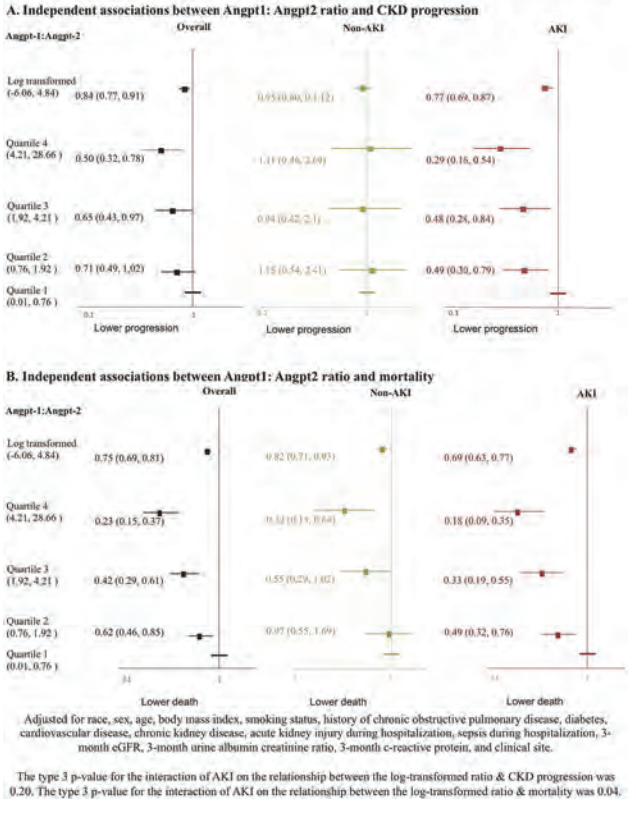
Methods: Using plasma samples from ASSESS-AKI, we measured Angiopoietins 3 months after hospitalization. We assessed the ratio of Angpt-1:Angpt-2 with CKD progression (composite of incident and progression of CKD, and end stage kidney disease), and all-cause mortality.

Results: Angiopoietins were measured in 1503 hospitalized patients, among whom 746 (49.6%) had AKI. Median (IQR) age was 65.8 (56.6, 73.9) years, 555 (37%) were female, and 196 (13%) were black. Median times to CKD progression, and all-cause mortality were 4.4 (2.5, 5.7), and 4.9 (3.6, 6.0) years, respectively. CKD progression developed in 293 (19%) and mortality in 314 (21%) participants. The highest quartile of Angpt-1:Angpt-2 ratio was independently associated with 50% reduced risk of CKD progression and 77% reduced risk of mortality as compared to the lowest quartile. Stratified analyses by AKI status revealed stronger associations between Angpt-1:Angpt-2 ratio and both outcomes in the AKI group (**Figure**).

Conclusions: A higher Angpt-1:Angpt-2 ratio was strongly associated with lower risk of CKD progression and mortality after hospitalization, particularly in patients with AKI. Angiopoietins may help risk stratify patients with AKI after discharge for those in need of close follow-up and CKD management.

Funding: Private Foundation Support

Figure. Associations between Angpt-1:Angpt-2 ratio and CKD progression and all-cause mortality



Adjusted for race, sex, age, body mass index, smoking status, history of chronic obstructive pulmonary disease, diabetes, cardiovascular disease, chronic kidney disease, acute kidney injury during hospitalization, sepsis during hospitalization, 3-month eGFR, 3-month urine albumin creatinine ratio, 3-month c-reactive protein, and clinical site.

The type 3 p-value for the interaction of AKI on the relationship between the log-transformed ratio & CKD progression was 0.20. The type 3 p-value for the interaction of AKI on the relationship between the log-transformed ratio & mortality was 0.04.

FR-OR07

Determinants of Major Adverse Kidney Events (MAKE) in Extra Corporeal Membrane Oxygenation (ECMO) Survivors

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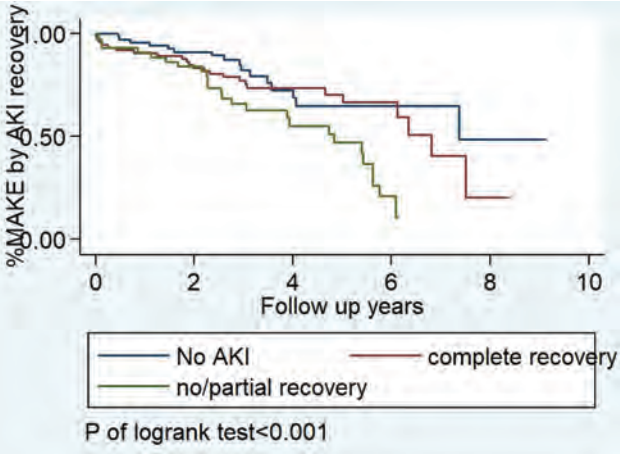
Background: The majority of ECMO patients develop acute kidney injury (AKI) and 40-60% require renal replacement therapy (RRT). Little is known about the effects of AKI on long-term renal outcomes after ECMO. The aim of this study was to examine the determinants of MAKE in ECMO survivors.

Methods: Patients who were admitted to a single-center between 2008 and 2017, were on ECMO for more than 24 hours & survived to hospital discharge were included. MAKE was defined as either doubling of serum creatinine (Scr), incident ESRD or death. USRDS and NDI databases were used to obtain information about ESRD and death. AKI was defined as KDIGO stages 2-3. Complete AKI recovery was defined as a return to 50% of baseline Scr and partial recovery as an improvement in the AKI stage without a return to 50% of baseline Scr. Survival analysis plots & Cox regression models were fitted to examine the associations of AKI status, AKI recovery and other factors with MAKE

Results: Among 188 ECMO patients who survived until hospital discharge, 63% had AKI, and 41% required RRT. The mean follow-up time was 3.4 years. Patients with AKI were more likely to be on ECMO for a cardiac rather than respiratory indication and had a longer length of stay compared to patients with no AKI. Kaplan-Meier survival curves showed that patients with no/partial recovery from AKI had a higher rate of MAKE compared to those with no AKI (Figure 1). Results of the unadjusted analysis showed that ECMO type and timing of initiation of RRT were associated with MAKE. Multivariate analysis showed that AKI [aHR=1.79 (95%CI=1.00-3.21)], no/partial recovery from AKI [aHR= 2.94 (95%CI=1.46-5.92)] and initiation of RRT after ECMO [aHR 5.4 (95%CI=1.14-25.6)] were significant determinants of MAKE after adjustment for potential confounders.

Conclusions: AKI, AKI recovery status, and timing of initiation of RRT are determinants of major adverse kidney events in patients who received ECMO.



FR-OR08

AKI Among African Americans with Sickle Cell Trait and Disease

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Background: Sickle cell trait (SCT) and disease (SCD) are independent risk factors for estimated glomerular filtration rate (eGFR) decline among African Americans (AA). However, our understanding of the risk for acute kidney injury (AKI) and the role of AKI in eGFR decline in patients with SCT/D remains limited. We aimed to describe the relative risk for AKI in SCT/D and the effect of AKI on eGFR decline in SCT/D.

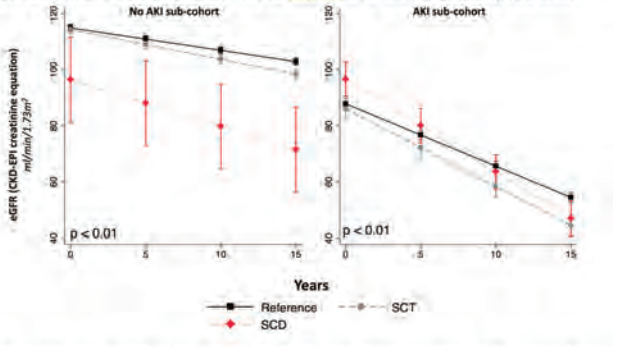
Methods: We performed a multi-center observational study of adult AA patients with a baseline eGFR ≥15 ml/min, and ≥1 year follow-up between 2005-2018. The presence of SCT/D (exposure) and normal hemoglobin phenotype (reference) was determined by hemoglobin electrophoresis. Outcomes of interest (incident All AKI [Kidney Disease: Improving Global Outcomes criteria], incident Severe AKI [doubling of baseline creatinine] and incident Sustained AKI [AKI persisting for ≥72 hours]) were adjudicated by chart review and evaluated by Cox regression. Only first AKI events were used. The effect of All AKI on eGFR decline (mixed linear models) was also investigated. Models were adjusted for predictors of AKI.

Results: We identified 8968 reference, 1279 SCT, and 254 SCD patients with a median follow-up of 7.6 years and mean serum creatinine of 0.8 mg/dl. SCT was associated with Sustained AKI (adjusted hazard ratio [aHR] 1.42; 95% CI, 1.08-1.88) compared to the reference. SCD was associated with All AKI (aHR 3.13; 95% CI, 2.33-4.21), Severe AKI (aHR 3.04; 95% CI, 1.90-4.87) and Sustained AKI (aHR 2.10; 95% CI, 1.24-3.53) compared to the reference. Effect of AKI on eGFR is shown in Figure 1.

Conclusions: The risk for AKI is increased in both SCT (Sustained) and SCD (all forms) and may contribute to faster eGFR decline in SCT/D. Further studies are needed to understand the mechanisms of AKI in SCT/D. Such studies will inform best practices that will help attenuate the burden of kidney disease in SCT/D.

Funding: Private Foundation Support

Figure 1. Difference in eGFR decline between the reference, SCT and SCD patients by AKI status.



Both models were adjusted for baseline age, sex, hypertension, diabetes mellitus, cardiovascular disease, hemoglobin electrophoresis indications and baseline eGFR. Among non-AKI patients, SCT was associated with a 0.26 (95% CI, 0.20-0.31) ml/min faster decline in eGFR compared to the reference. Also, among non-AKI patients, SCD was associated with a 0.86 (95% CI, 0.78-0.94) ml/min faster decline in eGFR compared to the reference. Among AKI patients, SCT was associated with a 0.54 (0.42–0.67) ml/min faster decline in eGFR compared to the reference. Also, among AKI patients, SCD was associated with a 1.09 (95% CI, 0.94-1.23) ml/min faster decline in eGFR compared to the reference.

FR-OR09

Assessment of Kidney Proximal Tubular Secretion in Critical Illness

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Background: Serum creatinine concentrations (SCr) are used to determine the presence and severity of acute kidney injury. SCr is primarily eliminated by glomerular filtration; however, most mechanisms of kidney injury in critical illness involve kidney proximal tubules, where tubular secretion occurs. Proximal tubular secretory clearance is not currently measured in the ICU. To estimate the kidney clearance of secretory solutes in critically ill adults.

Methods: We collected matched blood and spot urine samples from 170 ICU patients and from a comparison group of 70 adults with normal kidney function. We measured seven endogenously produced secretory solutes using liquid chromatography-tandem mass spectrometry. We computed a composite secretion score incorporating all seven solutes, and evaluated associations with 28-day major adverse kidney events ($MAKE_{28}$), defined as doubling of SCr, dialysis dependence, or death.

Results: The urine/plasma ratio of six of seven secretory solutes were lower in critically ill patients compared with normal individuals after adjustment for SCr. The composite secretion score was moderately correlated with SCr and cystatin C (r = -0.51 and r = -0.53, respectively). Each standard deviation higher composite secretion score was associated with a 52% lower risk of $MAKE_{28}$ (95% CI 25% - 70% lower) independent of ICU severity of illness and SCr. Higher urine to plasma ratios of individual secretory solutes isovalerylglycine and tiglylglycine were associated with $MAKE_{28}$ after accounting for multiple testing (p<0.001).

Conclusions: Among critically ill adults, tubular secretory clearance is associated with adverse outcomes, independent of SCr and SOFA score, and measurement could improve assessment of kidney function.

Funding: NIDDK Support

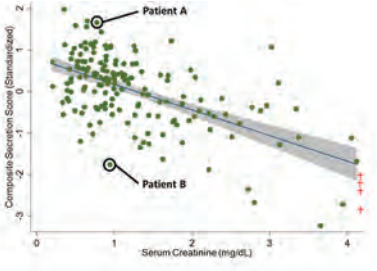

Figure 1. Visualization of correlations between ranges of composite secretion score and SCr measured at study enrollment in a critically ill population. The scatter plot allows for visual examination of the range, variability, and interindividual differences between the composite secretion score and SCr. To ease comparison of different tubular solutes, we standardized or rescaled solute measurements to have a mean of 0 and a standard deviation of 1. We then computed the composite secretion score as the average of the seven standardized U/P ratios. Red crosses at the right represent participants with extremely high SCr who are displayed at an arbitrary maximal-range value for graphic examination purposes; these participants are included in all statistical analyses using the true data value. Regression line is fit with 95% confidence intervals. To demonstrate the interindividual variability in tubular secretion, we highlight two patients (A and B) with similar SCr (approximately 1 mg/dL) but extremes of tubular secretion. Patient A is in the highest tertile of tubular secretion, while patient B is in the lowest tertile of tubular secretion.

FR-OR10

Endotrophin, Released During Collagen Type VI Formation, Predicts Long-Term Mortality After AKI

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Background: Acute kidney injury (AKI) is defined as a rapid decrease in kidney function which may be associated to structural damage. Early markers predicting AKI are emerging, but tools to monitor patients subsequent to AKI are still lacking. The novel biomarker PRO-C6 reflects formation of collagen type VI (COL6) and levels of endotrophin, a bioactive molecule derived from COL6. Here we evaluated the potential of PRO-C6 as a biomarker of mortality in AKI patients.

Methods: We measured PRO-C6 in plasma samples collected 1 year after the episode of AKI, using a novel ELISA in 801 patients from the AKI Risk in Derby (ARID) study, who were then followed prospectively until year three. 393 of the patients had been hospitalized for an episode of AKI, and 408 patients who did not sustain AKI were included as controls (non-AKI). The groups were matched for age, baseline renal function and diabetes.

Results: PRO-C6 levels were significantly higher in the AKI compared to the non-AKI group (median (m): 10.85 vs 9.23 ng/mL, P<0.0001). By year 3, a total of 70 patients died; 43 in the AKI group and 27 in the control group. In the AKI group, patients who died had significantly higher PRO-C6 levels than the patients who did not die (m: 12.66 vs 10.68 ng/mL, P=0.004), whereas there was no difference between patients who died and did not die in the non-AKI group (m: 9.97 vs 9.21 ng/mL, P=0.23). In a multivariate Cox regression analysis with backwards elimination including age, gender, baseline CKD and diabetes status, albuminuria, serum creatinine, eGFR and PRO-C6, only age (P=0.04) and albuminuria (P=0.007) remained in the final model for the non-AKI group. In the AKI group, PRO-C6 had a stronger association with mortality than eGFR, as only age (P=0.005), albuminuria (P=0.04) and PRO-C6 (P=0.004) remained in the final model. When stratified into tertiles, patients with higher levels of PRO-C6 at year 1 were significantly more likely to die (P=0.009).

Conclusions: In this study, we compared levels of PRO-C6 in patients with and without AKI, and show that PRO-C6 levels measured in plasma can predict mortality in patients with AKI. Our findings may indicate that PRO-C6 identifies patients with active fibrogenesis after AKI, suggesting that long-term renal injury after AKI is important for patient outcome.

FR-OR11

Association of Use of Kidney Disease Education Benefit with ESKD-Related Outcomes

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Background: ESKD onset in the US is marked by poor outcomes, including little use of home dialysis, widespread catheter dependence among patients on hemodialysis, and high mortality. Consequently, in 2010, the Centers for Medicare and Medicaid Services (CMS) initiated a new kidney disease education (KDE) benefit to ensure that beneficiaries with stage 4 CKD are informed about the effects and treatment of kidney disease, diet and nutrition, transplantation, dialysis modalities, and vascular access. Following the US president's Executive Order on Advancing American Kidney Health in 2019, CMS plans to expand KDE. However, the current use and efficacy of KDE have not been examined.

Methods: We used USRDS data to identify eligible patients and to ascertain KDE and ESKD outcomes. We examined use of KDE in the 2 years prior to ESKD onset in 2013-2017 among 106,465 individuals aged ≥67 years who had CKD stage 4. We examined patient characteristics associated with receipt of KDE. We matched each KDE recipient with 4 controls using propensity scores and estimated the association between receipt of KDE and ESKD outcomes in this matched cohort using logistic regression.

Results: 3171 patients (3%) received KDE, 56% of whom received a single session. 49.5% of KDE sessions were delivered by nephrologists and 42% by physician extenders. Younger patients, men, and non-Hispanics were more likely to receive KDE. There was substantial regional variation in KDE utilization, and rural residents were less likely to receive KDE. In the matched cohort, receipt of KDE was associated with higher odds of transplant waitlisting before dialysis initiation, pre-emptive transplantation, home dialysis, or in-center HD initiation with an AVF or AVG (vs. catheter; Table).

Conclusions: A very small percentage of eligible patients reaching dialysis receive Medicare-reimbursed KDE within the previous 2 years. KDE was associated with favorable outcomes, at least among those who advanced to ESKD.

Funding: NIDDK Support

Outcome	KDE	No KDE	OR (95% CI)
Transplant waitlisting prior to ESKD	4.0	2.9	1.41 (1.15 - 1.74)
Pre-emptive transplant	1.9	1.4	1.34 (1.00 - 1.80)
Home dialysis	18.1	11.5	1.70 (1.53 - 1.89)
Hemodialysis with AVF or AVG	41.6	26.3	2.00 (1.84 - 2.19)
Optimal ESKD start*	52.2	34.7	2.06 (1.90-2.23)

*Pre-emptive transplant or home dialysis or in-center HD with AVF or AVG

FR-OR12

Correlation Between Patient Activation and Quality of Life Among Patients with CKD

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Background: Quality of Life (QOL) is an important outcome in patients with chronic kidney disease (CKD). We have previously demonstrated that online peer mentoring (PM) improves patient activation and QOL. In this study, we evaluate the correlation between patient activation and QOL among patients with CKD who received online PM.

Methods: We randomized 155 patients with stage 4 or stage 5 CKD to one of 3 groups: online PM, face-to-face (FTF) PM, or usual care. Participants in all 3 groups received a book that contained detailed information about kidney disease. Participants assigned to intervention groups received 6 months of PM, either FTF or through a secure online platform. At baseline and at 18 months, the participants completed the Patient Activation Measure® (PAM) and the Kidney Disease QOL-36 (KDQOL-36) instrument. We used linear mixed effect models to estimate the slope of change of PAM and subsets of KDQOL over time. We then calculated the correlation between PAM and individual subscales of KDQOL by Pearson's Correlation Coefficient. We used SAS, version 9.4 (SAS Institute Inc., Cary, NC) for data analysis.

Results: Baseline KDQOL-36 and PAM scores, as well as demographic characteristics were similar among the 3 groups. Among the online PM group, there was a statistically significant improvement in: 1. The mean PAM score between baseline and 18 months (Slope estimate [SE]: 5.65; 95% confidence interval [CI]: 2.75, 8.52; P= 0.0001). 2. The following components of the KDQOL-36 score: Effects of Kidney Disease (EKD) (SE: 4.13; CI: 0.87, 7.4; P= 0.01); Burden of Kidney Disease (BKD) (SE: 5.44; CI: 1.24, 9.64; P= 0.01); Symptoms and Problems of Kidney Disease (SPKD) (SE: 6.00; CI: 3.09, 8.91; p= 0.006); SF-12 Physical Composite Score (PCS) (SE: 2.50; CI: 0.95, 4.06; P= 0.002); SF-12 Mental Composite Score (MCS) (SE: 3.46; CI: 1.78, 5.13; P<0.0001). Among the online PM group, the improvement in PAM was correlated with improvements in 4 components of the KDQOL-36: EKD (Pearson Coefficient [PC]: 0.36; p=0.04); BKD (PC: 0.44; p=0.01); SPKD (PC: 0.47; p=0.005), PCS (PC: 0.35; p=0.04). There was no correlation between PAM and MCS.

Conclusions: Among CKD patients who receive online PM, there is a correlation between the improvements in PAM and KDQOL, suggesting that improved QOL may be a result of improved activation. Funding: PCORI

FR-OR13

Breath Ammonia Is a Useful Biomarker Predicting Kidney Function in CKD Patients

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Background: Chronic kidney disease (CKD) is a public health problem and its prevalence has increased worldwide; patients are commonly unaware of the condition. Early identification and immediate intervention are crucial to delay CKD progression. Finding a tool to predict kidney function without visiting hospitals is an attractive method for CKD monitoring in COVID-19 pandemic. The present study aimed to investigate whether exhaled breath ammonia measurement could be used for rapid CKD screening.

Methods: CKD patients (n=121), including CKD stage 1-5 patients, were enrolled and breath ammonia was detected. Correlation between breath ammonia and blood urea nitrogen (BUN) levels, serum creatinine levels, estimated glomerular filtration rate (eGFR) were determined. The predictive value of breath ammonia for the presence of CKD was assessed.

Results: Correlation analysis demonstrated a good correlation between breath ammonia and blood urea nitrogen levels (R=0.756, p<0.0001), serum creatinine levels (R=0.735, p<0.0001), eGFR (R=-0.535, p<0.0001) and inversed eGFR (R=0.685, p<0.0001). Breath ammonia concentration was significantly elevated with increased CKD stage compared with the previous stage (CKD stage 1/2/3/4/5: 636±94; 1020±120; 1943±326; 4421±1042; 12781±1807 ppb, p<0.05). The receiver operating characteristic curve analysis showed an area under curve (AUC) of 0.835 (p<0.0001) for distinguishing CKD stage 1 from other CKD stages at 974 ppb (sensitivity, 69%; specificity, 95%, positive predictive value [PPV] 0.99; negative predictive value [NPV], 0.36). The AUC was 0.831 (p<0.0001) for distinguishing between patients with/without eGFR ≥60 mL/min/1.73 m^2 (cut-off 1187 ppb: sensitivity, 71%; specificity, 78%; PPV, 0.84; NPV, 0.61). At 886 ppb, the sensitivity increased to 80% but the specificity decreased to 69%. For a non-life threating or non-serious CKD, breath ammonia at a cut-off concentration of 886 ppb is a good screening tool for detection of patients with potential CKD and suitable for kidney function monitoring.

Conclusions: Because CKD is non-life threating and breath ammonia detection was conducted in real time, inexpensive, easy to administer, and had an acceptable diagnostic accuracy, breath ammonia can be used as a good surrogate for kidney function and a reliable tool for CKD screening.

Funding: Government Support - Non-U.S.

FR-OR14

Estimated Glomerular Filtration Rate Equations: Do We Need to Use the Ethnicity Correction Factor in People of African Ancestry Outside of the United States?

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Background: Recent African studies suggest ethnicity factors in estimated glomerular filtration rate (eGFR) equations is not required.

Methods: To assess accuracy of eGFR equations, with and without ethnicity factors compared with gold standard ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA) clearance assays. Patients with albumin <30g/dl, hepatology referrals, <18 years old, non-white or black, mixed ethnicities were excluded. Accuracy of CKD-EPI and MDRD equations compared to ^{51}Cr-EDTA GFR were assessed with and without correction factor.

Results: 2,776 ^{51}Cr-EDTA studies were identified (Mean age-54yrs; 43% female; 12% Black ethnicity). In Black patients, CKD-EPI and MDRD eGFR equations significantly overestimated GFR compared to White (p<0.001) but without ethnicity correction factor estimates were considerably improved (p<0.001)(Table 1). Accuracy was superior for GFR≥60ml/min/1.73m^2 compared to <60ml/min/1.73m^2 using CKD-EPI equation for both White and Black patients (p<0.001).

Conclusions: Overestimation of measured GFR with eGFR equations using ethnicity correction factors identified in this study may lead to reduced rates of CKD diagnosis and under-recognition of CKD severity in people of Black ethnicity in the UK. These findings require prospective validation in other countries.

Table 1: Estimated Glomerular Filtration equations bias, precision and accuracy compared with ^{51}Cr-EDTA clearance for people of Black and White ethnicities according to ^{51}Cr-EDTA GFR categories

			GFR Mean (SD)	Bias	Precision	Limits of agreement	30% Accuracy (%)
Black	Corrected ^{51}Cr-EDTA GFR <60 (N=56)	Corrected ^{51}EDTA	41.0 (13.8)				
		CKD-EPI adjusted	59.4 (27.3)	18.4	19.8	-21.2 to 58	39.3
		CKD-EPI unadjusted	51.2 (23.6)	10.2	16.7	-23.2 to 43.6	55.4
		MDRD adjusted	57.2 (24.8)	16.2	17.5	-18.8 to 51.2	48.2
		MDRD unadjusted	47.2 (20.5)	6.2	14.1	-22.0 to 34.4	64.3
	Corrected ^{51}Cr-EDTA ≥GFR 60 (N=249)	Corrected ^{51}EDTA	87.2 (16.0)				
		CKD-EPI adjusted	107.9 (22.3)	20.7	21.9	-23.1 to 64.5	59.4
		CKD-EPI unadjusted	93.1 (19.3)	5.9	19.7	-33.5 to 45.3	81.1
		MDRD adjusted	107.3 (30.2)	20.1	28.1	-36.1 to 76.3	59.4
		MDRD unadjusted	88.5 (24.9)	1.3	23.7	-46.1 to 48.7	77.5
White	Corrected ^{51}Cr-EDTA GFR <60 (N=399)	Corrected ^{51}EDTA	46.6 (11.2)				
		CKD-EPI	64.2 (21.2)	17.6	16.1	-14.6 to 49.8	44.1
		MDRD	61.4 (21.6)	14.8	17.1	-19.4 to 49.0	51.4
	Corrected ^{51}Cr-EDTA ≥GFR 60 (N=1568)	Corrected ^{51}EDTA	83.2 (15.4)				
		CKD-EPI	96.7 (16.0)	13.5	14.9	-16.3 to 43.3	74.4
		MDRD	97.7 (25.2)	14.5	22.8	-31.1 to 60.1	70.0

Adjusted = including ethnicity correction factor; Unadjusted = excluding ethnicity correction factor

FR-OR15

Mechanism of Higher Incidence of ESKD Among Blacks and Hispanics vs. Whites in the United States

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Background: In the U.S., Blacks and Hispanics have higher incidence of ESKD than Whites. Whether this is driven by lower mortality prior to ESKD or inherently faster progression to ESKD has not been clearly determined because most studies used prevalent cohorts that created survival bias. We examined this issue using a newly constructed national cohort of patients with new-onset CKD.

Methods: We identified 834,270 individuals with new-onset CKD in the US Veterans Health Administration (VHA) between 2002 and 2015, followed through 2016. CKD onset was defined as the first occurrence when there were two eGFR values (CKD-EPI equation) <60 mL/min/1.73 m^2 that were >90 days apart, not in ESKD. We excluded patients in VHA for <2 years prior to the first eGFR<60. Thus, the time of study entry should be close to the CKD onset for each individual. We examined jointly the cause-specific (CS) hazards ratios for two competing events, occurrence of ESKD and pre-ESKD death.

Results: Upon study entry, 704,557 Whites, 98,082 Blacks, and 31,631 Hispanics had similar mean eGFRs (49-50 ml/min/1.73m^2). Ten years after CKD onset, fractions of patients entering ESKD were 1.3-2.5 times greater for Blacks and Hispanics vs. Whites across six age groups (Table). CS hazards for ESKD was 2.1-2.9 times greater for Blacks and 1.2-2.7 times greater for Hispanics vs. Whites. CS hazards for pre-ESKD death were similar for Blacks and only modestly lower for Hispanics vs. Whites across ages.

Conclusions: More Blacks and Hispanics to ESKD were driven by their greater hazards for ESKD due to more rapid decline in kidney function, not through lower mortality prior to ESKD. Delineation and elimination of the causes of faster kidney function declines are therefore the appropriate strategies to improve clinical outcomes in Blacks and Hispanics with CKD, instead of attributing the higher incidence to pre-ESKD survival bias.

Funding: NIDDK Support

Crude CS hazards ratios and 95% confidence intervals (CI) for ESKD and for pre-ESKD death

Age (years)	10-year cumulative incidence of ESKD following CKD onset (%)			Black vs White Cause-specific hazards ratios (95% CI)		Hispanic vs White Cause-specific hazards ratios (95% CI)	
	Black	Hispanic	White	ESKD	pre-ESKD death	ESKD	pre-ESKD death
18-45	45.7	32.6	20.9	2.46 (2.17-2.80)	1.15 (0.96-1.38)	1.77 (1.37-2.29)	1.01 (0.67-1.51)
46-55	32.7	30.9	13.9	2.65 (2.51-2.81)	0.90 (0.86-0.95)	2.57 (2.32-2.85)	0.92 (0.82-1.03)
56-65	21.0	20.0	8.3	2.90 (2.79-3.01)	0.98 (0.95-1.01)	2.67 (2.50-2.85)	0.86 (0.81-0.90)
66-75	10.0	7.7	4.3	2.48 (2.34-2.62)	1.04 (1.01-1.06)	1.82 (1.65-2.01)	0.87 (0.84-0.91)
76-85	4.2	3.3	2.0	2.39 (2.18-2.62)	1.10 (1.07-1.12)	1.66 (1.44-1.93)	0.94 (0.91-0.97)
86-100	1.3	0.8	0.6	2.11 (1.54-2.89)	0.97 (0.93-1.00)	1.21 (0.66-2.20)	0.97 (0.92-1.03)

FR-OR16

Incidence of CKD and Environmental Inequities: An Integration of Ecological and Spatial Approaches in US Veterans

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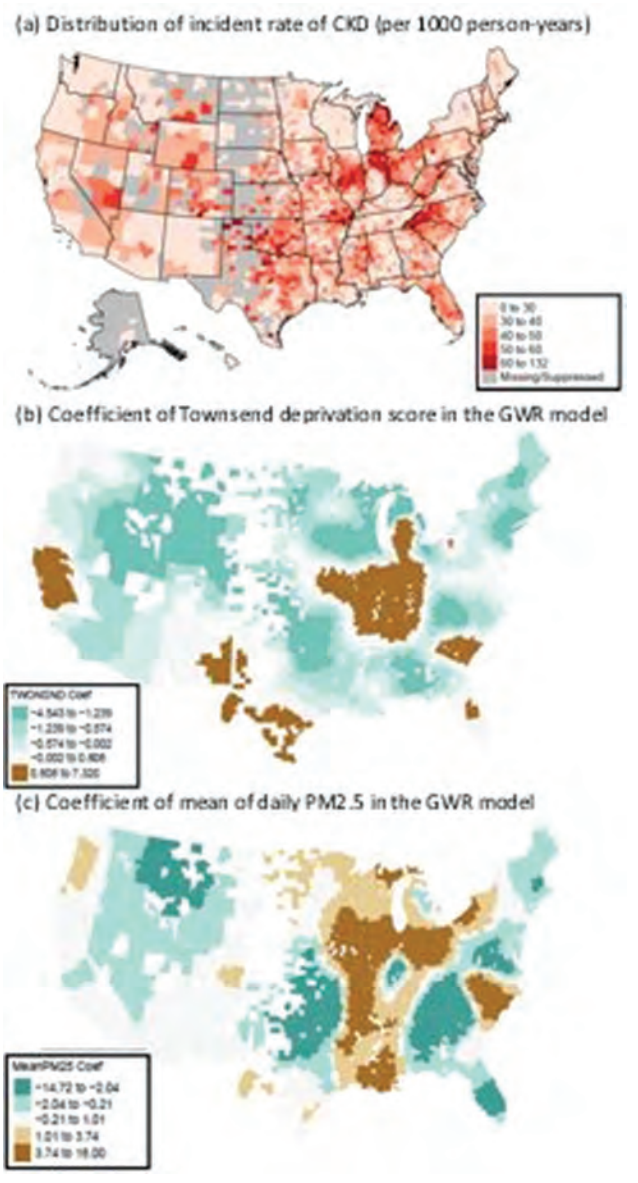
Background: Disparities in chronic kidney disease (CKD) can be linked to social and environmental determinants of health, which vary geographically across the US. We assessed geographic variation and the impact of environmental factors on incident CKD in US veterans.

Methods: We used a linked dataset from Veterans Health Administration (2014-18), the American Community Survey(2018); National Environmental Public Health Tracking Network(2018); EPA(2019) and Reference USA(2017). Incident cases of CKD were individuals with eGFR < 60 mL/min/1.73m^2 and without prior indication of CKD for at least 3 years. The county-level incidence rate of CKD was number of cases/1000 person-years during 2016-18. County-level environmental factors included Townsend deprivation index; neighborhood indices; average daily PM2.5; walkability index; number of recreational facilities and fast-food restaurants. A geographically-weighted regression model(GWR) was applied to investigate the relationship between environmental factors and incidence rate of CKD.

Results: Average of incident rate of CKD was 34.8/1000 person-years (SD=12.3, n=2,718). Incident rate was higher in the rust-belt area and Appalachian region (Fig 1.a). Townsend deprivation index associated with higher incident rate in the Midwest, Northern California and Texas (Fig 1.b). PM2.5 was associated with higher incident rate in the East North Central and East West Central regions (Fig 1.c).

Conclusions: Different environmental factors were associated with incident CKD in US counties. This highlights the potential importance of allocating resources for varied approaches to preventing and slowing the progression of CKD based on residence.

Funding: Veterans Affairs Support



FR-OR17

Chlorthalidone and Bumetanide in Advanced CKD: HEBE Trial

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Background: Current treatment for hypertension and volume overload in chronic kidney disease consists of loop diuretics, nevertheless, chronic use leads to adaptive changes at the distal nephron, which in turn decreases their efficacy. The use of thiazide diuretics could be another treatment option in these patients, notwithstanding, there's not enough evidence to justify their use in this population.

Methods: To evaluate the efficacy and safety of treatment with bumetanide plus chlorthalidone in patients with advanced chronic kidney disease a double-blind randomized controlled trial was conducted.

Results: Thirty-two patients with hypertension, chronic kidney disease stage IV/V, and chronic loop diuretic use where divided in two groups. The dual treatment group received bumetanide (2 mg BID) plus chlorthalidone (50 mg BID), while the control group was given bumetanide (2 mg BID) plus placebo, both for twenty-eight days. There was a decrease of systemic blood pressure in the dual treatment group when compared with the control group; systolic blood pressure -26.1±15.3 vs. -10±23.3 mmHg (p=0.028), diastolic blood pressure -13.5±10.7 vs. -3.4±11.9 mmHg (p=0.018), and mean arterial pressure -18.1±8.7 vs. -5.4±14.3 mmHg (p=0.006). There was also a decrease of volume overload in the dual treatment group when compared to the control group; total body water -4.36±3.29 vs. +0.075±1.78 liters (p<0.001), extracellular water -2.55±1.1 vs. +0.150±1.2 liters (p<0.001), and extracellular water to total body water ratio -2.92±4.76 vs. -0.24±1.42 (p=0.039).

Conclusions: In advanced chronic kidney disease plus hypertension patients whose treatment with loop diuretics is insufficient, combined use of bumetanide plus chlorthalidone can be useful for systemic blood pressure and volume overload control.

Funding: Commercial Support - Senosian

FR-OR18

Benefits of Icosapent Ethyl Across a Range of Baseline Renal Function in Patients with Established Cardiovascular Disease or Diabetes: Results of REDUCE-IT RENAL

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Background: Chronic kidney disease is associated with adverse outcomes among patients with established cardiovascular disease (CVD) or diabetes. Medications for treatment of CVD among patients with low estimated glomerular filtration rate (eGFR) may be ineffective.

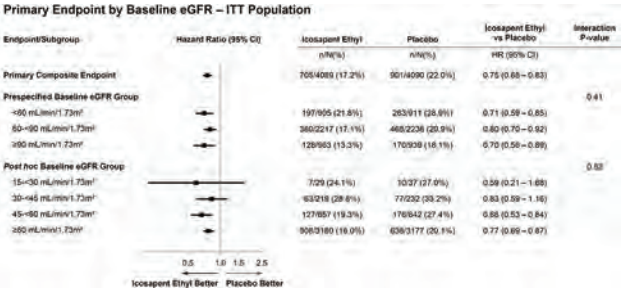
Methods: The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) randomized patients with CVD or diabetes and one additional risk factor to treatment with icosapent ethyl or placebo. Patients from REDUCE-IT were categorized by prespecified eGFR categories for analysis of the effect of icosapent ethyl (IPE) on the primary endpoint (composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina) and key secondary endpoint (a composite of CV death, nonfatal MI, or nonfatal stroke). In post hoc analysis, patients were categorized by additional eGFR cutoffs consistent with current medical guidelines.

Results: Among the 8179 REDUCE-IT patients, median baseline eGFR was 75 mL/min/1.73m^2 (range: 17 to 123 mL/min/1.73m^2). There were no meaningful changes in median eGFR for IPE versus placebo across study visits. IPE benefit was consistent across baseline eGFR for the primary (Figure) and key secondary endpoints. The numerical reduction in CV death was greatest in the eGFR <60 mL/min/1.73m^2 group (IPE: 7.6%; placebo: 10.6%; HR 0.70, 95%CI 0.51, 0.95, p=0.02). The rate of microalbuminuria in adverse event reporting was lower among IPE-treated patients (0.1% versus 0.3%, p=0.01).

Conclusions: In REDUCE-IT, icosapent ethyl reduced fatal and nonfatal ischemic events across the broad range of baseline eGFR categories.

Funding: Commercial Support - Amarin

Primary Endpoint by Baseline eGFR – ITT Population



FR-OR19

Dapagliflozin Reduces the Risk of Hyperkalaemia in Patients with Heart Failure and Reduced Ejection Fraction: A Secondary Analysis from DAPA-HF

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Background: Hyperkalaemia often limits the use of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure and reduced ejection fraction (HFrEF), denying these patients a life-saving therapy.

Methods: The risk of developing mild hyperkalaemia (potassium > 5.5 mmol/L) and moderate/severe hyperkalaemia (>6.0 mmol/L) was examined in the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) according to background MRA use, and randomized treatment assignment, by use of Cox regression analyses.

Results: Overall, 3370 (70.1%) patients in DAPA-HF were treated with an MRA. Mild hyperkalaemia and moderate/severe hyperkalaemia occurred in 182 (11.1%) and 23 (1.4%) patients treated with dapagliflozin as compared to 204 (12.6%) and 40 (2.4%) of patients given placebo (Table and Figure). This yielded a hazard ratio (HR) of 0.86 (0.70-1.05) for mild hyperkalaemia and 0.50 (0.29, 0.85) for moderate/severe hyperkalaemia, comparing dapagliflozin to placebo.

Conclusions: Patients with HFrEF and taking an MRA who were randomized to dapagliflozin had half the incidence of moderate/severe hyperkalaemia, compared with those randomized to placebo.

Funding: Commercial Support - AstraZeneca

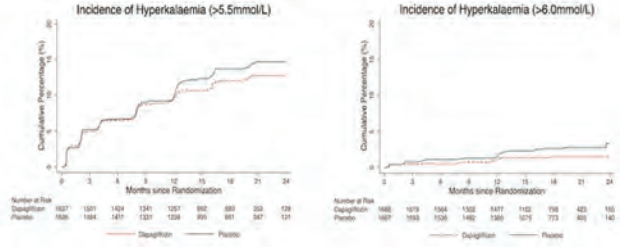
Table: Incident hyperkalaemia in DAPA-HF

	Dapagliflozin		Placebo			
	No. events/patients	Rate per 100py	No. events/patients	Rate per 100py	HR (95% CI)	P-value
Mild hyperkalaemia (>5.5 mmol/L)*						
No MRA at baseline	63/661	7.1	58/684	6.5	1.20 (0.84-1.72)	0.32
MRA treated at baseline	182/1637	8.6	204/1626	9.8	0.86 (0.70-1.05)	0.14
All patients	245/2298	8.2	262/2310	8.8	0.93 (0.78-1.11)	0.42
Moderate/Severe hyperkalaemia (>6.0 mmol/L)**						
No MRA at baseline	13/676	1.4	11/697	1.1	1.17 (0.52-2.62)	0.71
MRA treated at baseline	23/1688	1.0	40/1667	1.7	0.50 (0.29-0.85)	0.010
All patients	36/2364	1.1	51/2364	1.6	0.64 (0.42-0.99)	0.046

Models adjusted for baseline potassium and stratified by diabetes status at randomization. * Excluding those with baseline K+ >5.5 (n=136) ** Excluding those with baseline K+ >6.0 (n=16) Abbreviations: CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; PY, patient-years.

Incident hyperkalaemia in DAPA-HF

Figure: Cumulative incidence of hyperkalaemia in patients taking MRA at baseline



Cumulative incidence of hyperkalaemia in patients taking MRA at baseline

FR-OR20

Metformin Improves Vascular Function in CKD Patients with Metabolic Syndrome

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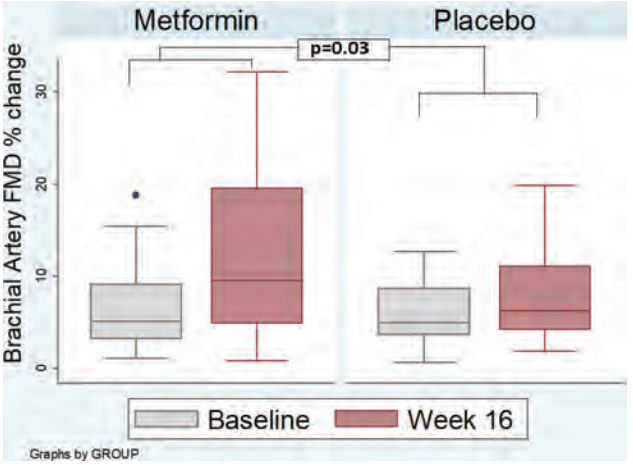
Background: Cardiovascular (CV) risk is increased in CKD. Insulin resistance (IR), highly prevalent in CKD patients, contributes to endothelial dysfunction and arterial stiffness, leading to poor CV outcomes. It remains unknown if insulin sensitization with metformin improves CV risk, in patients with CKD Stage 3-4 and metabolic syndrome (MS).

Methods: In a double-blinded randomized trial (NCT02252081), 50 patients with CKD Stage 3, and MS and/or pre-diabetes, received either metformin or placebo for 16 weeks. Dosing was initiated at 500 mg and up-titrated over 7-14 days based on GI tolerance up to 1500 mg/day in CKD3a and 1000 mg/day in CKD 3b. Co-therapies for optimal CV risk reduction were continued. The co-primary outcomes included change in brachial artery flow-mediated dilation (FMD), aortic pulse-wave velocity (aPWV), and carotid intima-media thickness (CIMT) in common (CCA) and internal (ICA) carotid arteries, at 16 weeks. Lactic acid was obtained throughout the study for safety.

Results: Participants were 65 ± 10 years old and 80% were men. Mean [SD]: BMI 31.4 ± 5.1 kg/m^2; SBP 130.5 ± 16 mmHg; DBP 74 ± 9 mmHg; HDL 46.4 ± 15 mg/dl; fasting glucose (FG) 92.3 ± 10.3 mg/dl; HbA1c 5.7 ± 0.24%; HOMA-IR 2.4±1.5, and eGFR was 50 ± 7 ml/min/1.73 m^2. There were 8 patients (16%) in CKD Stage 3b, 3 in the metformin and 5 in the placebo group. Compared with placebo, metformin improved FMD_{BA} (baseline: 6.24% ± 4.5% [mean±SD], 16 weeks: 12.06% ± 8.4% [mean±SD] with metformin and baseline: 6.12% ± 3.34% [mean±SD], 16 weeks: 7.6% ± 4.6% [mean±SD] with placebo, *P*=0.03 [**Fig 1**]), without changing aPWV (*P*=0.84) or CIMT: R CAA (*P*=0.10) L CCA (*P*=0.96) R ICA (*P*=0.74) L ICA(*P*=0.44).

Conclusions: Treatment with metformin improved FMD_{BA} but not aPWV or CIMT in patients with CKD and IR. Studies of larger sample size and longer duration are required to further evaluate the effects on cardiovascular outcomes.

Funding: Veterans Affairs Support



FR-OR21

Associations Between Enrollment in ESRD Special Needs Plans and Outcomes

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Background: Chronic condition special needs plans (C-SNPs) are Medicare Advantage plans that offer care coordination and specialized services for patients with conditions such as end-stage renal disease (ESRD) via specific benefits packages and provider networks. Although ESRD C-SNPs have been offered for over 10 years, an understanding of their impact on patient outcomes is lacking.

Methods: This observational study considered dialysis patients receiving care at a large dialysis organization who enrolled in a C-SNP from January 2013 to September 2017; study data were derived from deidentified medical records. As of C-SNP enrollment date (or matched date for controls), enrollees and controls were matched on the basis of index month, sex, race, etiology, and dialysis modality, as well as a propensity score. Eligible controls were patients who (separately): 1) dialyzed in the same facility as the C-SNP patient but had not enrolled in the C-SNP; 2) dialyzed in counties with no C-SNP but that were otherwise socio-demographically similar to C-SNP counties. Outcomes were evaluated from enrollment date through the first of study end (31 Dec 2018) or censoring for death, insurance change, or loss to follow-up. Within each matched cohort, outcomes were compared using generalized linear or Fine and Gray subdistribution hazard models.

Results: Hospitalization rates were 10% to 24% lower among C-SNP enrollees compared to controls, with an incidence rate ratio of 0.90 (95% confidence interval [CI] 0.84, 0.97) for patients in the same facility and 0.76 (95% CI 0.70, 0.83) for patients in similar counties. The mortality rate for C-SNP enrollees was approximately 23% lower than that of controls, with a hazard ratio of 0.77 (0.68, 0.88) for patients in the same facility and 0.77 (0.68, 0.88) for patients in similar counties. No meaningful differences were observed between groups with respect to serum calcium, phosphate, potassium, parathyroid hormone levels, or Kidney Disease Quality of Life scores.

Conclusions: C-SNP enrollment is associated with markedly lower rates of hospitalization and mortality, compared to non-enrollment.

FR-OR22

Organizational Characteristics Associated with High Performance in Medicare's ESRD Seamless Care Organizations

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Background: In 2016, the 1% of beneficiaries with end-stage renal disease (ESRD) constituted >7% of Medicare spending ($35 billion). To improve the value of care for the ESRD population, CMS implemented an alternative payment model (APM) for ESRD care, the ESRD Seamless Care Organization (ESCO), which shares savings with provider groups that reduce spending for ESRD patients below a defined benchmark. This study evaluated the relationship between key organizational, provider, community characteristics, and ESCO performance.

Methods: We constructed a novel ESCO-level dataset capturing key information for Wave 2 (2017) ESCOs using data from CMS reports, the National Provider Identification registry, and the Area Health Resource File. After describing all 37 ESCOs, we performed bivariate comparisons of high- and low-performing (above vs below median) ESCOs based on gross savings/losses, composite quality score, and standardized mortality ratio (SMR). We then estimated generalized logistic regression models of ESCO performance as a function of organizational, provider, and community characteristics.

Results: ESCO composition and performance were highly varied (ranges: savings/losses -3.9-10.2%; quality 76.4-100%; SMR 0.75-1.14). Bivariate analysis showed that ESCOs with above (vs below) median savings had more aligned physicians (58 vs 29, p=0.06), fewer dialysis facilities (8.7 vs 17, p=0.07), a smaller non-Hispanic Black population (14% vs 22%, p=0.06), and higher median household income ($56k vs $49k, p<0.01). Facilities reporting a quality score of 100% (vs <100%) had fewer practices (22 vs 43, p=0.05) and smaller non-Hispanic Black (16% vs 21%, p=0.06) and Medicaid eligible (6.5% vs 8.9%, p=0.14) populations. Low (vs above-median) SMR was associated with higher median household income ($58k vs $46k, p<0.01). Regression model results were consistent with these findings, though small sample size prevented statistically significant estimates.

Conclusions: Our findings offer the first evidence of the impact of organizational composition and social disparities on ESCO performance. We show that the diversity in ESCOs' composition and settings partially explained the high variation in performance. This study provides crucial evidence that will inform the design and implementation of APMs in nephrology and the decisions of provider groups considering participation.

FR-OR23

Progress in Preventing Bloodstream Infections in Hemodialysis: Data from the National Healthcare Safety Network, 2014-2018

Shannon Novosad, Lucy V. Fike, Minn Soe, Shunte Moon, Preeti Ravindhran, Erikka J. Woolfolk, Lauren Moccia, Duc B. Nguyen, Priti R. Patel. *Centers for Disease Control and Prevention, Atlanta, GA.*

Background: Patients on hemodialysis are at high risk of bloodstream infections (BSIs) and associated morbidity and mortality. National prevention efforts have resulted in widespread practice changes, including central venous catheter (CVC) care. We analyzed Dialysis Event surveillance data submitted to the National Healthcare Safety Network (NHSN) to describe BSI rates among hemodialysis outpatients from 2014 to 2018.

Methods: Outpatient hemodialysis facilities report BSIs (positive blood cultures collected in the outpatient setting or within 1 day after hospital admission) and the number of hemodialysis patients treated during the first 2 working days of each month to NHSN. For each BSI, the suspected source and vascular access type [e.g., CVC, arteriovenous fistula (AVF) or arteriovenous graft (AVG)] are indicated. Pooled mean rates (per 100 patient-months) were calculated. Annual BSI rate trends were evaluated using a negative binomial regression model including access type, year, and an access-year interaction variable.

Results: More than 6,000 outpatient hemodialysis facilities reported 134,961 BSIs from 2014 to 2018. Of these BSIs, 102,505 (76%) were categorized as access-related. Pooled mean BSI rates decreased 27% from 0.64 to 0.47 per 100 patient-months. Significant decreases in rates occurred across vascular access strata (Table); the reduction was most pronounced among patients with CVCs. BSI rates in patients with CVCs decreased 32% from 2.16 per 100 patient-months to 1.46 (annual average decrease 9.5%).

Conclusions: Substantial reductions in BSI rates among hemodialysis patients occurred during this 5-year period. Improvements in infection prevention practices, including CVC care, have likely contributed. Efforts to increase uptake of known prevention practices and identify new strategies for prevention might contribute to continued decreases in infections.

Funding: Other U.S. Government Support

BSI rates per 100 patient-months and annual trends, by access type, NHSN 2014-2018

Event	Access type	2014	2015	2016	2017	2018	Annual incidence rate ratio (95% CI)	Average annual % change (95% CI)
BSI	All	0.64	0.60	0.56	0.51	0.47		
BSI	Fistula	0.26	0.24	0.22	0.21	0.18	0.92 (0.91, 0.93)	-8.2 (-9.1, -7.3)
	Graft	0.39	0.39	0.37	0.35	0.33	0.95 (0.93, 0.98)	-4.7 (-7.1, -2.2)
	CVC	2.16	2.01	1.86	1.72	1.46	0.90 (0.88, 0.93)	-9.5 (-11.5, -7.5)

FR-OR24

Efficacy and Safety of Difelikefalin for Moderate-to-Severe CKD–Associated Pruritus: A Global Phase 3 Study in Hemodialysis Patients (KALM-2)

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Background: Chronic kidney disease (CKD)-associated pruritus (CKD-aP) is a common and distressing condition in CKD patients (pts) and has a serious negative impact on quality of life (QoL). Difelikefalin (DFK), a novel, peripherally restricted and selective kappa opioid receptor agonist, demonstrated efficacy in a US phase 3 study (KALM-1) in hemodialysis (HD) pts with CKD-aP. Here we report primary results from the global phase 3 study of DFK in HD pts with CKD-aP (KALM-2; NCT03636269).

Methods: HD pts with moderate-to-severe CKD-aP in the US, Europe, and Asia were randomized to receive intravenous DFK 0.5 mcg/kg (N=237) or placebo (PBO; N=236) after dialysis sessions. The primary endpoint was the proportion of pts who achieved ≥3-point improvement from baseline (BL) in the weekly mean of the daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) score at wk 12. Secondary endpoints were the proportion of pts who achieved ≥4-point improvement in WI-NRS score and mean change in itch-related QoL scores (5-D Itch and Skindex-10) from BL to wk 12.

Results: BL mean weekly WI-NRS scores were 7.3 and 7.1 in the DFK and PBO groups. The primary endpoint was met, with 54% of pts who received DFK achieving

a ≥3-point improvement in WI-NRS score vs 42% in the PBO group (*P*=.020). The proportion of pts who achieved a ≥4-point improvement in WI-NRS score was also significantly greater with DFK vs PBO (41% vs 28%, *P*=.010). Itch reduction was evident at wk 1 and was sustained through wk 12. Improvement in itch-related QoL assessed by 5-D Itch and Skindex-10 was observed. Treatment-emergent AEs ≥5% with DFK vs PBO were diarrhea (8.1% vs 5.5%), fall (6.8% vs 5.1%), dizziness (5.5% vs 5.1%), vomiting (6.4% vs 5.9%), and nausea (6.4% vs 4.2%). The incidence of serious AEs was similar across the groups.

Conclusions: In this second phase 3 study, IV DFK demonstrated rapid and sustained itch reduction in HD pts with CKD-aP in multiple regions of the world. DFK was generally well tolerated; safety was consistent with findings in prior studies. With no approved therapies for CKD-aP in the US or Europe, DFK is a potential therapeutic that may address this unmet need.

Funding: Commercial Support - This study was funded by Cara Therapeutics

FR-OR25

Efficacy and Safety of Roxadustat in Patients with Dialysis-Dependent CKD and Anemia on Hemodialysis

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Dialysis modality in patients with ESRD may impact clinical outcomes and survival. Thus, evaluation of safety and efficacy of roxadustat in patients on hemodialysis (HD) is of clinical importance.

Methods: Pooled data from three pivotal, phase 3, randomized, open-label, epoetin alfa-controlled studies of roxadustat for the treatment of anemia in patients with dialysis-dependent (DD) CKD were assessed in the subgroup of patients on HD. Endpoints evaluated were: mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy and Hb CFB averaged over Weeks 28–36 censored for rescue therapy. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs).

Results: In the DD-CKD study population, 90% (3515/3887) of patients were on HD (roxadustat=1761, epoetin alfa=1754). Baseline characteristics were generally similar between treatment groups. Mean (SD) Hb levels (mg/dL) at baseline were 9.64 (1.31) in the roxadustat group and 9.67 (1.31) in the epoetin alfa group. Patients achieved a larger mean (SD) CFB to Weeks 28–52 in Hb with roxadustat vs. epoetin alfa (1.20 [1.49] vs. 0.98 [1.51]), corresponding to a least-squares mean (LSM) difference of 0.25 (95% CI: 0.19, 0.31) (p<0.0001). Patients achieved a larger mean (SD) CFB to Weeks 28–36 in Hb with roxadustat vs. epoetin alfa (1.27 [1.63] vs. 1.02 [1.60]), corresponding to a LSM difference of 0.25 (95% CI: 0.16, 0.33) (p<0.0001). TEAE rates were comparable between treatment groups.

Conclusions: Roxadustat was efficacious vs. epoetin alfa for increasing and maintaining Hb levels in patients with DD-CKD on HD. The safety and tolerability profiles were similar to the overall population and consistent with that observed in this patient subgroup.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

FR-OR26

Stroke and Bleeding Risk Among US Veterans with Preexisting Atrial Fibrillation Transitioning to ESRD

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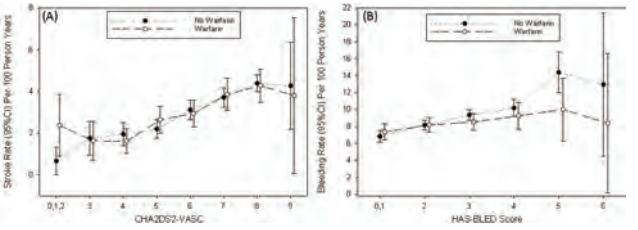
Background: Anticoagulation has been the mainstay of stroke prevention among patients with atrial fibrillation (AF). However, end stage renal disease (ESRD) patients on hemodialysis are at higher risk of bleeding and stroke outcomes, even without anticoagulation. It is unclear if patients should be continued on anticoagulation at the time of transition to ESRD.

Methods: We retrospectively examined a cohort consisting of 29,054 pre-dialysis US veterans that had a diagnosis of AF prior to transition to ESRD without a history of stroke. Patients were first stratified by CHA_2DS_2-VASC and modified HAS-BLED scores, ascertained at the time of transition. Prescriptions for warfarin were determined 180 days prior to and 90 days post transition. Incidence Rate Ratios (IRR) for stroke and bleeding events prior to ESRD transition stratified by warfarin vs no warfarin across risk scores were estimated with Poisson regression.

Results: The median age was 77±9 years, 4% were female, 85% were white, and 13% were African American. The median (IQR) CHA_2DS_2-VASC and HAS-BLED scores were 7 (5,8) and 2 (2,3), respectively. Stroke rates by CHA_2DS_2-VASC scores ranged from 0.67 (scores 0/1/2) to 4.27 (score 9) per 100 pt-years while bleeding rates by HAS-BLED scores ranged from 6.83 (score 0/1) to 46.3 (score 7) per 100 pt-years (Figure). Those with a CHA_2DS_2-VASC score of 0/1/2, had a stroke IRR of 0.28 (95% CI: 0.09-0.90, p=0.03) favoring no warfarin. Among patients with other CHA_2DS_2-VASC scores, there was no difference in stroke risk between warfarin and non-warfarin users. No difference was also seen in bleeding risk among warfarin vs non-warfarin users by HAS-BLED score.

Conclusions: In low stroke risk individuals (CHA_2DS_2-VASC score of 0, 1, or 2), warfarin use was associated with a higher risk of stroke. There was no significant difference in stroke and bleeding outcomes among other ESRD patients with AF transitioned to dialysis regardless of CHA_2DS_2-VASC and HAS-BLED scores.



FR-OR27

Forecasting the Distribution of Dialytic Modalities in the Era of Advancing American Kidney Health

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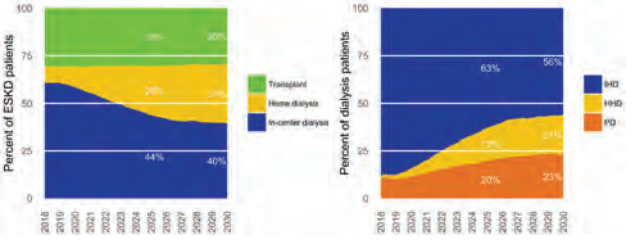
Background: The Executive Order on Advancing American Kidney Health aims to increase home dialysis utilization in patients with end stage kidney disease (ESKD). We constructed a simulation projecting dialytic modality distributions between 2019 and 2030 as a function of changing modality transition rates.

Methods: We specified the US ESKD population in Dec. 2018 and used Markov chain Monte Carlo methods to randomly assign patients to a dialytic modality, transplant, or death each month until Dec. 2030, according to parameters that regulate the inflow and outflow of each state. Incident ESKD patients entered the cohort each month and were subject to the same transition parameters. We assessed how changing transition parameters affects projected dialytic modality distributions.

Results: By prevailing conditions, the simulation projects home dialysis will comprise 12% of the dialysis population in 2025. Increasing home hemodialysis (HD) and peritoneal dialysis (PD) utilization among incident ESKD patients from rates of 0.3% to 7.5% and from 11.5% to 37.5%, respectively, by 2025 results in home dialysis utilization of 25% in 2025 and 29% in 2030. Concurrently increasing the rate of conversion from in-center HD to home dialysis from 3.0 to 15.0 events per 100 patient-years by 2025 results in home dialysis utilization of 37% in 2025 and 44% in 2030, as displayed. Decreasing home dialysis attrition rates has a smaller effect on home dialysis utilization.

Conclusions: Substantial growth of home dialysis utilization in the next decade will require a two-pronged approach to inflow: higher utilization of home dialysis in incident patients, emphasizing PD, and increased conversion of patients from in-center HD to home dialysis.

Funding: Commercial Support - Fresenius Medical Care



FR-OR28

Hospitalization and Day of the Week: Comparing Peritoneal Dialysis, Home Hemodialysis, and In-Center Hemodialysis

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Background: Studies have shown that there are daily variations in mortality for patients receiving in-center hemodialysis (HD) but not home HD, peritoneal dialysis or more frequent in-center HD. Less is known about daily variations in hospitalization according to dialysis modality.

Methods: We analyzed all chronic dialysis patients in Canada (excluding Manitoba and Quebec) from 1 Jan 2005 to 31 Dec 2014 using the Canadian Organ Replacement Register (CORR). Dialysis modalities were defined (using CORR) as peritoneal dialysis, conventional HD or frequent HD (nocturnal or short daily) and HD modalities were furthered categorized as home versus in-center. All switches between modalities after dialysis initiation were included provided the duration of the switch was >30 days.

The absolute number of hospitalizations for each day of the week was reported for each treatment type and differences in the distribution of hospitalizations were compared using the Chi-Square test.

Results: The cohort consisted of 36,334 individuals. Median age was 67 and 61% were of male sex. A total of 81% of patients were receiving hemodialysis at dialysis initiation and the cause of end-stage kidney disease was secondary to diabetes in 37%. Overall, there were 119,466 hospitalizations over the observation period. The cumulative number of hospitalizations was highest for conventional in-center HD (92,707) and lowest for conventional home HD (701). Day of the week admissions for each treatment type are noted in Table 1 (P<0.001). Hospitalizations were least frequent on saturday and sunday for all groups. The proportion of admissions was highest on monday or tuesday for conventional HD (regardless of location) and frequent in-center HD. In contrast, frequent home HD had a higher proportion of admissions on wednesday.

Conclusions: There are daily variations in hospitalization comparing dialysis modalities. Future planned analyses will evalute whether there are adjusted differences in day of the week hospitalization across modalities accounting for differences in patient characteristics.

Treatment Group	Total	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Conventional In-Center HD*	92707	8971 (10)	15496 (17)	16138 (18)	14643 (16)	14108 (15)	13508 (16)	9843 (11)
Frequent In-Center HD	1426	137 (10)	262 (18)	228 (16)	211 (15)	219 (15)	201 (14)	168 (12)
Conventional Home HD	701	60 (9)	137 (20)	129 (18)	115 (16)	93 (13)	95 (14)	72 (10)
Frequent Home HD	1439	149 (10)	213 (15)	231 (16)	273 (19)	230 (16)	191 (13)	152 (11)
Peritoneal Dialysis	23193	2562 (11)	3684 (16)	3800 (16)	3727 (16)	3533 (15)	3473 (15)	2414 (10)

* Hemodialysis

Day of the week hospitalization for each dialysis treatment type (N, %)

FR-OR29

Improving Supportive Care of Seriously Ill Dialysis Patients with Goals-of-Care Conversations

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Background: Dialysis patients are frequently known to receive unwanted high intensity end-of-life care. Families rate the quality of this care lower than families of patients with other chronic diseases. The purpose of this study was to test the feasibility of a supportive care intervention--the Pathways Project, an evidence-based change package of best practices--to identify seriously ill patients (SI), engage them in goals of care discussions, and track outcomes for patient goal concordance.

Methods: Pathways researchers recruited 10 dialysis centers with 1,546 patients. Dialysis staff screened patients with the surprise question (SQ)-"Would I be surprised if this patient died in the next 6-12 months?"- to identify those who were SI and recorded patient outcomes including the number screened, SI, goals of care conversations, hospitalizations, referred to hospice, death, and place of death. An odds ratio was calculated for the odds of SI dying versus those who were not SI, and one-sided Cochran-Armitage trend tests were used to assess for increasing goals of care conversations and deaths at home. The study was interrupted at 9 months due to COVID-19.

Results: On average, 98.8% of patients were screened monthly, and 18.4% were identified as SI. Of 114 patients who died, the SI constituted 66% of deaths though only 18.4% of patients. The mortality for the SI was 27% versus 3% for those who were not, and the odds ratio for SI dying was 11.22 (95% CI 7.42 to 16.98, P < .0001). Dialysis interdisciplinary teams implemented site-specific approaches to adding goals of care conversations into usual workflow; the number conducting conversations with SI within 30 days of hospital discharge increased from 30% to 80% (P=.02). The proportion of the patients who died at home in the last 2 months was higher than baseline (32.6% vs 18.8%), but a trend was not yet evident (P=.12).

Conclusions: The Pathways intervention is feasible to implement supportive care best practices into existing workflow of dialysis centers. It takes time for teams to get comfortable with new processes and communication approaches; after 9 months more centers were conducting goals of care conversations and more patients were dying at home. Future research is needed to determine if the Pathways intervention results in outcomes more aligned with patient preferences.

Funding: Private Foundation Support

FR-OR30

Implementation of a Decision Aid for Recognition and Correction of Volume Alterations (Recova®) in Hemodialysis

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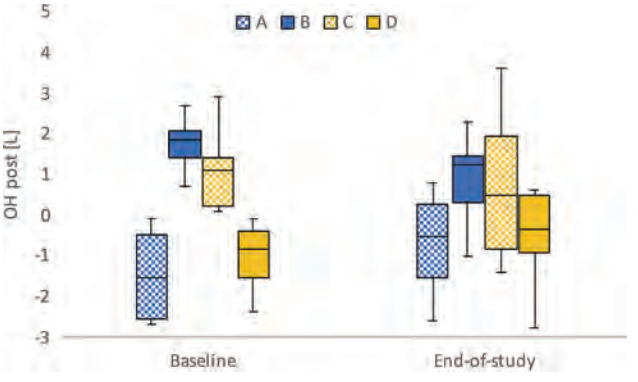
Background: Chronic fluid overload is an independent predictor of mortality in hemodialysis. Clinical assessment of fluid status is subjective and unprecise, and 30% of the patients remain fluid overloaded at dry weight. This study evaluates the effects of implementing a recently developed decision aid, Recova®, which combines a systematized fluid status procedure with bioimpedance spectroscopy, for individualized dry weight determination in hemodialysis.

Methods: The study was a prospective implementation intervention carried out at two hemodialysis units. The impact of the intervention was measured as the proportion of participants at an adequate dry weight at the end of the study, assessed as change in symptoms, hydration status, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Hemodialysis nurses were instructed to use Recova® every two weeks, assessing the study participants' fluid status and adjusting their dry weights as appropriate. The process of the intervention was measured as frequencies of fluid status assessments, bioimpedance measurements, and dry weight adjustments.

Results: Forty-nine patients were enrolled. In participants with fluid overload (n = 10), both bioimpedance-measured overhydration and fluid overload symptom score decreased. In fluid-depleted participants (n = 20), dry weight adjustment frequency and dry weight increased. The post-dialytic negative overhydration was reduced, but NT-proBNP increased. In the remaining 19 participants, with low volume status scores, no significant changes were observed.

Conclusions: Recova® defines how and when dry weight should be evaluated in hemodialysis patients. Its purpose is to provide the multidisciplinary team with a common language, and thereby facilitate early recognition and appropriate response to fluid alterations. Implementation of Recova® in hemodialysis care increased the monthly frequencies of bioimpedance measurements and dry weight adjustments, and contributed to symptom reduction.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



Overhydration at base-line and at end-of-study

FR-OR31

Development of Alport-Syndrome-on-a-Chip to Study the Glomerular Filtration Barrier Pathophysiology

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Background: Alport Syndrome (AS) is a genetic disorder in which podocytes fail to correctly assemble the COL4α3α4α5 trimer, a major constituent of the GBM. Disruption of the COL4 network leads to podocyte depletion and progressive kidney failure. While important advances in our understanding of AS progression have been made possible by animal models, we still lack an efficient and faithful in vitro model that can mimic the human AS disease. We have recently developed a glomerulus-on-a-chip system (GOAC) that replicates the features of the glomerular filtration barrier and generated AS chips by combining this novel tool with COL4-defective podocytes.

Methods: Podocytes derived from amniotic fluid of patients affected by AS (AS-POD) were seeded with human glomerular endothelial cells (hGEC) on Organoplates in a barrier-free system to generate AS-GOAC. The system was assessed by confocal microscopy, WB, proteomics and RNA-seq. Permselectivity was assessed by measuring albumin leakage. Transcriptomics studies were performed on podocytes by RNA-seq and qPCR and results confirmed in vivo in a mouse model of AS. Primary human podocytes were used as control.

Results: We confirmed AS phenotype in AS-POD by RNA-seq and WB. GOAC generated with AS-POD show absence of COL4A3-4-5 confirmed by WB. AS-GOAC

present impaired permselectivity to albumin, due to a dysfunctional assembly of the GBM, typical of AS. Our data confirmed high upregulation of miR-193a, a microRNA known to target key players in AS and CKD like WT1, osteopontin, vinculin as well as VEGF and TGFβ pathways. Results were confirmed in vivo in glomeruli of AS mice, further validating the AS-GOAC as an efficient tool for AS studies. Proteomics analysis of the filtrate revealed a distinctive signature in AS-GOAC, including presence of apoliprotein A, vWF and ceruloplasmin.

Conclusions: We have successfully developed an Alport-on-a-chip system that closely mimics the GFB structure and provides a powerful tool for studying the effect of a defective GBM at the cellular level. We have also identified some specific AS proteins, indicative of disease manifestation. This system has the potential to improve our knowledge on AS patho-physiology, able novel therapeutic targets and become a transformative tool, thus ultimately benefiting patients affected by renal failure.

Funding: Private Foundation Support

FR-OR32

Development of a Personalized Medicine Platform for Nonsense Readthrough Therapy in Alport Syndrome

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Background: Alport syndrome (AS) is characterized by glomerular basement membrane (GBM) abnormalities leading to progressive glomerulosclerosis. Mutations in the COL4A3, COL4A4 or COL4A5 genes encoding type IV collagen α3α4α5 cause AS. Nonsense mutations resulting in premature termination codons (PTCs) account for about 6% of AS cases. Type IV collagen chains have a C-terminal NC1 domain, which is essential for assembly of heterotrimers inside cells and for network formation in the GBM. Truncated α3, α4, α5 chains without an intact NC1 domain due to PTCs cannot assemble in the GBM. Therefore, achieving full-length protein expression is a potential therapy for AS due to nonsense mutations. Small compound-based nonsense readthrough therapy has been well studied in other genetic diseases, but whether nonsense readthrough therapy is applicable to Alport syndrome is unexplored.

Methods: To investigate the feasibility of PTC readthrough in AS, we made a C-terminal NanoLuc-fusion COL4A5 reporter cDNA to monitor full-length translation. The full-length COL4A5-NLuc produces luminescence, but truncated forms do not. To screen for COL4A5 nonsense mutants susceptible to PTC readthrough therapy, we introduced 49 nonsense mutations found in X-linked AS patients into the COL4A5-NLuc gene. We transfected these individually into HEK293 cells and measured luminescence in the presence of Geneticin (G418), which is known to have high readthrough activity.

Results: The COL4A5-NLuc gene produced luminescence when wild type, but not when carrying COL4A5 nonsense mutations. Among 49 nonsense mutants, we found that 11 were susceptible to PTC readthrough. The efficacy of readthrough was higher for UGA nonsense codons than for UAG and UAA. Gentamicin also induced readthrough of these same 11 PTCs.

Conclusions: We found 11 nonsense mutations in COL4A5 susceptible to PTC readthrough drugs. This luciferase-based COL4A5 translation reporter system will contribute to the development of PTC readthrough therapy in a personalized medicine approach to treating AS.

Funding: NIDDK Support

FR-OR33

A ROBO2 Fusion Protein (PF-06730512) Traps SLIT Ligands and Therapeutically Ameliorates Podocyte Injury

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Background: ROBO2/SLIT2 signaling negatively regulates nephrin-induced actin polymerization and destabilizes podocyte focal adhesions and attachment to the glomerular basement membrane (GBM) by inhibiting non-muscle myosin IIA. Mice lacking ROBO2 in podocytes are protected from podocyte injury. Based on these findings we hypothesized that blocking this pathway might have therapeutic potential in podocytopathies. Here we provide evidence to support that hypothesis from a case with a genetic defect in ROBO2 and a rodent model of podocyte injury.

Methods: We investigated a patient with a chromosomal translocation that disrupted the ROBO2 gene, produced transcripts encoding dominant negative proteins, and caused high-grade vesicoureteral reflux (VUR). We designed a novel therapeutic ROBO2 fusion protein (ROBO2-Fc, PF-06730512) that inhibits the ROBO2/SLIT2 pathway. In vivo efficacy of ROBO2-Fc was tested in the rat Passive Heymann Nephritis (PHN) model. We also studied the molecular and cellular functions of SLIT2 in kidney glomeruli.

Results: In contrast to most adults with long-standing VUR that develop focal and segmental glomerulosclerosis (FSGS) and proteinuria, the patient with a disrupted ROBO2 gene had stable renal function without proteinuria. In vitro, ROBO2-Fc bound to SLIT ligands with high affinity and dose-dependently inhibited SLIT binding to cell surface ROBO2, and it inhibited ROBO2-dependent cell migration ex vivo. ROBO2-Fc has a terminal half-life of about 5 days in rat and 8 days in monkey. Treatment with ROBO2-Fc reduced proteinuria, shortened podocyte foot process width, and increased slit-diaphragm density in the rat PHN model. Mechanistically, we found that SLIT2 is localized to the GBM and binds to COL4A3/laminin to inhibit podocyte adhesion.

Conclusions: We have generated a novel therapeutic ROBO2 fusion protein that functions as a SLIT ligand trap to treat podocyte injury in a pre-clinical animal model. Inhibiting the ROBO2/SLIT2 pathway therapeutically reduces proteinuria and improves podocyte ultrastructure. A phase 2 clinical trial to evaluate the safety and efficacy of ROBO2-Fc (PF-06730512) in patients with FSGS is currently ongoing (NCT03448692).

Funding: Other NIH Support - National Institute of Health (NIH), Commercial Support - Pfizer Inc

FR-OR34

Semaphorin 3B-Associated Membranous Nephropathy

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Background: Membranous nephropathy (MN) results from subepithelial antigen-antibody complex deposition along the glomerular basement membrane (GBM). Although PLA2R, THSD7A, and NELL-1 account for a majority (approximately 80%) of the target antigens, the target antigen in the remaining MN is not known.

Methods: We performed laser microdissection and mass spectrometry (MS) of glomeruli in kidney biopsies of 70 cases of PLA2R-negative MN. We detected high spectral counts of a unique protein Semaphorin 3B (Sema3B) in 3 cases. Immunohistochemistry (IHC) for Sema3B was then performed to confirm MS results. Next, we analyzed 3 validation cohorts (2 French and 1 Italian) of 118 PLA2R-negative MN cases by immunofluorescence microscopy (IF). Confocal microscopy studies were done to confirm colocalization of IgG and Sema3B along the GBM. Next, serum antibodies were detected by Western blotting (WB).

Results: MS identified a unique protein, Sema3B in 3 cases of PLA2R-negative MN. MS failed to detect Sema3B in the remaining 67 PLA2R-negative MN, in 23 PLA2R-associated MN, and 88 controls that included IgA nephropathy, diabetes, FSGS and minimal change disease. Semaphorin 3B in all 3 positive cases localized as granular deposits along the GBM by IHC (Figure 1). Next, an additional 8 cases of Sema3B-associated MN were identified in 3 validation cohorts by IF. Confocal microscopy showed that both IgG and Sema3B co-localized to the GBM. In 4 of 11 cases, kidney biopsy also showed tubular basement membrane (TBM) IgG deposits, the TBM deposits were negative for Sema3B. WB analysis in 5 available sera showed reactivity to reduced Sema3B in 4 of 4 patients with active disease and no reactivity in 1 patient in clinical remission; there was also no reactivity in control sera. Eight (73%) of the 11 cases of Semaphorin 3B-associated MN were pediatric cases. In 5 of the 8 children, the disease started below the age of 2 years.

Conclusions: Semaphorin 3B-associated MN is a distinct type of MN, and is predominantly present in pediatric patients.

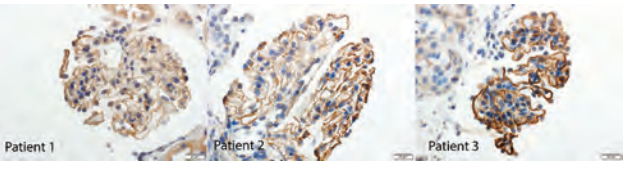

Figure 1 shows bright granular capillary wall staining for Sema3B in 3 cases of Sema3B-associated MN.

FR-OR35

High Temperature Recombinant Protein A1 (HTRA1): A Novel Antigen in Membranous Nephropathy

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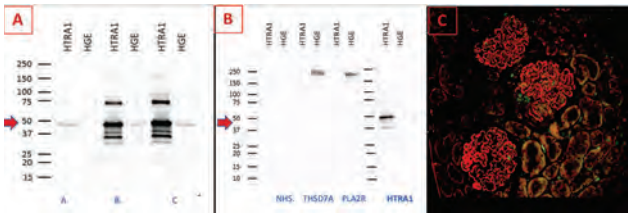
Background: Previous discoveries in MN included identification of PLA2R, THSD7A and NELL-1 as target antigens in 80-85% of primary MN cases. However, target antigens in the remaining 15-20% of cases remain unidentified.

Methods: We present a multi-pronged approach using traditional and modern technologies to converge on a novel target antigen. Instead of a case-vs-control design, we capitalized on the temporal variation in autoantibody titer for our biomarker discovery. Western blotting (WB) of human glomerular extract (HGE) proteins followed by differential immunoprecipitation and mass spectrometric analysis was complemented by laser-capture microdissection / mass spectrometry as well as autoimmune profiling on a protein expressed sequence tag microarray. Commercial antibodies to the candidate antigen were used for immunostaining MN biopsies, and reactivity of patient sera with a recombinant HTRA1 (rHTRA1) by WB and ELISA was assessed.

Results: Using these combined approaches, we identified HTRA1 as a novel antigen in a subset of patients with primary MN. Serum from those patients reacted by WB with a 51 KDa protein in non-reduced HGE as well as rHTRA1, which correlated with clinical disease activity.(Fig A and B) Consistent with PLA2R and THSD7A, anti-HTRA1 antibodies were predominantly IgG4. HTRA1 specifically was detected in a capillary loop fine granular pattern. (Fig C) and colocalized with IgG4. Whole-proteome peptide microarrays detected significantly higher titer (6.9 SD) of anti-HTRA1 antibody in the active stage as opposed to the remission stage which was informative of its candidacy as a podocyte targeted protein. We have 3 confirmed cases of HTRA1-associated MN and are currently screening several large biopsy cohorts of MN that are negative for PLA2R, THSD7A, and NELL-1 to better assess the prevalence of this novel form of MN.

Conclusions: This report demonstrates the convergence of conventional with more modern techniques to identify HTRA1 as a target podocyte antigen in MN.

Funding: Private Foundation Support



FR-OR36

Protocadherin 7-Associated Membranous Nephropathy

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Background: Membranous nephropathy (MN) results from subepithelial antigen-antibody complex deposition along the glomerular basement membrane (GBM). Although PLA2R, THSD7A, and NELL-1 account for a majority (approximately 80%) of the target antigens, the target antigen in the remaining MN is not known.

Methods: We performed laser microdissection and mass spectrometry (MS) of glomeruli in kidney biopsies of 85 cases of PLA2R-negative MN. We detected high spectral counts of a unique protein Protocadherin 7 (PCDH7) in 8 cases. Immunohistochemistry (IHC) for PCDH7 was then performed to confirm MS results.

Results: MS identified a unique protein, PCDH7 in 8 cases (9.4%) of PLA2R-negative MN. MS failed to detect PCDH7 in remaining 77 PLA2R-negative MN, 23 PLA2R-positive MN, and 88 controls that included IgA nephropathy, diabetes, FSGS and minimal change disease. Among the 77 PLA2R-negative MN, MS detected NELL1 (14 cases), EXT1/EXT2 (6 cases), PLA2R (4 cases labeled PLA2R-negative on IF), Sema3B (3 cases), THSD7A (2 cases), and DNAJB9 (4 cases of fibrillary GN, misdiagnosed as MN as EM was not done). PCDH7 localized as granular deposits along the GBM by IHC (Figure 1). Kidney biopsy showed a grade II MN in 6 cases, grade I in 1 and grade III in 1 case. Immunofluorescence microscopy showed GBM staining for IgG and C3 in all cases. IgG subtyping done in 2 cases showed IgG4 in both. The mean age was 64 years (+/- 11) and 7 of the 8 patients were males. The average serum creatinine and proteinuria was 1.28 mg/dL (+/- 0.3) and 4.9 gm/L (+/- 3.0), respectively. Interestingly, 3 of 8 cases had associated malignancies. Further studies including evaluation for circulating antibodies are ongoing.

Conclusions: Protocadherin 7-associated MN may represent distinct type of MN.

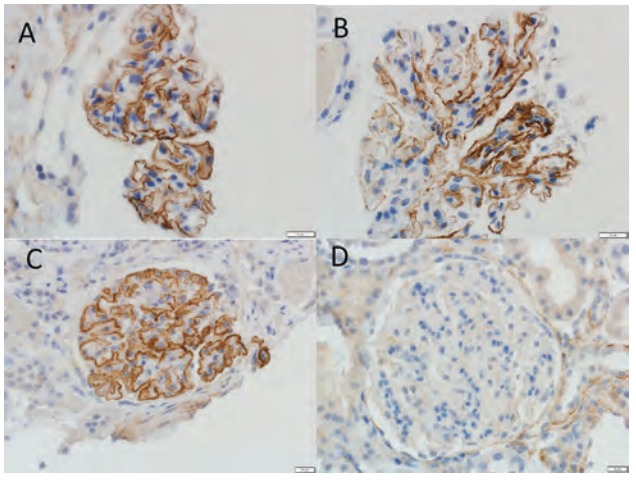

Figure 1 shows bright granular capillary wall staining for PCDH7 in 3 cases (A, B, C) of PCDH7-associated MN, and negative staining in a case (D) of PLA2R-negative MN.

FR-OR37

Nefecon® (Budesonide) Selectively Reduces Circulating Levels of BAFF (BLyS) and Soluble BCMA and TACI in IgA Nephropathy

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Background: Evidence supports a pivotal role for gut-associated lymphoid tissue (GALT) as a major source of poorly *O*-galactosylated immunoglobulin A (IgA) 1 in patients with IgA nephropathy (IgAN). IgA synthesis in GALT is regulated by B-cell activating factor (BAFF) [B-lymphocyte stimulator (BLyS)] and A PRoliferation-inducing ligand (APRIL). BAFF and APRIL bind to specific cell-surface receptors: transmembrane activator and calcium modulator and cyclophilin-ligand interactor (TACI), B-cell maturation antigen (BCMA), and the BAFF receptor. Elevated levels of BAFF and APRIL have been linked to worse clinical outcomes in IgAN. The therapeutic potential of targeting GALT was demonstrated in the NEFIGAN trial (NCT01738035), which assessed the efficacy of a novel targeted-release formulation of budesonide (Nefecon®), designed to deliver budesonide to the GALT-rich distal ileum in patients with IgAN. The trial comprised 6-month run-in, 9-month treatment, and 3-month follow-up phases: 48 patients received Nefecon® 16 mg/day, 51 patients received Nefecon® 8 mg/day, and 50 patients received placebo. As a result, Nefecon® 16 mg/day, added to optimised renin–angiotensin system blockade, reduced proteinuria and stabilized estimated glomerular filtration rate in patients with IgAN. This study investigated whether Nefecon® treatment altered serum levels of BAFF and APRIL and their receptors.

Methods: Serum levels of BAFF, APRIL, BCMA, and TACI were measured using Luminex technology. Changes in the levels of each biomarker with treatment were compared using a one-way analysis of variance. Significance was set as $p<0.05$.

Results: A significant, dose-dependent reduction in serum BAFF levels was seen with Nefecon®, which reversed on cessation of Nefecon®. There were similar significant reductions in the levels of soluble BCMA and TACI with treatment, but no effect was seen on circulating levels of APRIL. These changes were mirrored by parallel changes in soluble CD27 levels and were consistent with our previous reports on dose-dependent reductions in circulating IgA–IgG immune complexes, secretory IgA, and galactose-deficient IgA levels with Nefecon®.

Conclusions: Delivering budesonide to the GALT-rich distal ileum modulates key regulators of GALT B-cell maturation and IgA class switch recombination in patients with IgAN.

Funding: Commercial Support - Calliditas

FR-OR38

KZR-616, A Selective Inhibitor of the Immunoproteasome: Preclinical and Clinical Mechanism of Action Studies in Lupus Nephritis

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Background: Selective inhibition of the immunoproteasome blocks progression of nephritis in a mouse model of systemic lupus erythematosus (SLE). Here we describe the effects of KZR-616 in this model and in patients from MISSION (KZR-616-002; NCT03393013), an open-label study of KZR-616 in patients with SLE with and without nephritis.

Methods: 24-week old NZB/W mice were treated weekly with subcutaneous administration of 5 mg/kg KZR-616 for 11 weeks. SLE patients with active disease and stable background medication (N=34) were dosed subcutaneously with KZR-616 at 30, 45 or 60 mg weekly for 13 weeks with a 12-week follow-up. Clinical samples were evaluated for proteasome subunit binding, and immune cell profile was evaluated by flow cytometry. Gene expression analysis was performed by RNAseq in mouse tissue (whole blood, spleen, and kidneys) and patient (whole blood) samples.

Results: KZR-616 treatment resulted in complete resolution of proteinuria, prevention of glomeruli damage, and absence of renal IgG deposition. Depletion of splenic activated T- and B-cells and short and long-lived plasma cells in treated animals was noted and correlated with decreased gene expression associated with inflammation, T helper (Th) 1 and Th17 pathways, interferon signaling, antibody secreting cells, and differentiation of plasma cells (PC). KZR-616 reduced kidney tissue transcripts associated with inflammation, cell and myeloid glomerulus trafficking and renal genes implicated in LN pathogenesis. In SLE patients, KZR-616 treatment was determined to be safe and tolerated at all dose levels and reductions in disease activity parameters were noted. KZR-616 treatment was associated with a reduction in class-switched memory B cells and PC in peripheral blood. Decreased expression of gene modules for PC, T-cell activation, inflammation, neutrophil, and type I IFN responses were seen in response to treatment.

Conclusions: KZR-616 resolves nephritis in a mouse model of SLE/LN by regulating immune effector cell gene expression and glomerular injury. In SLE patients, KZR-616 demonstrated broad anti-inflammatory activity across T, B, and innate immune effector cells. These results support further clinical evaluation of KZR-616 in patients with LN.

Funding: Commercial Support - Kezar Life Sciences

FR-OR39

NCAM1 Is an Autoantigen in Membranous Lupus Nephritis

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Background: Membranous lupus nephritis is a frequent cause of proteinuria in patients with systemic lupus erythematosus. In patients with membranous lupus nephritis, the target autoantigens are largely unknown. Determination of a target autoantigen can have diagnostic significance, inform prognosis, and enable non-invasive monitoring of disease activity. We utilized mass spectrometry to identify target autoantigens in membranous lupus nephritis and report neural cell adhesion molecule-1 (NCAM1) as a novel target podocyte antigen.

Methods: We utilized mass spectrometry for antigen discovery of laser capture microdissected (LCMD) glomeruli and protein G immunoprecipitation studies to interrogate immune complexes. Confocal microscopy was used to examine co-localization with IgG within glomerular immune deposits. Case series of biopsies from PLA2R-negative membranous nephropathy patients (n=101) and patients with membranous lupus nephritis (n=212) were used to determine the overall frequency of these antigens. Western blotting reacting patient sera against recombinant NCAM1 protein was used to detect circulating anti-NCAM1 antibodies.

Results: NCAM1 was uniquely identified in a subset of patients with membranous lupus nephritis in LCMD glomeruli and protein G immunoprecipitations by mass spectrometry. NCAM1 co-localized with IgG within glomerular immune deposits. The prevalence of NCAM1 positivity by immunofluorescence was 6.1% of cases of membranous lupus nephritis and 2.0% of idiopathic membranous nephropathy cases. Additionally, serum from NCAM1 patients showed reactivity to NCAM1 recombinant protein, demonstrating the presence of circulating antibodies.

Conclusions: We propose that NCAM1, a cytoskeleton-linked transmembrane protein, is a target autoantigen in a subset of patients with membranous lupus nephritis and within rare cases of idiopathic membranous nephropathy. The presence of anti-NCAM1 antibodies in sera could allow for non-invasive monitoring.

Funding: Other NIH Support - SBIR funding from the National Institute on Minority Health and Health Disparities, awarded to Dr. Christopher Larsen

FR-OR40

Alpha1-Antitrypsin Diminishes Neutrophil Activation by PR3-ANCA and Endothelial Injury by Neutrophil Serine Proteases

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Background: Neutrophil serine proteases (NSPs) contribute to ANCA-associated vasculitis (AAV). PR3 is a unique NSP family member because it is both a proteolytic enzyme and an ANCA antigen. Alpha1-antitrypsin (AAT) is the major natural NSP inhibitor. We hypothesized that AAT protects from ANCA-induced neutrophil activation and neutrophil-mediated glomerular endothelial cell injury.

Methods: We produced recombinant wild-type (wt) AAT and a mutant (mu) form that does not inhibit proteolytic NSP activity. We used flow cytometry to study membrane PR3 (mPR3) and MPO (mMPO), ferricytochrome C assay for superoxide release, FRET assays for proteolytic NSP activity, human neutrophils and glomerular microvascular endothelial cells (gMVEC), confocal and electron microscopy, and assessed ECs by phalloidin staining and gene expression.

Results: Wt-AAT reduced mPR3 on TNF-primed neutrophils dose-dependently from 0.1 to 10 μM (n=3). Five μM wt-AAT, but not mut-AAT, reduced neutrophil mPR3 in suspension, on fibronectin, and on an EC monolayer to approximately 25% (n=3). Parallel comparisons in neutrophil-EC co-cultures using antibodies to different PR3 epitopes showed that 5 μM AAT reduced mPR3 but not mMPO. Importantly, reduced mPR3 by AAT resulted in significantly less superoxide release by TNFa-primed neutrophils when activated with PR3-, but not with MPO-ANCA IgG from AAV patients (n=4). Next, we studied the NSP transfer from activated neutrophils to gMVEC and found that gMVEC acquired NSPs, exemplified by PR3, from both cell-free supernatants (cf-SN) and under neutrophil-EC co-culture conditions. Importantly, wt-, but not muAAT abrogated the PR3 transfer from cf-SN. In contrast, AAT did not inhibit the PR3 transfer under neutrophil-EC co-culture conditions. Finally, we observed by RT-PCR that cf-SN from activated neutrophils increased two NF-κB dependent genes in gMVEC, namely IkBa and IL-8. This effect was reduced by wt-, but not by mu-AAT suggesting an NSP-dependent activation mechanism.

Conclusions: AAT has protective effects by reducing neutrophil activation in response to PR3-ANCA, and NSP-mediated glomerular microvascular endothelial cell injury. Disturbances of the AAT-NSP balance possibly contribute to neutrophil-mediated vascular injury in AAV, particularly, but not exclusively, in patients with PR3-ANCA.

Funding: Government Support - Non-U.S.

FR-OR41

Harnessing Expressed Single-Nucleotide Variation and Single-Cell RNA Sequencing to Define Immune Cell Chimerism in the Rejecting Kidney Transplant

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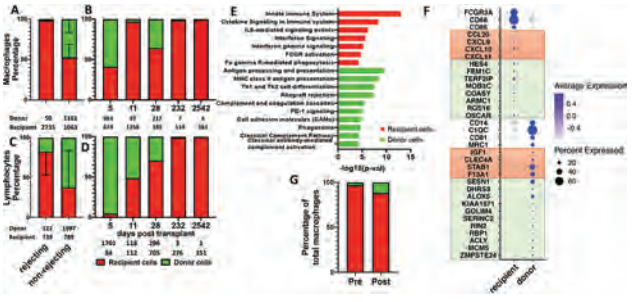
Background: In solid organ transplantation, donor derived immune cells are assumed to decline with time after surgery. Whether donor leukocytes persist within kidney transplants or play any role in rejection is unknown, however, in part because of limited techniques for distinguishing recipient and donor cells.

Methods: We performed paired whole exome sequencing of donor and recipient DNA and single cell RNA sequencing (scRNA-seq) of 5 human kidney transplant biopsy cores. Exome sequences were used to define single nucleotide variants (SNV) across all samples.

Results: By analyzing expressed SNVs in the scRNA-seq dataset we could define recipient vs. donor cell origin for all 81,139 cells. The leukocyte donor to recipient ratio varied with rejection status for macrophages and with time post-transplant for lymphocytes. Recipient macrophages were characterized by inflammatory activation and donor macrophages by antigen presentation and complement signaling. Recipient origin T cells expressed cytotoxic and pro-inflammatory genes consistent with an effector cell phenotype whereas donor origin T cells are likely quiescent expressing oxidative phosphorylation genes relative to recipient T cells. Finally, both donor and recipient T cell clones were present within the rejecting kidney, suggesting lymphoid aggregation. Our results indicate that donor origin macrophages and T cells have distinct transcriptional profiles compared to their recipient counterparts and donor macrophages can persist for years post transplantation.

Conclusions: This study demonstrates the power of this approach to accurately define leukocyte chimerism in a complex tissue such as the kidney transplant coupled with the ability to examine transcriptional profiles at single cell resolution.

Funding: NIDDK Support, Private Foundation Support



A-D) Donor origin Macrophage and Lymphocyte population variations with time and rejection status E) Macrophage pathway analysis by cell origin F) Dotplot of genes that define donor and recipient macrophages

FR-OR42

Proteomics Reveals Extracellular Matrix Injury in the Glomeruli and Tubulointerstitium of Kidney Allografts with Early Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) accounts for >50% of kidney allograft losses. AMR is caused by donor-specific antibodies (DSA) against HLA antigens in the glomeruli and the tubulointerstitium, which together with interferon-γ and tumor necrosis factor-α (TNFα), trigger graft injury. The reasons behind cell-specific injury in AMR remain unclear. Identifying compartment-specific proteome alterations may help uncover mechanisms of early antibody-mediated injury.

Methods: We studied 30 for-cause kidney biopsies with early AMR, acute cellular rejection (ACR) or acute tubular necrosis (ATN). We laser-captured microdissected glomeruli and tubulointerstitium and subjected them to unbiased proteome analysis.

Results: We found 107 glomerular and 112 tubulointerstitial proteins significantly differentially expressed in AMR vs ACR ($p<0.05$). Similarly, 112 (glomeruli) and 124 (tubulointerstitium) proteins were altered in AMR vs ATN. Basement membrane and extracellular matrix (ECM) proteins were decreased in both compartments in AMR, compared to ACR and ATN. We verified decreased glomerular and tubulointerstitial LAMC1 expression, and decreased glomerular NPHS1 and PTPRO expression in AMR. Cathepsin-V (CTSV) was predicted to cleave ECM-proteins in the AMR glomeruli. We identified galectin-1, an immunomodulatory protein increased in AMR glomeruli and linked to the ECM. An external dataset (GSE36059) also demonstrated increased galectin-1 expression in AMR. Anti-HLA class-I antibodies induced inflammation and significantly increased CTSV expression, and galectin-1 expression and secretion, in human glomerular endothelial cells. We also studied GSTO1, an ECM-modifying enzyme, increased in the AMR tubulointerstitium. GSTO1 expression was significantly increased in TNFα-treated proximal tubular epithelial cells.

Conclusions: Basement membranes are often remodeled in chronic AMR, and we demonstrated that this remodeling begins early in glomeruli and tubulointerstitium. ECM-remodeling in AMR may represent a new therapeutic target.

FR-OR43

Interim Update of the MDR-101-MLK Phase 3 Trial: MERCURY Study

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Background: The goals of tolerance in patients with kidney transplants (Ktxp) are to eliminate the lifelong need for immunosuppressive (IS) drugs and to prevent graft loss due to rejection or drug toxicity. MDR-101 is a novel cellular immunotherapy, to produce persistent mixed chimerism without graft versus host disease (GvHD) to allow elimination of all IS therapy without rejection, and, thus, to produce operational tolerance. The randomized study evaluated the need for chronic IS therapy in recipients of HLA-matched living donor (LD) kidney transplants as compared to standard of care (SOC) (NCT03363945).

Methods: Eligible adult pairs (donor/recipient) of a first kidney allograft from an HLA-identical LD were enrolled and randomized 2:1 to either the Investigational Arm (IA; n=20) or Control Arm (CA; n=10). Donors in the IA received G-CSF mobilization for 5 days before undergoing apheresis (1 or 2 cycles). IA recipients receive ATG conditioning, low-dose total lymphoid irradiation (TLI) over 10 days and IS followed by an infusion of MDR-101 on d11. After 180 days of persistent mixed chimerism, IA subjects initiated a 6-month taper of CNI and could withdraw all IS on D365. CA subjects were treated as institutional SOC.

Results: As of June 1 2020, 26 subject pairs (donor/recipient) have been enrolled, comprising 18 pairs randomized to the IA and 8 pairs randomized to the CA. MDR-101 infusion was completed in 12 subjects in the IA. To date, 9 subjects in the IA have reached Day 180 with 6 months of positive mixed chimerism. Five subjects have reached D365 and were able to withdraw from all IS. Two subjects lost chimerism – 1 at D545 (off IS) and 1 at D240 continue to wean IS. There have been no events of GvHD, biopsy-proven acute rejection, dnDSA. There have been no graft losses or deaths in either group.

Conclusions: Administration of MDR-101 in HLA-identical LD Ktxp recipients conditioned with ATG and TLI have produced promising results to date. These results show that MDR-101 induces mixed chimerism without GvHD and permits withdrawal of IS without rejection or dnDSA. Further analysis continues.

Funding: Veterans Affairs Support, Commercial Support - Medeor Therapeutics

FR-OR44

Single-Cell Profiling of Peripheral Blood Mononuclear Cell Identifies Immune Populations Associated with High Risk of Early Acute Rejection

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Background: Our previous transcriptomic analysis of pre-transplant peripheral blood of 235 kidney transplant recipients in a multi-center GoCAR cohort revealed a 23-gene set predictive of early acute rejection (EAR) post kidney transplant, but the associated immune profile is unknown.

Methods: We first developed a reliable targeted RNA expression (TREx) sequencing assay based on the EAR prediction gene set and applied the assay to assess the EAR risk of 21 dialysis patients who were recruited at Mount Sinai Hospital. We next performed extensive singe-cell immune profiling of PBMCs of these patients using 33 surface markers with CyTOF technology. Lastly, using 10X genomics technology, we performed single cell RNA sequencing (scRNAseq) of the PBMCs to identify immune cell (sub) populations and their transcriptomic signatures from two patients with high and low risk of EAR, respectively.

Results: Using the established TREx assay to stratify patients, we identified had 6 high, 9 intermediate and 6 low risk patients. CyTOF immune profiling of PBMCs of these patients indicated that NK cell population was negatively associated with the risk score ($p=0.008$) while CD4 T cells were positively associated ($p=0.056$). scRNAseq analysis of the transcriptomic profiles of a total number of 11,966 cells confirmed these findings. In addition, scRNA sequencing profiling identified NK and T cell subsets and their transcriptomic signatures associated with the EAR risk, especially decreased NK $CD56^{Dim}$ and increased CD4 CTL populations in EAR high risk patients, which was further validated using PBMC composition deconvoluted from bulk RNAseq profiles of GoCAR cohort (n=235).

Conclusions: The Baseline Acute Rejection assay is associated with clear cellular and molecular Phenotype which may help us further understand the underlying mechanisms that lead to the development of acute rejection.

FR-OR45

Single-Cell RNA-Sequencing Analysis of Kidney Transplant Biopsies Demonstrates a Proinflammatory Role for Renal Tubular Cells in Rejection

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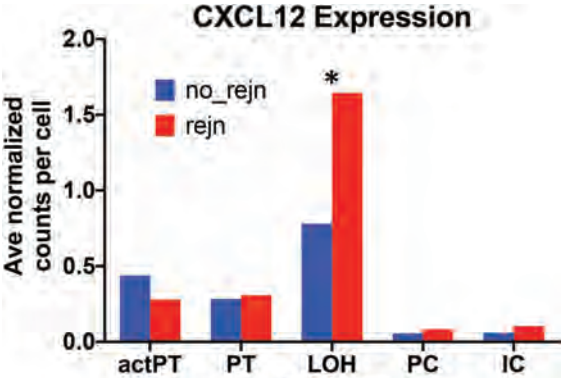
Background: Antibody mediated rejection (AMR) remains one of the major causes of allograft failure and our understanding of this disease process is poor. CXCL12 is thought to contribute to allograft rejection through T cell recruitment and a CXCL12 promotor variant is associated with worse graft outcomes. We performed single cell RNAseq on biopsies from transplant patients to examine ligand expression in kidney cells.

Methods: The 10X Genomics platform was used to make libraries which were sequenced to a depth of ~50k reads/cell. Gene-cell matrices were obtained from CellRanger and the downstream analysis (clustering, integration analysis, expression analyses) were done using R and Seurat. This study had IRB approval.

Results: 81139 cells in total (avg = 1124 genes/cell) from 5 kidney transplant biopsy samples (2 non-rejecting, 3 ABMR) were included in the final integrated analysis using UMAP. All major kidney cell types were identified as well as macrophages, B cells and T cells. Renal epithelial cells from rejection samples differentially expressed ligands with cognate receptors found on immune cells. All renal tubular cell types increase HLA gene expression allowing allowing for ligation of macrophage and T cell cognate receptors LILRB and CD3, respectively. Interestingly, only loop of Henle cells increased expression of *CXCL12* whereas stromal cells decreased *CXCL12* expression in rejection samples.

Conclusions: Comprehensive single cell RNAseq of human kidney transplant biopsies suggests a role for loop of Henle cells in rejection though expression of *CXCL12*. We also demonstrate that stromal cells, known to express *CXCL12*, downregulate *CXCL12* expression in rejection. These data suggest a pro-inflammatory role for tubular cells in rejection.

Funding: NIDDK Support, Private Foundation Support



	actPT	PT	LOH	PC	IC
cells no_rejn	696	434	1033	45	30
cells rejn	288	129	2277	49	53

* adj P value < 10^{-56}

FR-OR46

Modified Immune Cell Infusion in Kidney Transplantation

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Background: We have shown that donor blood cells, modified *in vitro* by an alkylating agent (MIC, modified immune cells), induced specific immunosuppression against the allogeneic donor when administered prior to transplantation. An additional finding was an up to 68-fold increase in the frequency of immunosuppressive $CD19^+CD24^{hi}CD38^{hi}$ transitional B lymphocytes compared to transplanted controls without MIC infusions. The question arises whether donor-specific immunosuppression and increased regulatory B lymphocytes (Breg) are permanently detectable in MIC-treated patients.

Methods: Four patients from a phase-I trial who had received $1.5x10^8$ MIC per kg b.w. on day -7 before living donor kidney transplantation and who were on low immunosuppression were compared to 12 transplanted control patients without MIC infusions.

Results: MIC-treated patients showed an excellent clinical course with no donor-specific HLA antibodies or rejection. On day 1080 after transplantation, median serum creatinine was 1.59 mg/dL. Patients had absent *in vitro* lymphocyte reactivity against stimulatory donor blood cells while reactivity against third party cells was preserved as an indication of continued donor-specific unresponsiveness. $CD19^+CD24^{hi}CD38^{hi}$ and $IL10^+CD19^+CD24^{hi}CD38^{hi}$ Breg were with 2.2/µL and 1.0/µL, respectively, strikingly higher than the 0.0/µL (P<0.001) and 0.0/µL (P<0.001) in transplanted controls and in the range of the numbers of healthy individuals (N=34, P=0.73 and P=0.60). In addition, significantly higher Breg numbers were found for $CD1d^+$ (P=0.0071), $CD19^+CD38^+CD147^+CD1d^+$ (P=0.0071), $CD19^+CD25^+$ (P=0.0077), $CD19^+CD25^+CD73^+CD71^+$ (P=0.013), $CD19^+CD25^+CD73^-CD71^+$ (P=0.0011), $CD19^+CD24^{hi}CD27^+$ memory (P=0.029), and $IL10^+CD19^+CD24^{hi}CD27^+$ memory Breg (P=0.042). No such differences were observed for $CD4^+CD25^+CD127^-FoxP3^+$ Treg (P=0.68) or different Treg subsets when comparing the four MIC-treated patients to transplanted controls without MIC infusions.

Conclusions: Donor-specific immunosuppression after MIC infusion is long-lasting and is associated with a striking increase in Breg at various stages of B cell development, including memory Breg.

Funding: Commercial Support - TolerogenixX GmbH, Government Support - Non-U.S.

FR-OR47

Normothermic Ex Vivo Kidney Perfusion in a Porcine Auto-Transplantation Model Preserves the Expression of Key Mitochondrial Proteins: An Unbiased Proteomics Analysis

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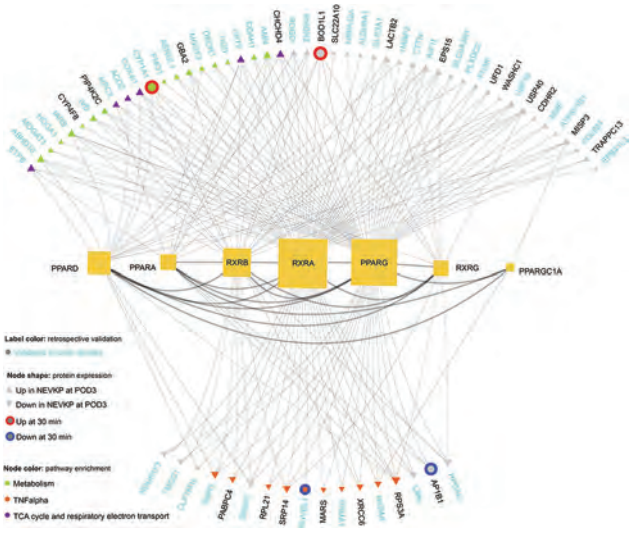
Background: Normothermic *ex-vivo* kidney perfusion(NEVKP) results in significantly improved graft function in porcine auto-transplant models of DCD injury compared to static cold storage (SCS); however, the molecular mechanisms underlying these beneficial effects remain unclear.

Methods: We performed an unbiased proteomics analysis of 28 kidney biopsies obtained at 3 timepoints from pig kidneys subjected to 30-minutes of warm ischemia, followed by 8 hours of NEVKP or SCS, and auto-transplantation.

Results: Of 6593 proteins quantified, 70 were differentially expressed between NEVKP and SCS groups (2-way ANOVA, q<0.05). Proteins increased in NEVKP mediated key metabolic processes including fatty acid ß-oxidation, the TCA cycle and oxidative phosphorylation. Comparison of our findings with external datasets of ischemia-reperfusion, and other models of kidney injury confirmed that 47 of our proteins represent a common signature of kidney injury reversed or attenuated by NEVKP. We validated key metabolic proteins (ETFB, CPT2) by immunoblotting. Integrated transcription factor databases identified PPARGC1A, PPARA/G/D and RXRA/B as the upstream regulators of our dataset, and we confirmed their increased expression in NEVKP with RT-PCR.

Conclusions: The proteome-level changes observed in NEVKP mediate critical metabolic pathways that may explain improved graft function with NEVKP compared to SCS. These effects may be coordinated by PPAR-family transcription factors, and may represent novel therapeutic targets in ischemia-reperfusion injury.



FR-OR48

Cyclosporine-Induced Endothelial Injury and Complement Activation Is Caused by Impaired Complement Factor H Binding to the Glycocalyx

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Background: Calcineurin inhibitors are associated with nephrotoxicity, endothelial cell (EC) dysfunction and thrombotic microangiopathy. Evolving evidence suggests a central role for complement dysregulation in the pathogenesis of CNI-induced thrombotic microangiopathy. However, the exact mechanism of calcineurin-induced complement-mediated injury remains unknown.

Methods: In an in-vitro model utilising Blood Outgrowth EC (BOEC) from healthy donors, we evaluated the effects of cyclosporine (CsA) on EC injury, complement activation (C3c, C9) and regulation (CD46, CD55, CD59 and complement factor H [CFH]) on EC surfaces, and on the EC glycocalyx, utilising flow cytometry, Western blot, and immunofluorescence imaging. Functional activity of CFH was assessed via CFH co-factor assay. Co-immunoprecipitation of Angiopoietin-2 (Angpt-2), Angiopoietin-1 (Angpt-1) and Tie2 was assessed by Western blot.

Results: CsA resulted in a dose and time dependent enhancement of EC complement deposition and EC death. CsA (10 µg/ml for 24 h) led to upregulation of CD46, CD55 and CD59 on EC surface. CsA led to Angpt-2 mediated breakdown of the EC glycocalyx, which was mitigated by Angpt-1. This EC glycocalyx breakdown led to decrease in CFH surface binding and surface cofactor activity.

Conclusions: Our findings confirm a role for complement in CsA-induced EC injury, and suggest Angpt-2 mediated glycocalyx abolishment, induced by CsA, as a mechanism leading to complement alternative pathway dysregulation via decreased CFH surface binding. Insights into this mechanism may provide a potential therapeutic target that might lead to improved patient outcomes which is subject to further studies. It might also apply to other thrombotic microangiopathies, in which a role for complement has so far not been recognized.

FR-OR49

Epigenome-Wide Microarray Analysis of Pre- and Post-Transplant Methylation Profiles in Kidney Transplant Recipients

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Background: Kidney transplantation is the optimal treatment for suitable individuals with end-stage kidney disease (ESKD). Serious post-transplant complications include infections, cardiovascular events, malignancy, and new onset of diabetes after transplant (NODAT). Our regional nephrology centre has the highest living kidney donor transplant rate per million population in Europe, and promotes research to improve patient outcomes. We compared pre and post-transplant methylation profiles in samples derived from matched participants.

Methods: Epigenome-wide analysis was conducted using the Illumina Infinium MethylationEPIC array to interrogate 862,987 sites across the genome and identify any differentially methylated regions (DMR) in samples derived from peripheral blood mononuclear cells of age and sex matched pre (n=25) and post (n=25) kidney transplant recipients. DNA was extracted in a uniform manner and stored carefully undergoing minimal freeze thaw cycles. Samples were run on the same instrument and regression calibration was performed in R to estimate leukocyte cell proportions.

Results: Association analysis using Partek® GenomicsSuite® identified 53 DMR (FDR adjusted p≤0.1 x 10^{-8}, fold change +/-2). Within the top ranked CpG probes we identified DMR within genes dysregulated in melanoma (*e.g. EXOC2, VEPH1*), genes encoding extracellular matrix proteins that could influence structural glomerular changes (e.g. *SPAM1*) and genes with prior chronic kidney disease associations (e.g. *FNTA*). A DMR was also identified within the long intergenic non-protein coding RNA *LINC01544*, suggesting possible regulatory function. Additionally, Partek® Pathway™ identified enrichment of DMR in the mitogen-activated protein kinase (MAPK) signalling pathway, primarily implicated in malignancy but also ESKD and cardiovascular disease. Gene ontology analysis identified enrichment of terms associated with localization and binding within cells.

Conclusions: This analysis provides a novel epigenomic perspective on molecular changes caused by kidney transplantation, and highlights markers that may be of relevance to post-transplant complications. We provide evidence supporting further methylation and transcriptomic analyses in larger cohorts to help identify epigenetic risk factors associated with post-transplant complications.

FR-OR50

Impact of Caspase-1 Deletion on Apoptosis and AKI in a Murine Transplant Model

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Background: Prolonged cold ischemia (CI) is a known risk factor for acute kidney injury (AKI) after kidney transplantation. However, the mechanism by which CI leads to AKI is unknown. Caspase-1 knockout mice (Casp1KO) are protected from AKI after warm ischemia/reperfusion injury. We hypothesized that Casp1KO mice would be protected from AKI following transplant.

Methods: Renal tubular cells (RTECs) were subjected to cold storage and rewarming (CS/REW). C57Bl/6J wild type or Casp1KO kidneys were subjected to CI for 30 min and then transplanted into wild type recipients (CI+Txp). The recipients underwent bilateral native nephrectomy at the time of transplant. Serum creatinine (sCr) was measured 24hrs after native nephrectomy to assess transplant function.

Results: In vitro: We observed significantly increased expression of NLRP1 inflammasome protein and Caspase-1 in cells subjected to CS/REW. Using Imagestream flow cytometer we observed spatial overlap between two different fluorescent labels of Caspase-1 and NLRP1 in RTECs exposed to CS/REW compared to control cells. **In vivo studies:** Wild-type kidneys subjected to CI+Txp demonstrated significantly increased Caspase-1 and NLRP1 protein expression. Caspase-1 deletion results in significantly decreased RTEC apoptosis in transplanted Casp1KO vs WT kidneys. Renal function, brush border injury, cast formation, tubular simplification were similar in both groups and not significantly different [Table 1].

Conclusions: CS/REW and CI+Txp increase NLRP1 and Caspase-1 expression and co-localization. Deletion of Caspase-1 improves tubular cell apoptosis following CI+Txp. However, Caspase-1 deletion did not prevent AKI and necrosis in kidneys subjected to CI+Txp, suggesting that other triggers of inflammation and programmed necrosis may need to be inhibited in addition to deletion of Caspase-1 to fully prevent AKI after kidney transplant.

Funding: Veterans Affairs Support

Histological assessment of transplanted kidneys

	WT-WT	Casp1KO-WT
Apoptotic cell death	6.78 ± 1.21	4.13 ± 0.75 ***
Brush border injury (BBI)	2.67 ± 0.30	2.59 ± 0.20
% of tubule displaying BBI	79.11 ± 8.99	93.15 ± 3.61
Tubular injury	0.95 ± 0.21	0.93 ± 0.24
Casts	0.59 ± 0.16	0.53 ± 0.20
Serum Creatinine	1.58 ± 0.44	0.53 ± 0.20

***p<0.001 vs. WT-WT

SA-OR01

Studying Proteinuria in COVID-19 to Define Markers of Severity and New Treatments

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Background: The recent SARS-CoV-2 pandemic has led to ~375,000 fatalities worldwide as of June 1st. Nearly, 43% of COVID-19 patients have been reported to have proteinuria, which can result from direct podocyte infection, podocytopathy related to cytokine storm, or both. This association between respiratory viruses, proteinuria, and primary kidney disease has also been observed in the context of respiratory syncytial virus (RSV), where patients can develop nephrotic syndrome. Therefore, studying primary and virus-dependent models of proteinuria and podocyte injury is critical to shed light into COVID-19 pathobiology, severity of disease and potential treatments.

Methods: We accessed transcriptomic data (RNA-seq) for lung cell lines (A549) infected with three different viruses and identified differentially expressed genes (DEGs) for SARS-CoV-2, RSV and IAV. In parallel, we also investigated DEGs for FSGS and MCD using LIMMA R package. We investigated the statistical correlation between the log-fold change of DEGs (Nephroptic syndrome and SARS-COV-2) using R. Pathway analysis was performed using WebGestalt. Possible drugs correcting the skewed gene expression in FSGS and SARS-COV-2 were identified using the Connectivity map (cMAP).

Results: 120 gene signatures were specific to SARS-CoV-2. By using gene expression data from glomeruli of FSGS/MCD we identified 902 DEGs for FSGS and 5 for MCD. Out of these, 6 were overlapping and upregulated in COVID-19 and FSGS/MCD (*B2M, EIF2AK2, IFI16, IFI27, TCIM* and *UBE2L6*). Strikingly, *IFI27* has been recently reported as a marker of disease severity in COVID-19. We found significant positive correlation between the log2 fold change of 94 FSGS/MCD genes intersecting with the 120 COVID-19. The results were specific to glomeruli and to high proteinuric diseases, supporting a common cellular response in lung and podocytes. We then searched the cmap data and identified 59 drugs significantly inversely associated with SARS-COV-2 and 72 for FSGS. Out of these, 7 drugs were in common, representing novel potential drugs for COVID-19 and podocytopathies.

Conclusions: Overall, our results suggest transciptional congruency between NS and SARS-COV-2 which can possibly be used to design novel therapies treat these diseases.

SA-OR02

Machine Learning for Predication of Severe AKI in Hospitalized Patients with COVID-19

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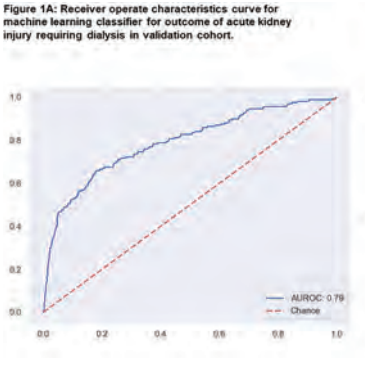
Background: Preliminary reports indicate that acute kidney injury (AKI) is common in coronavirus disease (COVID-19) patients and is associated with worse outcomes. Identification of patients at high risk for developing severe AKI in hospitalized COVID-19 patients in the United States is not well-described.

Methods: This is a retrospective observational study of patients aged ≥18 years with laboratory confirmed COVID-19 admitted to the Mount Sinai Health System between February 27 and April 15, 2020. We trained and tested a machine learning algorithm, extreme gradient boosting (XGBoost), a boosted decision-tree based machine learning (ML) model, with 5-fold cross validation to predict AKI requiring dialysis. Patients from the Mount Sinai (MSH) were randomly split into a training and validation set for the model. To increase model generalizability and help minimize bias, the model's performance was assessed on a test set composed entirely of patients from the other hospitals in the Mount Sinai Health System (MSHS). Input features for the model included demographics, laboratory values, and vital signs that occurred in the first 48 hours of admission.

Results: Of 3,235 hospitalized patients with COVID-19, AKI occurred in 1406 (46%) patients and 280 (20%) with AKI required dialysis. In the training set (n=1,317 patients), the classifier achieved good performance with an area under the receiver operating characteristic curve (AUROC) of 0.79 and area under the precision recall curve (AUPRC) of 0.38 for predicting AKI requiring dialysis. Performance was similar in the testing set (n=1,918) with 0.79 AUROC and 0.36 AUPRC. The features that had a larger impact on the model included serum creatinine, age, potassium, and heart rate.

Conclusions: A machine-learned model using admission features had good performance for dialysis prediction and could be used for resource allocation.



SA-OR03

SARS-CoV-2 Detection in Urine Sediment Suggests Infection of Kidneys and Correlates with Risk of AKI and Poor COVID-19 Prognosis

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Background: Since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most of the focus has been on the respiratory failure caused by the resulting disease, COVID-19. However, the effects of COVID-19 in the kidney are increasingly recognized. Acute kidney injury (AKI) has been identified with varying prevalence around the world with higher rates (37-46%) reported in the USA. It is debatable whether AKI is an indirect consequence of systemic inflammation or a consequence of viral renal cell infection and tropism. We hypothesize that SARS-CoV-2 directly infects kidney tissue and increases the risk of developing AKI, worsening prognosis of COVID-19 patients.

Methods: We studied 88 COVID-19 patients admitted to the Henry Ford Hospital, Detroit after April 15, 2020. Demographics were: mean age 60, 71% African American, 55% male. We quantified viral copies by RT-PCR (S and N genes) in urine sediments from 52 PCR-confirmed COVID-19 patients. We performed immunofluorescence for Membrane and Spike viral proteins in two COVID-19 biopsies.

Results: The prevalence of AKI was 72%, with 32% of patients admitted to the ICU. The overall mortality rate was 14%, with no deaths in non-AKI patients. Viral proteins M and S were detected in the glomerulus, parietal cells and tubules of COVID-19 patients. In some tubules, positive SARS-CoV-2 overlapped with ACE2, the receptor for viral entry. Virus was detected in 61% of urine sediments, with 6-fold greater viral load in AKI-patient urines (copies/ng RNA: AKI, 7422±1338 vs No-AKI: 1523 ± 404; $p<0.05$, n=52). The highest viral loads were detected three weeks post-AKI at 11,374±2248 copies/ng RNA ($p<0.01$). Among COVID-19 AKI-patients who died, the urine viral load exceeded 8000 copies/ng RNA. Above this threshold, the mortality rate was 55%.

Conclusions: Our data support that direct viral renal cell infection occurs in COVID-19 AKI patients with urinary viral genome detection. Greater urinary viral loads portend increased mortality. Urinary viral detection can facilitate management and treatment of COVID-19 and improve outcomes. Future research should focus on studying whether urine contains infective virus or sheds non-infective genomic fragments.

Funding: NIDDK Support

SA-OR04

SARS-CoV-2 Receptor Networks in Diabetic Kidney Disease, BK Virus Nephropathy, and COVID-19 Associated AKI

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Background: COVID-19 shows increased disease burden in patients with diabetic kidney disease (DKD). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) for host cell entry, so ACE2 levels may influence SARS-CoV-2 susceptibility. We investigated how pre-existing conditions and drug treatments alter receptor expression in kidney cells (Figure 1).

Methods: Single cell RNA profiling of 7 healthy living donor kidneys, 44 DKD, 3 BK virus nephropathy (BKVN) and a urine COVID19 patient with acute kidney injury (COV-AKI) revealed ACE2 expression primarily in proximal tubular epithelial cells (PTEC).

Results: ACE2 mRNA expression levels were higher in proximal tubule epithelial cells (PTEC) in DKD versus LD, but unaltered by exposures to renin angiotensin aldosterone system inhibitors. Bayesian integrative analysis of public -omics datasets identified molecular network modules induced in ACE2 positive versus negative PTEC in DKD and BKVN (hb.flatironinstitute.org/covid-kidney), that were linked to viral entry, immune activation, endomembrane reorganization, and RNA processing. Similar programs were seen in COV-AKI ACE2-positive PTEC, and overlapped with programs in SARS-CoV-2 infected cells.

Conclusions: A consistent ACE2-coregulated expression program in PTEC may interact with SARS-CoV-2 infection processes. These networks can seed further research into developing therapeutic strategies and assessing risk in patients with COVID-19.

Funding: NIDDK Support, Private Foundation Support

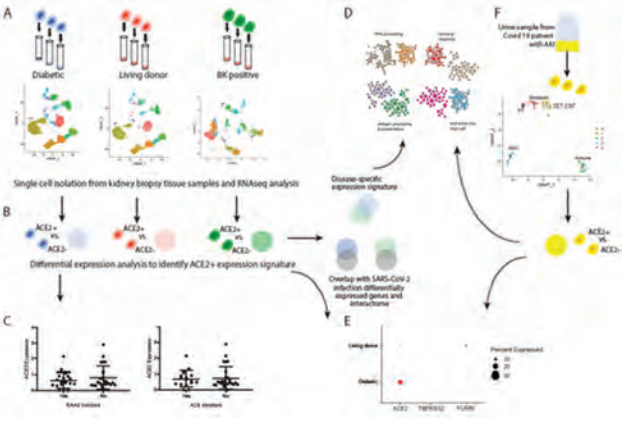

Figure 1: Study overview. Identifying SARS-CoV-2 receptor networks in DKD, BKVN and COV-AKI using scRNAseq and integrative network analyses

SA-OR05

Genomic Datasets from Traditional Murine Models of AKI and AKI-Lung Cross-Talk Reveal Molecular Pathways Relevant to COVID-19 Infection

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Background: COVID-19 infection leads to ARDS and AKI, and there are established mechanistic links between acute kidney injury (AKI) and lung injury. SARS-CoV-2 uses for cell entry angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2), which are expressed in kidney and lung. Using publicly available genomics data of ischemic and sepsis induced AKI in mice, we searched for established and novel molecular players of AKI and AKI-lung cross-talk relevant to COVID-19.

Methods: The microarray datasets GSE6730 (AJP Renal 2007, JASN 2008) and GSE60088 (Shock 2016) were downloaded from Gene Expression Omnibus (GEO). GSE6730: lungs from mice with moderate and severe ischemic AKI were studied at 6h and 36h. GSE60088: kidneys were studied from mice after 6h of pneumonia+mechanical ventilation (PMV). Isolated RNA was hybridized to MG_430 microarray. To identify differentially expressed genes, GEO-built in GEO2R tool was used.

Results: AKI led to downregulated kidney ACE2 gene at both 6h (fold change (FC)=-2.41) and 36h (FC=-3.23) after severe (60min clamp) but not moderate ischemia (30 min clamp; 6 h: FC=-1.3, 36h: FC=-1.16). In lung from AKI mice, ACE2 was significantly downregulated (FC=-2.89, $P=5.56*10^{-5}$). Ischemic AKI and PMV led to a decrease in lung TMPRSS2 FC=-1.83, $P=1.19*10^{-2}$ and FC=-1.68, $P=6.58*10^{-6}$, respectively. The filtering for known genes with P-value<0.01 and FC>4 identified 53 kidney genes upregulated by PMV; and 254 lung genes upregulated by AKI, of which 9 genes were common to both organs. 3 of 9 genes were previously linked to kidney-lung cross-talk: Lcn2 (FC_{Lung}=18.6, FC_{Kidney}=6.32), Socs3 (FC_L=10.5, FC_K=10.4), Inhbb (FC_L=6.20, FC_K=6.17). This finding validates our approach and makes other 6 genes appealing candidates, especially Maff (FC_L=7.21, FC_K=5.98). This gene participates in the cellular stress response and also binds the oxytocin receptor promoter, which may be involved in gender differences in disease severity.

Conclusions: We identified changes in COVID-19 related genes ACE2 and TMPRSS2 in traditional mouse models of AKI and lung cross talk. We also found new candidate genes activated in kidney during pneumonia+mechanical ventilation and in lung during AKI, which warrants further investigation of their involvement in the combined kidney-lung injury during COVID-19.

SA-OR06

AKI in Patients Hospitalized with COVID-19

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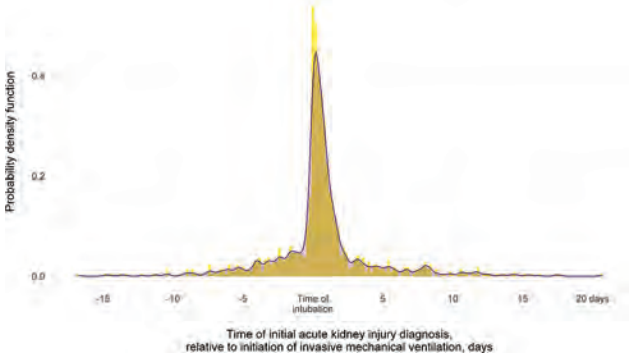
Background: The rate of AKI associated with patients hospitalized with Covid-19, and associated outcomes are not well understood.

Methods: We reviewed the health records for all patients hospitalized with Covid-19 between March 1, and April 5, 2020, at 13 hospitals in metropolitan New York. Patients younger than 18 years of age, with ESKD or with a kidney transplant were excluded. AKI was defined according to KDIGO criteria. The primary outcome was the development of AKI. Secondary outcomes included need for RRT and hospital disposition, i.e., discharge or death. The RRT modalities offered to patients with AKI in our health system were intermittent HD or CRRT. All patients were followed up through April 12th, 2020. We additionally analyzed urine results including urine electrolytes and urinalysis with automated microscopy that were obtained within 24 hours before or 48 hours after the initial development of AKI.

Results: Of 5,449 patients admitted with Covid-19, AKI developed in 1,993 (36.6%). The peak stages of AKI were stage 1 in 46.5%, stage 2 in 22.4% and stage 3 in 31.1%. Of these, 14.3% required renal replacement therapy (RRT). AKI was primarily seen in Covid-19 patients with respiratory failure, with 89.7% of patients on mechanical ventilation developing AKI compared to 21.7% of non-ventilated patients. 276/285 (96.8%) of patients requiring RRT were on ventilators. Of patients who required ventilation and developed AKI, 52.2% had the onset of AKI within 24 hours of intubation(Figure and Table). Risk factors for AKI included older age, diabetes mellitus, cardiovascular disease, black race, hypertension and need for ventilation and vasopressor medications. Among patients with AKI, 1136 died (57%), 519 (26%) were discharged and 338 (17%) were still hospitalized.

Conclusions: AKI occurs frequently among patients with Covid-19 disease. It occurs early and in temporal association with respiratory failure and is associated with a poor prognosis.



The probability of acute kidney injury diagnosis relative to time of mechanical ventilation.

SA-OR07

A Multicenter Observational Study of Clinical Features and Outcomes of AKI in Critically Ill Patients with COVID-19

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Background: Acute kidney injury (AKI) is emerging as an important sequela of COVID-19 infection. Existing data on the incidence and clinical features of AKI in patients with COVID-19 are mainly limited to single-center studies. Given the high incidence of severe AKI among patients with COVID-19 and its strong association with mortality in other settings, we conducted a multicenter nationally representative cohort study to examine the incidence, clinical features, risk factors, and outcomes of AKI in critically ill patients with COVID-19.

Methods: We used data from a multicenter observational study that collected granular, patient-level data from >3,000 critically ill adults with laboratory-confirmed COVID-19 admitted to participating ICUs from 67 centers across the United States. Using multivariable logistic regression, we examined risk factors for the primary composite outcome, AKI requiring renal replacement therapy or death (RRT/death) in the 14 days following ICU admission.

Results: Among 3099 patients, 1205 (38.9%) developed the primary outcome of RRT/death (n=637 required RRT, n=792 died within 14 days, and n=224 both required RRT and died within 14 days). Independent risk factors for RRT/death included chronic kidney disease (odds ratio [OR], 5.02; 95% CI, 3.55-7.10 for eGFR<30 vs. ≥60; OR 1.90; 95% CI, 1.55-2.33 for eGFR 30-59 vs. ≥60), as well as older age, male sex, higher body mass index, and greater severity of hypoxemia on ICU admission (**Figure**). Patients admitted to hospitals with higher degrees of strain also had a greater risk of RRT/death (OR 1.49; 95% CI, 1.06-2.06 for highest versus lowest quintile of hospital strain).

Conclusions: This multicenter study identifies several key insights into the risk factors for RRT/death in critically ill patients with COVID-19.

Funding: NIDDK Support, Other NIH Support - NIDCD F32DC017342

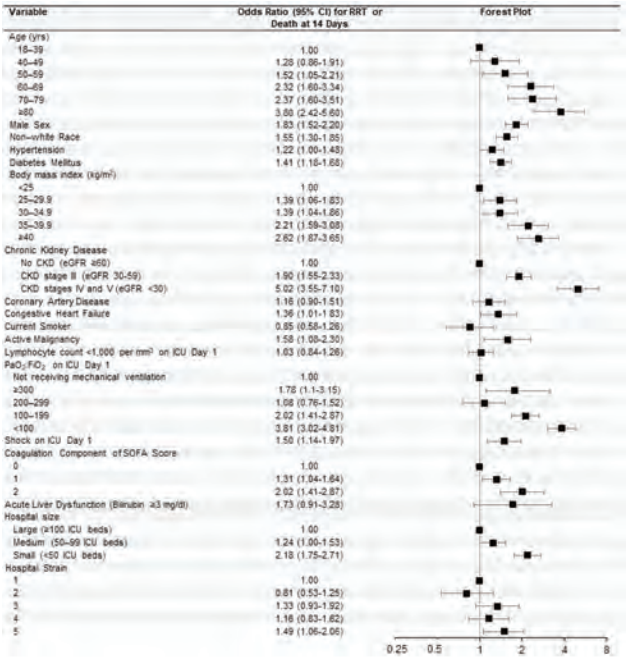

Figure 1

SA-OR08

Screening for SARS-CoV-2 (COVID) Infection in Chronic Dialysis Patients: A Nonprofit Provider's Experience

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Background: The CDC recommends screening of all patients for COVID exposure history and or signs and symptoms prior to treatment. In order to limit the spread of COVID within our facilities, Dialysis Clinic Inc. screens all patients prior their in-center hemodialysis treatment or peritoneal dialysis visit consistent with recommendations.

Methods: We describe the outpatient screening results of our dialysis patients having a positive screen as patients under investigation (PUI) to activate local protocols for isolation and testing. We determined the frequencies of positive screening parameters and rate of identifying COVID patients.

Results: From 2/17 to 5/1, 2020, facilities screened 15,602 patients over 402,002 in-person visits, identifying 959 PUI's (6%). Among PUIs, 61 of 351 (17%) COVID+ patients were correctly triaged prior to COVID+ diagnosis. In the subset of 788 PUIs screened prior to 4/11/20 where we were able to catalogue reasons for positive screening, 149 (19%) had exposure only and 639 exhibited symptoms (81%), of which 15 had exposure; 34 resided in group home (GH) and 7 had both exposure and GH residence. It was determined 41 (6.4%) were COVID+. Frequency of symptoms elicited by PUI are shown below.

Conclusions: 959 PUIs were identified and isolated by our screening process, resulting in the successful preemptive triage of 61 COVID+ (6%) patients before testing positive, potentially limiting infection spread in the facility. Cough and fever were the most common reasons for positive screen, and fever was most commonly associated with COVID+ diagnosis. However, the majority (83%) of COVID+ patients were primarily asymptomatic and hence not captured by screening.

COVID-related Symptom	COVID+ (n=41)	Non-COVID (n=598)	Overall (n=639)
Cough	11 (27%)	320 (54%)	331 (52%)
Fever (≥100 F)	30 (73%)	153 (26%)	183 (29%)
Shortness of Breath	8 (20%)	132 (22%)	140 (22%)
Sore Throat	1 (2%)	138 (23%)	139 (22%)
O2 Saturation ≤90%	6 (15%)	60 (10%)	66 (10%)
Other Symptom	2 (5%)	43 (7%)	45 (7%)
Chills	3 (7%)	24 (4%)	27 (4%)
Diarrhea	5 (12%)	16 (3%)	21 (3%)
Headache	1 (2%)	13 (2%)	14 (2%)
Vomiting	2 (5%)	7 (1%)	9 (1%)
Abdominal pain	0 (0%)	3 (1%)	3 (0%)

SA-OR09

Urgent Peritoneal Dialysis Catheter Placement at a New York City Hospital During the COVID-19 Pandemic

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Background: During the COVID-19 pandemic, there has been an unparalleled burden on nephrology services to provide kidney replacement therapy to patients admitted to the hospital with COVID-19, who develop severe AKI. Given the unprecedented surge in COVID-19 admissions, ability to provide inpatient hemodialysis and continuous kidney replacement therapy (CKRT) was quickly saturated. We present data from our acute peritoneal dialysis (PD) program that was quickly assembled to provide kidney replacement therapy due to shortage of hemodialysis and CKRT resources.

Methods: Patients admitted to an academic NYC hospital during COVID-19 pandemic with AKI requiring kidney replacement therapy were evaluated for candidacy for bedside PD catheter placement via cut-down method with the majority having COVID respiratory failure. A dedicated surgery team was assembled to place PD catheters within 12-24 hours of request by the nephrology team. Catheters were placed in patients with BMI up to 51. Patients requiring proning were not excluded. Exclusion criteria were prior lower abdominal surgery, known varices, or imminent death.

Results: Thirty-eight PD catheters were placed during the 4 week time period from April 8 to May 8, 2020. Majority of the catheters were placed bedside in an ICU setting (36/38 - 95%), with 2 being placed laparoscopically in the OR. There were no episodes of peritonitis. Three catheters required revision due to poor flows. Six catheters required floseal for bleeding along the catheter tract, which resolved without additional intervention. There were no major bleeding complications during PD catheter placement despite many patients being on systemic anticoagulation. Dwell volumes of up to 2.2L did not appear to have negative effects on the ability to ventilate patients. One patient required transition to hemodialysis due to catheter malfunction.

Conclusions: Acute peritoneal dialysis successfully allowed kidney replacement therapy for patients with severe AKI during the peak phase of the COVID-19 pandemic at our hospital in NYC. There were no major complications with acute PD catheter placements.

SA-OR10

Recovery from AKI and Acute Respiratory Distress Syndrome (ARDS) with the Use of Low-Dose Steroids During COVID-19 Infection in an African American Population: A Retrospective Analysis

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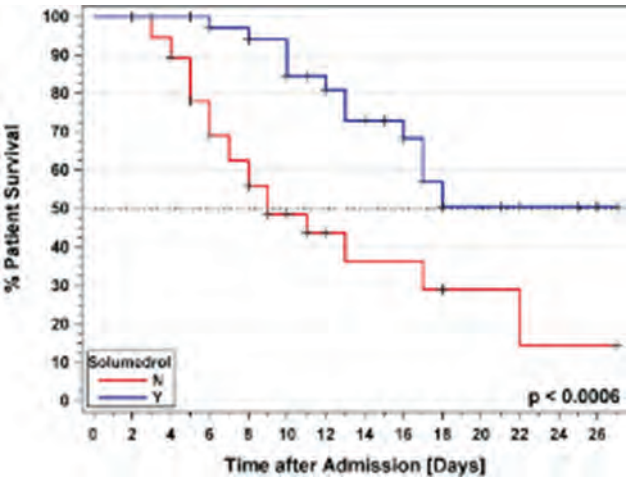
Background: Corona Virus Disease-19 (CoVID-19) infection associated with AKI and ARDS results in a mortality of 80%. In AA population COVID 19 presentations and outcomes are worse. NIH and Interim WHO guidelines suggest against steroids use unless in the context of clinical trials. We conducted a retrospective analysis on the impact of 2 different doses of IV steroids in AA adult population.

Methods: 75 patients between March 1 and April 30, 2020 were enrolled. Primary outcomes (21-day mortality) and secondary outcomes (improvement in lung function and renal function) were analyzed. Comparisons between the steroid doses (methylprednisolone 1 mg/kg/day or 2 mg/kg/day) and no-steroid groups were performed with the Wilcoxon, Kruskal-Wallis, and Chi-Square tests. Factors affecting the recovery of AKI or ARDS were analyzed. AKI recovery was defined as 50% increase of GFR, and cessation of RRT; lung function recovery was defined as improved oxygenation by P/F ratio > 200 and extubation.

Results: 38 out 75 patients received steroids. Survival in the steroids group reached 73% at 21 days compared to 36% in the non-steroids group ($p<0.0006$). Steroids improved the likelihood of renal function improvement by 300% ($p=0.06$). Lung functionwas 73% in the steroids group versus 45% in the other ($p=0.01$). Use of anticoagulants (16% vs 51%, $p= 0.001$) seemed to be interacting with steroids on outcomes. Low dose steroids had the most beneficial impact.

Conclusions: In patients with COVID-19 infection and ARDS with AKI, low dose IV methylprednisolone was associated with a significantly lower incidence of mortality and higher likelihood of renal and lung function recovery. Further investigation with a randomized control trial consisting of low dose steroids seems warranted.



Mortality in stroids and non-steroids groups

SA-OR11

p53/MicroRNA-214/ULK1 Axis Impairs Renal Tubular Autophagy in Diabetic Kidney Disease

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Background: The pathogenesis of diabetic kidney disease (DKD) is unclear. Dysregulation of autophagy in DKD has been reported, but the underlying mechanism and its pathogenic role in DKD remain elusive.

Methods: Autophagy changes in DKD were investigated in high glucose treated renal tubular cells in vitro and in Akita mice and streptozotocin (STZ)-induced diabetic mice in vivo. Autophagy-related gene 7 (Atg7), microRNA-214 (miR-214), or p53 were ablated specifically from kidney proximal tubules to elucidate the pathogenic role and underlying mechanism of autophagy dysregulation in DKD. The expression of autophagy-related proteins, miR-214, and p53 were analyzed in human diabetic kidney tissues along with renal pathologies to determine their correlations.

Results: Autophagy was inhibited in DKD models and in human diabetic kidneys. Ablation of Atg7 from kidney proximal tubules led to autophagy deficiency and worsened renal hypertrophy, tubular damage, inflammation, fibrosis, and albuminuria in diabetic mice, indicating a protective role of autophagy in DKD. Autophagy impairment in DKD was associated with the downregulation of ULK1, a key serine/threonine protein kinase for the initiation of autophagy. ULK1 downregulation in DKD involved miR-214, which was induced in diabetic kidney cells and tissues to repress ULK1 expression. Ablation of miR-214 from kidney proximal tubules prevented ULK1 decrease and autophagy impairment in diabetic kidneys, resulting in less renal hypertrophy and albuminuria. Furthermore, blockade of p53 attenuated miR-214 induction in DKD, leading to higher levels of ULK1 and autophagy, accompanied by the amelioration of DKD. Compared to non-diabetic samples, renal biopsies from human diabetic patients showed the induction of p53 and miR-214, associated by the downregulation of ULK1 and autophagy. There was a significant positive correlation between p53/miR-214 and renal fibrosis, whereas a negative correlation between ULK1/LC3 and renal fibrosis in diabetic patients.

Conclusions: Autophagy dysfunction occurs in renal tubules in DKD, and contributes to renal hypertrophy and related pathologies. Mechanistically, p53 is activated in DKD to induce miR-214, which represses ULK1 resulting in autophagy dysfunction. The results identify the p53/miR-214/ULK1 axis of autophagy impairment for the development and progression of DKD.

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SA-OR12

Podocytes-Derived Extracellular Vesicles Mediate Renal Proximal Tubule Cells Dedifferentiation via MicroRNA 221 in Diabetic Nephropathy

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Background: Podocyte injury is a key event in the initiation of diabetic nephropathy (DN), and the proximal tubule has been regarded as a target of injury. Evidence suggests that cross-talk between podocytes and tubular epithelium is a key component in the pathogenesis of DN, but the mechanisms are not fully understood.

Methods: The podocytes and proximal tubular epithelial cells (PTECs) were co-cultured in high glucose conditions to detect the intercellular communication. Podocytes-derived extracellular vesicles (EVs) was isolated and identified by specific morphology and surface markers. Immunofluorescence, PCR, western blot, electron microscope, and transwell were conducted to assess the dedifferentiation of PTECs. The expression level of miRNA in EVs was detected and Cy3-labeled mimics was used to demonstrate its direct transfer into target cells. A dual-luciferase reporting system was utilized to confirm the binding of miRNA to its target gene. The roles of miRNA and target gene were assessed using specific miRNA inhibitors, mimics and shRNA. In addition, Streptozotocin-induced mice models were construct, and miRNA antagomir were used to explore its role in proximal tubule injury.

Results: Podocytes induced dedifferentiation of PTECs in high-glucose conditions and EVs mediated the interaction. The podocytes-derived EVs were extracted and identified as exosome, and the EVs treatment induced PTECs injury. miR-221 was remarkably increased in EVs and could be directly transferred into target cells, moreover, this miRNA was shown to play a key role in PTECs dedifferentiation. The dual-luciferase reporter assay confirmed that miR-221 direct target DKK2, and miR-221 positively regulated β-catenin activation. Importantly, inhibition of β-catenin markedly diminished the EVs and miRNA induced PTECs dedifferentiation. Furthermore, inhibition of miR-221 in diabetic mice reversed the PTECs injury and relative β-catenin activation.

Conclusions: Podocyte-derived EVs in diabetes acted as key mediators of proximal tubule cell injury and the exosomal-miR-221 mediated the cells damage through Wnt/β-catenin signaling. These findings provide unique insights in the mechanisms of proximal tubule cell injury in diabetic nephropathy, and miR-221 can be used as a new target for the treatment of renal fibrosis in DN.

Funding: Government Support - Non-U.S.

SA-OR13

Whole-Genome Sequencing Identifies a Dominant Negative ADIPOQ Mutation in a Type 2 Diabetic Family Enriched for ESRD

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Background: Diabetic nephropathy (DN) is a complex, heterogeneous complication of diabetes. Despite evidence of its strong genetic predisposition, identification of the genetic factors that contribute to DN and the risk of end-stage renal disease (ESRD) has been challenging.

Methods: We performed whole genome sequencing (WGS) in a multi-generational family enriched for both type 2 diabetes and ESRD followed by unified linkage analysis and rare variant association testing using pVAAST.

Results: Using WGS to evaluate this family, we identified a rare loss-of-function mutation in adiponectin (*ADIPOQ*^{Gly93GlufsTer73}; seen only once among 56,810 non-Finnish Europeans included in the gnomAD database) observed among 6 ESRD cases in this family. This 10-nucleotide deletion results in a premature termination codon and a complete loss of adiponectin's globular domain. We found that carriers of this mutation have low circulating adiponectin (15% of normal levels) and dramatically high ceramide levels (double the level of C16 ceramides as compared with *ADIPOQ*^{wt} diabetic patients). In cell culture, we observed that *ADIPOQ*^{Gly93GlufsTer73} is degraded by the proteasome. Likely due to its incorporation to trimeric adiponectin, over-expression of the mutant protein decreases stability of wildtype adiponectin and exerts a dominant-negative effect that results in reduced adiponectin levels.

Conclusions: Here we report the first human family with a dominant-negative mutation in adiponectin. Importantly, while adiponectin is known to play important roles in insulin sensitivity, it also has a protective role in mitigating renal injury in patients with diabetes. Moreover, adiponectin knockout mice are prone to DN and podocyte apoptosis. Together, these data provide strong evidence supporting the role of adiponectin in kidney disease in patients with diabetes.

SA-OR14

Enhancing Kidney DDAH-1 Expression by Adenovirus Delivery Reduces Asymmetric Dimethylarginine and Ameliorates Diabetic Nephropathy

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Background: Endothelial dysfunction, characterized by reduced bioavailability of nitric oxide and increased oxidative stress, is a hallmark characteristic in diabetes and diabetic nephropathy (DN). High levels of asymmetric dimethylarginine (ADMA) are observed in several diseases including DN and are a strong prognostic marker for cardiovascular events in patients with diabetes and end-stage renal disease. ADMA, an endogenous endothelial nitric oxide synthase (NOS3) inhibitor, is selectively metabolized by dimethylarginine dimethylaminohydrolase (DDAH). Low DDAH levels have been associated with cardiac and renal dysfunction, but its effects on DN are unknown. We hypothesized that enhanced renal DDAH-1 expression would improve DN by reducing ADMA and restoring NOS3 levels.

Methods: DBA/2J mice injected with multiple low doses of vehicle or streptozotocin were subsequently injected intrarenally with adenovirus expressing DDAH-1 (Ad-h-DDAH-1) or vector control [Ad-green fluorescent protein (GFP)], and mice were followed for 6 wk.

Results: Diabetes was associated with increased kidney ADMA ($p<0.05$) and reduced kidney DDAH activity ($p<0.05$) and DDAH-1 expression ($p<0.05$) compared to normal mice but had no effect on kidney DDAH-2 expression. Ad-GFP-treated diabetic mice showed significant increases in albuminuria ($p<0.005$), histological changes ($p<0.005$), glomerular macrophage recruitment ($p<0.001$), inflammatory cytokine ($p<0.01$) and fibrotic markers ($p<0.01$), kidney ADMA levels ($p<0.05$), and urinary thiobarbituric acid reactive substances excretion ($p<0.001$) as an indicator of oxidative stress, along with a significant reduction in kidney DDAH activity ($p<0.05$) and kidney NOS3 mRNA ($p<0.05$) compared with normal mice. In contrast, Ad-h-DDAH-1 treatment of diabetic mice reversed these effects.

Conclusions: These data indicate, for the first time, that DDAH-1 mediates renal tissue protection in DN via the ADMA-NOS3-interaction. Enhanced renal DDAH-1 activity could be a novel therapeutic tool for treating patients with diabetes.

Funding: NIDDK Support

SA-OR15

Cell Type Specificity of Hypoxia Signaling in Early Diabetic Kidney Disease (DKD)

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Background: Chronic hypoxia is considered a driver of kidney disease progression. Given the spatial heterogeneity of hypoxia, we evaluated the cell type specificity of Hypoxia Related Genes (HRG) in DKD along the nephron and the association of HRG with structural parameters.

Methods: Cell-specific expression and normalized gene signatures (Z scores) were calculated for 237 HRG in single cell RNA profiles of 44 kidney biopsies from American Indians with Type 2 Diabetes (T2D) and 7 healthy living donor kidneys (LD), and replicated in 49 independent micro-dissected biopsies of T2D with DKD (DN).

Results: Mean measured glomerular filtration rate was 159 ml/min (SD 54) in T2D and 147 ml/min (SD 45) in DN, and mean urine albumin/creatinine ratio was 304 mg/g (SD 1542) for T2D and 35 mg/g (SD 90) for DN. Average HgA1c was 9.2 for T2D and 9.3 for DN. HRG expression showed highly cell-type specific elements in both LD and T2D (**Figure 1**). HRG signature in stressed proximal epithelial cells (sPEC), unique to T2D, was dominated by apoptosis and glycolysis signals, while endothelial cells (EC) signatures expressed more genes involved in fibrosis in T2D compared to LD. In DN, Z score of the EC signature was associated with increased mesangial volume (R 0.33, p-value 0.02) and Z score of sPEC signature was associated with interstitial fibrosis (R 0.35, p-value 0.02), which are strong predictors of long-term outcomes in this cohort.

Conclusions: HRG expression varies by cell type in LD and DKD, suggesting transcriptional regulation changes of HRG in diabetes and DKD. Association of HRG signatures with morphometrics that are associated with progressive GFR loss implicate chronic hypoxia processes in early DKD.

Funding: NIDDK Support

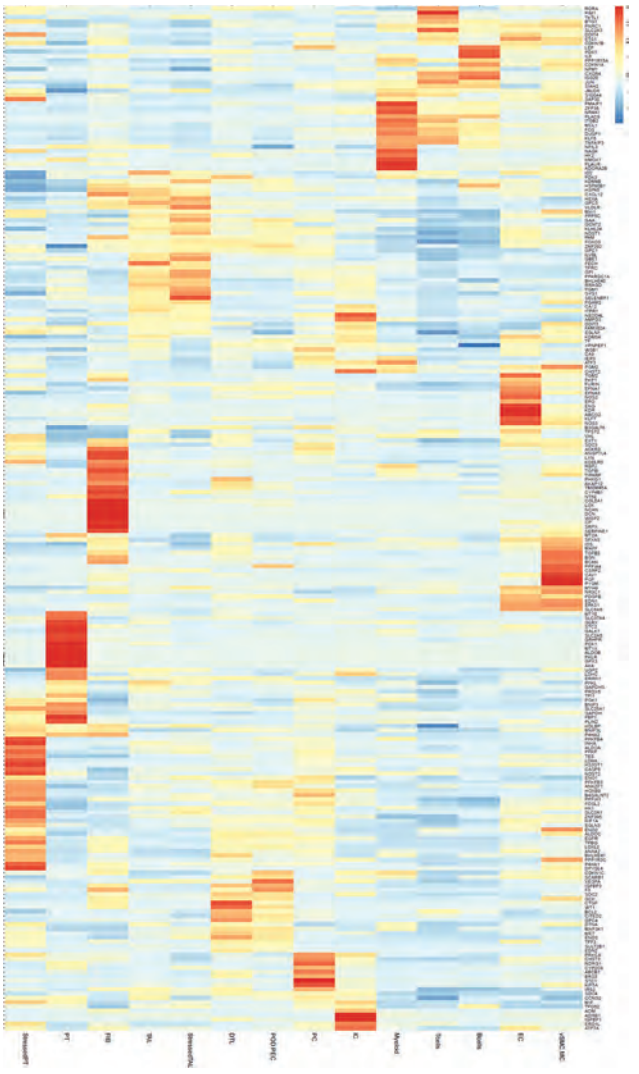

Figure 1: Heatmap of HRG in T2D

SA-OR16

Loss of Functional SCO2 Attenuates Diabetic Kidney Disease in db/db Mice

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Background: Synthesis of Cytochrome C Oxidase 2 (SCO2), a Cu^{2+} metallochaperone located in the inner mitochondrial membrane, is essential for the assembly of Complex IV (COX IV) of the electron transport chain, maintenance of the proton gradient, and redox signaling. Altered COX activity and reduced mitochondrial function have been reported in diabetic kidney disease (DKD), but the mechanism mediating this process remains to be explored.

Methods: *db/db* mice were bred with *Sco2* mutant mice (E129K, most common human missense mutation in the Cu^{2+} binding domain) to generate $Sco2^{KO/KI}$*;db/db* and $Sco2^{KI/KI}$*;db/db* mice. $Sco2^{KO/KI}$, $Sco2^{KI/KI}$, *db/db*, and wildtype mice served as controls. All mice were euthanized at 24 weeks of age and assessed for functional and histological changes in the kidney.

Results: Data mining in *Nephroseq* showed that *SCO2* expression was increased in micro-dissected glomeruli in human DKD kidney biopsies (Ju et al. 2013), which we confirmed by immunostaining in human kidney biopsies with DKD as compared to healthy donor nephrectomies. Since $SCO2^{-/-}$ mice are embryonically lethal, we ascertained the role of mutant and heterozygous knockout SCO2 in DKD ($SCO2^{KI/KI}$, $SCO2^{KO/KI}$). As compared to *db/db* mice, $SCO2^{KO/KI}$*;db/db* and $SCO2^{KI/KI}$*;db/db* mice had a significant reduction in albuminuria, serum creatinine, glomerular hypertrophy, glomerular oxidative stress (8-oxoG staining) with an increase in podocyte number (WT1+ cells per glomerular cross-sectional area), synaptopodin expression, and overall survival. $SCO2^{KO/KI}$*;db/db* and $SCO2^{KI/KI}$*;db/db* mice also exhibited less glomerular endothelial injury with a decrease in glomerular capillary loop dilatation and a trend towards decrease in *Icam* and *Vcam1* and an increase in *Angpt1*, *Vegfa*, *Kdr* and *Klf2* expression as compared to *db/db* mice.

Conclusions: Loss of *SCO2* and mutant *SCO2* reduced glomerular endothelial injury, oxidative stress, and early diabetic injury in the kidney with improved mice survival in a murine model of DKD.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

SA-OR17

Reversal of Diabetic Nephropathy After 10 Years of Pancreas Transplantation Occurs Despite Parallel Podocyte Loss

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Background: Diabetic nephropathy (DN) is associated with podocyte (PC) injury and loss. PC injury is believed to play important role in DN progression. DN reversal following 10 years (10Y) of euglycemia after pancreas transplantation (PTx) is documented (N Engl J Med 1998; 339:69-75). We hypothesized that if PC loss is crucial for DN development, DN reversal would be associated with PC regeneration and improvement in PC structure

Methods: Paired kidney biopsies prior to PTx (BL) and 10Y after PTx were compared for classical DN lesions, PC number and foot process width (FPW) using electron microscopy morphometry in 10 type 1 diabetic (T1D) patients with age 33 (30-54) years [median (range)], diabetes duration 23 (16-33) years and albumin excretion rate (AER) 134 (0-951)µg/min at BL. The results were compared with biopsies from 10 age matched living donor biopsies [controls (C)].

Results: Glomerular basement membrane (GBM) width, fractional volume of mesangium/glomerulus [Vv(Mes/glom)] and fractional volume of mesangial matrix/glomerulus [Vv(MM/glom)] and FPW were all increased at BL compared to C (data not shown). There were significant reductions in GBM width (30%; p=0.0002), Vv(Mes/glom) (21%; p=0.001), Vv(MM/glom) (30%; p=0.002), and glomerular volume (27%; p=0.02) at 10Y compared to BL. However, while PC number density did not change from BL to 10Y, there was a significant decrease in PC number/glomerulus (31%; p=0.049). FPW in T1D patients at BL (p=0.0008) or 10Y (p=0.002) was greater than C with no significant change from BL to 10Y. No relationship was found between change in GBM width, Vv(Mes/glom) or Vv(MM/glom) and PC number density, PC number per glomerulus or FPW. Creatinine clearance was reduced by 25% from BL to 5y post PTx in these calcineurin treated patients, and remained stable between 5 and 10Y. AER did not change significantly.

Conclusions: Substantial reversal of GBM and mesangial extracellular matrix (ECM) accumulation in T1D occurs following long term PTx despite decrease in PC number, persistence of foot process widening and no change in PC density. This study does not support PC loss to be an important mediator of glomerular extracellular dynamics in DN in T1D. Moreover, despite long-term normoglycemia, PC do not regenerate and PC injury does not regress in T1D patients.

Funding: Private Foundation Support

SA-OR18

Urinary Proteomics Identifies Proteins Associated with Rapid eGFR Decline in Type 1 Diabetes

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Background: Varying rates of eGFR decline have been observed in patients with type 1 diabetes (T1D), the pathophysiologic mechanisms of which remain poorly understood.

Methods: We performed a case-control study nested within four T1D cohorts (EDC, CACTI, STENO, FinnDiane) to identify urinary proteins associated with rapid eGFR loss. Cases and controls were defined by annual eGFR decline ≥3ml/min/1.73m^2 and <1ml/min/1.73m^2, respectively. We developed a targeted liquid chromatography-tandem mass spectrometry assay to measure 38 peptides of 20 proteins implicated in diabetic kidney disease. Peptide associations with rapid eGFR loss in discovery and validation sets were compared using logistic regression. Associations of significant peptides with diabetic kidney disease were investigated in the Nephroseq transcriptomic database.

Results: 1271 participants (508 cases, 763 controls) with baseline median eGFR 95ml/min/1.73m^2 and ACR ≥30mg/gCr in 36% were included. Over 8 years median follow-up, mean eGFR slope was -5.65 and 0.57ml/min/1.73m^2 per year for cases and controls, respectively. Out of 38 urine peptides, 2 cathepsin D (CatD) peptides were associated with rapid eGFR loss adjusting for demographic and clinical variables with a false discovery rate of <5% in the discovery set (fully-adjusted OR per SD 1.52, 95%CI 1.22-1.88; 1.41, 95%CI 1.14-1.74). In the validation set, CatD peptides were associated with rapid eGFR decline adjusting for demographic but not clinical variables (1.26, 95%CI 0.99-1.60; 1.15, 95%CI 0.91-1.46). When stratified by baseline urine albumin creatinine ratio (UACR), CatD peptides were associated with rapid eGFR loss among those with UACR 30-300mg/g in both discovery (2.36, 95%CI 1.39-4.03; 2.28, 95%CI 1.32-3.92) and validation (1.93, 95%CI 1.10-1.39; 1.84, 95%CI 1.08-3.13) sets. Across several Nephroseq cohorts, CatD transcription was increased in tubulointerstitial but not glomerular specimens in diabetic kidney disease compared to healthy living donors.

Conclusions: Among patients with T1D and largely normal kidney function, differences in renal lysosomal function as suggested by increased urine CatD may represent a mechanism of rapid eGFR loss early in the course of T1D.

Funding: Private Foundation Support

SA-OR19

Reduction in the Rate of eGFR Decline with Semaglutide vs. Placebo: A Post Hoc Pooled Analysis of SUSTAIN 6 and PIONEER 6

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Background: The SUSTAIN 6 cardiovascular outcomes trial (CVOT) indicated that once-weekly (OW) subcutaneous (s.c.) semaglutide may have beneficial effects on kidney function in subjects with type 2 diabetes (T2D) at high CV risk. SUSTAIN 6 and the PIONEER 6 CVOT (once-daily [OD] oral semaglutide) had similar designs and populations, and both evaluated the effects of semaglutide vs placebo (PBO) on macro- and microvascular outcomes. This *post hoc* analysis of pooled data from the two trials evaluated the effects of semaglutide vs PBO on kidney function decline.

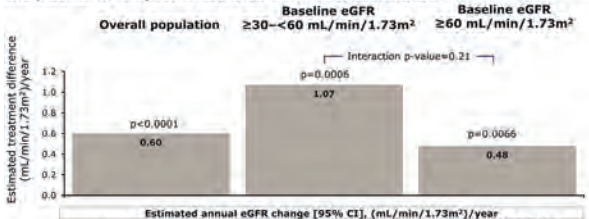
Methods: Data for 6,480 subjects with T2D from SUSTAIN 6 (OW s.c. semaglutide 0.5 and 1.0 mg or PBO, N=3,297; median follow-up 2.1 years) and PIONEER 6 (OD oral semaglutide 14 mg or PBO, N=3,183; median follow-up 1.3 years) were pooled into two groups: semaglutide and PBO. Annual change in estimated glomerular filtration rate (eGFR) was compared (semaglutide vs PBO) in the overall population and subgroups by baseline (BL) eGFR (≥30–<60 or ≥60 mL/min/1.73 m^2). Changes in eGFR from BL during trial were analyzed using a linear random regression model with individual intercept and time slope. The estimated treatment difference (ETD) at 1 year between annual rates of eGFR slope from BL was calculated; an interaction p-value <0.05 indicated difference between subgroups.

Results: In the overall population, the annual rate of eGFR change was 0.60 mL/min/1.73 m^2 (p<0.0001) lower with semaglutide vs PBO. In the eGFR ≥30–<60 mL/min/1.73 m^2 and ≥60 subgroups, the ETDs for semaglutide vs PBO were, respectively, 1.07 and 0.48 mL/min/1.73 m^2/year, with a non-significant interaction p-value (Figure).

Conclusions: Semaglutide was associated with a significantly smaller decline in kidney function than PBO in subjects with T2D at high CV risk across tested BL eGFR categories; the data suggest the main benefit might be observed in those with kidney disease.

Funding: Commercial Support - Novo Nordisk

Figure: Estimated treatment difference in annual eGFR change between semaglutide and placebo in the pooled SUSTAIN 6 and PIONEER 6 trials



Estimated annual eGFR change [95% CI], (mL/min/1.73m²)/year					
Overall population		≥30–<60 mL/min/1.73m² at baseline		≥60 mL/min/1.73m² at baseline	
Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo
N=3,232	N=3,231	n=779	n=777	n=2,375	n=2,374
−0.95 [−1.16;−0.74]	−1.55 [−1.77;−1.34]	−0.29 [−0.73;0.14]	−1.36 [−1.80;−0.92]	−1.15 [−1.40;−0.91]	−1.63 [−1.87;−1.38]

eGFR was calculated using the CKD-EPI equation. Change in eGFR from baseline were analyzed using a linear random effects regression model with individual intercept and time slope, and for subgroups interaction between time slope and subgroups. p-values above bars sre from tests for difference between treatments. Estimated treatment difference calculated for pooled semaglutide – placebo.
CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

SA-OR20

Patiromer to Enable Spironolactone in Patients with Resistant Hypertension and CKD (AMBER): Results in the Prespecified Subgroup with Diabetes

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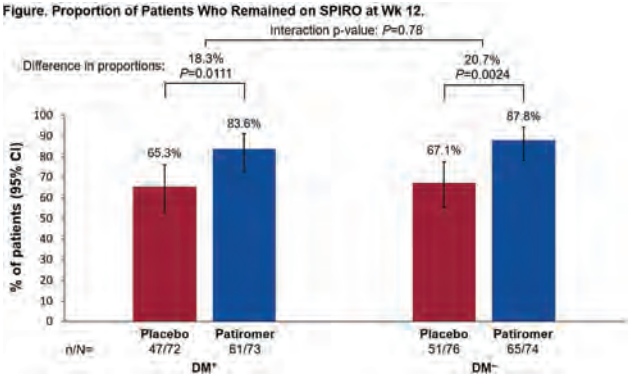
Background: Spironolactone (SPIRO) reduces BP in patients (pts) with resistant hypertension (RHTN); however, its use in pts with advanced chronic kidney disease (CKD) is often limited by hyperkalemia (HK). In AMBER, patiromer (PAT) enabled more persistent use of SPIRO in pts with RHTN and CKD. As SPIRO is recommended in RHTN and diabetes mellitus (DM) increases HK risk, we report results in prespecified subgroups with Type 1 or 2 DM (DM$^+$) and without (DM$^-$).

Methods: Randomized, double-blind, placebo (PBO)-controlled trial in adults with RHTN and eGFR 25 to ≤45 mL/min/1.73 m^2. Pts were assigned (1:1) to PBO or PAT, and SPIRO 25 mg QD, with dose titrations permitted after 1 wk for PAT/PBO and 3 wks for SPIRO. The primary endpoint, between-group difference at Wk 12 in % of pts on SPIRO, was assessed prospectively in prespecified DM subgroups.

Results: 295 pts were randomized, 145 (49%) DM$^+$ and 150 (51%) DM$^-$. Baseline mean (SD) serum K$^+$ (mEq/L) was 4.76 (0.34) in DM$^+$ and 4.67 (0.39) in DM$^-$. Significantly more pts treated with PAT than with PBO remained on SPIRO at Wk 12 in both subgroups (**Figure**). LS Mean (SE) cumulative SPIRO dose was higher with PAT than PBO, by 438.7 (177.7) mg in DM$^+$ and 317.8 (175.0) mg in DM$^-$. Adverse events occurred in 61% (PBO) and 60% (PAT) of DM$^+$ pts and in 46% (PBO) and 51% (PAT) of DM$^-$ pts. Four pts had serum magnesium (Mg^{2+}) <1.4 mg/dL between baseline and Wk 12 (none <1.2 mg/dL), including 3 DM$^+$ (1 PBO, 2 PAT) and 1 DM$^-$ (PAT) pts. None of these pts had cardiac arrhythmias temporally associated with low Mg^{2+} levels, neuromuscular abnormalities, or serum K$^+$ below the LLN (3.5 mEq/L).

Conclusions: PAT enabled more pts with advanced CKD and RHTN to continue treatment with SPIRO, regardless of DM status.

Figure. Proportion of Patients Who Remained on SPIRO at Wk 12.



SA-OR21

Single-Cell Transcriptomic Analysis to Define Cellular Heterogeneity in Human ADPKD

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Background: Deciphering the molecular pathogenesis of human autosomal dominant polycystic kidney disease (ADPKD) requires a detailed understanding of the distinct cell types and cell states driving cyst growth. Unlike single cell RNA-seq, single nucleus RNA-seq can be performed on cryopreserved samples, and we hypothesized that it might reveal unique cell states from biobanked human ADPKD samples.

Methods: We performed snRNA-seq on 8 ADPKD kidney samples (4 males and 4 females, mean = 50 +/- 8.5 years old, all had ESRD). Cystic kidneys weighed 1631 +/- 728 g. Nuclear preparations were processed using 10x Genomics Chromium 3' kit and sequenced by NovaSeq. Reads were counted with CellRanger 3.1.0 and analyzed with Seurat v3. Gene expression was validated by fluorescence in situ hybridization.

Results: Samples were stored at -80°C prior to processing (median, 20 mo; range 7-40 mo). All samples yielded good libraries (Avg. genes/nucleus = 1560 +/- 526). 63,289 nuclei originating from all 8 ADPKD kidneys passed quality control filters. Large clusters of cystic epithelial cells could be distinctly identified as originating from PT, TAL and CD. Compared to non-cystic epithelia, TAL-derived cystic epithelia showed strong induction of ERBB4 and gene ontology terms including fibroblasts/ECM and secretion of TGFb. CDH6^{high} /LRP2^{high} cystic epithelia expressed the PT injury markers HAVCR1 and VCAM1, suggesting stress-induced dedifferentiation. Cyst-specific marker gene expression was validated by RNAscope on human ADPKD sections. Analysis also revealed four separate fibroblast subtypes, most expressing markers of activation and inflammation, as well as endothelial clusters, podocytes and four separate macrophage sub-clusters.

Conclusions: To our knowledge this is the first single cell transcriptomic atlas of human ADPKD. We demonstrate the utility of this approach by revealing (1) excellent gene expression from all samples including those stored > 3 yrs, (2) segment specific cystic epithelial expression profiles, (3) activated interstitial fibroblast subsets and (4) pro-inflammatory macrophage cell types and states.

Funding: NIDDK Support, Commercial Support - Chinook Therapeutics

SA-OR22

Single-Cell RNA Sequencing Provides Insights into the Mechanism Through Which Adaptive Immune Cells Promote Injury-Induced Cyst Formation

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Background: Inducible disruption of cilia related genes in adult mice results in slow progressing cystic disease, which can be greatly accelerated by renal injury. However, cells that promote accelerated cystogenesis following renal injury are poorly understood.

Methods: To identify cells that may be responsible for driving rapid, injury induced cystic disease, we performed single cell RNA sequencing on cells isolated from sham operated CAGGCre^{ERT2+} *Ift88*$^{f/f}$ (hereafter referred to as cilia mutant mice), ischemia-reperfusion (IR) injured cre negative control, and IR injured cilia mutant mice 56 days post injury, a time point in which injured cilia mutant mice had mild cystic disease.

Results: Comparison of single cell RNA sequencing data from sham- and injured-cilia mutant mice indicate that renal injury in the setting of cilia loss results in alterations in T cell clusters with limited differences in other cell populations. In contrast, single cell RNA sequencing data comparing injured cre negative control and injured cilia mutant mice reveals that loss of primary cilia in the setting of IR injury resulted in major changes in clusters of tubular epithelia and macrophages with minimal effects on T cells. These data suggest that accelerated cystogenesis in cilia mutant mice requires both injury induced changes in T cells as well as cilia-dependent alterations in the injured epithelium and macrophages. Using NicheNet to identify ligand-receptor-gene regulatory networks, we show that T cells from injured cilia mutant mice produce ligands that cause alterations in the gene expression signature of the cilia mutant epithelium and macrophages suggesting that these cells are master regulators of injury induced cystic disease. In agreement with this hypothesis, our data indicate that loss of adaptive immune cells (including T cells) significantly reduced injury induced cystic disease. In contrast, loss of adaptive immune cells did not affect cyst progression in the absence of injury in multiple cystic models, even when animals were aged out several months.

Conclusions: Collectively, our data indicate that IR injury creates a unique population of ligand-producing T cells that crosstalk with macrophages and epithelium of cilia mutant mice to drive rapid, injury induced cystogenesis.

Funding: NIDDK Support, Other NIH Support - University of Alabama at Birmingham (UAB) Hepato/Renal Fibrocystic Disease Core Center P30-DK-074038, R01 DK097423(M.M), 1-I01-BX002298 from the Office of Research and Development, Medical Research Service, Department of Veterans Affairs (M.M) and by the Detraz Endowed Research Fund in Polycystic Kidney Disease (to M. M.). Additional support was provided by the Polycystic Kidney Disease Research Foundation grant 214g16a (B.K.Y.); University of Alabama at Birmingham (UAB) School of Medicine AMC21 grant (B.K.Y., M.M.); the National Institutes of Health T32 training grant in Basic Immunology and Immunologic disease 2T32AI007051-38 (to K.A.Z); an NIDDK K01 DK119375 (K.A.Z.), two Pilot and Feasibility grant from the Baltimore PKD Center 2P30DK090868 (K.A.Z, K.H.); a Pilot and Feasibility grant from the UAB Hepato/Renal Fibrocystic Disease Core Center 5P30DK074038 (to K.A.Z), an NIH R01 DK115752 (B.K.Y.), a PKD Foundation Research Award (to K.H.), and the Zell Family Foundation (to K.H.), Veterans Affairs Support, Private Foundation Support

SA-OR23

Activation of AMP-Activated Protein Kinase In Vivo Leads to a Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a genetic disorder in which numerous fluid-filled cysts form in the kidney. Despite having identified the causative genes that are mutated in PKD, our understanding of the molecular signalling pathways involved in cystogenesis is limited, hindering PKD drug discovery. In this project, we generated a mouse model of AMP-activated protein kinase (AMPK) activation and observed a polycystic kidney phenotype, reminiscent of PKD. AMPK is known for its role in regulating energy homeostasis and is activated in response to cellular stress. It is currently unknown whether AMPK could play a role in PKD pathogenesis.

Methods: AMPK activation mouse models were generated by expressing the AMPKγ1 isoform with a D316A mutation under the control of β-actin (global) and Ksp (kidney-specific) promoters using the Cre-LoxP system. A constitutively active form of AMPK is produced when AMPKγ1-D316A is incorporated into the enzyme complex. Renal function was assessed using metabolic cages, serum and urine samples were collected for analysis. Kidneys were collected and snap-frozen for biochemical studies or wax-embedded for histological studies.

Results: Global activation of AMPKγ1 resulted in a striking polycystic kidney phenotype. Tubule dilations were evident from 11 days of age, which progressed to heavily cystic kidneys by 3 weeks of age. Adult mice showed signs of polyuria associated with a concentrating defect, polydipsia, kidney damage and compromised renal function. Cysts were observed in the collecting ducts of these mice, consistent with the distal nephron being most heavily afflicted in PKD. Mechanistically, the cystic kidneys had increased cAMP levels and ERK activation (a pathway known to be dysregulated in PKD), increased hexokinase I expression and altered lysosomal protein expression. Kidney-specific activation of AMPKγ1 also produced polycystic kidneys in mice, demonstrating that AMPK activation within the kidney was causative.

Conclusions: These results show that activation of AMPK causes polycystic kidneys to form in mice, raising the possibility that AMPK activation could be a contributing factor in PKD pathogenesis. Dysregulation of the cAMP-ERK pathway in this model suggests a possible mechanism for how AMPK activation could be implicated in renal cystogenesis. Future studies should investigate whether AMPK has a pathogenic role in other PKD models.

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SA-OR24

CU062, the Product of the *C21orf62* Gene, Is a Polycystin-1 Ligand

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Background: The *PKD1* gene, encoding the protein polycystin-1 (PC1), is responsible for 85% of cases of mutation positive autosomal dominant polycystic kidney disease (ADPKD) and is the most common genetic cause of renal failure (1:800). PC1 has been shown to be present on easily accessible urinary exosome-like vesicles (ELVs) and to be decreased in individuals with *PKD1* mutations. Label-free mass spectrometry comparison of ELVs from normal and *PKD1* urine showed that several other proteins were decreased to a degree similar to PC1, including a small signal peptide bearing protein of unknown function, CU062, the product of the *C21orf62* gene.

Methods: To determine whether this novel protein is involved in cystogenesis, we applied a genetic approach and deleted the entire *C21orf62* open reading frame in c57Black6/J mice. We also investigated the ability of CU062 to interact with the entire 4302 aa ORF of PC1 and mapped the interacting domains. Furthermore, we probed its ability to gate the PC1/PC2 channel using primary cilium patch clamp.

Results: A TALEN induced deletion of the entire *C21orf62* ORF generated mice that were grossly phenotypically normal, and both sexes were fertile. Close inspection of the kidney showed that about 25% of the homozygous null animals had mild tubular dilation in the loop of Henle and collecting duct. The *C21orf62*^{del} allele exacerbated the *Pkd1*^{R3277C} phenotype as assessed by kidney weight/body weight ratio, ANOVA interaction p=0.0017. *In vitro* binding studies indicated that CU062 interacts with PKD domains 2-17 and most tightly with domains 15-17 in an SDS stable manner. We subsequently showed that extracellular application of pure CU062 activated polycystin-2 (PC2) dependent currents in primary cilia of mIMCD-3 cells. CU062 was shown to be expressed most prominently in the *vasa recta* (VR) and the endothelium of large blood vessels but not in kidney tubules.

Conclusions: These data suggest that CU062 might be a circulating ligand for PC1 and may be filtered through the glomerulus to interact with PC1 on exosomes. CU062 accounts for a subset of PC1 functions as its genetic deletion leads to a milder phenotype than that observed in *Pkd1* homozygous null mice.

Funding: NIDDK Support

SA-OR25

Intercalated Cells and the Transcription Factor FOXI1 Drive the Kidney Cystogenesis in Tuberous Sclerosis Complex

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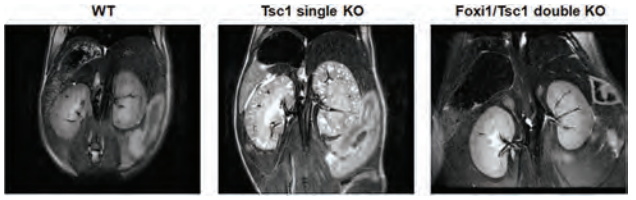
Background: Tuberous sclerosis complex (TSC) is caused by mutations in either the TSC1 or TSC2 gene and affects multiple organs, including the kidney. Patients can present with benign tumors (angiomyolipomata) and cysts, which can lead to kidney failure. Factors that promote cyst formation and tumor growth in TSC are poorly understood.

Methods: Mice with principal cell specific inactivation of Tsc1 were generated. In addition, mice with double deletion of Foxi1 and Tsc1 (Foxi1/Tsc1 double KO) or carbonic anhydrase 2 (CAII) and Tsc1 (CAII/Tsc1 double KO) were generated based on RNA-seq and expression studies.

Results: Tsc1 KO mice showed numerous kidney cortical cysts, which were overwhelmingly comprised of A-intercalated (A-IC) cells that showed strong expression of apical V H^+-ATPase. RNA-seq studies demonstrated a 3-fold enhanced expression of Foxi1, which is critical to the development of IC cells and regulation of V H^+-ATPase and CAII. The expression of Foxi1 in Pkd1 mice remained unchanged vs. WT mice. Deleting Foxi1 completely abrogated the cyst burden in Foxi1/Tsc1 dKO mice (Kidney MRI in image 1) and caused a profound reduction in V H^+-ATPase expression in the A-IC cells. Mice with double deletion of Tsc1 and CAII, a regulator of V H^+-ATPase, showed significant reductions in cyst burden and increased longevity vs. Tsc1 KO mice.

Conclusions: We propose that A-IC cells, V H^+-ATPase and CAII are critical to cystogenesis, and their inhibition or inactivation is associated with a significant protection against cyst generation and/or enlargement in TSC. Carbonic anhydrase inhibitors may be viable treatments for the prevention of kidney cyst expansion in TSC. Supplementing carbonic anhydrase inhibitors with HCO_3^- (to minimize the untoward side effects of metabolic acidosis) may be warranted.

Funding: Veterans Affairs Support, Private Foundation Support



MRI examination of kidneys of Tsc1 and Foxi1/Tsc1 double Ko mice

SA-OR26

Genome-wide Analyses Provide Insights into the Architecture of Kidney Function and CKD in African Americans in the Million Veteran Program (MVP)

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Background: End-stage kidney disease (ESKD) incidence rates for African Americans are more than 3 times higher than for European-Americans. This disparity has been only partly explained by known determinants of ESKD and the presence of high-risk APOL1 variants. The identification of "second hit" triggers may explain kidney outcome disparities observed in African Americans.

Methods: We performed a GWAS of eGFR among 84,544 African Americans from the MVP at or closest to enrollment. Exclusion criteria were: dialysis, kidney transplant, and BMI<18. We evaluated the association of common (minor allele frequency > 1%) SNPs with linear eGFR (by CKD-EPI equation), adjusted for age, sex, BMI, and the top ten principal components of ancestry. Analyses were performed by strata of diabetes and estimates were aggregated with fixed-effects meta-analysis.

Results: We identified 2,275 SNPs in 22 independent loci associated with eGFR ($p<5x10^{-8}$). The SNP with the strongest signals replicated previously detected associations at *SPATA5L1*/*GATM* (rs2486272, $p = 1.7 \times 10^{-60}$). Of these, 19 represented previously reported loci from GWAS of kidney function or CKD. Known CKD genes from case-control studies such as *APOL1* (rs73885319 p=9.09x10-28) were included in the known loci. Three were novel loci for the association with kidney function in African Americans. Of the novel variants, we discovered SNPs in *ABCA1* (rs10991574 $p = 2.97x10^{-8}$) associated with accelerated atherosclerosis and lipid metabolism through PPAR alpha, *PIK3AP1*(rs556476 $p = 3.1 x10^{-09}$) associated with leukocyte count and *BLNK*(rs9664029 p=2.49 10-8) associated with colorectal adenoma. Some of the strongest signals previously reported for kidney phenotypes included: *DAB2* (rs2542713 $p=1.5 \times 10^{-8}$), *OCT2* (rs2279463, $p=1.98\ 10^{-14}$), *UNCX* (rs62435145 $p=1.97\ 10^{-12}$) and *PRKAG2* (rs10253736 $p=3.0x10^{-8}$). 70 SNPs were exonic variants overall. SNPs within *UMOD/PDILT*, the top hits for kidney function GWAS and CKD progression among European-Americans, did not reach genome-wide ($p=9.19x10^{-8}$) significance.

Conclusions: In this large GWAS of eGFR among African Americans to date, we replicate over 19 previously identified loci, identify 3 novel loci associate with kidney function.

Funding: Veterans Affairs Support

SA-OR27

3D Genome Architecture of Human Renal Cortex and Medulla

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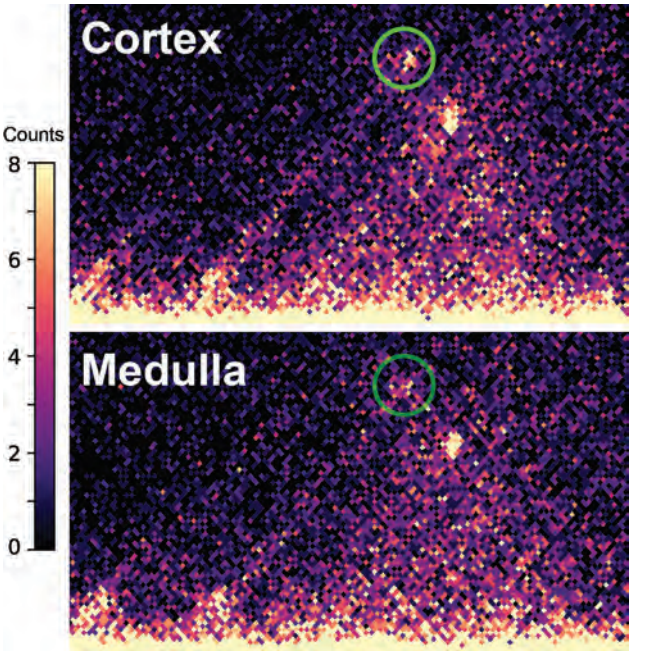
Background: Genomic DNA is organized in a non-random manner within the mammalian nucleus. How this three-dimensional genome architecture influences cell-type specific phenotypes is poorly understood. Genome-wide methods such as Hi-C can systematically map out 3D genome architecture. However until now, technical and cost limitations have prevented these powerful approaches from being applied to intact human kidney tissues.

Methods: We performed global genome conformation (Hi-C) analysis on macrodissected human renal cortex and medulla from the same individual. Since existing algorithms to identify intra and inter-chromosomal interactions in Hi-C sequencing data are plagued by low concordance, we developed a novel machine learning algorithm used in the domain of computer vision to identify significant contacts in our Hi-C data.

Results: Each kidney Hi-C sample was deeply sequenced to >400 million mapped contacts enabling visualization of topologically associated domains (TADs) and contacts at 10kb resolution. Comparing even these highly similar samples, our novel algorithm identified significantly different genome conformation at multiple intra-chromosomal contacts in renal cortex (n=1789) and medulla (n=1841) (figure). Further validation by DNA-FISH and comparison to orthogonal functional genomic data sets (ATAC-seq, RNA-seq) are ongoing.

Conclusions: These high-resolution chromatin conformation maps of intact human kidney will provide an valuable resource for the study of kidney genome regulation. Our novel loop-calling algorithm enabled identification of fine genome architectural differences between renal cortex and medulla. Our data can also be used to link genetic risk loci to target genes in genome-wide association studies.



Hi-C contact matrices for cortex and medulla for chr2:117,860,000-118,850,000; Green circle = differential loop.

SA-OR28

Clonal Hematopoiesis of Indeterminate Potential and Somatic Mutation Role in CKD: The First Study

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related somatic mutagenesis associated with inflammation and increased risk of death due to cardiovascular disease. Chronic kidney disease (CKD) is strongly associated with cardiovascular disease, suggesting shared pathophysiologic mechanisms. Inflammation is a well-established component of CKD but CHIP has never been investigated in CKD.

Methods: We analyzed whole-exome sequencing data to determine CHIP prevalence and variant allele frequency (VAF) in a cohort of 2,187 CKD patients and 1,686 age-matched controls. Somatic variants were called using Mutect2 and filtered using strict standard criteria. The presence of CHIP mutations was evaluated for associations with demographic and clinical variables, including age, sex, CKD etiology, treatment with immunosuppressive therapies, end-stage renal disease (ESRD), and history of renal transplant.

Results: In a multivariate logistic regression model focused on the most frequently mutated CHIP genes (DNMT3A, TET2, ASXL1, JAK2), we observed an age-independent association between CHIP and CKD, where both prevalence (p=0.04, OR: 1.62) and VAF (3.48% vs. 1.89%, p=0.004) were higher in CKD cases than in controls. Among CKD cases, CHIP was independently associated with history of renal transplant >10 years (p<0.01, OR: 5.8) and treatment with immunosuppressive therapies (p<0.01, OR: 2.6). Differences were primarily driven by TP53, DNMT3A, ASXL1, ATM, and JAK2. In univariate analysis, we also found a higher prevalence of CHIP in patients with lupus nephritis and other autoimmune glomerulonephritis than in patients with other diagnoses (p=0.04), but this association did not persist in multivariate analyses.

Conclusions: Our analysis of a large case-control cohort suggests an independent association between CHIP and CKD. This association was most evident in patients with ongoing inflammation due to renal transplantation or immune-mediated conditions. These data will require replication in larger human cohorts and validation in animal models.

SA-OR29

Loss of Diacylglycerol Kinase ε Causes Thrombotic Microangiopathy by Impairing Endothelial Vascular Endothelial Growth Factor A Signaling

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Background: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) accompanied by hemolytic anemia, thrombocytopenia, and acute renal failure due to glomerular damage. Mutations in complement genes have been identified in about 50% of aHUS cases. We reported that mutations in the gene *DGKE*, encoding the lipid kinase diacylglycerol kinase epsilon (DGKε) that is unrelated to the

complement system, also cause aHUS. In the glomeruli, *DGKE* is expressed in endothelial cells and podocytes. The molecular mechanisms by which loss of DGKε causes TMA are not known. Phosphatidyl-inositol diphosphate [PtdIns(4,5)P_2] levels are reduced in *Dgke* knockout cells. Since the disruption of vascular endothelial factor A (VEGFA) signaling in humans and mice results in glomerular lesions that resemble those in humans with loss-of-function mutations in *DGKE*, we hypothesized that loss of *DGKE* may impair VEGF signaling in endothelial cells due to shortage of PtdIns(4,5)P_2.

Methods: To test this hypothesis, we performed in vitro studies on *DGKE* knockdown human umbilical vein endothelial cells (HUVECs) and generated endothelial-specific ^{Tie2Cre}*Dgke*$^{f/f}$ conditional knockout mice.

Results: We found that signaling downstream of VEGFA receptor 2 (VEGFR2) is compromised in *DGKE* knockdown HUVECs due to decreased activation of Akt, a phenotype that is rescued by supplementation the culture medium with PtdIns(4,5)P_2. Endothelial-specific ^{Tie2Cre}*Dgke*$^{f/f}$ conditional knockout mice spontaneously developed thrombocytopenia, schistocytosis, and renal insufficiency, indicating that the endothelium is the cellular compartment responsible of the DGKE disease. Remarkably, these mice also developed albuminuria at later times, indicating that the impairment of the glomerular barrier, which is characteristic of the DGKE disease, is a later and secondary event.

Conclusions: Our data indicate that loss of *DGKE* compromises signaling downstream of VEGFR2 in endothelial cells by decreasing cellular levels of PtdIns(4,5)P_2, inducing aHUS and, secondarily, disruption of the glomerular barrier. These results also implicate that pharmacological manipulation of the VEGFA signaling may be used to modify the clinical course of other forms of aHUS.

SA-OR30

Re-Envisioning the APOL1 Cation Channel Structure

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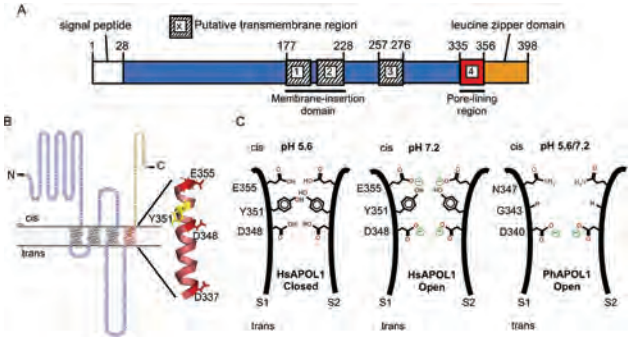
Background: Apolipoprotein L-I (APOL1) is a channel forming protein that protects humans and other primates from African trypanosome infection. African Americans have inherited common APOL1 variants with increased trypanolytic potential; however, these variants are responsible for an increased risk of kidney disease compared with other variants. Human APOL1 forms non-selective cation channels in a strictly pH dependent manner: channel formation requires acidic pH, whereas channel opening requires pH neutralization. Current APOL1 structural models rely on tenuous comparisons with unrelated channel forming proteins. Here we introduce a new model of APOL1 channel structure and topology based on functional characterization of divergent APOL1 orthologs and interspecies chimeras in a planar lipid bilayer system.

Methods: We tested interspecies APOL1 chimeras and point mutations in planar lipid bilayers to identify molecular determinants of pH dependence and ion selectivity.

Results: Strikingly, we demonstrate that cation conductance depends on the C-terminal domain, rather than the N-terminal region as previously suggested, with both pH gating and selectivity functions largely governed by a single residue - aspartate-348. Dual substitution of Asp-348 and nearby glutamate-355 eliminated pH gating, with tyrosine-351 having a steric influence. Acidic residues within a putative hairpin region (residues 177-228) affected the pH-dependence of channel formation.

Conclusions: Based on these data we present a radically updated domain structure of APOL1, including a putative 4-pass transmembrane topology and a pore-lining helix near the C-terminus (see Image abstract). We propose a mechanism of channel gating based on dual proton-sensing residues (Asp-348 and Glu-355) within the pore-lining helix, with Asp-348 also determining selectivity for cations over anions.

Funding: Other U.S. Government Support



(A) Domain structure. (B) Topology model and pore-lining helix. (C) Model of the pore. Two APOL1 subunits (S1 and S2) are brought into apposition via the C-terminal leucine zipper domain.

SA-OR31

Small Molecule Inhibitor of TMEM16A Chloride Channel Blocks Vascular Smooth Muscle Contraction and Lowers Blood Pressure in Spontaneously Hypertensive Rats

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Background: Hypertension is a major cause of cardiovascular morbidity and mortality, despite the availability of antihypertensive drugs with different targets and mechanisms of action. There is an unmet need for antihypertensive drugs with novel mechanisms of action for better BP control. TMEM16A (transmembrane member 16A or anoctamin-1) is a Ca^{2+}-activated Cl^- channel expressed in vascular smooth muscle. TMEM16A activation produces membrane depolarization that results in secondary activation of voltage-dependent ion channels that modulate vasoconstriction. TMEM16A is a potential target for hypertension treatment.

Methods: We recently identified by high-throughput screening and subsequent medicinal chemistry, small molecule TMEM16A inhibitor TM_{inh}-23 that inhibits TMEM16A current fully, with IC_{50} ~ 30 nM. Here we tested TM_{inh}-23 pharmacokinetics in rodents and its effects on vascular smooth muscle contraction (via wire myograph) and BP in spontaneously hypertensive rats (SHR) and wild type rodents.

Results: TM_{inh}-23 pretreatment blocked maximum in vitro vascular smooth muscle contractions induced by a thromboxane mimetic (U46619) in rat mesenteric arteries by 90%. Intraperitoneal (ip) administration of TM_{inh}-23 to rodents at 10 mg/kg produced sustained serum concentrations of >10 μM for >4 hours. BP measurements by tail-cuff and telemetry showed a maximum ~45 mmHg reduction in SBP in spontaneously hypertensive rats (SHR) after a single dose TM_{inh}-23 (10 mg/kg, ip) compared to vehicle administration, with BP gradually returning to baseline values within 6-8 hours after TM_{inh}-23 treatment. Minimal effect on BP (less than 10 mmHg decrease in SBP) was seen in wild-type rats and mice with TM_{inh}-23 treatment (10 mg/kg, ip). Chronic 5-day treatment of SHR with TM_{inh}-23 (10 mg/kg, ip, twice daily) caused sustained decreases (~25 mmHg) in daily average SBP, DBP and MAP during the treatment period. TM_{inh}-23 action was reversible, with BP returning to baseline (~170/115 mmHg) by 3 days after discontinuation of treatment.

Conclusions: These studies provide validation for TMEM16A as a target for hypertension therapy, and demonstrate the proof-of-concept for efficacy of TM_{inh}-23 as an antihypertensive with a novel mechanism of action.

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SA-OR32

Intravital Imaging of Afferent Arteriole Calcium Dynamics and the Role of Connexin 45

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Background: The glomerular afferent (AA) and efferent (EA) arterioles are the most critical resistance vessels in the autoregulation of renal blood flow and glomerular filtration rate. Calcium dynamics of vascular smooth muscle cells (VSMC), in part mediated by gap junction communication via connexin 45 (Cx45), are important regulators of AA contractility and myogenic tone. We aimed to study the role of Cx45 in renal hemodynamics in vivo.

Methods: Intravital imaging with multiphoton microscopy (MPM) of renal functional parameters was performed in mice expressing a genetically encoded calcium indicator (GCaMP3 or GCaMP5) in cells of renin lineage with or without connexin 45 knockout (KO). Suramin treatment was used to test the effects of purinergic receptor blockade.

Results: Compared to the uniform upstream AA segment, high baseline and $\Delta(Ca^{2+})_i$ were observed in a few AA VSMCs at the glomerular entrance, which appeared to function as sphincter cells. The diameter of the AA (9.24±0.27μm WT, vs. 11.39±0.37μm KO) and EA (7.18±0.36μm WT, vs. 8.58±0.30μm KO) were larger in KO animals, although no difference was found in SBP, snGFR and glomerular diameter. Blood flow in AA was also increased (1.42±0.15μm/ms WT, vs. 2.0±0.12μm/ms KO). AA myogenic tone was visualized 3-4 weeks after unilateral ureteral obstruction (UUO). In WT animals, regular AA contractions were observed uniformly in all AAs with an average frequency of 0.12±0.01 Hz, with large magnitude $\Delta(Ca^{2+})_i$ in VSMCs during every contraction ($\Delta(Ca^{2+})_i$ = 5564±855 AU). In contrast, KO animals showed highly heterogeneous and irregular AA vascular activity. In those AAs that did exhibit some myogenic tone-like contractions, a higher frequency was observed (0.28±0.02 Hz), however the magnitude of $\Delta(Ca^{2+})_i$ in AA VSMCs was much lower than in the WT ($\Delta(Ca^{2+})_i$ = 395±249 AU). In both WT and KO animals, treatment with suramin rapidly blocked AA VSMC calcium increases and the myogenic contractions, and the AA became dilated.

Conclusions: AA sphincter cells have robust effects on AA $(Ca^{2+})_i$ dynamics and contractility in vivo, and Cx45 and purinergic signaling are essential components of AA calcium signaling and vascular contractility. Cx45 and purinergic signaling in the AA regulate the myogenic response and renal blood flow, and may be culprit and potential target in vascular pathologies.

Funding: NIDDK Support

SA-OR33

Inorganic Nitrite Supplementation Improves Endothelial Function with Aging: Translational Evidence for Suppression of Mitochondria-Derived Oxidative Stress

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Background: We previously observed improvements in vascular endothelial function with inorganic nitrite supplementation in old mice, which we translated to older humans in a pilot study of sodium nitrite supplementation.

Methods: Here, we sought to confirm the efficacy of sodium nitrite in humans and determine mechanisms of action using: 1) a randomized, placebo-controlled, parallel-group clinical trial with sodium nitrite (80 mg/day, 12 weeks) in older adults (n=49, 68±1 yr) and 2) reverse translation experiments in young (6 mo) and old (27 mo) male C57BL6 mice.

Results: In humans, sodium nitrite increased plasma nitrite ($p<0.05$) and was well-tolerated over 12 weeks. Endothelial function (brachial artery flow-mediated dilation) was increased by 28% vs. baseline after nitrite supplementation ($p<0.05$), but unchanged with placebo. Serum from nitrite-treated subjects reduced whole-cell (CellROX) and mitochondria (mito)-specific (MitoSOX) reactive oxygen species (ROS) in human umbilical vein endothelial cell culture ($p<0.05$), whereas serum from placebo-treated subjects had no effect. Old mice (OC, n=9) had ~30% lower *ex vivo* carotid artery endothelium-dependent dilation (EDD) vs. young mice (YC, n=9) due to reduced nitric oxide (NO) bioavailability ($p<0.05$). Nitrite supplementation (drinking water, 50 mg/L, 8 weeks) restored EDD and NO bioavailability in old mice (ON, n=10). MitoROS suppression of EDD was present in OC (increased EDD with a mito-targeted antioxidant, $p<0.05$), but not in Y or ON. A mito stressor (rotenone) further impaired EDD in OC ($p<0.05$), whereas Y and ON were protected.

Conclusions: Nitrite supplementation improves age-related endothelial dysfunction and is associated with increased NO, reduced mito ROS and improved mitochondrial stress resistance.

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SA-OR34

Paracrine FGF-23 Signaling in the Heart Causes Cardiac Hypertrophy

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Background: Elevated serum levels of the phosphaturic hormone, fibroblast growth factor (FGF) 23, contribute to cardiac hypertrophy in chronic kidney disease (CKD). FGF23 directly targets cardiac myocytes via FGF receptor (FGFR) 4 to induce hypertrophic growth and FGFR4 blockade not only protects rodent models of CKD from cardiac hypertrophy but also from fibrosis. Our cell culture studies indicate that cardiac fibroblasts do not directly respond to FGF23. It is known that a miscommunication between cardiac myocytes and fibroblasts contributes to pathologic cardiac remodeling. It has been shown that in rodent models and patients with CKD, as well as in mice on high phosphate diet without kidney injury, the heart starts to produce FGF23. Here, we studied if by targeting cardiac myocytes FGF23 promotes paracrine signaling that drives fibrosis. We aimed to determine the cardiac cell type(s) that act as FGF23 source and study if FGF23 serves as a novel paracrine signal mediator between cardiac cell types.

Methods: We treated cultured cardiac myocytes with FGF23 and determined expression levels of established paracrine signal mediators (IL6, LIF, TGFβ, FGF2), or with high phosphate and analyzed FGF23 expression, all by qPCR. We isolated cardiac fibroblasts from wildtype mice on a high phosphate (2%) diet or control chow (0.7%) for 12 weeks. We analyzed paracrine signal mediators by qPCR, as well as FGF23 by qPCR and ELISA. After plating cardiac fibroblasts for 24 and 48 hours, we transferred cell supernatants to myocytes and analyzed hypertrophy.

Results: FGF23 did not increase the expression of paracrine signal mediators in cardiac myocytes or fibroblasts. Phosphate elevations induced FGF23 expression in cardiac fibroblasts, but not in myocytes. Cardiac fibroblast-derived supernatants showed pro-hypertrophic activity when transferred to myocytes, which could be inhibited by co-administration of blocking antibodies for FGF23 or FGFR4.

Conclusions: FGF23 does not affect cardiac fibroblasts by regulating paracrine signal mediators in myocytes. However, FGF23 acts as a novel fibroblast-derived paracrine signaling mediator that induces hypertrophic growth of cardiac myocytes in an FGFR4-dependent manner in scenarios of hyperphosphatemia, such as CKD.

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SA-OR35

A Renal Potassium-Switch Prioritizes Dietary Potassium Over Sodium, Driving Salt-Sensitive Hypertension

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Background: Reducing dietary salt (NaCl) is well appreciated to lower blood pressure (BP), but a growing body of evidence indicates that increasing dietary potassium (K) intake is equally important. A 'renal K switch' that turns on the thiazide-sensitive NaCl cotransporter (NCC) in response to low dietary K intake and off in response to high K intake has been implicated. Here we test this idea in genetically engineered mice (CA-SPAK) in which the K switch is 'locked on.'

Methods: Kinase-activating mutations were introduced in SPAK. Expression of the constitutively active (CA) SPAK mutant was limited to the early DCT and results in NCC hyperactivation. BP responses to small changes in plasma [K+] (P[K]) in CA-SPAK were compared to control mice. Dietary K content was varied over 4 days to titrate P[K] over a narrow range (3.7mM (LK), 4.4mM (MK), and 5.1mM (HK)). Blood pressure was monitored by telemetry at each P[K] level in mice consuming control or high salt diet (HNa). At the end of each treatment, the BP response to hydrochlorothiazide (HCTZ) was measured to assess the contribution of NCC to BP.

Results: BP decreased by ~10 mmHg when P[K] increased from 3.7 to 5.1 mM in control mice, coincident with the inactivation of NCC. When the switch was on (LK and MK groups), HNa significantly elevated BP but had no effect when the switch was inactivated by HK. HCTZ significantly reduced BP in the LK/HNa and MK/HNa groups but had no effect on BP in the HK/HNa group, supporting the idea that low K-dependent activation of NCC exacerbates the effects of Na. Studies in CA-SPAK mice reveal a causal relationship between switch activation and BP responses to Na and K. In contrast to control mice, increasing P[K] in CA-SPAK mice had no effect on BP under control salt conditions and failed to blunt the significant hypertensive effects of HNa. HCTZ significantly decreased BP in all CA-SPAK groups to near control levels, consistent with NCC-driven salt reabsorption. Thus, locking on the K switch prevents the anti-hypertensive effects of HK. No sex differences were found.

Conclusions: In summary, low K consumption, common in modern diets, presses the switch pathway to turn on to conserve K at the expense of increasing Na retention, even in the face of high dietary Na, and this elevates BP. Thus, switch activation can drive salt-sensitive hypertension.

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SA-OR36

Risk of Cardiovascular Events Is Higher in Patients with Glomerular Disease Compared with the General Population

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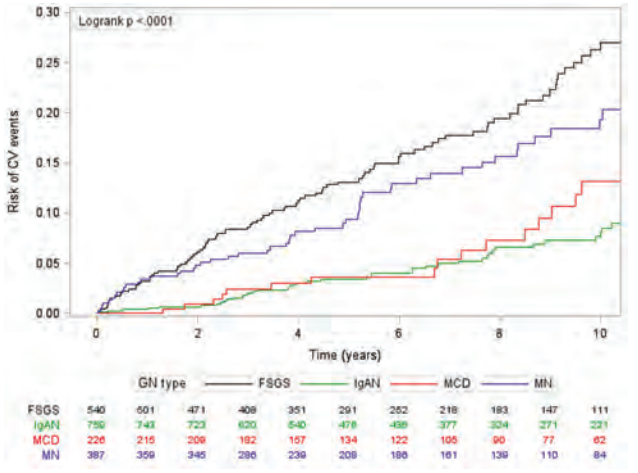
Background: Cardiovascular (CV) disease is a recognized cause of morbidity and mortality in chronic kidney disease; however, understanding of CV risk in patients with glomerular disease (GN) is limited. We sought to define CV risk in GN patients and compare incidence rates to the general population.

Methods: A centralized kidney pathology registry (2000-2012) was used to capture all incident cases of focal segmental glomerulosclerosis (FSGS, n=540), IgA nephropathy (IgAN, n=759), membranous nephropathy (MN, n=387), and minimal change disease (MCD, n=226) in British Columbia, Canada. The primary outcome was a composite of major CV events, ascertained from a hospital discharge registry and evaluated using the Kaplan-Meier method. Hazard ratios (HR, 95% CI) were determined using Cox proportional hazards regression. Event rates were age and sex standardized to the general adult population to generate standardized incidence ratios (SIR, 95% CI).

Results: Over a median follow-up of 6.8years there were 338 CV events; 10-year risk (95% CI) was 16.0% (13.8-18.3) and differed by GN type (Figure): IgAN=7.7% (5.4-10.4), MCD=13.2% (7.6-20.4), MN=19.4% (14.3-25.0), and FSGS=27.0% (21.9-32.4). Compared to IgAN, MN (HR=2.6, 1.7-3.9) and FSGS (HR=3.7, 2.6-5.3) had higher risk, but MCD (HR=1.3, 0.8-2.4) did not. Results were similar when comparing CV events before versus after ESKD. CV risk in GN patients was 2.5-fold higher than the general population (SIR 2.5, 2.1-2.8), and was higher in each GN subtype (IgAN=1.4, 1.0-1.8; MCD=1.8, 1.0-2.8; MN=3.0, 2.2-4.0; FSGS=4.0, 3.2-4.9).

Conclusions: Patients with GN are at high risk of CV disease, both before and after ESKD onset. The CV risk for all GN subtypes was higher than the general population, including MCD and IgAN. This suggests CV preventive strategies should be considered in all patients with GN.



Kaplan-Meier Curve by GN Type

SA-OR37

Prediction of Atrial Fibrillation Using Clinical and Cardiac Biomarker Data: The CRIC Study

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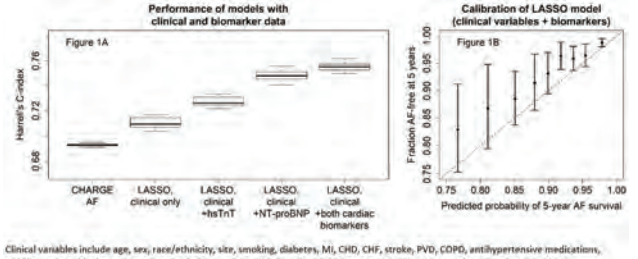
Background: Clinically available biomarkers of myocardial injury (high sensitivity troponin T, hsTnT) and hemodynamic stress (N-terminal brain natriuretic peptide, NT-proBNP) are strongly associated with atrial fibrillation (AF) in chronic kidney disease (CKD), and have been included in AF prediction models in community-based populations. We investigated the incremental prognostic value of NT-proBNP and hsTnT for AF prediction compared to standard clinical variables in CKD patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) using machine learning methods.

Methods: Among 2690 CRIC participants without prior AF with complete cardiac biomarker, demographics, medical history/lifestyle, medications, physical characteristics, and laboratory data, we evaluated the utility of Cox regression, LASSO, ridge regression, elastic net, and boosting methods, as well as a previously validated clinical prediction model (CHARGE-AF, using both original and re-estimated coefficients) to predict incident AF. Discriminatory ability of each model was assessed using 10-fold cross-validation; calibration was evaluated graphically.

Results: Mean (SD) age of participants was 57 (11) years, 55% men, 38% black, and mean (SD) eGFR 45 (15) mL/min/1.73m^2; 251 incident AF events occurred during 7.3 (SD 2.8) years of follow-up. CHARGE-AF prediction equations using original and re-estimated coefficients each had a cross-validated C-index of 0.69 (Figure 1a). A LASSO model using only clinical data had a C-index of 0.69, while adding NT-proBNP, hsTnT, or both biomarkers improved the C-index to 0.75, 0.73, and 0.76, respectively (p for difference compared to clinical only model <0.0001 for all). Calibration of top biomarker models was generally adequate (Figure 1b).

Conclusions: Cardiac biomarkers NT-proBNP and hsTnT can improve AF prediction in CKD, particularly when paired with machine learning algorithms.

Funding: NIDDK Support



Clinical variables include age, sex, race/ethnicity, site, smoking, diabetes, MI, CHD, CHF, stroke, PVD, COPD, antihypertensive medications, ACEi/ARBs, beta blockers, CCBs, diuretics, height, weight, BMI, SBP, DBP, ECG heart rate, eGFR, 24-hour urine albumin, PTH, FGF-23, hemoglobin, HDL, LDL.

CHARGE-AF model uses published coefficients from Alonso et al (JAHA, 2013).

SA-OR38

Renal Hyperfiltration and the Effect of Intensive vs. Standard Blood Pressure Lowering on Cardiovascular Outcomes

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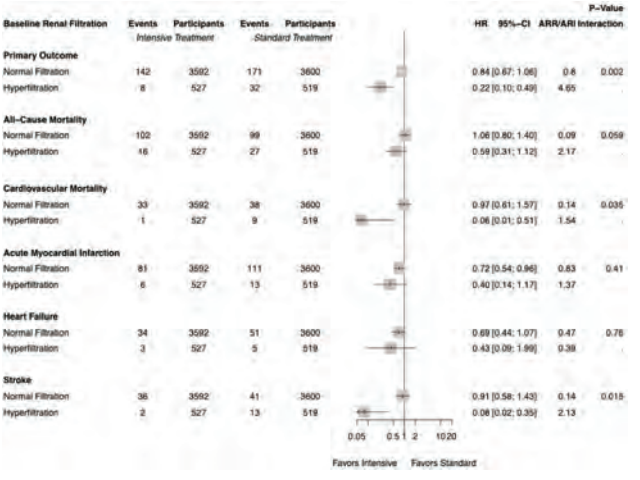
Background: Using the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Systolic Blood Pressure Intervention Trial (SPRINT), we examined whether the effect of intensive versus standard blood pressure (BP) lowering on cardiovascular outcomes varies by the presence of renal hyperfiltration (RHF).

Methods: We pooled data on adults in ACCORD and SPRINT without chronic kidney disease (eGFR>60 and urine albumin-to-creatinine ratio <30 mg/g). RHF was defined as an eGFR above the 95th percentile for healthy adults in the National Health and Nutrition Examination Survey. Outcomes of interest were major adverse cardiovascular events (MACE, as defined in the ACCORD primary outcome): a composite of cardiovascular (CV) mortality, acute myocardial infarction (AMI) and stroke. Secondary outcomes were all-cause mortality, CV mortality and CV events. We used fixed effect cox regression.

Results: There were 1046 (13%) adults with RHF and 7192 adults with normal filtration. RHF modified the effect of intensive versus standard BP lowering on MACE (p-interaction=0.002) but not all-cause mortality (p-interaction=0.059). For adults with RHF, intensive BP lowering reduced incidence of MACE compared with standard BP lowering (HR: 0.22, 95%-CI: 0.10-0.49). The risk reduction was smaller in adults with normal filtration (HR: 0.84, 95%-CI: 0.67-1.06). Intensive BP lowering was also associated with a larger reduction in the incidence of CV mortality and stroke among adults with RHF (Figure, p-interaction≤0.035) but not AMI or heart failure (p-interaction≥0.41). Separate analyses of ACCORD and SPRINT were similar.

Conclusions: RHF modified the effect of intensive versus standard BP lowering on cardiovascular outcomes.



Intensive Versus Standard Blood Pressure Lowering and Cardiovascular Outcomes in Adults With and Without Renal Hyperfiltration (Pooled Analysis)

SA-OR39

Pooled Analyses of the Phase 3 Roxadustat Studies: Congestive Heart Failure Hospitalization Rates in Dialysis and Non-Dialysis Patients with Anemia Treated with Roxadustat vs. Comparators

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Background: Roxadustat is an orally bioavailable hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Phase 3 roxadustat studies were performed to treat anemia of chronic kidney disease (CKD). Congestive heart failure (CHF), a common comorbidity in CKD, was also analyzed. CHF is associated with a poorer prognosis in CKD patients, with a prevalence that increases with CKD severity; approximately 20% in mild CKD (>65 years) to 40% in patients on hemodialysis.

Methods: Safety data were pooled from pivotal phase 3 studies comparing roxadustat to placebo in Stage 3-5 non-dialysis-dependent (NDD) CKD patients, and to epoetin alfa in the overall dialysis-dependent (DD) patients, and subgroup of incident-dialysis (ID-DD) patients. Patients with baseline (BL) moderate to severe CHF were not enrolled. CHF hospitalization events were a component of the MACE-plus endpoints that were adjudicated by a blinded independent committee, and analyzed by a Cox proportional hazards regression model; these analyses were not powered for individual component endpoints.

Results: In the pooled NDD studies, 4270 patients were analyzed (2386 roxadustat; 1884 placebo). BL CHF history was comparable between roxadustat (13.0%) and placebo (13.6%) arms. Using ITT long-term follow-up, the HR (95% CI) of hospitalization for CHF among the NDD pooled population was 0.89 (0.72, 1.12) for roxadustat vs placebo. In the pooled DD studies, 3880 patients were analyzed (1940 roxadustat; 1940 epoetin alfa). BL CHF history was comparable between roxadustat (25.7%) and epoetin alfa

(25.3%) arms, and in the incident dialysis (ID-DD) subgroup (≤4 months of dialysis at BL, n=1526) of 26.4 vs 27.0%, respectively. Using on-treatment analysis comparing roxadustat with epoetin alfa in the DD studies, the HR (95% CI) of hospitalized CHF was 0.73 (0.58, 0.94; p=0.013). In the ID-DD subgroup, the HR (95%CI) was 0.77 (0.42, 1.40).

Conclusions: Roxadustat showed a 27% reduction in risk for CHF hospitalization compared to epoetin alfa in the DD population, and a trend based on the point estimates toward reduction of risk compared to placebo in NDD, and to epoetin alfa in ID-DD patients.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

SA-OR40

Effect of Apabetalone on Major Adverse Cardiovascular Events in Patients with CKD, Diabetes, and Recent Acute Coronary Syndrome: Results from the BETonMACE Trial

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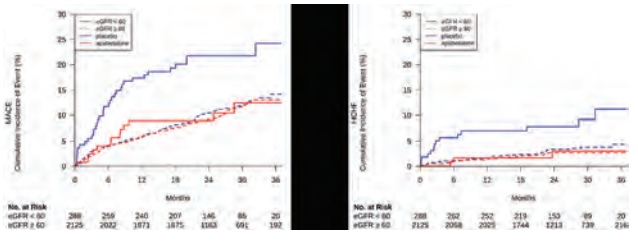
Background: Chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) patients (pts) is associated with increased cardiovascular disease (CVD) and heart failure risk. We hypothesized that a maladaptive epigenetic response engaging the bromodomain and extraterminal (BET) protein transcription system contributes to excess CVD risk. Hence, the efficacy of BET inhibition (BETi) treatment with apabetalone (APB) was assessed according to presence of CKD in the phase 3 BETonMACE trial.

Methods: BETonMACE compared APB with placebo in 2425 pts with T2DM and recent acute coronary syndrome. The primary outcome was CV death, non-fatal myocardial infarct or stroke (MACE). Hospitalization for congestive heart failure (HCHF) was a secondary endpoint. Both outcomes were evaluated according to the presence of CKD (estimated GFR <60 mL/min/1.73 m2 at baseline).

Results: CKD pts were older (71 vs. 61 years), more likely female (42% vs. 23%) or non-white (18% vs. 12%), had longer duration of diabetes (mean 11.3 vs. 8.2 years) and higher serum alkaline phosphatase (91 vs. 81 U/L), and were less likely to receive metformin (69% vs. 84%) or SGLT2 inhibitors (6% vs. 13%) (P<0.05 for all). Under placebo, risk of endpoints was higher in CKD vs. non-CKD pts [MACE: 35/164 (21.3%) vs.114/1041 (11.0%), HR=2.40, 95% CI [1.67, 3.44]; HCHF: 14/164 (8.5%) vs. 34/1041 (3.3%), HR=3.19, 95% CI [1.66,6.12]; P<0.001 for both). Under APB treatment, pts with CKD had significant reductions in MACE (HR=0.50, 95% CI [0.26, 0.96], P=0.034) and HCHF (HR=0.26, 95% CI [0.07,0.94], P=0.028) vs. placebo, see Kaplan-Meier figures.

Conclusions: CKD patients with T2DM and recent acute coronary syndrome have a high risk of MACE that was substantially reduced with APB BETi in the phase 3 BETonMACE trial.



SA-OR41

Racial-Ethnic and Socioeconomic Disparities in Healthcare Utilization Among Children with Glomerular Disease in the CureGN Project

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Background: Inpatient charges for nephrotic syndrome differ across racial-ethnic groups. This study compares rates of ACU (acute care utilization i.e., hospitalization or ED visit) across racial-ethnic groups in children with glomerular disease (GD) and explores demographic, socioeconomic (SE), and disease-related factors that might explain any observed differences.

Methods: CureGN is a multinational prospective cohort study of prevalent patients with GD. We compared patient and disease characteristics at enrollment and rates of ACU during follow-up across racial-ethnic groups. We used multivariable recurrent event proportional rate models to determine rate ratios of ACU, serially adjusting for potential confounders.

Results: In 785 children with GD (median age 11.3 yrs, 58% male, 66% White, 88% residing in US, 51% privately insured, median urine protein/creatinine 0.4g/g, 34% with edema, 39% receiving steroids, 48% receiving other immunosuppression), with a median follow-up of 2.4 yrs, the ACU rate was significantly higher in Black, lower in Asian, and similar in Hispanic, vs. White children (0.85, 0.22, 0.55, and 0.56 events per patient yr, respectively, p<0.001). After multivariable adjustment, poorer SE status and more severe disease explained the excess events observed in Black Children, while an independent association between Asian race-ethnicity and lower rate of ACU was maintained (adjusted RR 0.42, 95% CI 0.25 - 0.72), Table.

Conclusions: The higher rate of ACU observed in Black children with GD enrolled in CureGN was largely explained by poorer SES and more severe disease. Strategies to prevent socioeconomic consequences of GD, or more effectively treat GD, among Black children with GD might begin to target ACU disparities.

Table: Unadjusted and serially adjusted associations between race-ethnicity and rate of hospitalization or ER visit in children with glomerular disease enrolled in CureGN

	Model 1		Model 2		Model 3		Model 4		Model 5	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Race/Ethnicity		<0.001		<0.001		<0.001		<0.001		0.009
Black vs White	1.42 (1.22, 1.66)	<0.001	1.49 (1.28, 1.75)	<0.001	1.30 (1.10, 1.53)	0.002	1.09 (0.91, 1.29)	0.346	1.10 (0.90, 1.34)	0.360
Asian vs White	0.35 (0.22, 0.56)	<0.001	0.34 (0.21, 0.54)	<0.001	0.35 (0.22, 0.57)	<0.001	0.34 (0.21, 0.54)	<0.001	0.42 (0.25,0.72)	0.002
Hispanic vs White	0.88 (0.78, 1.24)	0.895	0.94 (0.75, 1.19)	0.621	0.81 (0.63, 1.02)	0.077	0.79 (0.62, 1.00)	0.054	0.88 (0.74, 1.30)	0.912
Age at enrollment			0.45 (0.39, 0.52)	<0.001	0.52 (0.45, 0.60)	<0.001	0.63 (0.54, 0.74)	<0.001	0.71 (0.59, 0.86)	<0.001
Country						0.037		<0.001		0.001
Canada vs USA					0.80 (0.50, 1.27)	0.343	0.82 (0.52, 1.31)	0.419	1.26 (0.77, 2.05)	0.360
Italy vs USA					1.26 (1.03, 1.53)	0.022	1.46 (1.19, 1.79)	<0.001	1.54 (1.22, 1.94)	<0.001
Insurance Status at enrollment						<0.001		<0.001		<0.001
Public vs Private					2.11 (1.79, 2.49)	<0.001	1.93 (1.63, 2.28)	<0.001	1.69 (1.39, 2.06)	<0.001
Other vs Private					2.30 (1.64, 3.23)	<0.001	2.14 (1.52, 3.01)	<0.001	1.36 (0.81, 2.28)	0.238
None vs Private					3.90 (2.35, 6.47)	<0.001	3.48 (2.08, 5.82)	<0.001	2.64 (1.26, 5.52)	0.010
Hypertension Status at enrollment								<0.001		0.1356
Pre-Hypertension vs Normal							1.22 (1.00, 1.49)	0.046	1.09 (0.87, 1.36)	0.595
Hypertensive vs Normal							1.48 (1.27, 1.74)	<0.001	1.20 (0.10, 1.44)	0.052
Disease Group								<0.001		0.009
FSGS vs IgA							1.86 (1.53, 2.27)	<0.001	1.43 (1.14, 1.80)	0.002
MCD vs IgA							1.60 (1.33, 1.93)	<0.001	1.29 (1.04, 1.61)	0.019
MN vs IgA							1.09 (0.75, 1.56)	0.657	0.93 (0.68, 1.45)	0.965
UPCR at enrollment (per 1g/g increase)									1.01 (1.00, 1.02)	0.027
eGFR at enrollment (per 1mL/min/1.73m² increase)									0.997 (0.995,0.999)	0.003
Serum Albumin at enrollment (per 1 g/dL increase)									0.72 (0.66, 0.78)	<0.001
On immunosuppression at enrollment									1.22 (1.04, 1.43)	0.017

Modeling used Cox proportional hazards regression to run proportional rates models with model selection done using backwards selection. Covariates tested for inclusion in models as follows: Model 1, race; Model 2, other demographics (sex, age) added; Model 3, socioeconomic variables (country, insurance status, family history of kidney disease, parent's education status) added; model 4, general health indicators (hypertension status as defined by blood pressure measurement at enrollment, weight status as defined by BMI group at enrollment, disease diagnosis, disease duration) added; model 5, disease severity (edema, UPCR, eGFR, serum albumin, steroid use, other immunosuppressant use) added.

SA-OR42

Prevalence of Left Ventricular Hypertrophy in Pediatric Patients on Maintenance Dialysis and After Kidney Transplantation: A NAPRTCS Study

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Background: Left ventricular hypertrophy (LVH) is recognized as the most common cardiovascular complication in children on maintenance dialysis. There have been small single-center, or cross-sectional multi-center studies but there has been no large multi-center studies looking at prevalence of LVH during long-term maintenance dialysis. Using the NAPRTCS database, we determined the prevalence of LVH at time of initiation of maintenance dialysis and changes during long-term dialysis and post kidney transplantation. We also assessed the risk factors associated with LVH in children initiating maintenance dialysis.

Methods: Echocardiographic data were obtained from the NAPRTCS database which initiated collection of echo data in 2013 with the last data obtained in March 2020. LVH was defined as left ventricular mass index (LVMI, height-indexed) >95th percentile for age and sex. Patients with cardiovascular diagnoses, those younger than 1 year old at the time of echocardiography, LVMI values >200 g/m$^{2.7}$, and LVMI values based on outlying heights were excluded from analysis. Multivariable logistic regression to assess risk factors for LVH at baseline (within first 3 months after initiation of dialysis) was performed.

Results: The study cohort included 606 patients between 1 and 18 years of age (median 10y (IQR 3.8-15.1), 53% females, 48% whites, 27% African-American, and 25% others/unknown) who had LVH data during time on dialysis. Of 182 patients who had echocardiography within first 3 months after initiation of dialysis (baseline), 67% had LVH. In logistic regression, hypertension (OR 2.9, 95% CI 1.4-6.3), anemia

(OR 2.8, 95% CI 1.3-6.2), and higher serum phosphorus level (OR 2.4, 95% CI 1.1-5.1) were significantly associated with the presence of LVH at baseline, while adjusting for age, race, and sex. Prevalence of LVH remained about 40-50% during long-term dialysis, with no improvement in LVH seen in patients within 6 months (47%) as well as 12 months post-transplant (43.5%), Table 1.

Conclusions: LVH remains very prevalent, difficult to control in chronically dialyzed children, and persistent after kidney transplantation.

Table 1: Percent with LVH by dialysis and transplant visit

	Baseline (0-3mo.)	6 months	12 months	18 months	24 months	Any Time Post-Dialysis	Post Transplant (<6 months)	Post Transplant (12 ± 3 months)
N	182	183	169	106	83	606	49	46
% with LVH (95% CI)	67 (59.9,73.4)	51.9 (44.7,59)	41.4 (34.3,49)	35.8 (27.4,45.3)	45.8 (35.5,56.4	56.4 (52.5,60.3)	46.9 (33.7,60.6)	43.5 (30.2, 57.8)

SA-OR43

Biomarker Panels for Discriminating Risk of CKD Progression in Children

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Background: We used multivariate survival trees to identify plasma and clinical biomarkers to predict CKD progression in children.

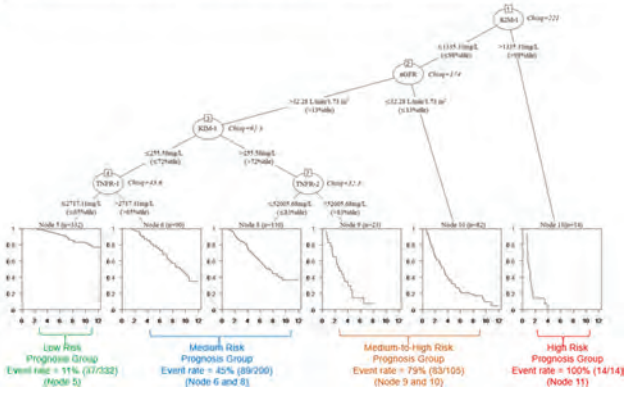
Methods: The CKiD study prospectively enrolled children aged 6 months to 16 years old with an eGFR of 30-90 and eGFR was assessed annually. The primary outcome of CKD progression was a composite of 50% decline in eGFR or incident ESKD. We used multivariate survival trees to determine combinations of baseline clinical predictors and plasma biomarkers as well as identify optimal thresholds for predicting the time to the composite event.

Results: Of the 651 children included, median age was 11 years [IQR,8-15], 405(62%) were male, 195(30%) had a glomerular cause of CKD, and baseline eGFR was 53 [IQR,40-67]. 223(34%) out of 651 children reached the primary outcome over a median follow-up time of 5.7 years. The Figure shows the best-sized multivariate survival tree and 4 prognosis groups selected after bootstrapping the sample. Plasma KIM1, TNFR1, TNFR2, and baseline eGFR were used to define branching patterns, while MCP1, YKL40, suPAR and the known risk factors of sex, age, glomerular diagnosis, BMI, hypertension, and proteinuria were not included as they did not reach a level of predictive importance. In the final model, KIM1 was the variable with the highest importance, with a level of 1335 mg/L(98th percentile) determining the first branching split and identifying the highest risk group of 14 children with predominantly glomerular types of kidney disease and nephrotic range proteinuria. When the tree-based prognosis classification was added to the clinical risk factors, the C-statistic increased from 0.81[95%CI:0.78-0.84] to 0.85[95%CI:0.83-0.88].

Conclusions: Using multivariate survival trees we identified a biomarker panel of plasma KIM1, TNFR1, TNFR2 and baseline eGFR which improved discrimination for CKD progression.

Funding: NIDDK Support

Figure. The best-sized multivariate survival tree and corresponding survival curves to predict CKD progression in children



SA-OR44

Puberty Is Associated with Decline in Estimated Glomerular Filtration Rate in Children with CKD

Hannah Kim,[1] Derek Ng,[1] Matthew Matheson,[1] Meredith A. Atkinson,[1] Yasmin Akhtar,[1] Bradley A. Warady,[2] Susan L. Furth,[3] Rebecca Ruebner.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Children's Mercy Hospitals and Clinics, Kansas City, MO; [3]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Puberty is a high-risk period for decline in kidney function among children with CKD. We aimed to describe changes in eGFR before and after pubertal onset using different objective markers of puberty among children with CKD.

Methods: We conducted a prospective cohort study using data from the Chronic Kidney Disease in Children (CKiD) study. Children who had onset of CKD after pubertal onset were excluded. GFR was estimated annually using the bedside and complete CKiD equations. Pubertal onset was defined by three separate definitions: transition to Tanner Stage 2, peak growth velocity, and menarche. A mixed effects model with random intercept and random slope was used to compare the slope of eGFR before and after pubertal onset. The model was adjusted for age, race, glomerular diagnosis, baseline proteinuria, and BMI.

Results: 339 girls and 552 boys were included; Median age of pubertal onset for girls was 11.0 years (IQR 9.8, 12.1), 14.1 years (IQR 12.4, 17.0), and 14.4 years (IQR 13.1, 15.7) as defined by Tanner stage 2, peak growth velocity, and menarche, respectively. Median age of pubertal onset for boys was 12.4 years (11.3, 13.3) and 14.6 years (IQR 13.4, 16.6) as defined by Tanner stage 2 and peak growth velocity, respectively. Annual percent change in eGFR declined faster among girls and boys after pubertal onset when defined by all measures, after adjustment. For example, annual percent decrease in eGFR was seen to increase from 2.6% prior to 9.0% after Tanner stage 2 in boys using the complete CKiD equation (p<0.001).

Conclusions: Estimated GFR declined faster after the onset of puberty among girls and boys with CKD. Clinicians should be aware that puberty may be an important time of kidney function decline among children with CKD.

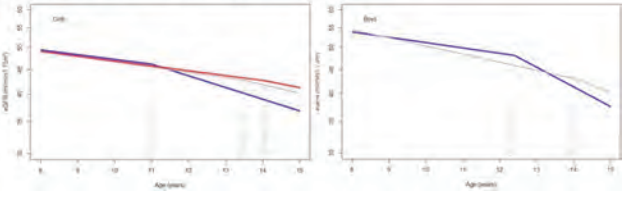
Funding: NIDDK Support

Table 1. Mixed effects model of association between pubertal onset and change in eGFR

	% change in eGFR per year Tanner Stage 2			% change in eGFR per year Peak Growth Velocity			% change in eGFR per year Menarche		
	Pre	Post	p-value	Pre	Post	p-value	Pre	Post	p-value
Girls (n=339)									
Bedside CKiD**	-3.3%	-7.6%	<0.001	-4.2%	-6.7%	<0.001	-2.9%	-10.5%	<0.001
CKiD Creatinine-Cystatin C	-2.2%	-5.5%	0.003	-2.5%	-4.1%	<0.001	-2.3%	-3.5%	<0.001
Boys (n=552)									
Bedside CKiD**	-3.8%	-9.4%	<0.001	-5.2%	-9.9%	<0.001			
CKiD Creatinine-Cystatin C	-2.6%	-9.0%	<0.001	-3.9%	-6.7%	<0.001			

*Adjusted for age, race, BMI, glomerular disease diagnosis, and baseline proteinuria
** For those 18 years or older, the average of the CKiD bedside and CKD-epi equation was used to estimate GFR

Figure 1. Change in eGFR Before and After Pubertal Onset



SA-OR45

CLVS1 H310Y Is a Novel Cause of Familial Childhood Steroid-Sensitive Nephrotic Syndrome

Brandon M. Lane,[1,2] Megan Chryst-Stangl,[2] Guanghong Wu,[2] Mohamed A. Shalaby,[3] Sherif M. El desoky,[3] Jameela A. Kari,[3] Rasheed A. Gbadegesin.[1,2] *[1]Department of Pediatrics, Duke University School of Medicine, Durham, NC; [2]Duke Molecular Physiology Institute, Durham, NC; [3]King Abdulaziz University Hospital, Jeddah, Saudi Arabia.*

Background: Nephrotic syndrome (NS) is the most common glomerular disease seen in children. It is estimated that up to 30% of steroid resistant NS (SRNS) may be due to mutations in one of sixty genes reported in cohort of patients with familial or idiopathic SRNS. However, the genetic causes of the more common steroid sensitive NS (SSNS) and the molecular basis for variability in glucocorticoid response have remained elusive. Our overarching hypothesis is that single gene causes of SSNS can be identified in cohorts of sibling pairs with SSNS and identification of such genes can provide insight into the molecular basis of glucocorticoid response.

Methods: To identify single gene causes of SSNS in a cohort of patients with familial SSNS and examine the molecular basis of glucocorticoid response, we carried out whole genome sequencing in forty families with hereditary SSNS. After identifying a potential disease-causing variant, we examined the effects of loss of gene function in cultured human podocytes through the creation of lentiviral shRNA knockdown and CRISPR-Cas9 knockout cell lines as well as morpholino-based gene knockdown in zebrafish.

Results: We identified a rare homozygous variant, *CLVS1 H310Y*, that segregates with disease in a consanguineous family with two affected siblings and a cousin. *CLVS1* encodes clavesin1, a component of clatherin mediated endocytosis. This variant was not present in a homozygous state in >200,000 chromosomes and is predicted to be pathogenic by *in silico* analyses. Morpholino knockdown of the orthologous *CLVS1* gene in zebrafish resulted in edema phenotypes indicative of loss of glomerular filtration barrier (GFB) integrity. This edema phenotype could be rescued with wildtype human *CLVS1* mRNA but not the *H310Y* variant. Knockdown of *CLVS1* in cultured human podocytes as well as overexpression of the *H310Y* variant in HEK 293 cells decreased endocytosis of fluorescently labeled dextran and increased susceptibility to apoptosis. These aberrant podocyte phenotypes could be rescued in the presence of glucocorticoid, mimicking the steroid responsive phenotype in patients bearing the *CLVS1 H310Y* variant.

Conclusions: We identified a mutation in *CLVS1* as a new cause of hereditary SSNS. Our data demonstrates the requirement of functional *CLVS1* in the maintenance of podocyte viability and GFB integrity.

Funding: NIDDK Support, Private Foundation Support

SA-OR46

Cross-Talk Between Neutrophils and Macrophages Dictates the Outcome of Acute Pyelonephritis

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Background: Pediatric urinary tract infections (UTI) account for 1.5 million clinician visits annually in the United States. Uropathogenic *Escherichia coli* (UPEC) causes over 80% of UTIs. Up to 50% of infants with a UTI develop a kidney infection (acute pyelonephritis, APN). Despite prompt diagnosis and treatment with appropriate antibiotics, a population of children with APN develops renal scarring, which can lead to kidney injury and renal dysfunction. The cellular immune mechanisms underlying renal scarring after an APN episode remain incompletely understood. In this study, we determined the contribution of neutrophils and monocytes to the development of kidney pathology following experimental APN.

Methods: C3H/HeOuJ female mice were treated with monoclonal antibodies to deplete neutrophils (anti-Ly6G), monocytes (anti-CD115), or both neutrophils and monocytes (anti-Gr1). After cell depletion, the animals were transurethrally infected with UPEC strain CFT073. Bacterial ascent was assessed via biophotonic imaging and quantification of bacterial burden in the kidney. The cell dynamics of monocytes and neutrophils were determined by flow cytometry and immunofluorescence microscopy. Renal inflammation and fibrosis were assessed by H&E and Sirius-Red, respectively. Transcriptomic analyses of infected kidneys were performed using TaqMan Arrays.

Results: Our data indicate that neutrophils, not monocytes, are required to prevent widespread UPEC dissemination during APN. In contrast, monocyte-derived macrophages promote bacterial dissemination and induce an early inflammatory response upon UPEC infection. Exacerbated, macrophage-dependent inflammation during APN leads to increased renal abscess formation, tubular injury, renal fibrosis, and azotemia.

Conclusions: While highlighting the essential antimicrobial role for neutrophils, our findings point to a novel detrimental function for macrophages during APN, and the potential utility of macrophage targeted therapies to reduce long-term sequelae following APN.

Funding: NIDDK Support, Other NIH Support - NIDCD

SA-OR47

Proliferation Control of Interstitial Cells in the Neonatal Kidney

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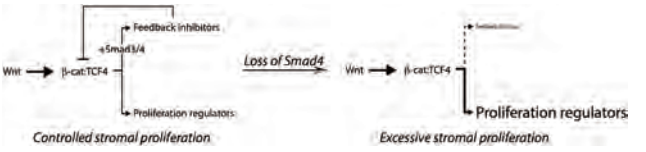
Background: Expansion of interstitial cells in the adult kidney is a hallmark of chronic disease, whereas their proliferation during fetal development is necessary for organ formation. An intriguing difference between adult and neonatal kidneys is that the neonatal kidney has the capacity to control interstitial cell proliferation when the target number has been reached. In this study, we define the consequences of inactivating the TGFb/Smad response on proliferation control of the renal interstitium in the neonatal mouse.

Methods: Smad4 was inactivated using the Foxd1cre mouse strain, which is specifically expressed in interstitial progenitor cells in the developing kidney. Loss of Smad4 in interstitial cells was confirmed by single cell genotyping and immunostaining. Interstitial cell lines with tamoxifen-inducible loss of Smad4 were generated from primary interstitial cells for molecular interaction studies.

Results: We find that loss of *Smad4* leads to over-proliferation of interstitial cells regionally in the kidney medulla. Analysis of signaling pathway markers in tissue showed that activation of Smad3 is deficient, whereas activation of Smad1/5 is largely unaffected, indicating an effect specifically on TGFb signaling. Genetic and molecular interaction studies showed that Smad3/4 participates in the Wnt/b-catenin signaling pathway in interstitial cells, which is responsible for promoting their proliferation. Specifically, *Smad4* is required for the expression of the Wnt feedback inhibitor *Apcdd1*.

Conclusions: Based on these findings, we propose a model for interstitial cell proliferation control in which the Wnt/b-catenin proliferative signal is attenuated by TGFb/Smad signaling to ensure that proliferation ceases when the target number of interstitial cells has been reached in the neonatal medulla.

Funding: NIDDK Support



Model for proliferation control of medullary interstitial cells

SA-OR48

Single-Cell Resolution Regulatory Landscape of the Kidney Highlights Cellular Differentiation Programs and Renal Disease Targets

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Background: The kidney cells undergo complex differentiation during development, among which the nephron progenitors differentiate to more than 10 different epithelial cells. However, the driver pathways, cell type specific transcription factors and regulatory circuits are not fully understood.

Methods: Here we conducted single-nucleus ATAC sequencing (snATAC-seq) and single cell RNA-sequencing (scRNA-seq) of kidneys from developing and adult mice. After quality control, we obtained 66,254 scRNA-seq and 28,316 snATAC-seq profiles.

Results: Through clustering analysis, we identified all major cell types in the kidney. By integrating snATAC-seq and scRNA-seq data, we revealed cell type- and developmental stage-specific cis-regulatory elements and inferred promoter-enhancer regulatory units. We defined key cell identity TFs and their gene targets through co-expression patterns. To study cell-type specification of renal epithelial cells, we conducted trajectory analysis and resolved the developmental pseudotime along cell differentiation from nephron progenitors. We show that early differentiation of podocytes from the nephron progenitor pool is associated with sustained *Foxl1* expression. Differentiation of renal tubule cells followed a more complex pattern, where *Hfn4a* expression is associated with a more proximal fate, while *Tfap2b* is coupled to the distal tubule differentiation. After cell specification, terminal differentiation was strongly linked to metabolic nuclear receptors such as *Essra* and *Ppara* for proximal tubules and *Esrrb* and *Ppargc1a* in loop of Henle. We also implemented snATAC-seq data to leverage our understanding of human kidney disease development. By overlapping the chromatin landscape with kidney disease GWAS signals, we inferred key cell types for GWAS loci in the proximity of *Shroom3* and *Dab2* genes. Interestingly, we observed that some kidney disease-associated loci, such as those in the vicinity of *Uncx*, are only accessible in the developing kidney cells, indicating a developmental stage regulatory role of genetic variants.

Conclusions: Here we present a comprehensive open chromatin and gene expression landscape for developing mouse kidney and illustrate the use of single-cell multi-omics data to study gene regulatory dynamics and its relationship to complex human disease genetics.

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SA-OR49

Expansion of Human Induced Pluripotent Stem Cell-Derived Ureteric Bud Organoids with Repeated Branching Potential

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Background: The mammalian adult kidney, metanephros, develops by the reciprocal interaction between two embryonic progenitor tissues, metanephric mesenchyme and ureteric bud (UB). UB has epithelial polarity and tubular lumens, consists of two domains, the tip and trunk, and repeats branching morphogenesis. The tip cells produce both new tip and trunk cells that further differentiate into collecting ducts (CDs). Recently, we reported a stepwise protocol to induce human induced pluripotent stem cells (hiPSCs) and embryonic stem cells (hESCs) into UB-like structures through anterior intermediate mesoderm. However, the generation of hiPSC/ESC-derived UB-like tissues that show tubular lumens or sufficient branching has not been achieved.

Methods: We established a novel method to induce hiPSCs to differentiate into induced UB (iUB) organoids. We evaluated our iUB organoids using immunostaining and single cell RNA sequencing analysis.

Results: Our iUB organoids showed RET^+ tip and $CK19^+$ trunk domains, epithelial polarity, tubular lumens and developmental potential to repeat branching morphogenesis. The isolated tip regions from the iUB organoids showed repeated branching to reconstitute the iUB organoids. We also succeeded in establishing *in vitro* monitoring and expansion methods for tip cells that can efficiently reconstitute iUB organoids and differentiate into CD progenitors. In addition, we confirmed that our iUB organoids recapitulate *in vivo* development accompanied by spatiotemporal regulation of the gene network by high-resolution transcriptome analysis using single cell RNA sequencing, which showed the reciprocal expression of UB tip and trunk markers.

Conclusions: Our induction method for iUB organoids will help elucidate the developmental mechanisms of UB branching and develop a selective differentiation method for CD cells, contributing to the creation of disease models for congenital renal abnormalities.

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SA-OR50

Rhesus Macaque Serves as a Model for Human Lateral Branching Nephrogenesis

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Background: Premature infants are at risk for chronic kidney disease later in life due to low nephron endowment. Lateral branching nephrogenesis (LBN), not occurring in the mouse, is a poorly understood but critical period of human nephrogenesis. Here, we analyze third trimester LBN in the rhesus macaque at the molecular and morphological level.

Methods: The morphology of third trimester rhesus kidneys was assessed by immunostaining after tissue clearing. 3D renderings were created using Bitplane Imaris. Single-cell RNA sequencing (scRNA-seq) and single-nucleus RNA sequencing (snRNA-seq) were performed on 4 kidneys from 4 rhesus using cold protease digestion and 10xGenomics platform. Unsupervised analyses using ICGS2 were used to identify distinct cell populations and GO-Elite was used to compare rhesus with human and mouse datasets.

Results: The gestational period of the rhesus lasts 165 days. We determined that cessation of rhesus nephrogenesis occurs between 136- and 138-days gestational age (GA). LBN was observed along the ureteric stalks at 126-138 days GA. We noted rosette-like patterns of ureteric tips and nephron progenitor cells (NPC) in both rhesus and human third trimester archival samples. scRNA-seq was performed on 4 cortically enriched rhesus samples 129-131 days GA revealing 37 transcriptionally distinct cell clusters. C25 was predicted to contain the naïve NPCs and included CITED1, MEOX1, and EYA1. snRNA-seq yielded 5,972 nuclei, corresponding to 29 ICGS2 clusters. We found a single cluster (c26), with a near identical GO-Elite enrichment profile to that the naïve NPC scRNA-seq cluster (c25). snRNA-seq c26 contained many unique markers not found in the matching scRNA-seq c25 (e.g., BMPER, DPP6, KIRREL3). GO-ELITE showed that late-gestation rhesus NPC markers more closely aligned to late-gestation murine NPCs, whereas the 2nd trimester human NPCs more closely aligned to mid-gestation murine NPCs. Novel surface markers predicted in the rhesus include CACNA1E, KIRREL3, and KCNB2.

Conclusions: The rhesus is the first animal model to demonstrate LBN, suggesting that LBN is conserved in old world primates. We identified novel genes upregulated during LBN and surface markers that could be used during cell-sorting. snRNA-seq of naïve NPC nascent transcripts may provide mechanistic insights that would otherwise be missed.

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SU-OR01

Keap1 Gene Edited T Cells Using CRISPR/Cas9 Improve Outcomes from Experimental AKI

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Background: T cells have been demonstrated to modulate responses in ischemic AKI, and *Keap1/Nrf2* pathway regulates T cell functions. We hypothesized that using the gene editing technique CRISPR/Cas9 could set the stage for T cell therapy for human AKI. We therefore edited *Keap1* gene in murine CD4 T cells using CRISPR technology and tested its effects in an ischemic AKI model.

Methods: Primary CD4 T cells isolated from spleen of WT mice were used for *ex vivo* CRISPR/Cas9 mediated *Keap1* editing. Control CD4 T cells were electroporated without sgRNA and Cas9. *Keap1* editing was confirmed by sequencing, qRT PCR of *Nrf2* target genes and immunophenotyping using flow cytometry. *Keap1* edited CD4 T cells were studied under hypoxic or normoxic conditions *in vitro*. For *in vivo* studies, *Keap1* edited or control CD4 T cells were adoptively transferred into T cell deficient nu/nu mice (n=6-8/group). Mice were subjected to bilateral IR surgery, serum creatinine, histology, kidney immune cell trafficking and cytokine production were measured.

Results: *Keap1* editing resulted in significant increase in *Nrf2* targets *Nqo1* (8.5-fold), *Hmox1* (4.4-fold) and *Gclc* (2-fold) mRNA. *Keap1* edited CD4 T cells displayed higher expression of *Hif1a* mRNA than control cells in hypoxic conditions (1.5-fold, p=0.02). *Ifng* mRNA expression was significantly decreased in *Keap1* edited cells compared to control cells under normoxic (0.4-fold, p=0.04) or hypoxic (0.6-fold, p=0.01) conditions. nu/nu mice that received *Keap1* edited CD4 T cells showed significantly reduced SCr (0.55±0.05mg/dl vs 1.14±0.19mg/dl, p=0.05) at 24h compared to mice that received control cells. They also had significantly reduced percentage of necrotic tubules (40±16% vs 63±15%, p=0.055). Kidney *Keap1* edited CD4 T cells had significant reduction in TNFα protein expression (43±9% vs 54±7%, p=0.03) compared to control cells post IRI. Kidney CD4 IFN-γ (p=0.16), CD25 (p=0.16) and CD69 (p=0.46) expression was similar in *Keap1* edited and control cells.

Conclusions: CRISPR/Cas9 mediated *Keap1* editing increases murine CD4 T cell *Nrf2* regulated antioxidant gene expression and modifies responses to *in vitro* hypoxia. Adoptive transfer of *ex-vivo Keap1* edited CD4 T cells ameliorates ischemic AKI in mice. These results are important to set the stage for T cell-based therapy for AKI in humans.

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SU-OR02

Cyclin G1/CDK5-Mediated Dedifferentiation of Proximal Tubular Cells Drives AKI-to-CKD Transition

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Background: Acute kidney injury (AKI) is associated with increased morbidity and mortality in hospitalized patients and predisposes patients to chronic kidney disease (CKD). While kidney cells, particularly proximal tubule cells (PTCs), can undergo dedifferentiation, proliferation, and re-differentiation to facilitate kidney repair after injury, maladaptive repair resulting in prolonged dedifferentiation of PTCs drives fibrosis. We have found that cyclin G1 (CG1), an atypical cyclin, not only promotes G2/M cell cycle arrest, but also regulates dedifferentiation of PTCs. The aim of the current study is to determine if CG1 regulates dedifferentiation through its cyclin dependent kinase, CDK5.

Methods: 1; Aristolochic acid nephropathy (AAN) was induced by administration of three doses of AA in 8 to 12-week-old male wild-type (WT) and CG1 globally knockout mice (CG1KO). 2; Unilateral ureteral obstruction (UUO) was performed and kidneys were harvested on day 9. 3; To determine the interacting partners of CG1, immunoprecipitation (IP) was performed in CG1-overexpressing LLC-PK1 cells treated with AA. 4; To examine the pathological role of CDK5, LLC-PK1 cells or primary PTCs with or without siRNA or pharmacological inhibitors of CDK5 were treated with AA.

Results: CG1 was rapidly upregulated in PTCs in response to kidney injury and remained high in chronic phase following AAN and UUO. Kidney fibrosis and markers of dedifferentiation, such as SOX9, Vimentin, and Snail, were reduced in CG1KO animals following AAN and UUO injuries, compared to WT. IP demonstrated that CG1 binds to p53, mouse double minute 2 homolog (MDM2), and CDK5. Of these, the interaction of CG1 activates CDK5 and translocates the complex into nuclei. Phosphorylation of CDK5 in response to injury was reduced by genetic ablation of CG1. Genetic or pharmacological inhibition of CDK5 preserved E-cadherin in AA-induced cellular injury with reduction of profibrotic markers; however, it showed no additional effect in CG1KO PTCs.

Conclusions: CG1 partnering with CDK5 drives a maladaptive dedifferentiation of PTCs after kidney injury, resulting in increased secretion of profibrotic cytokines and progression of fibrosis. As CG1 is highly expressed in injured PTCs, it represents a potential therapeutic target for prevention of kidney fibrosis.

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SU-OR03

Incorporation of Urine-Derived Stem Cells into Kidney Organoids Derived from Human Induced Pluripotent Stem Cells

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Background: Donor-derived somatic cells or stem cells can be differentiated into renal cell types for disease modeling, drug screening, or therapeutic studies. Modeling of kidney disease with kidney organoids derived from human induced pluripotent stem cells (hiPSCs) has been termed a "kidney in a dish." The recent advances in stem cell-based therapies have shown great promise for the treatment of kidney injuries. To evaluate the therapeutic properties, we studied the incorporation of urine-derived stem cells (USCs) into a kidney organoid model of acute kidney injury. UCSs are viable cells from urine which can be expanded *in vitro* for more than ten passages. There is evidence suggesting that USCs are most likely cultured glomerular parietal epithelial cells.

Methods: For this project, we cultured kidney organoids from fibroblast-derived hiPSCs by the established protocol from Takasato and Little, following optimization. Co-culturing of USCs labeled with a membrane dye and Day 25 kidney organoids revealed that USCs incorporated into the organoids efficiently within two days of the co-culture. For injury models, we established nephrotoxicity in the proximal tubule by adding the nephrotoxic drug Cisplatin (5 μm) at Day 21 of kidney organoid culture.

Results: The kidney organoids derived form IPSCs expressed the kidney cell type markers ECAD (distal tubule), GATA3 (collecting duct), LTL (proximal tubule) and NEPHRIN (Glomeruli) at Day 21. The organoids were then treated with 5 x 10^4 USCs at Day 22 for 48 hours and evaluated for the expression of kidney injury molecule-1 (KIM-1). Immunostaining revealed that KIM-1 expression was significantly reduced in the organoids treated with USCs compared to the organoids without USCs, suggesting a positive therapeutic impact of USCs. We are currently performing RNAseq on three sets of whole kidney organoids (Control, +Cisplatin, +Cisplatin+USC) to provide detailed interrogation of cellular apoptosis and related signaling pathways in these three different sets of organoids.

Conclusions: The ability of USCs to reduce KIM-1 expression in human kidney organoids suggests that further investigation into the therapeutic potential of USC for treatment of acute kidney injury is warranted.

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SU-OR04

Supramolecular Nanofibers Containing Arginine-Glycine-Aspartic Acid (RGD) Boost Therapeutic Efficacy of Extracellular Vesicles in Kidney Repair

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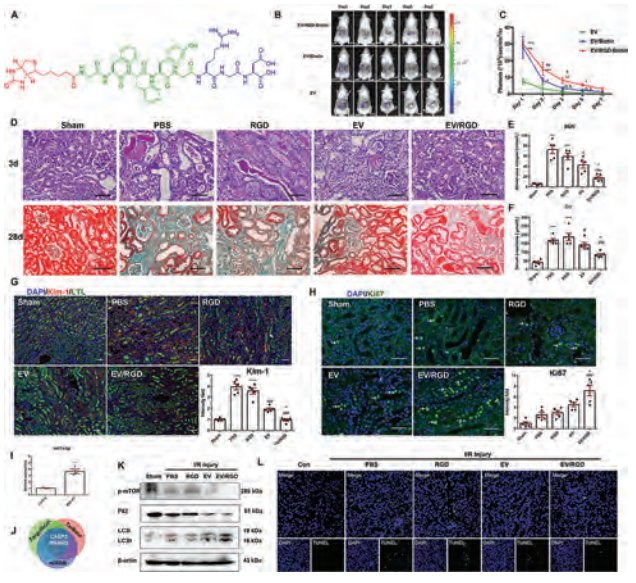
Background: Extracellular vesicles (EVs) derived from mesenchymal stem cells (MSC-EVs) have been recognized as a promising cell-free therapy for acute kidney injury (AKI), which avoids safety concerns associated with direct cell engraftment. However,

low stability and retention of MSC-EVs have limited their therapeutic efficacy. RGD peptide binds strongly to integrins, which have been identified on the surface of MSC-EV membranes, yet RGD has not been applied to EV scaffolds to enhance and prolong bioavailability.

Methods: Here, we developed RGD hydrogels, which we hypothesized could augment MSC-EV efficacy against AKI.

Results: *In vivo* tracking of the EVs revealed that RGD hydrogels increased retention and stability of EVs. Upon intrarenal injection, EV-RGD hydrogels provided superior rescuing effects at functional, histopathological and molecular levels. Further analysis revealed that the presence of microRNA let-7a-5p in MSC-EVs served as a novel mechanism contributing to the reduced cell apoptosis and elevated cell autophagy in AKI.

Conclusions: RGD hydrogels boosted the therapeutic efficacy of let-7a-5p-containing-EVs in AKI repair. This study developed an RGD-scaffold to increase the EV integrin-mediated loading and in-turn improved therapeutic efficacy, therefore this strategy shed light on MSC-EVs application as cell-free treatment for potentiated efficiency.



RGD Hydrogels Boost Therapeutic Efficacy of Extracellular Vesicles in Kidney Repair. (A) The structure of the hydrogels. (B-C) RGD hydrogels enhanced the stability and retention of EVs. (D-H) RGD hydrogels improved the therapeutic efficacy of EVs at functional, histopathological and molecular levels. (I-L) Underlying mechanisms of let-7a-5p-containing-EVs protected against AKI.

SU-OR05

Pannexin 1 Channel Regulates Mitochondrial Function and Cell Survival During AKI

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Background: Pannexin 1 (Panx1) is a membrane associated non-selective channel that, when activated, serves as a conduit for release of small metabolites that have pro- or anti-inflammatory function. We have previously shown that pharmacological inhibition or genetic deletion of *Panx1* in mice prior to injury is protective against renal ischemia-reperfusion injury (IRI). How Panx1 contributes to acute kidney injury (AKI) pathology is unknown. We hypothesized that Panx1 induces cell death by mediating both intracellular and extracellular events.

Methods: We subjected a novel human Panx1 overexpressing mouse (*hPANX1*-Tg) to IRI or cisplatin-mediated AKI and assessed plasma creatinine and renal expression of neutrophil gelatin associated lipocalin (*Ngal*). For *in vitro* studies, *PANX1* overexpressing TKPTS cells (OX) were challenged with cisplatin. Cell death was assessed by flow cytometry using Annexin-V/7AAD. Mitochondrial function was assessed by measuring oxygen consumption rate, mitochondrial membrane potential and ROS production. mRNA expression was measured using real-time PCR.

Results: *hPANX1-Tg* mice had significant rise in plasma creatinine and expression of *Ngal* in the kidneys in both models of AKI compared to their littermate controls. Cisplatin-induced cell death was greater in OX cells compared to control cells. Moreover, cisplatin induced greater death in OX cells than control cells when cultured together. Among genes involved in the cell death pathway, OX cells had reduced expression of *Bcl2* and a greater increase in *Ho-1* after cisplatin exposure. Assessment of mitochondria showed that OX cells had reduced mitochondrial DNA, *Pgc1a* expression, and mitochondrial respiration at baseline, a greater reduction in mitochondrial function and a higher increase in mitochondrial ROS production after cisplatin exposure compared to controls.

Conclusions: Our data demonstrate that PANX1 overexpression results in overt renal injury during AKI that is in part mediated by reduced mitochondrial function and in part by metabolites released via Panx1 channels, which facilitates cell death. These results complement our prior studies demonstrating that Panx1 deficiency protects kidneys from IRI and provide strong rationale for the development of selective strategies to inhibit Panx1 in the prevention or treatment of AKI.

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SU-OR06

Targeting Angiopoietin-Tie2 Signaling in Kidney Ischemia-Reperfusion Injury

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Background: The endothelial angiopoietin (ANG)–Tie2 signaling pathway is required for vascular development and homeostasis. Dysregulation of ang-Tie2 pathway has been implicated in diseases including venous malformation, glaucoma, diabetic nephropathy, and septic acute kidney injury (AKI). The endothelial-specific phosphatase VE-PTP/PTPRB is a negative regulator of Tie2 phosphorylation. Here we investigate the therapeutic roles of Angiopoietin/Tie2 signaling in kidney ischemia-reperfusion injury (IRI).

Methods: A bitransgenic doxycycline-inducible system (Veptp$^{flox/flox}$, Rosa26-rtTA$^{+/+}$, tetO-Cre$^{Tg/+}$) was used to knockout VE-PTP at postnatal day 0 (VE-PTPiKO). Adult male VE-PTPiKO and littermate control mice underwent bilateral IRI or sham surgery. Serum creatinine was measured on day1, day3 and day7 after surgery by HPLC method. Data were analyzed using two-way ANOVA. Tissues were harvested on day 7 for histology, immunohistochemistry and RNA/protein analysis. Bulk RNAseq was performed with RNA extracted from whole kidney 5 hours after IRI. Normalization and differential expression were determined using DESeq2. For pharmacological studies, adult male C57BL/6J mice were used. A new soluble ANGPT1 mimetic (C4BP-ANG1) or vehicle were administered by intraperitoneal injection.

Results: Western blot analysis showed VE-PTP protein levels were increased in kidneys post-IRI and following hypoxia-inducible factor stabilization. Genetic deletion of VE-PTP rescued declined Tie2 phosphorylation in kidney after IRI. While serum Creatinine was elevated 1day post-IRI in control mice, this increase was minimal in VE-PTP iKO mice (p=0.0055). Global gene expression analysis indicated minimal kidney transcriptome change at base line whereas in the setting of IRI, VEPTPiKO mice showed a less activated renal endothelium and downregulation of acute stress response gene signature. A corresponding decrease in pro-fibrotic genes was observed in VE-PTPiKO mice on day7. In the pharmacological study, systemic administration of C4BP-ANG1 activated Tie2 and its downstream AKT/eNOS/NO pathways in mouse kidney in physiological condition. Ongoing studies are analyzing its protective effect in ischemic AKI.

Conclusions: Our data provide evidence for augmenting Tie2 activation-induced vascular protection as a promising therapeutic strategy for renal protection following IR-AKI.

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SU-OR07

Exosome-Based Delivery of Super-Repressor IκBα Ameliorates Kidney Ischemia-Reperfusion Injury

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Background: Ischemia-reperfusion (IR) injury (IRI) is a major cause of acute kidney injury (AKI). Recent studies on the pathophysiology of IR-induced AKI showed that immunologic responses significantly affect renal IRI and repair. Nuclear factor (NF)-κB signaling, which controls cytokine production and cell survival, is significantly involved in IR-induced AKI; its inhibition can ameliorate ischemic AKI. We assessed whether the systemic delivery of the NF-κB inhibitor using exosomes could alleviate the course of ischemic AKI.

Methods: Using EXPLOR, a novel, optogenetically engineered exosome technology, we successfully delivered the exosomal super-repressor inhibitor of NF-κB (Exo-srIκB) into B6 wildtype mice before/after kidney IR surgery, and compared outcomes with those of the control exosome (Exo-Naïve)-injected group. To better understand the protective mechanism of Exo-srIκB in renal IRI, the expression of pro-inflammatory cytokines/chemokines and adhesion molecules and the level of apoptosis were measured using quantitative real-time PCR (qRT-PCR), enzyme-linked immunosorbent assay, western blot, and immunohistochemical/immunofluorescent (IF) staining. Immune cell populations of post-ischemic kidneys and spleens were analyzed using flow cytometry and IF staining.

Results: Exo-srIκB treatment resulted in lower levels of serum blood urea nitrogen (BUN), creatinine, and neutrophil gelatinase-associated lipocalin (NGAL) in post-ischemic mice than in the Exo-Naïve treatment group (24-h/48-h BUN, creatinine, and NGAL, $P < 0.001$). Systemic delivery of Exo-srIκB decreased NF-κB activity in post-ischemic kidneys, leading to reduced apoptosis levels. Post-ischemic kidneys showed decreased gene expression of pro-inflammatory cytokines and adhesion molecules with

Exo-srIκB treatment as compared with the control. Exo-srIκB treatment also significantly affected post-ischemic renal immune cell populations, lowering neutrophil, monocyte/macrophage, and T cell frequencies than those in the control.

Conclusions: Thus, the modulation of NF-κB signaling through exosomal delivery can be used as a novel therapeutic method for IR-induced AKI.

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SU-OR08

Enhancer and Super-Enhancer Dynamics in Repair After Ischemic AKI

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Background: The endogenous repair process of the mammalian kidney allows rapid recovery after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. There is currently limited understanding of which transcriptional regulators activate these repair programs. Here we investigate the existence of enhancer and transcription factor dynamics in the regenerating mouse kidney.

Methods: RNA-seq and ChIP-seq (H3K27ac, H3K4m3, BRD4, BRD2, BRD3, Pol II, HNF4A, GR, STAT3 and STAT5) were performed on samples from repairing kidney cortex 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Furthermore we investigated the role of enhancer dynamics in kidney repair through pharmacological BET inhibition using the small molecule JQ1 in AKI models in vivo.

Results: Response to injury leads to genome-wide alteration in enhancer repertoire *in*-vivo. We identified 16,781 enhancer and 380 super-enhancer sites (H3K27ac and BRD4 positive) with dynamic binding in SHAM and IRI samples; 6,512 enhancer, 164 super-enhancer lost and 9,774 enhancer, 214 super-enhancer gained after IRI. The lost and gained enhancer sites can be annotated to 62% and 63% of down- and up-regulated transcripts after AKI, respectively. ChIP-seq profiles of predicted transcription factors show specific binding at corresponding enhancer sites with dynamic binding of HNF4A, GR and STAT3. HNF4A and GR show a reduced binding at enhancer and super-enhancer sites after injury, whereas STAT3 binding can be observed at injury gained enhancer and super-enhancer sites. BET (BRD4) inhibition before IRI leads to suppression of 40% of injury-induced transcripts associated with cell cycle regulation, genome-wide Pol II pausing and significantly increased mortality after AKI.

Conclusions: This is the first demonstration of enhancer and super-enhancer and transcription factor binding dynamics in the repairing kidney. In addition, our data call attention to potential caveats for use of BET inhibitors that are currently being tested in clinical trials. Understanding of enhancer dynamics after kidney injury in vivo has the potential to lead to indentification of new targets for therapeutic intervention.

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SU-OR09

Developmental Reprograming of Kidney Resident Macrophages During Human AKI and Its Implications to CKD

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Background: Kidney tissue-resident macrophages (KRM) promote naturally progressing or AKI-induced cystic renal disease in mice. AKI also reprograms KRM into an early development state in mice. The relevance of KRM to human AKI and chronic kidney disease (CKD) remains mostly elusive.

Methods: We characterized KRM expression in renal biopsies and urine sediment from patients with AKI and non-AKI controls using a 255 gene Nanostring Inflammation panel. We mapped differentially expressed genes to single-cell RNA sequencing (scRNAseq) data from the Mouse Cell Atlas. We identified candidate injury-induced KRM markers and supported their validity in several available gene expression AKI- and CKD-relevant datasets (using limma package empirical Bayes smoothing in R).

Results: Both acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) trigger transcriptional changes in similar genes (more prominently in AIN despite higher serum creatinine in ATN). Mapping of these AKI-regulated genes to normal adult kidney single scRNAseq data revealed the best fit for cell clusters defined by transcriptional signatures of KRMs. Such a fit was even stronger when the AKI-regulated genes were mapped to fetal kidney scRNAseq data. A similar fit was obtained by analyses of bulk RNAseq data of urine sediment from patients with AKI. Based on the strength of these associations, we prioritized *C1qa*, *C1qb*, *C3ar1*, *Tlr1*, *Itgb2*, *Ccr7* and *Ifit1* as transcriptional signatures of injury-induced KRMs. We validated the relevance of these candidate markers to the following: renal aging, protective effects of caloric restriction, and drug-induced forms of AKI in mice, pre-cystic kidney milieu in the model of polycystic kidney disease in a rat, and CKD including focal segmental glomerulosclerosis in human patients.

Conclusions: Together, we point to a KRM-like transcriptional response as a hallmark feature of AKI and CKD across species. The better fit of this response to fetal scRNAseq data supports the AKI-induced developmental reprogramming in human kidneys. A similar pattern of these responses in kidney tissues and urine cells points to urine-derived KRM assessment as an alternative to renal biopsies.

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SU-OR10

Endothelial-Derived miR-17~92 Promotes Angiogenesis to Protect Against Renal Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI), resulting from renal ischemia reperfusion injury (IRI) among others, is an independent predictor of morbidity and mortality, and is identified in as many as 50% of ICU patients. Damage to the renal microvasculature is a hallmark of renal IRI. miR-17~92 encodes 6 polycistronic microRNAs that show potent pro-angiogenic capacity by targeting anti-angiogenic factors. The function of miR-17~92 in renal microvasculature after renal IRI remains unknown.

Methods: Antibodies bound to magnetic beads were utilized to selectively enrich for renal endothelial cells from mice. Endothelial-specific miR-17~92 knockout (miR-17~92endo-/-) mice were generated and a renal IRI model was performed. Mice were monitored for the development of AKI using serum chemistries and tissue analysis, and for renal blood flow using a magnetic resonance imaging (MRI). Mice were treated with miRNA mimics during renal IRI to test its therapeutic efficacies.

Results: we demonstrate that miRs-17, -18a, -20a, and -19b are up-regulated in renal endothelial cells after renal IRI in mice. miR-17~92endo-/- exacerbates ischemic AKI in male and female mice. Specifically, miR-17~92endo-/- promotes renal tubular injury, reduces renal blood flow, promotes microvascular rarefaction, increases renal oxidative stress and promotes macrophage infiltration to injured kidneys. The potent anti-angiogenic factor, thrombospondin 1 (TSP1), is highly expressed in renal endothelium in miR-17~92endo-/- after renal IRI and is a target of miR-18a and miR-19a/b. Beyond defining a critical role for miR-17~92 in the angiogenic response after ischemic AKI, we show that co-treatment with a combination of miR-18a and miR-19b mimics is sufficient to mitigate ischemic AKI.

Conclusions: These data suggest that endothelial-derived miR-17~92 stimulates a reparative response in damaged renal vasculature during ischemic AKI by regulating angiogenic pathways.

Funding: NIDDK Support, Private Foundation Support

SU-OR11

Inhibition of Cadherin 11 Improves Outcomes in Murine Models of CKD

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Background: Chronic kidney disease (CKD) represents a massive unmet clinical need, as there are virtually no pharmaceutical options for treatment of renal injury. A recent study identified cadherin-11 (CDH11) as a potential biomarker for CKD, as it is present in kidney biopsies and urine samples of CKD patients and its expression is increased in CKD mouse models. We have investigated the role of CDH11 as both a mediator and therapeutic target of CKD.

Methods: In the current study, we used three mouse models of CKD to evaluate the role of CDH11: aristolochic acid nephropathy, unilateral ureteral obstruction, and uninephrectomy/angiotensin II administration. In each of these models, we inhibited CDH11 genetically using transgenic mice and pharmacologically with the administration of a functional blocking antibody to CDH11.

Results: Although CDH11 has been found on immune cells and fibroblasts in other fibrotic diseases, we found that in the kidney CDH11 is exclusively expressed in injured proximal tubules (PTs). PTs play a significant role in CKD, as they are both a target and mediator of chronic injury. In our models of CKD, we found that both genetic and pharmacologic CDH11 inhibition improves renal function (BUN and ACR), diminishes cytokine production (TGF-β1 and IL-6 expression), and reduces tubular injury (expression of KIM-1 and histological analysis). Using primary PT cells, we found that genetic ablation of CDH11 improves cell survival *in vitro*. Although the specific mechanism by which CDH11 mitigates PT injury is still under investigation, preliminary data shows that inhibition of CDH11 increases Wnt/β-catenin activity in the kidneys of injured mice. Wnt/β-catenin signaling promotes cell survival, which in this context could result in reduced tubular atrophy, cytokine production, and fibrosis. Such pro-survival signaling could be driving the reduction in renal injury we see when CDH11 is inhibited, as PT death strongly correlates with outcomes in CKD.

Conclusions: These results clearly identify CDH11 inhibition as a novel means of improving outcomes in murine CKD models. The mechanism by which CDH11 inhibition mitigates renal injury is likely through CDH11 interactions with the Wnt/β-catenin signaling pathway to enhance PT survival. These results could prove an important step towards developing new therapeutic strategies for the treatment of CKD.

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SU-OR12

METTL10: A Kidney Disease Risk Gene by Altering Protein Methylation

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Background: Genome-wide association studies (GWAS) have identified more than 300 loci where genetic variants are associated with kidney function, however, the causal variants, genes, cell types and the disease mechanism remain mostly unknown.

Methods: We have generated expression of quantitative trait (eQTL) data from microdissected human kidney tubules and glomeruli. We used Bayesian colocalization of eQTL and GWAS to identify likely causal genes for kidney function. We used single cell RNA and ATACseq data to identify causal cell types. Finally, we generated mice with genetic deletion to study kidney disease mechanism.

Results: Kidney disease associated genetic variants showed a strong association with METTL10 expression. Methyltransferase-like protein 10 (METTL10), is a non-histone lysine methyltransferase. Patients with CKD variants showed lower level of METTL10 in their kidneys. METTL10 was relatively broadly expressed in kidney tubule cell by single cell expression analysis. Its expression was markedly reduced in mice and patients with kidney disease. We found that Mettl10 controls methylation and the activity of the eukaryotic translation elongation factor 1 alpha (eEF1A). eEF1A is the alpha subunit of the eukaryotic elongation complex, controlling RNA translation. Methylation of eEF1A was markedly reduced in kidneys of Mettl10 KO mice. The reduction in eEF1A activity lead to lower protein translation and tubule cell proliferation. Mettl10 KO mice was more susceptible to kidney injury, it showed increased structural damage and collagen expression in the folic acid induced kidney injury model.

Conclusions: Taken together, GWAS and eQTL studies identified Mettl10 a kidney disease risk gene. METTL10 controls the methylation of eEF1A, downstream RNA translation, cell proliferation altering kidney disease risk, defining a novel mechanism for kidney disease development.

Funding: NIDDK Support

SU-OR13

Renal Proximal Tubule Cell Differentiation and Metabolism Are Coupled by Nuclear Receptors

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Background: Kidney proximal tubule (PT) cells have high mitochondrial density to perform their highly energy demanding function to secrete and reabsorb metabolites and electrolytes. Chronic kidney disease is characterized by tubule epithelial atrophy and dedifferentiation, resulting in a decline in kidney function. In this study, we aimed to define upstream regulators that control PT differentiation.

Methods: We performed scRNA and snATACseq analysis on kidneys of developing and adult mice, kidney organoids, and kidneys from control and folic acid-induced kidney injury model. Bioinformatic methods included dimension reduction, differential expression, cell fraction and cell trajectory analysis. Functional studies included mice and cultured tubule cells with genetic deletion of ESRRA.

Results: Single cell differential expression analysis identified PT cells as the key vulnerable cell type in kidney fibrosis. Cell trajectory analysis showed a sequential differentiation path from precursor to differentiated PT cell state in development and in healthy adult and diseased kidneys. But this differentiation path showed more complexity in fibrosis, such as enhanced cell proliferation and a blockade of terminal differentiation. Pathway analysis indicated fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) were key variable genes along the PT cell differentiation path in the adult, and developing mouse PT cells and organoids. Single cell epigenetics data identified the critical role of nuclear receptors; HNF4A, HNF1B, PPARA, and ESRRA driving the PT cell differentiation program. These transcription factors did not only directly control FAO and OXPHOS but also the expression of PT differentiation genes. Genetic and pharmacological deletion of these transcription factors lead to marked changes in differentiation state of cultured PT cells. Analysis of healthy and disease human kidneys samples and mice with ESRRA deletion showed a defect in FAO, OXPHOS and PT differentiation and was more susceptible for injury, defining a novel role for ESRRA in PT cells and CKD.

Conclusions: The coupling of cell state and metabolism is established by nuclear receptors such as PPARA and ESRRA that not only control cellular metabolism but also the expression of PT cell-specific genes in mice and patient samples.

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SU-OR14

COX17-Mediated Abnormal Mitochondrial Copper Metabolism Promotes Renal Fibrosis

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Background: Copper is a trace element essential for almost all living organisms. Previously, we found that elevated intracellular copper contributes a unique role to kidney fibrosis. Furthermore, copper ions in cells were mainly accumulated in mitochondria, which damage the structure and function of mitochondria. However, the mechanisms of the accumulation of copper ions in the mitochondria and how a disturbed copper balance induces mitochondrial dysfunction remain to be identified. Copper chaperone COX17, a protein required for cytochrome c oxidase (COX) assembly, was previously hypothesized to shuttle copper between the cytosol and mitochondria based on its dual localization. We found that in the fibrosis model COX17 was highly expressed and COX activity decreased. Therefore, we speculated that COX17 might be involved in mitochondrial copper overload and renal fibrosis.

Methods: Expression level and pattern of COX17 were examined in ischemia-reperfusion injury (IRI) AKI mice. The regulatory mechanisms of COX17 was investigated in renal tubule epithelium cell line (NRK-52E) and rat fibroblast(NRK-49F) by treating with copper or copper chelator tetrathiomolybdate (copper-chelating agent). ICP-MS, mitoSOX, electron microscopy, realtime-PCR and western blot analysis were applied in the current study.

Results: Firstly, the expressions of COX 17, Col1 in the kidney of IRI group were extremely upregulated compared with the sham group. Unexpected, we found dysfunction of mitochondria in IRI kidneys evidenced by it's appearing swollen and ruptured. Secondly, stimulated by TGF-β1, COX activity was declined, and mitochondrial copper content, mitochondrial reactive oxygen species and the expression of cox17, Col1 were significantly upregulated. More importantly, mitochondrial copper content and col1, fibronectin expression were reduced and mitochondrial function was improved after transfecting with COX17 shRNA. Meanwhile, treatment with copper chelator tetrathiomolybdate also alleviated renal fibrosis both in vivo and in vitro.

Conclusions: COX17 was significantly increased in renal fibrosis and transported excessive intracellular copper ions into the mitochondria. Copper overload inhibits the activity of COX and impairs mitochondria, subsequently leading to renal fibrosis.

SU-OR15

Protective Effect of Prostacyclin in Renal Fibrosis

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Background: Inadequate repairing process to injury has been reported to play an important role in renal fibrosis. Mounting evidence suggests that prostaglandins are important in serving as a "buffer" in response to physiological changes or pathophysiologic insults to tissues including the kidney. Importantly, under certain conditions such as aging and hypertension, prostacyclin (PGI_2), an active production of COX/PGI_2 Synthase (PGIS), is reduced. The present study provides data showing that low levels of PGI_2 are associated with enhanced renal fibrosis.

Methods: Unilateral ureteral obstruction (UUO) was used as a renal fibrosis model. At days 10 after UUO, the mice were sacrificed. Ischemia-reperfusion (I/R) model was induced by clamping the left renal pedicle for 35 minutes on D0. After 4 weeks, the right kidney was removed. The mice were treated with beraprost sodium (300μg/kg bodyweight per day by twice daily gavage) or vehicle from D32 to D55, and were sacrificed on D56.

Results: The PGIS heterozygous (PGIS+/-) mice had normal body weight, blood pressure and blood urea nitrogen (BUN) level. Losing one allele of PGIS significantly attenuated the increase of PGIS expression after UUO and aggravated UUO -induced renal fibrosis, showing increased levels of fibronectin, collagen I and α-SMA compared with wild-type littermates. Masson trichrome staining shows more extracellular matrix accumulation in the kidney of $PGIS^{+/-}$ mice after UUO. Endothelial PGIS gene deletion also significantly attenuated the increase of PGIS expression after UUO and aggravated UUO-induced renal fibrosis. I/R model was performed on wild-type mice. Treatment with beraprost sodium (BPS), a analog of PGI2, inhibited the expression of fibronectin, collagen I and α-SMA in the kidney and ameliorated extracellular matrix deposition in the histology study. Furthermore, the level of phosphorylated PKA substrates in the ureteral obstructed kidney of deficient mice was significantly reduced, suggesting the role of IP receptor. IP agonist treatment reduced the expression of fibronectin, collagen I and α-SMA in rat renal fibroblasts (NRK-49F), which were induced by TGF-β.

Conclusions: PGIS/PGI_2 plays an important role in protecting the kidney from fibrosis. Lack of PGIS enhances renal fibrosis, and supplementation with PGI_2 analog ameliorates renal fibrosis. PGIS/PGI_2 is a potential target for CKD.

SU-OR16

Proteomic Risk Assessment of CKD Progression in the Chronic Renal Insufficiency Cohort

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Background: Quantification of thousands of plasma proteins simultaneously is now feasible in large cohorts using the SomaScan aptamer assay. In this study, we applied large-scale proteomics to patients with chronic kidney disease (CKD) to discover new biomarkers and risk models of CKD progression.

Methods: We measured 4638 unique plasma proteins among 3249 participants in the Chronic Renal Insufficiency Cohort(CRIC), with follow-up to 13 years. Mean age was 59 years, mean estimated glomerular filtration rate (eGFR) 42 ml/min/1.73m^2, and 50% were diabetic. The study outcome was 10-year risk of 50% decline in eGFR, end-stage renal disease or renal transplant (n=1171 events). Associations of individual proteins with the composite outcome were analyzed in Cox survival models adjusted for demographics, comorbidities, eGFR and proteinuria. Protein-only risk models were constructed using elastic net regression and compared to the 4-variable Kidney Failure Risk Equation

(KFRE). KFRE variables (age, gender, eGFR and proteinuria) were refit to CRIC. For risk modeling, the cohort was split into 80% derivation/20% validation.

Results: Among the 4638 assayed proteins, after adjustment for eGFR, 1535 proteins were associated with CKD progression at FDR <0.05; 529 were significant at Bonferroni $p<1x10^{-5}$. After full adjustment, 459 proteins met FDR significance and 77 proteins met Bonferroni significance. A 58 protein risk model for 10-year CKD progression derived by elastic net achieved a c-statistic of 0.860 (95% CI: 0.834, 0.885) in the validation set, equal to the refit KFRE c-statistic of 0.857 (95% CI 0.831, 0.884). The c-statistic for the proteomic model was not enhanced by addition of clinical risk factors. Additionally, we were able to identify protein biomarkers that are unique to progression of diabetic vs. non-diabetic CKD.

Conclusions: Through large-scale proteomics, we discovered numerous novel biomarkers that predict the risk of CKD progression. The proteomic risk model has excellent discrimination, equal to the refit clinical model. Ongoing analyses of the biological functions of the newly discovered biomarkers may identify new therapeutic targets to slow CKD progression.

Funding: NIDDK Support

SU-OR17

Molecular Mechanisms Underlying Sex-Specific Association of Circulating Transforming Growth Factor B1 with the Risk of Accelerated Kidney Function Decline

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Background: Study of sex differences in kidney function decline and risk of chronic kidney disease (CKD) is a stated research goal. We recently found serum transforming growth factor β1 (TGF-β1), a key mediator in kidney fibrosis development, to be associated with risk of accelerated age-related loss of glomerular filtration rate (GFR) in women, but not men, in the general population. We therefore investigated the effect of sex on intrarenal TGF-β1 pathway and structural damage in kidney biopsies from a cohort of patients with early kidney impairment.

Methods: Kidney tissue samples from 22 female and 33 male patients undergoing nephrectomy included in the PRECISE study (age 31 to 83 years) were used for transcriptomic analysis of micro-dissected glomeruli (Affymetrix Human Gene 2.1 ST Array). Interaction of the expression of genes in the TGF-β1 signaling pathway with sex was evaluated between expression level and global glomerulosclerosis (GGS), a structural parameter of kidney disease. Genes exhibiting significant interaction with sex were used to generate a sex-dependent TGF-β1 pathway activity score.

Results: Out of the 136 genes downstream of TGF-β1, expression of 20 genes exhibited significant interaction with sex for GGS. BMP6, ID1, MYC, and TNF were among the genes that showed the most significant interaction. An increased activity score for sex-specific TGF-β1 downstream effectors was associated with higher degree of GGS in women (p<0.001), but with less GGS in men (p=0.01, p for interaction with sex <0.001, Figure 1).

Conclusions: Higher levels of the sex-specific TGF-β1 pathway activity was associated with higher GGS in women, but with less GGS in men. These results, along with our findings of an association between higher serum TGF-β1 and accelerated GFR decline in women only, point to a sex-specific TGF-β1 driven mechanism of kidney fibrosis that may shed light on sex differences in age-related GFR loss and CKD.

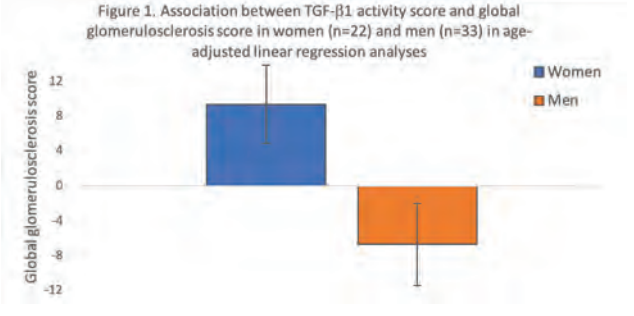

Figure 1

SU-OR18

Defining the Correlation Between Kidney Function and Histopathological Changes

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Background: Estimated glomerular filtration rate (eGFR) is an imperfect measure of kidney function and does not correlate well with prognosis. Histopathologic analysis of renal biopsy is considered the gold standard to establish disease etiology and prognosis. Kidney biopsy, however, is rarely performed in patients with diabetes due its associated risks. Here we examined whether we could predict the degree of histological damage and kidney function decline based on clinical and demographic information.

Methods: Descriptor based histopathological analysis was performed in 759 human kidney tissue samples obtained from unaffected portion of tumor nephrectomies. Samples were limited to healthy, hypertensive and diabetic kidney disease. Changes in the glomeruli, tubules, interstitium and the vasculature were scored in an unbiased manner. Regression analyses were performed to assess the association between histopathology based on eGFR quantiles. Decline in renal function over time (eGFR slope in ml/min/1.73m² per year) was assessed in subjects with at least 3 months of follow up. Validation analysis was performed on 467 clinically indicated kidney biopsies.

Results: Mean subject age was 61, eGFR was 66 ml/min/1.73m², 70% had hypertension and 37% had diabetes. The association between eGFR and interstitial fibrosis was relatively weak (r^2=0.3, p <0.001). There was no association between fibrosis and eGFR greater than 45 ml/min/1.73m2. Samples with eGFR below 45 ml/min/1.73m² showed a reasonably strong association between eGFR and fibrosis (r^2=0.51, p <0.001) indicating a non-linear relationship. Hypertension and black race were independently associated with more severe histopathologic changes (p<0.05). Similar non-linear trends and significant associations were observed in our validation cohort. There was an association between severity of histopathologic findings and kidney function decline which did not reach significance in the primary cohort but was significant in the validation cohort.

Conclusions: The eGFR is a poor predictor of fibrosis at values > 45 ml/min/1.73m² but predicts renal structural changes well at lower eGFR. Hypertension and black race were independently associated with renal fibrosis, which may warrant more aggressive therapy in these cohorts. Predictions of kidney function decline are enhanced when eGFR and histopathology are used in combination.

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SU-OR19

Low Birth Weight for Gestational Age and Risk of Different Groups of Kidney Disease During the First 50 Years of Life

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Background: Previous studies have shown that Low Birth Weight (LBW) is associated with increased risk of end-stage renal disease. Few population based studies have investigated risk of Small for Gestational Age (SGA) on kidney disease. Our study investigates SGA and risk of chronic kidney disease (CKD), other kidney diagnoses as well as different stages of kidney failure.

Methods: The Norwegian Patient Registry (NPR) has registered ICD diagnostic codes for all admissions and outpatient visits to Norwegian hospitals since 2008. The Norwegian Medical Birth Registry (MBR) has registered birth weight, gestational age and several other data on maternal and offspring health for all birth in Norway since 1967. Data from these registries were linked and risk of CKD and other groups of kidney disease were analyzed with logistic regression statistics. Based on birth weight, gestational age and gender, a z-score of birth weight for gestational age has been calculated. SGA defined as birth weight less than the 10th percentile for gestational age and gender with cut-off -1.30 for male and -1.28 for female. LBW (less than the 10th percentile) and preterm birth (less than 37 weeks) were analyzed as risk markers. Adjusted analyses were performed for the main analyses by including birth year, gender, maternal disease, maternal marital status and malformations in the newborn

Results: Of the 2,663,010 included sunjects, 4495 had been diagnosed with CKD and 12,818 with acute kidney disease, glomerulonephritis, hereditary kidney disease or kidney disease due to kidney or urinary tract malformations. SGA was associated with odds ratio (OR) for CKD of 1.79 (1.65-1.94), LBW with an OR of 1.72(1.59-1.86) and preterm birth with an OR of 1.48 (1.32-1.67). There were no significant gender differences. Analyses of CKD stage 3, 4 and 5 showed similar results. An adjusted odds ratio (aOR) for other groups of kidney disease showed that SGA was associated with aOR of 1.60 (1.49-1.73) for acute kidney disease, 1.18 (1.070-1.30) for glomerulonephritis, 1.31 (1.12-1.52) for hereditary kidney disease and 1.13 (1.03-1.23) for kidney disease due to kidney or urinary tract malformations

Conclusions: SGA is a strong risk maker for diagnosis of all stages of CKD during the first 50 years. The risks seem to increase also for other groups of kidney disease.

SU-OR20

Large-Scale Kidney Volumetry from MRI: Initial Results and Relations to Sex, Age, and Body Size in UK Biobank

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Background: Kidney volume has been associated with age, kidney function, diabetes, and other cardiovascular risk factors. Body size, body surface area (BSA) and lean tissue mass are important confounders. UK Biobank (UKB) is a large-scale study aiming to examine 100,000 subjects aged 44 to 82 years using MRI. Resulting images allow measurements of kidney volume. Currently 40,264 scans have been released.

Methods: A deep learning-based method for direct kidney parenchymal volume (KPV) segmentations was developed and validated (Accuracy: Dice 0.956, R^2=0.95) and applied to UKB MRI. Absolute and relative change with age and associations to body weight, BSA and fat free mass from bioimpedance analysis (BIA-FFM) and lean tissue volume from MRI (MRI-LT) were studied using linear regression. Rate changes were compared below and above group mean ages. MRI-LT values (n=8,524) were inferred for 30,308 additional subjects by MRI-based deep learning regression with validated R^2=0.96(arXiv:2002.06862).

Results: Resulting KPVs from 37,468 subjects (47,6% males) and age changes are shown in Fig1a and Table 1. Correlations between total KPV and BSA and MRI-LT over age are shown in Fig1b. The associated overall correlations were (males / females): Body weight: 0.568/0.460, BSA: 0.574/0.496, BIA-FFM: 0.597/0.536, MRI-LT: 0.636/0.600.

Conclusions: Both sexes show continuous volume decline in the studied age interval. Males show an increasing rate of decline with age. MRI-LT showed strongest correlations to KPV.

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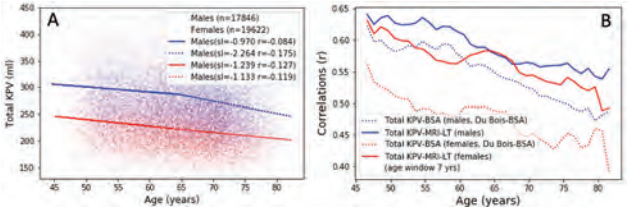
Table 1

	Kidney Volume (ml)		Absolute age change (ml / year)		Relative age change (% / year)	
	Males	Females	Males	Females	Males	Females
Total	281.9±51.4	224.0±39.7	-0.970, -2.264	-1.239, -1.133	-0.397, -0.926	-0.635, -0.580
Left	142.5±29.0	113.5±22.4	-0.478, -1.185	-0.682, -0.607	-0.392, -0.973	-0.699, -0.622
Right	139.2±27.8	110.4±21.6	-0.494, -1.081	-0.555, -0.525	-0.413, -0.903	-0.584, -0.551

Age changes are given as two regression slopes, from below and above the sex-specific mean age.



A) Scatter plot of total KPV and age for males and females including regression lines for subjects below and above respective mean age. An increasing rate of decline is found in males ($p<10^{-15}$) but not in females. B) Correlation between total KPV and BSA and MRI-LT for males and females over age.

SU-OR21

Variation in Peritoneal Dialysis-Related Peritonitis Outcomes and Treatment Practices: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study

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Background: Peritoneal dialysis (PD)-associated peritonitis is a leading cause of technique failure and transition to hemodialysis. In the Optimizing Peritonitis Prevention in The United States (OPPUS) study, we explored the impact of various patient, facility and treatment factors on the likelihood of cure following a peritonitis episode.

Methods: Using Peritoneal Dialysis Outcomes and Practice Patterns Study phase 1 (2014-2017) data from Australia and New Zealand, Canada, Japan, Thailand, the UK, and the US, cure was defined as the absence of a peritonitis relapse or recurrence, PD catheter removal, transition to hemodialysis or death during the 50 days following a peritonitis episode. Multivariable logistic regression was used to test associations between cure and patient, facility, and treatment characteristics.

Results: We identified 1677 peritonitis episodes in 1190 patients across 126 facilities. Overall, 63% of episodes resulted in a cure. Cure was associated with APD (OR v. CAPD=1.35, 95% CI 1.02-1.80), higher serum albumin (OR=1.04 per 0.1 g/dL, 95% CI=1.01, 1.06), facility icodextrin use (OR=1.06 per 10% greater icodextrin use, 95% CI = 1.01-1.12), and aminoglycoside use for Gram-negative peritonitis (OR v. ceftazidime=3.10, 95% CI=1.02, 9.36). Prior peritonitis (OR v. no prior peritonitis episodes during follow-up=0.84, 95% CI=0.74, 0.97) and concomitant exit-site infection (OR= 0.42, 95% CI=0.28, 0.63) were associated with lower cure odds. Higher odds of peritonitis relapse were seen among patients with greater residual urine volume (OR= 1.14 per 200 ml, 95% CI=1.07, 1.22).

Conclusions: Different characteristics and management practices can impact the likelihood of cure following a peritonitis episode. Our findings can inform future guidelines in addressing the effect of different modifiable patient, facility, and treatment factors on reducing morbidity associated with PD peritonitis.

Funding: Other NIH Support - Agency for Healthcare Research and Quality (AHRQ)

SU-OR22

Rate of Decline in Residual Kidney Function Before and After Peritoneal Dialysis Initiation: A Post Hoc Analysis of the IDEAL Study

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Background: Residual kidney function (RKF) is associated with improved survival and quality of life in dialysis patients. Previous studies have suggested that commencement of peritoneal dialysis (PD) may slow RKF decline compared to the pre-dialysis period. We sought to evaluate the association between PD initiation and RKF decline in the Initiating Dialysis Early And Late (IDEAL) trial.

Methods: In this *post hoc* analysis of the IDEAL randomized controlled trial, PD participants were included if results from 24-hour urine collections had been recorded within 30 days of dialysis initiation (-30 to +30 days from start), and at least one value pre- and one value post-dialysis commencement were available. The primary outcome was slope of RKF decline, calculated as mean of urinary creatinine and urea clearances. Secondary outcomes included slope of urine volume decline and time from PD initiation to anuria.

Results: The study included 151 participants (79 early-start group, 72 late-start group). The slope of RKF decline was slower after PD commencement (-2.69±0.18 mL/min/1.73m^2/yr) compared to before PD commencement (-4.09±0.33 mL/min/1.73m^2/yr; change in slope +1.19 mL/min/1.73m^2/yr, 95% CI 0.48-1.90, p<0.001). In contrast, urine volume decline was faster after PD commencement (-0.74±0.05 L/yr) compared to beforehand (-0.57±0.06 L/yr; change in slope -0.18 L/yr, 95%CI -0.34—-0.01, p=0.04). No differences were observed between the early- and late-start groups with respect to RKF decline, urine volume decline or time to anuria.

Conclusions: Commencement of PD was associated with a slower decline of RKF compared to the pre-dialysis period.

Funding: Government Support - Non-U.S.

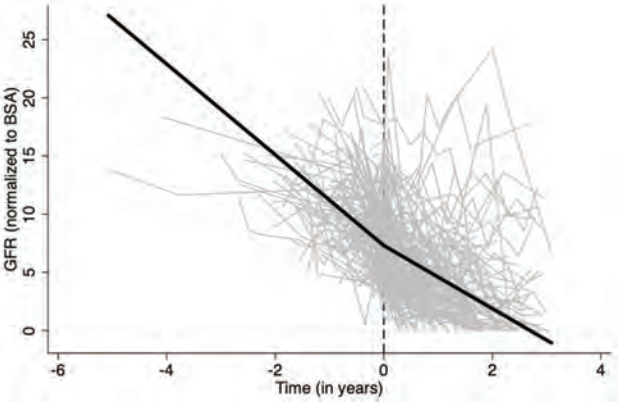

Figure 1. Trend of glomerular filtration rate (normalized to BSA) over time. Gray lines: individual patient measurements; black lines: predicted slopes in the pre- and post-dialysis initiation periods.

SU-OR23

Steady Concentration Peritoneal Dialysis Increases Ultrafiltration and Sodium Removal Compared with Continuous Ambulatory Peritoneal Dialysis (CAPD)

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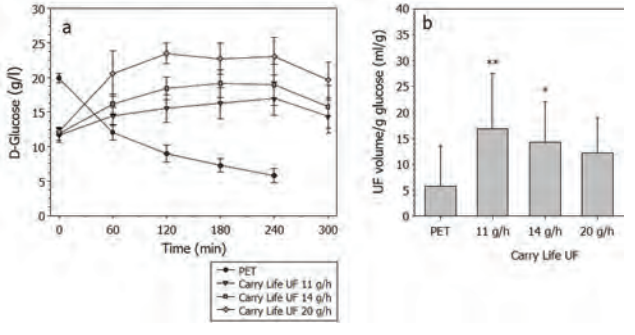
Background: Fluid and sodium removal (NaR) may be a challenge during glucose-based PD, leading to increased use of high glucose solutions to maintain sufficient fluid removal. This may lead to increased sodium sieving, resulting in reduced NaR. Carry Life® UF uses steady concentration PD (SCPD), where the intraperitoneal (IP) glucose concentration is maintained by infusion of glucose to provide a continuous ultrafiltration (UF) throughout the dwell. The present study investigated the effect of Carry Life® UF *vs.* CAPD regarding UF, NaR and glucose absorption.

Methods: Eight stable PD patients were included in the study. Subjects were treated with 5-hour Carry Life® UF treatments using three different glucose doses (11, 14, 20 g/h). An initial fill with 1.5 l, 1.36% glucose PD solution was used. A small volume of dialysate was drained hourly to avoid overfill. A 4-hour peritoneal equilibration test (PET) (2.0 l, 2.27% glucose) served as control. Data expressed as mean±SD, statistical analysis using ANOVA.

Results: UF volumes were significantly increased during Carry Life® UF treatments (646±256, 739±312, 863±380 ml for 11, 14 and 20 g/h) *vs.* PET (162±242 ml, p<0.01). NaR increased significantly during Carry Life® UF treatments (86±27, 92±33 110±37 mmol/dwell for 11, 14 and 20 g glucose/h) compared to PET (22±33 mmol/dwell, p<0.001).

Conclusions: SCPD performed with Carry Life® UF maintained a stable IP glucose concentration during the treatment (figure a) which generated significantly higher UF volumes compared to PET. During the Carry Life UF treatments glucose was used more efficiently, particularly for the two lowest doses, in comparison to PET (figure b). In summary, SCPD using Carry Life® UF increases the efficiency of PD compared to standard, glucose-based CAPD with respect to UF and NaR.

Funding: Commercial Support - Triomed AB



IP glucose concentration in g/l during treatments (a).UF efficiency expressed as UF volume in ml per gram of glucose absorbed during treatments, *p<0.05, **p<0.01 (b).

SU-OR24

Efficacy and Safety of Roxadustat in Patients with Dialysis-Dependent CKD and Anemia on Peritoneal Dialysis

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Dialysis modality in patients with ESRD is associated with different incidence rates of anemia and clinical outcomes. Therefore, evaluating the safety and efficacy of roxadustat in patients with dialysis-dependent (DD) CKD on peritoneal dialysis (PD) is of clinical importance.

Methods: Pooled data from three pivotal, phase 3, randomized, open-label, epoetin alfa-controlled studies of roxadustat for the treatment of anemia in patients with DD-CKD were assessed in the subgroup of patients on PD. Endpoints evaluated were: mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy, Hb CFB averaged over Weeks 28–36 censored for rescue therapy, and risk for blood/RBC transfusion during the treatment period. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs).

Results: In the DD-CKD study population, 10% (372/3887) of patients were on PD (roxadustat=180, epoetin alfa=192). Baseline characteristics were generally similar between treatment groups. Mean (SD) Hb levels (g/dL) at baseline were 9.58 (1.22) in the roxadustat group and 9.56 (1.23) in the epoetin alfa group. Patients achieved a larger mean (SD) CFB to Weeks 28–52 in Hb (g/dL) with roxadustat vs. epoetin alfa (1.41 [1.45] vs. 1.08 [1.53]), corresponding to a least-squares mean (LSM) treatment difference of 0.37 (95% CI: 0.11, 0.63) (p=0.0048). Patients achieved a larger mean (SD) CFB to Weeks 28–36 in Hb (g/dL) with roxadustat vs. epoetin alfa (1.53 [1.54] vs. 1.01 [1.63]), corresponding to a LSM treatment difference of 0.46 (95% CI: 0.17, 0.74) (p=0.0018). Risk for blood/RBC transfusion was significantly reduced with roxadustat vs. epoetin alfa (HR, 0.50 [95% CI: 0.26, 0.98]; p=0.0422). TEAE rates were comparable between treatment groups.

Conclusions: Roxadustat was efficacious vs. epoetin alfa for increasing/maintaining Hb levels and reducing the risk for blood/RBC transfusion in patients with DD-CKD on PD. Safety and tolerability profiles were similar to the overall population and consistent with that observed in this patient subgroup.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

SU-OR25

Development and Content Validity of a Patient-Reported Experience Measure for Home Dialysis

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Background: The population of patients with kidney failure in the United States utilizing home dialysis modalities is growing rapidly. Unlike for in-center hemodialysis, there is no patient-reported experience measure for assessment of patient experience of care for peritoneal dialysis or home hemodialysis. We sought to develop and establish content validity of a patient-reported experience measure for patients undergoing home dialysis using a mixed-methods multiple stakeholder approach.

Methods: We conducted a systematic literature review, followed by concept elicitation focus groups and interviews among 65 participants, including 21 home dialysis patients, 33 home dialysis nurses, 3 patient care partners, and 8 nephrologists. We generated a list of candidate items for possible measure inclusion, and conducted a national aspects of care prioritization exercise among 91 home dialysis patients and 39 providers using a web-based platform. We drafted the Home Dialysis Care Experience (Home-DCE) instrument and conducted 3 rounds of cognitive debriefing interviews to evaluate item comprehensibility, order, and structure. We iteratively refined the measure based on interview findings.

Results: The literature review and concept elicitation phases supported 15 domains of home dialysis care experience in 6 general areas: communication and education of patients; concern and helpfulness of the care team; proficiency of the care team; patient-centered care; care coordination; and amenities and environment. Focus groups results showed that domains of highest importance for measure inclusion were home dialysis staff education and patient-centered communication, care coordination, and personalization of care (Figure). Aspects of care prioritization exercise results confirmed focus group findings. Cognitive debriefing indicated that the final measure was easily understood and supported content validity.

Conclusions: The Home-DCE instrument is a 26-item patient-reported experience measure for use in peritoneal dialysis and home hemodialysis. Qualitative focus group and prioritization survey data support measure content validity. To our knowledge, the Home-DCE instrument represents the first rigorously developed and content valid English language survey instrument for assessment of patient-reported experience of care in home dialysis.

FIGURE. Home dialysis care domains and aspects of care from concept elicitation focus groups

Grouped area	Home Dialysis Care Domain	Number of mentions	Key aspects of care
Communication and Education	Dialysis center staff education of patients and patient-centered communication	107	• Clarity and quality of communication between staff, patient, caregiver • Accuracy, completeness, flexibility of education content • Effectiveness in addressing patient's questions
	Nephrologist education of patients and patient-centered communication	15	• Frequency of communication between nephrologist, patient, caregiver • Availability of nephrologist and communication with dialysis staff
Concern and helpfulness of the care team	Concern and helpfulness of the dialysis center staff	36	• Perception by patient that staff are caring, informed, respectful • Perception by patient that staff are proactive and helpful when asked
	Concern and helpfulness of the nephrologist	7	• Perception by patient that nephrologist is caring, informed • Nephrologist shows respect and takes patient seriously
	Support services	38	• Availability of social work, dietitian, transportation services • Availability of backup and respite care
	Caregiver training and support	7	• Degree to which care partners receive training and support from staff
Proficiency of the care team	Dialysis center staff proficiency	36	• Perception by patient that dialysis staff can manage problems, deliver timely care, and show/perform technical aspects of dialysis
Patient-centered care	Personalization of care	39	• Patient perception that staff take patients' values and preferences into account in treatment decisions and integration of treatment into life
	Patient involvement in care	12	• Inclusion of patients in decisions regarding dialysis modality • Patient comfort in asking questions about care
	Access and convenience of care	31	• Accessibility of home dialysis center • Ease of contacting dialysis center staff • Accessibility of different dialysis modalities
	Confidence and safety to perform dialysis at home	33	• Confidence in performing all steps of dialysis procedure • Knowledge of response to complications, emergencies, disasters
	Handling of grievances	3	• Response by dialysis staff to complaints, and comfort of patients in raising complaints
Care coordination	Care coordination	39	• Perception of patient regarding cooperation among providers
Amenities and environment	Facility amenities and environment	15	• Cleanliness, convenience, quality of dialysis facility space
	Dialysis supplies, equipment, and home environment	30	• Convenience and accessibility of dialysis supply and delivery process • Helpfulness of staff in dealing with supply issues

SU-OR26

Cardiovascular Thromboembolic Outcomes by Dialysis Modality Following Primary Total Knee Arthroplasty

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Background: There is a paucity in the literature evaluating the impact of dialysis modalities on cardiovascular thromboembolic outcomes following primary total knee arthroplasty (TKA). Therefore, the purpose of this study was to investigate whether patients treated with hemodialysis (HD) or peritoneal dialysis (PD) have higher rates of: 1) medical complications, 2) readmission, and 3) cost of care.

Methods: Patients undergoing primary TKA while receiving HD served as the study group (n = 82,518) and matched 1:1 to a control group of PD patients (n = 82,518) by distribution, age, sex, and Elixhauser-Comorbidity Index (ECI). Outcomes analyzed included rates of 90-day medical complications, readmission rates, and cost of care. Logistic regression analysis was used to calculate odds-ratios (OR) for medical complications and readmission rates. Welch's t-test was used to test for significance on cost of care and ECI between cohorts. P-value less than 0.05 was considered statistically significant.

Results: Patients undergoing HD prior to primary TKA were found to have a significantly lower incidence and odds of cerebrovascular accidents (PD vs. HD: 0.19 vs. 0.13%; OR: 1.44, p=0.003) and venous thromboemboli (0.15 vs. 0.10%; OR: 1.52, $p<0.001$), specifically deep vein thromboses (0.13 vs 0.10%; OR 1.75, p<0.001). HD patients did however incur significantly higher 90-day cost of care ($104,341.89 vs. $209,611.67; p<0.001). No statistically significant differences were noted in myocardial infarction, pulmonary embolism, or 90-day readmission rates between the two groups.

Conclusions: While incurring a lower 90-day cost of care, patients treated with PD prior to primary TKA may have a greater odds of developing a cerebrovascular accident or deep vein thrombosis when compared to HD.

Table 1

Cardiovascular Thromboembolic Adverse Outcomes	Incidence (PD vs. HD)	Odds Ratio	95% Confidence Interval	P-Value
Myocardial Infarction	0.14 vs. 0.13%	1.11	0.85 - 1.45	0.42
Cerebrovascular Accident	0.19 vs. 0.13%	1.44	1.13 - 1.85	0.003
Venous Thromboembolism	0.15 vs. 0.10%	1.52	1.15 - 2.00	0.0003
Deep Vein Thrombosis	0.13 vs. 0.10%	1.75	1.28 - 2.40	<0.001
Pulmonary Embolism	0.02 vs. 0.03%	0.86	0.46 - 1.59	0.64
Readmission Rates & Cost of Care at 90 Days	Incidence (PD vs. HD)	Odds Ratio	95% Confidence Interval	P-Value
Readmission Rates	51.94 vs. 51.62%	1.01	0.99 - 1.03	0.18
Cost of Care	$104,341.89 vs. $209,611.67			<0.0001

Outcome comparisons by dialysis modality following TKA.

SU-OR27

Prognostic Roles of Peritoneal Dialysis Effluent Mitochondrial DNA Level

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Background: Circulating mitochondrial DNA (mtDNA) level is associated with the systemic inflammatory state and prognosis of peritoneal dialysis (PD) patients. We explore the relation between mtDNA level in PD effluent and peritoneal transport characteristics and outcomes of PD patients.

Methods: We measured PD effluent mtDNA levels by quantitative polymerase chain reaction and the result is expressed as copy per 1000 copies of the housekeeping gene. Both PD effluent sediment and cell-free supernatant mtDNA levels were measured. Peritoneal transport was determined by the peritoneal equilibration test and represented as mass transfer area coefficient (MTAC) of creatinine. All patients were followed for technique and overall survival.

Results: 168 PD patients were followed for 41.3 (IQR: 19.3-52.0) months. Their mean age was 60.4±11.8 years; 99 (58.9%) were men. Median PD effluent (PDE) supernatant mtDNA was 255.4 unit (IQR: 157.5-451.3); median PDE sediment mtDNA was 201.6 unit (147.8-267.3). PDE supernatant mtDNA level had a modest but significant correlation with MTAC creatinine (r = -0.364, p<0.001) and the number of previous peritonitis episode (r = -0.235, p=0.002). After adjusting for age, gender, Charlson's Comorbidity Score, total weekly Kt/V, and residual renal function, PDE sediment mtDNA was a significant predictor of technique survival (adjusted hazards ratio [AHR] 1.002, 95%CI 1.000-1.003, p=0.011). In contrast, PDE sediment mtDNA level did not predict patient survival (p = 0.7). In contrast, the PDE supernatant mtDNA level did not correlate with technique or patient survival.

Conclusions: PDE supernatant mtDNA level had a significant correlation with peritoneal transport. PDE sediment mtDNA level was a significant predictor of technique survival for PD patients. The mechanism of the differential implications between PDE sediment and supernatant mtDNA levels deserves further investigations.

SU-OR28

Hemodynamics and Geometry of Rat Arteriovenous Fistulas: Effect of Sildenafil Treatment

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Background: Arteriovenous fistula (AVF) maturation is dependent on hemodynamics and remodeling of the vessel wall to increase the AVF flow rate and lumen area for dialysis. Sildenafil is a phosphodiesterase 5 inhibitor that promotes vasodilation and is used clinically to treat erectile dysfunction and pulmonary hypertension. Here we investigate the effect of sildenafil on lumen geometry and hemodynamics in rat AVFs.

Methods: Femoral AVFs were created in 12-16 week-old male Sprague-Dawley rats. Sildenafil was administered at 90 mg/kg in drinking water starting 14 days prior to AVF creation surgery (n=4). 21 days post creation, animals were subject to non-contrast MRI scans, and the MR images were used for reconstruction of the AVF lumen and computational fluid dynamic simulations of the AVF blood flow. Hemodynamic parameters (flow rate, wall shear stress (WSS), vorticity, and oscillatory shear index (OSI)) and geometrical analysis (cross sectional lumen area, anastomosis angle (AA), tortuosity, and nonplanarity angle (NA)) were calculated.

Results: Sildenafil significantly increased the lumen area and flow rate of both the venous and arterial limbs of the AVFs when compared to no-treatment controls (p<0.0001) (Fig. 1). WSS, vorticity and OSI of treated rats were also significantly higher than controls (p<0.0001)(Fig. 1). AA, tortuosity, and NA were not significantly different between the two groups. AA was approximately 40° in both groups.

Conclusions: The AA of our AVF rat model is similar to the AA in human radiocephalic AVFs in the literature. Sildenafil leads to significantly higher flow rate and larger lumen in both vein and artery than controls. Vorticity, WSS, and OSI are significantly higher in treated rats compared to control, which may be due to the increased flow rate. Sildenafil may have therapeutic potential to enhance AVF maturation by affecting the hemodynamics.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

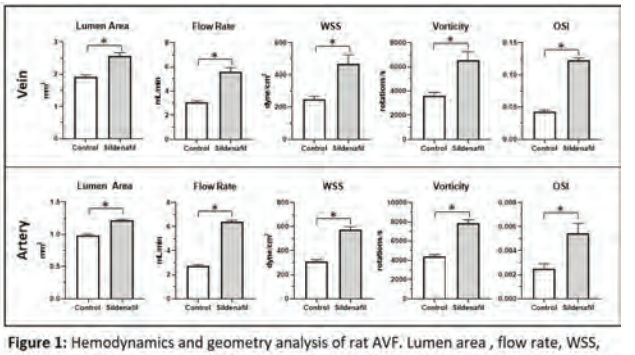

Figure 1: Hemodynamics and geometry analysis of rat AVF. Lumen area , flow rate, WSS, vorticity, and OSI were averaged from start of anastomosis to 10 mm in the vein or artery and throughout a cardiac cycle. Error bars show SEM. *: p<0.0001. Control: n=4, Sildenafil Treatment: n=4.

SU-OR29

Single-Center Real-World Experience with Endovascular Arteriovenous Fistulas

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Background: Endovascular arteriovenous fistulas (EndoAVFs) are created percutaneously via an anastomosis between the radial artery and the perforator vein (Ellipsys), or between the ulnar artery and vein or radial artery and vein (Wavelinq). Flow is directed via the perforator vein to the superficial veins.

Methods: We report partial outcomes for 69 technically successful endoAVF creations for patients on hemodialysis between 5/2019 and 4/2020 using 2 catheter-based devices.

Results: 12/69 endoAVFs failed (17%), all before reaching physiologic usability (ok to use) except for 1 which failed due to failure to cannulate at the dialysis center. The most common reason for failure was thrombosis of the perforator vein. In 49 endoAVFs that reached physiologic usability at time of data review, mean duration from creation to physiologic usability was 92 days and mean number of procedures between endoAVF creation and physiologic usability was 1. At time of data review, 9 endoAVFs were pending physiologic usability. 14/49 (29%) of endoAVFs that reached physiologic usability did so with 0 secondary procedures. Mean postoperative brachial artery flow in this subset was 718 ml/min (range 400-1100 ml/min). Mean flow at 4-6 weeks was 843 ml/min. 35/49 (71%) needed at least 1 procedure. Mean postoperative flow in this subset was 545 ml/min. Mean flow at 4-6 weeks was 721 ml/min. In 44 endoAVFs that had been cannulated at time of data review, mean duration from physiologic usability to cannulation was 9 days. In 33 patients whose dialysis catheters had been removed at time of data review, mean duration from first cannulation to dialysis catheter removal was 57 days.

Conclusions: Successfully created endoAVFs have shorter maturation time than surgical AVFs and require less maturation procedures. Immediate postoperative brachial artery flow is an important predictor of endoAVF behavior/outcome. All endoAVFs that reached physiologic usability with 0 secondary procedures had a postoperative flow above 400 ml/min, and mean postoperative flow was higher than those that needed at least 1 procedure. Time from first cannulation to dialysis catheter removal represents a pragmatic measure for endoAVFs. Cannulation injuries sometimes obligate a period of endoAVF rest. Removal of the dialysis catheter not only indicates functional usability of the endoAVF but also proficiency of the dialysis units in cannulating them.

SU-OR30

Association Between Antimicrobial Barrier Cap Use and Outcomes Among Hemodialysis Patients Using a Central Venous Catheter

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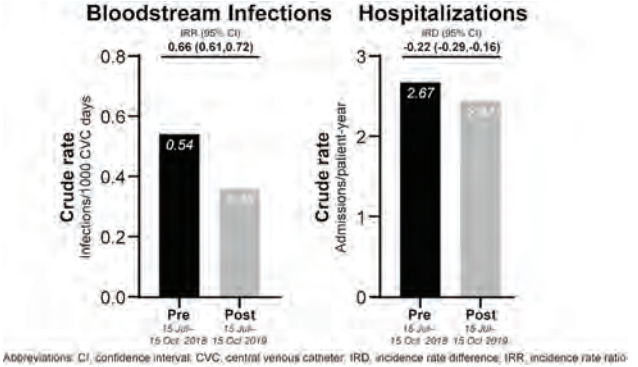
Background: Bloodstream infections (BSIs) are a common complication of central venous catheter (CVC) use and contribute to hospitalization, mortality, and high costs of care in patients on hemodialysis (HD). In a prior randomized clinical trial, patients using CVCs with antimicrobial barrier caps (AmBC; ClearGuard® HD, Pursuit Vascular Inc, Maple Grove, MN, USA) had significantly lower catheter-related BSI rates compared to patients using CVCs with the historical standard of care. Based on these findings, AmBCs were introduced in May 2019 as standard of care for CVC patients across a large dialysis organization (LDO). This study assessed changes in clinical outcomes in a real-world HD population following implementation of AmBC use.

Methods: Study data were derived from LDO electronic medical records over two 3-month periods: Pre (Jul-Oct 2018) and Post (Jul-Oct 2019) AmBC adoption. Included patients were adults receiving in-center HD treatment 3x/week using a CVC. Crude outcome rates were calculated for individual calendar months and for the pre- and post-periods overall; formal comparisons were made using generalized linear models.

Results: A total of 37,642 patients in the pre-period and 40,498 patients in the post-period met eligibility criteria. Overall BSI rate fell from 0.54/100 CVC days in the pre-period to 0.36/100 CVC days after AmBC implementation. Hospitalization rates were lower during the post-period versus the pre-period overall and within each calendar month; the contribution of underlying temporal changes (eg, background year-over-year change) could not be quantified.

Conclusions: Adoption of AmBCs for use in HD patients using a CVC for vascular access was associated with an early 34% reduction in infections assessed on the basis of positive blood cultures and 0.22 fewer hospital admissions per patient-year.



Abbreviations: CI, confidence interval; CVC, central venous catheter; IRD, incidence rate difference; IRR, incidence rate ratio

SU-OR31

Two-Year Results from a Randomized, Controlled Study of Obinutuzumab for Proliferative Lupus Nephritis

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Background: NOBILITY demonstrated improved renal responses and complete B-cell depletion with the humanized type II anti-CD20 monoclonal antibody obinutuzumab (OBI) compared with placebo (PBO) through 18 months in patients with proliferative lupus nephritis (LN) when added to standard of care therapies. Two-year results from NOBILITY are reported here.

Methods: Patients with class III/IV LN received mycophenolate and steroids and were randomized to OBI or PBO. The primary endpoint was complete renal response (CRR) at week 52. Patients were followed through week 104. Secondary endpoints included overall renal response (ORR) and modified CRR (mCRR).

Results: CRR was greater with OBI than PBO at week 52 (35% vs. 23%, $P = 0.115$), week 76 (40% vs. 18%, $P = 0.007$), and week 104 (41% vs 23%, $P = 0.026$; Table). At week 104, OBI patients had greater improvement in eGFR (+6.5 vs. -3.2 mL/min/1.73 m^2, $P = 0.018$), UPCR, anti-dsDNA, C3, and C4. Serious adverse events (OBI 25% vs. PBO 30%), serious infections (8% vs. 18%) and deaths (1 vs. 4) were not increased with OBI.

Conclusions: NOBILITY demonstrated a sustained benefit of OBI through week 104, approximately 18 months after the final OBI infusion. There were no unexpected safety findings. OBI use in LN will be further evaluated in the Phase 3 REGENCY trial.

Table. Week 104 Results

Week 104 Endpoint	OBI (n=63)	PBO (n=62)	Difference (80% CI)	P Value
CRR	41%	23%	19% (8, 29)	0.026
ORR	54%	29%	25% (14, 36)	0.005
mCRR	56%	33%	22% (11, 33)	0.015
C3 >90 mg/dL	76%	47%	29% (19, 40)	0.008
C4 >10 mg/dL	95%	74%	21% (13, 29)	0.001
Mean change in eGFR from baseline (mL/min/1.73 m^2)	+6.5	-3.2	9.7 (1.7, 18)	0.018
Mean change in UPCR from baseline	-2.3	-1.4	-0.96 (-1.4, -0.57)	0.002

CRR=UPCR <0.5, serum creatinine (SCr) ≤upper limit of normal (ULN) and ≤115% of baseline, <10 red blood cells per high power field (RBCs/HPF), and no RBC casts.

ORR = CRR or partial renal response=UPCR <1 (<3 if baseline UPCR ≥3) and ≤50% of baseline, SCr ≤115% of baseline, and ≤50% increase in urinary RBCs (or <10 RBCs/HPF).

mCRR = UPCR <0.5, SCr ≤ ULN.

SU-OR32

Complement C5a Receptor Inhibitor Avacopan Improves Renal Function in ANCA Vasculitis

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Background: Renal impairment is common in anti-neutrophil cytoplasmic autoantibody-associated vasculitis. The resulting chronic kidney disease and exacerbation of the toxicity risks of high dose or prolonged glucocorticoid use, a mainstay of ANCA treatment, are major consequences. Avacopan was tested for efficacy and effects on renal function compared to standard prednisone therapy in a randomized double-blind Phase 3 trial in ANCA vasculitis.

Methods: Subjects randomized 1:1 received either prednisone (60 mg tapered to 0 over 20 weeks) or avacopan (30 mg twice daily for 52 weeks), combined with *either* cyclophosphamide (CYC) followed by azathioprine, *or* rituximab (RTX). Primary endpoints: Disease remission at week 26 and sustained remission at week 52. Changes in urinary albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) were also assessed.

Results: 330 subjects were treated: 166 to avacopan and 164 to prednisone treatment groups. Avacopan remission at week 26 was 72.3% vs. 70.1%, for prednisone (P<0.0001 for non-inferiority); avacopan was superior to prednisone for sustained remission (week 52, 65.7%, avacopan vs. 54.9%, prednisone, P=0.0066). 81% percent of subjects had renal disease. UACR decreased more rapidly with avacopan than prednisone: week 4 avacopan was 40% below baseline vs. no change for prednisone (P<0.0001). Baseline to week 52 eGFR (mL/min/1.73 m²) improvement: avacopan eGFR +7.3 vs. prednisone +4.1 (P=0.029). In subjects with baseline eGFR <30: mean eGFR improved 67% more with avacopan than prednisone to week 52: avacopan eGFR +13.7 vs. prednisone +8.2 (P=0.01).

Conclusions: Treatment with avacopan for ANCA vasculitis compared with standard glucocorticoid therapy (both combined with either CYC or RTX) is as effective for remission induction at 26 weeks, and superior to prednisone for sustained remission after 52 weeks. Avacopan led to faster falls in UACR and greater recovery in eGFR when compared to standard prednisone therapy. These findings have important implications for the long term health of AAV patients through better overall disease control, reduced prednisone exposure and reduced severity of chronic kidney disease.

Funding: Commercial Support - ChemoCentryx, Clinical Revenue Support

SU-OR33

Prognostic Value of Persistent Proteinuria and Hematuria After Induction Therapy in ANCA-Associated Vasculitides

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Background: In ANCA-associated vasculitides (AAV), hematuria and proteinuria are biomarkers reflecting renal involvement at diagnosis. Yet, the prognostic value of their persistence after immunosuppressive induction therapy, which may reflect renal damage or persistent disease, remains uncertain.

Methods: This is a *post hoc* study including participants of 5 European randomized clinical trials on AAV (MAINRITSAN, MAINRITSAN2, RITUXVAS, MYCYC, IMPROVE). We examined the association of PCR (urine protein-creatinine ratio) and hematuria on spot urine samples collected at the end of induction therapy with the occurrence of i) a combined endpoint of death and/or end stage renal disease (ESRD), and ii) relapse during follow-up.

Results: Among 571 patients (59% men, median age 60 years), 60% had PR3-ANCA, 35% had MPO-ANCA, 77% had renal involvement. After induction therapy, 157/526 (29.8%) had persistent hematuria, 165/481 (34.3%) had PCR ≥ 0.05 g/mmol. After a median follow up of 28 months (IQR : 18-42), and adjustment for sex, age, ANCA serotype, initial eGFR, persistent hematuria, a PCR ≥ 0.05 g/mmol after induction was associated with risk of death and/or ESRD (adjusted Hazard Ratio (HR) = 4.08, 95% confidence interval (CI95) 1.48-11.25, p = 0.006). Persistent hematuria was associated with renal relapse (adjusted subdistribution HR = 2.18, CI95 1.14-4.18, p = 0.019) but not with any relapse (adjusted sHR = 1.10, CI95 0.78-1.56, p = 0.59) nor with death and/or ESRD (adjusted HR = 1.88, CI95 = 0.83-4.29, p = 0.132).

Conclusions: In this large cohort of AAV patients, persistent proteinuria after induction therapy was an independent predictor of death and/or ESRD, whereas persistent hematuria after induction therapy was an independent predictor of renal relapse. These parameters must be taken into account to assess long-term renal prognosis of AAV patients.

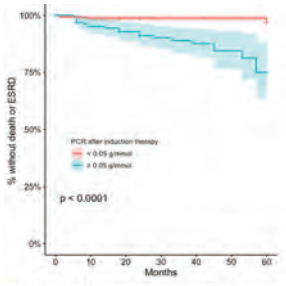

Figure 1. Freedom from composite outcome of death or ESRD

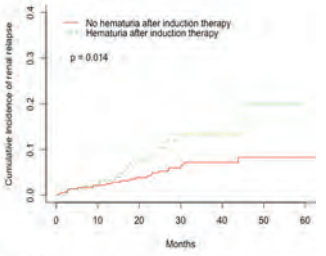

Figure 2. Cumulative incidence of renal relapse (with death, ESRD, non renal relapse as competive risks)

SU-OR34

Belimumab (BEL) Improves Renal Outcomes in Active Lupus Nephritis (LN): A Phase 3 Randomized, Placebo (PBO)-Controlled Trial

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Background: BEL is approved for patients (pts) with systemic lupus erythematosus (SLE). We evaluated intravenous (IV) BEL in active LN.

Methods: This 104-week trial (GSK Study BEL114054; NCT01639339) randomized adults with active LN (class III, IV, and/or V) 1:1 to monthly BEL 10 mg/kg IV or PBO, plus standard therapy (ST) with high-dose corticosteroids + either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) for induction at the investigator's discretion. CyC was followed by azathioprine (AZA), and MMF by MMF maintenance. The primary endpoint was Primary Efficacy Renal Response (PERR = urine protein:creatinine ratio [uPCR] ≤0.7; estimated glomerular filtration rate [eGFR] no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) at Week 104. Other endpoints were Complete Renal Response (CRR = uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73m^2; no rescue therapy) at Week 104; time to renal event (end-stage kidney disease, doubling of serum creatinine, increased proteinuria and/or impaired renal function, renal disease-related treatment failure) or death. Endpoints were analyzed by ST regimen.

Results: 224 pts were randomized to each arm. At Week 104, there were significantly more PERR and CRR responders on BEL vs PBO: (43.0% vs 32.3%, OR [95% CI] 1.6 [1.0, 2.3]; p=0.03) and (30.0% vs 19.7%, OR [95% CI] 1.7 [1.1, 2.7]; p=0.02), respectively. Risk of renal event or death was lower in BEL pts relative to PBO (HR [95% CI] 0.5 [0.3, 0.8]; p<0.01). Week 104 PERR response rates in pts on CyC/AZA were 33.9% with BEL and 27.1% with PBO, and 46.3% with BEL vs 34.1% with PBO in those on MMF. BEL reduced risk of renal event or death on background of CYC/AZA (HR [95% CI] 0.5 [0.2, 1.0]) and MMF (HR [95% CI] 0.5 [0.3, 0.8]) relative to PBO. Adverse events (AEs; ≥1) occurred in 95.5% of BEL and 94.2% of PBO pts, and 25.9% of BEL and 29.9% of PBO pts had ≥1 serious AE.

Conclusions: The addition of BEL to commonly used ST for the treatment of LN significantly improved renal responses with no unexpected safety signals.

Funding: Commercial Support - GSK

SU-OR35

24-Week Interim Analysis of a Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Atacicept in Patients with IgA Nephropathy and Persistent Proteinuria

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis and currently has no approved therapy. Its central pathogenic feature is circulating immune complexes of poorly O-galactosylated polymeric IgA1 (Gd-IgA1) that often deposit in the kidneys (causing inflammation and scarring) and trigger formation of IgA/G autoantibodies. Atacicept, a human TACI-Ig fusion protein, inhibits B cell-stimulating factors BLyS and APRIL and is associated with reduced serum IgA/G, mature B cells and plasma cells. This Phase II study (NCT02808429) examines atacicept safety and efficacy in reducing Gd-IgA1 and renal activity in IgAN.

Methods: Patients with IgAN and proteinuria ≥1 g/day or 0.75 mg/mg on 24-hr urine protein-creatinine ratio (UPCR) despite maximal standard of care (ACE inhibitor and/or ARB) were enrolled. Patients were randomized to subcutaneous placebo, atacicept 25mg or 75mg weekly. Primary endpoint: change in proteinuria at Week 48; secondary endpoints: changes in eGFR, serum IgA, IgG, and IgM, and Gd-IgA1.

Results: This interim analysis showed that, at Week 24, IgAN patients (placebo=5; atacicept 25mg=6; 75mg=5) had a consistent, dose-dependent reduction in IgA, IgG and IgM, and in Gd-IgA1 (Fig 1A), and a higher median % reduction from baseline in UPCR with atacicept than with placebo (Fig 1B); eGFR remained stable. TEAEs were reported by 81% of patients (mild/moderate, none severe), with no serious related events, severe hypogammaglobulinemia, or fatal outcomes.

Conclusions: These results provide proof of concept for the potential treatment of patients with IgAN and persistent proteinuria with atacicept.

Funding: Commercial Support - EMD Serono Research & Development Institute, Inc. (a business of Merck KGaA, Darmstadt, Germany)

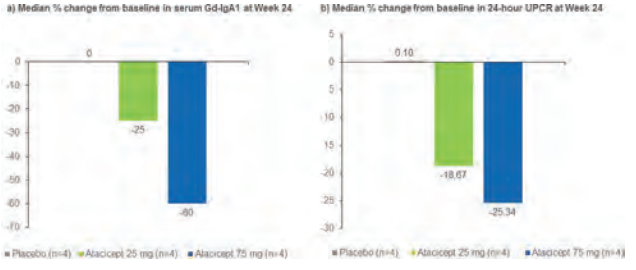

Figure 1. Median changes from baseline to Week 24 in a) serum Gd-IgA1 and b) 24-hour UPCR

SU-OR36

Grading System Utilizing Total Score of Oxford Classification for Predicting Renal Prognosis in IgA Nephropathy

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Background: The Oxford classification of IgA nephropathy (IgAN) can evaluate each MEST-C score individually. However, no research has evaluated the prognosis of IgAN patients using the MEST-C score comprehensively. Therefore, we aimed to analyze the usefulness of a new grading system that utilized the total score of each MEST-C score in predicting renal prognosis.

Methods: A total of 871 IgAN patients were classified into three groups using the new Oxford classification system (O-grade) that utilized the total score of each MEST-C score (O-grade I: 0-1, II: 2-4, and III: 5-7 points) according to the renal survival rate (<10%, 10%-30%, >30%, respectively). The 20-year renal prognosis was analyzed, and the O-grade combined with the Japanese clinical classification (C-grade) was also evaluated.

Results: The clinical findings became significantly severer with increasing O-grades, and the renal survival rate by the Kaplan-Meier method was 78.5%, 74.9%, and 42.2% for O-grades I, II, and III, respectively (P<0.001). The hazard ratios (HRs) for O-grades II and III with reference to O-grade I were 1.7 (95% confidence interval [CI], 1.0-2.9; P=0.036) and 4.7 (95% CI, 2.6-8.4; P<0.001), respectively. In the multivariate analysis,

mean blood pressure and renal function, proteinuria, and O-grade (HR, 1.39; 95% CI, 1.02-1.90; P=0.036) were the independent factors predicting the renal prognosis. The renal prognosis in the nine groups classified by the O-grade combined with the C-grade showed HR of 33.7 (P<0.001) in the severest group with reference to the mildest group.

Conclusions: The O-grade classified by the total score of the Oxford classification was associated with renal prognosis, and renal prognosis could be accurately predicted by combining the O-grade with the C-grade. The O-grade allows easier evaluation of the total activity and chronicity of IgAN and prediction of the renal prognosis of this disease.

SU-OR37

Development of a Deep Learning Model to Predict ESKD in Patients with Immunoglobulin A Nephropathy (IgAN) at Kidney Biopsy Time

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Background: Many prediction models to support clinical decision making have been developed for decades but they are based on traditional statistic linear methods. Another approach is the application of artificial intelligence (AI) that is based on machine learning or deep learning algorithms. We developed an artificial neural network (ANN) tool to predict ESKD in IgAN patients at kidney biopsy time.

Methods: The classifier model to predict ESKD was composed of 4 hidden layers with 100 neurons in each layer. The regression model to predict the time-to-event endpoint consisted of 3 layers containing 125 neurons each.

Results: Our tool, based on these two models, was developed in a cohort of 948 IgAN patients of the VALIGA and Greek cohort. Then, the tool was validated in an independent cohort of 167 IgAN patients from 6 nephrology units. After Cox's regression analysis 7 variables (age, sex, blood pressure values, serum creatinine, daily proteinuria, MESTC classification for the kidney biopsy and therapy at baseline) were chosen to develop the ANN model. The AUC of the ANN model in the study cohort was 0.80. The performance was 0.82 (precision 0.83, accuracy 0.80) for ESKD prediction at 5 years of follow-up and 0.89 (precision 0.81; accuracy 0.83) for patients with 10 years of follow-up. Stable renal function and ESKD were correctly predicted in 91% of IgAN patients in the test cohort.

Conclusions: (i) Our ANN is a promising alternative to the mathematical models in solving non-linear and multidimensional problems. (ii) We have developed a new clinical decision support system that provides additional information to identify IgAN patients at high risk of ESKD. (iii) This tool may stratify patients in the context of a personalized therapy. (iv) This tool will be validated in a clinical prospective study.

Funding: Government Support - Non-U.S.

SU-OR38

Complete Remission of Proteinuria in Patients with Focal Segmental Glomerulosclerosis Treated with Sparsentan, a Dual Endothelin and Angiotensin Receptor Antagonist, in the DUET Trial

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Background: In FSGS, partial remission (FSGS partial remission endpoint [FPRE]: 40% proteinuria reduction and urine protein/creatinine ratio (UP/C) <1.5 g/g) and complete remission (CR) of proteinuria are strong predictors of kidney survival. In the DUET trial, sparsentan (SPAR) resulted in greater reductions in proteinuria and higher rate of FPRE vs irbesartan (IRB) over the 8-week double-blind (DB) period. This antiproteinuric effect of SPAR was sustained during the open-label extension (OLE) period of DUET. Here we analyze patients who achieved CR (UP/C <0.3 g/g) in DUET.

Methods: DUET randomized patients age 8-75 years with biopsy-proven FSGS, UP/C>1 g/g, and eGFR>30 mL/min to SPAR or IRB for 8 weeks, followed by OLE with all patients receiving SPAR. UP/C and other parameters were measured every 12 weeks during OLE. This post-hoc analysis included all patients on SPAR treatment regardless of original randomization.

Results: Median follow-up on SPAR was 42.5 months. Of 108 subjects dosed with SPAR, 44 (41%) reached CR at least once and 30 (28%) patients reached CR in ≥2 visits (68% of CR patients). CR was achieved by 28 patients within the 1st year on SPAR (Kaplan-Meier estimate: 29%). A history of, or nephrotic syndrome at baseline, was documented in 8 (18%) of CR patients. Of subjects with CR, 14%, 41%, and 45% were originally assigned to 200, 400, and 800 mg/day of SPAR dose cohorts, respectively. No patient achieved CR while on IRB during the DB period. Compared to the overall DUET population, CR patients had similar age, sex, and baseline eGFR, but lower baseline mean UP/C (1.67 g/g vs 2.65 g/g), and higher proportion of baseline immunosuppression (45% vs 35%), in particular with mycophenolate mofetil (18% vs 12%). Achieving CR was associated with better preservation of kidney function compared to not achieving CR. In 6 patients (14%), occurrence of CR followed the initiation of new steroid treatment.

Conclusions: In the DUET trial, a high proportion of patients achieved CR on at least one occasion. These observations support the long-term nephroprotective potential of SPAR in FSGS.

Funding: Commercial Support - Retrophin, Inc.

SU-OR39

LNP023: A Novel Oral Complement Alternative Pathway Factor B Inhibitor Safely and Effectively Reduces Proteinuria in C3 Glomerulopathy

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Background: LNP023 is a highly selective oral low molecular weight inhibitor of complement Factor B, a key alternative pathway (AP) protease. The aim of the preliminary interim analysis (IA) of this Phase 2 study (NCT03832114) was to determine whether LNP023 safely and effectively reduces proteinuria in patients with C3 glomerulopathy (C3G).

Methods: Adults with biopsy-proven native C3G received open-label LNP023 for 12w (10-100mg bid during w1-3 then 200mg bid w4-12). All had proteinuria >1g/24h, low plasma C3, stable ACEi/ARB and were vaccinated vs. encapsulated bacteria. Complement inhibition was measured by the *ex vivo* Wieslab assay and fragment Bb and soluble C5b-9 (sC5b-9) levels. Study primary end-point was the ratio of UPCR at 12w vs. baseline. On study completion, all patients received ongoing LNP023 in a long-term extension study (NCT03955445).

Results: 7 patients completed therapy at the time of this IA: mean (range) age 25 (18-39)y, median (range) eGFR 80 (29-130)ml/min/1.73m^2. There were no treatment discontinuations. UPCR levels fell by 53% (80% CI 40-64%) from a Geo-Mean (Geo-CV%) value of 399 (67.6)mg/mmol at baseline to 187 (104.3)mg/mmol at 12w, p=0.0035. eGFR improved or stabilised; median (IQR) change +4.0 ml/min/1.73m2 (-0.5 - +7.5ml/min/1.73m^2). There were no deaths or treatment-emergent SAEs. Blood and urine complement biomarkers confirmed abnormal pre-dosing AP activity in all. Plasma C3 levels recovered, with complete normalisation in 5/7 at 12w. LNP023 inhibited AP activity, with maximal effects obtained at 100mg to 200mg bid (median percent changes from BL at maximum inhibition were Wieslab: -66.3% (N=5), plasma Bb: -13.6% (N=5), plasma SC5b-9 (N=6): -75.9%, urine SC5b-9: -94.9% (N=4)). There was little impact of reduced eGFR on LNP023 systemic exposure. In 6 patients who have entered the long-term extension study to date there has been further reduction in proteinuria; Geo-CV% UPCR value at 6m was 129 (109.9)mg/mmol, a fall of 67.7% from baseline.

Conclusions: LNP023 200mg bid resulted in AP blockade and reduced proteinuria in patients with C3G treated for 12w with excellent safety and tolerability. Extended treatment resulted in further proteinuria reduction.

Funding: Commercial Support - Novartis

SU-OR40

Characteristics and Outcomes of Pregnancy-Triggered Atypical Hemolytic-Uremic Syndrome (aHUS): Global aHUS Registry Analysis

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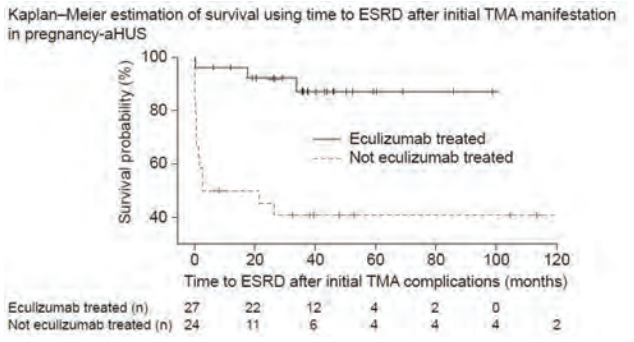
Background: Pregnancy-triggered aHUS (P-aHUS) accounts for 10–20% of aHUS diagnoses. Complement-mediated thrombotic microangiopathy (CM-TMA) may be associated with high maternal and fetal morbidity and mortality such as ESRD. The clinical characteristics of P-aHUS and survival probability in patients treated with the complement C5 inhibitor eculizumab are described, using the largest collection of P-aHUS data available in a single study.

Methods: Patients with a clinical diagnosis of aHUS were included in the global aHUS registry (NCT01522183). Patients with P-aHUS were selected as those with first TMA manifestations during pregnancy or within 60 days postpartum. Patients with other triggers of aHUS were excluded. Survival, based on time to ESRD, was calculated by the Kaplan-Meier method.

Results: In the registry, 51/1029 female patients were selected with P-aHUS and 27 received eculizumab. Mean ± SD age at pregnancy onset was 30.7 ± 5.9 years. P-aHUS occurred during pregnancy in 28 (54.9%) patients, with the remainder occurring postpartum. A diagnosis of pre-eclampsia or HELLP (hemolysis elevated liver enzymes low platelet count) syndrome was reported in 28 (54.9%) and 17 (33.3%) patients, respectively. A complement pathogenic variant was identified in 23 (45.1%) patients, of whom 3 (8.3%) also tested positive for anti-complement factor H antibodies. Mean ± SD eculizumab treatment duration was 1.8 ± 1.8 years. Survival probability was higher in eculizumab-treated patients compared with patients not receiving eculizumab (Figure).

Conclusions: Survival probability was higher in patients who received eculizumab compared with patients who did not receive eculizumab. Successful treatment with eculizumab, in addition to almost half of the patients having a complement pathogenic variant, confirms the appropriate classification of P-aHUS as a CM-TMA.

Funding: Commercial Support - Alexion Pharmaceuticals Inc.



SU-OR41

Differences in Kidney Failure Risk by Race/Ethnicity at the Time of GFR-Based Transplant Eligibility

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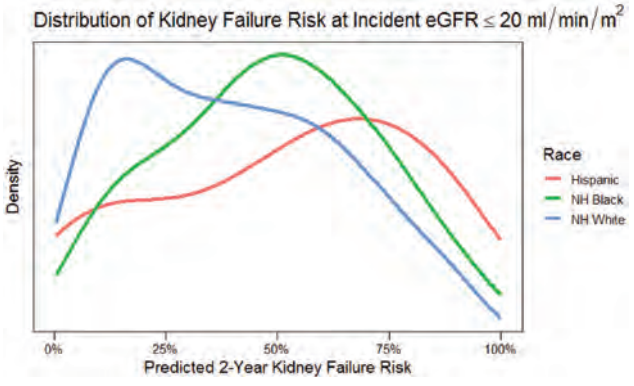
Background: Glomerular filtration rate (GFR) less than 20 ml/min/m^2 is a criterion for kidney transplant listing, but variation in underlying end-stage kidney disease (ESKD) risk distributions by race/ethnicity has the potential to produce systematic racial disparities due to under recognition of the higher progression risk when a singular eGFR threshold is used as a decision point.

Methods: We compared predicted kidney failure risk by race/ethnicity for patients at the time their eGFR fell below 20 ml/min/m^2 using the OptumLabs® Data Warehouse (OLDW), a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data. We identified patients 18-70 years old from 1/1/2014-6/30/2019 who had at least one eGFR >20 ml/min/m^2, and at least two later eGFR values ≤20 ml/min/m^2 that were ≥90 days separated, who also had a urine albumin/creatinine ratio (UACR) measured within 90 days of the first eGFR ≤20 ml/min/m^2. We calculated 2-year risk of ESKD for each patient using the 4-variable Kidney Failure Risk Equation and compared the distributions by race/ethnicity.

Results: Of 2926 patients, 2024 were non-Hispanic white (NHW), 649 non-Hispanic black (NHB), and 253 Hispanic. At the time of incident eGFR ≤20 ml/min/m^2, NHWs were older than NHB or Hispanic patients (mean age 59.2 versus 56.2 or 54.3 years, respectively) and had lower median UACR (0.67 versus 1.36 or 1.72 g/g, respectively). Compared to ESKD risk among NHWs (median predicted risk 38.7%), the risk distribution was skewed toward higher risk for NHB and Hispanic patients, who had median predicted risks of 49.4% and 55.8% respectively (Figure).

Conclusions: At the time of incident eGFR ≤20 ml/min/m^2, NHB and Hispanic populations had greater risk of ESKD. A racial/ethnic disparity in time from GFR-based transplant eligibility to ESKD may exist even with elimination of disparities in timing of transplant referral and waitlisting. Consideration of kidney failure risk might be given greater attention in access to transplantation.

Funding: NIDDK Support



SU-OR42

Exploration of Racial Disparities in the Kidney Transplant Process Among Dialysis Patients

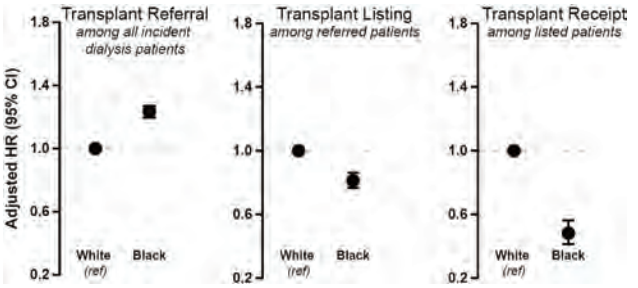
Steven M. Brunelli, Abigail Hunt, Carey Colson, Francesca Tentori. *Davita Clinical Research, Minneapolis, MN.*

Background: Kidney transplant is generally considered the best long-term treatment for dialysis patients. Before receiving a transplant, a patient must be referred to a transplant center, undergo extensive clinical evaluation, and then be placed on a wait list. Previous studies have observed that black patients are less likely to receive kidney transplants than white patients. However, it is unclear at which points in the transplant process inequity is imparted. In this analysis, we used a single source of data to compare the entire transplant process among black and white patients at a large dialysis organization (LDO).

Methods: Eligible patients were those who, between Jul 2015-Jun 2018, were 18-80 years old; were incident to dialysis and began care at the LDO within 30 days of first ever dialysis; and had not undergone a transplant evaluation or listing prior to dialysis start. Exposure was ascribed based on race as documented in LDO medical records (black or white). Patients were followed forward in time from study entry until 31 Mar 2019 or censoring or loss to follow-up. Transplant referrals, listings, and receipts were compared across exposure categories using time-to-event models adjusted for demographics, comorbidities, biochemistries, and socioeconomic factors

Results: We identified 60,229 eligible incident patients (23,499 black; 36,730 white). Compared to whites, black patients were 23% more likely to be referred for transplant (hazard ratio [HR] and 95% confidence interval [CI] = 1.23 [1.20, 1.27]). Among referred patients, black patients were 19% less likely to be placed on a wait list than whites (HR [95% CI] = 0.81 [0.77, 0.86]). Among wait-listed patients, black patients were 52% less likely to receive a transplant than whites (HR [95% CI] = 0.48 [0.41, 0.56]). Overall, black patients were only 46% as likely to receive transplants as white patients (HR [95% CI] = 0.46 [0.39, 0.53]).

Conclusions: These results support prior findings that racial disparities exist within the kidney transplant process and indicate that these disparities occur downstream of the referral.



SU-OR43

Do Social Determinants of Health Predict Patient-Reported Outcomes in Transplant-Eligible ESRD Patients?

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Background: Measuring and understanding patient reported outcomes [PRO, e.g., health related quality of life (HRQoL) and satisfaction with transplant clinic service] is a critical consideration for the care of kidney transplant (KT) eligible patients with end-stage renal disease (ESRD), because research has demonstrated that pre-transplant HRQoL predicts both the receipt of a KT as well as post-KT mortality. Although research demonstrated the importance of social determinates of health (e.g., cultural factors, psychosocial characteristics, transplant knowledge) on clinical outcomes, less is known about how they predict PRO in KT-eligible ESRD patients.

Methods: We examined whether social determinants of health (Time 1, assessed shortly after initiating KT evaluation) are risk or protective factors for PRO (Time 2, assessed after notification of KT evaluation outcome – accepted or not), controlling for evaluation outcome, in a prospective cohort study. Of the initial 1152 adults referred for KT evaluation (2010-2012), 955 completed a Time 2 interview, most within 1 year of completing KT evaluation [n≤6 months=70% (669), n>6 months to≤12 months=8% (76), n>12 months=22% (210)]. We used the Physical Composite Score (PCS), Mental Health Composite Score (MCS), and Kidney Summary Score (KSS), from the Kidney Disease Quality of Life Short Form (KDQoL-SF) to measure HRQoL, and the Client Satisfaction Questionnaire to measure satisfaction with KT clinic service.

Results: Participants completed KT evaluation in an average of 11.7 months (range= 0-43 months). In adjusted multivariable regression models, a stronger sense of mastery predicted higher PCS (β=4.5, p <0.001), MCS (β=5.4, p<0.001), and KSS (β=5.6, p=<0.001). Depression predicted lower MCS (β=-6.2, p=0.001), and lower KSS (β=-5.1, p=0.002). More medical mistrust predicted lower odds of higher patient satisfaction scores (OR= 0.6, 95% CI=0.4, 0.8, p=0.002).

Conclusions: Transplant teams should consider identifying and targeting patients with a low sense of mastery, greater depressive symptoms, or an increased sense of medical mistrust, with additional psychosocial support to improve PRO during the KT evaluation process.

Funding: NIDDK Support, Private Foundation Support

SU-OR44

Genetic vs. Self-Reported African Ancestry and Kidney Allograft Outcome: Analysis of Two Large Multiethnic Urban Transplant Cohorts

Francesca Zanoni,[1] Y. Dana Neugut,[1] Sumit Mohan,[1] Ali G. Gharavi,[1] Brendan Keating,[2] Krzysztof Kiryluk.[1] *[1]Columbia University Irving Medical Center, New York, NY; [2]University of Pennsylvania, Philadelphia, PA.*

Background: African-American (AA) kidney transplant recipients have higher risk of allograft rejection and failure. However, it is unknown to what extent the inferior outcomes in self-reported AA's are due to genetic versus environmental effects. Herein, we compared the effects of self-reported race versus genetic African admixture on graft outcomes.

Methods: A discovery multiethnic cohort of 1,083 kidney transplant recipients from Columbia University and a replication cohort of 761 kidney transplant recipients from University of Pennsylvania were genotyped with high resolution SNP arrays. African admixture proportions, a genetically-derived quantitative measure of African ancestry, was estimated with ADMIXTURE software. Multivariable Cox models were used to investigate associations between African ancestry measures and time to rejection and time to death-censored graft failure, with adjustments for relevant covariates. Akaike information criterion (AIC) was used to compare the models.

Results: 206 and 346 self-identified AA were included in the discovery and replication cohorts, respectively. Over a median follow-up time of 78 months, 432 patients had rejection and 193 had graft failure in the discovery cohort. Self-reported AA ancestry and African admixture were associated with acute rejection (self-report: HR 1.47, 95% CI: 1.18-1.83, AIC: 5540.1; admixture: HR 1.64, 95% CI: 1.22-2.19, AIC: 5541) and graft failure (self-report: HR 1.42, 95% CI: 1.02-1.97, AIC: 2281.9; admixture: HR 1.48, 95% CI: 0.96-2.29, AIC: 2282.9). In the replication cohort, during a median follow-up time of 49 months, 113 patients had rejection and 121 had failure. Self-reported AA ancestry and African admixture measures confirmed to be associated with both acute rejection (self-report: HR 3.06, 95% CI: 1.96-4.78, AIC: 1289.5; admixture: HR 3.69, 95% CI: 2.21-6.16, AIC: 1288.9) and failure (self-report: HR 2.16, 95% CI: 1.43-3.27, AIC: 1113.8; admixture: HR 2.46, 95% CI: 1.54-3.94, AIC: 1113.1). In this cohort, the models including African admixture proportion had a better fit when compared to self-report.

Conclusions: In conclusion, self-reported AA race and a genetically-derived continuous measure of African ancestry predict the risk of allograft rejection and failure in multiethnic and genetically diverse cohorts.

Funding: NIDDK Support

SU-OR45

Deceased Donor Families and Authorization for Research: Differences Among Ethnic Groups

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Background: Research in transplantation requires next of kin(NOK) to authorize for participation in research. Aim was to determine the rate of research authorization by the NOK within different ethnic groups: African American(AA), White (W) or Hispanic(H).

Methods: Single center study of all deceased donor kidney transplants referred to our institution during 3/1/2019-10/31/2019 from multiple organ procurement organizations(OPO) across the United States. We looked at the authorization for donation form in DonorNet. We searched for the NOK research authorization agreement at the time of organ donation. Donors were grouped by self-identified ethnic groups as W, AA or H

Results: We had a total of 297 donors, yielding 401 kidney offers. 71% were imported from 46 different OPOs and 29% from our local OPO. Mean donor age (±SE) was 45.7±0.9. Donor ethnicity distribution was W 180 (60.6%); AA 66 (22.2%) and H 50 (16.8%). Overall 226 (76.1%) donors' NOK authorized for research and 71 (23.9%) declined research. Donor age <35yr had a lower rate of authorization 62.9% vs 81.3% and 80.6% for 35-49yr and>50yr respectively p=0.006. Table 1 shows ethnic distribution on rate of NOK authorization for research, which was significantly lower within AA donors 38/66 (57.6%). Logistic regression showed donor age<35yr and AA donor as more likely to decline research authorization, yielding multivariable p=0.0001 for AA donor and p=0.002 for younger donor age. Multivariable percentages who declined research authorization had highest rate among AA donors<35yr at 55%(11/20) compared to 37.0%(17/46) in AA donors>35yr; 31.0%(18/58) in W/H donors <35yr; and 14.5%(25/173) in W/H donors>35yr. Out of 401 donated kidneys, 93(23%) were not authorized to participate in research, of which 38/93(40.9%) were AA; 15/93(16.1%) were H and 40/93(43.1%) were W donors

Conclusions: In deceased donors from local and imported OPOs, the rate of declined authorization for research participation from NOK was higher among donors from AA ethnicity compared to donors from W or H backgrounds, especially when donor age is <35. Community education is crucial in the field.

Table 1: Rate of NOK Authorization for Research

Agree to Research	W (n=181)	AA (n=66)	H (n=50)
yes n(%)	152 (83.9%)	38 (57.6%)	36 (72%)
no n(%)	29 (16.1%)*	28 (42.4%)*	14 (28%)*

p<0.0002 among 3 groups

SU-OR46

Minimum Diagnostic Criteria for Thrombotic Microangiopathy in Renal Allograft: The Banff TMA Working Group Phase I Results

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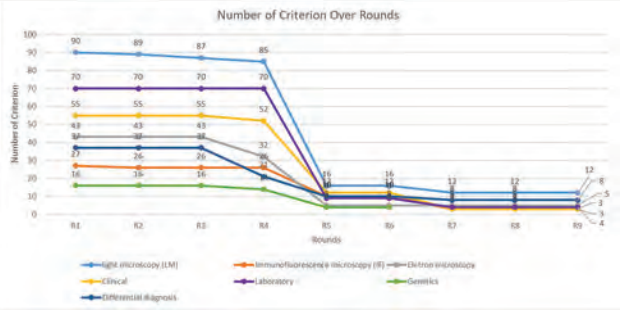
Background: Thrombotic Microangiopathy (TMA) TMA is a serious complication of renal transplantation, usually with poor outcome. The Banff TMA Working Group (TMA-WG) was formed to study renal transplant TMA (t-TMA) aiming to: 1- Survey current practices used in the diagnosis of t-TMA; 2- Define minimum diagnostic criteria (MDC); and 3- Develop recommendations for accurate diagnosis integrating morphological, clinical, laboratory and molecular findings, where available. The project started with Phase I (pathology phase) and is continuing in Phase II (Nephrology phase).

Methods: Using the Delphi methodology during phase I, 23 nephropthologists who had >3 years of experience with t-TMA were asked to list their MDC for t-TMA in the following categories: 1- Light, 2- immunofluorescence, and 3- electron microscopy, 4- clinical history, 5- laboratory findings, 6- genetic testing and 7- raised differential diagnoses. Nine rounds (R) of surveys were designed. At the end of each R, MDC were narrowed down following Delphi rules. R6 and R7 were designated as the validation Rs in which the narrowed criteria were validated on 37 renal biopsies (25 TMA and 12 non-TMA cases) using Aperio Imagescope and whole slide digital images scanned @ X400. For each biopsy, pertinent pathology/history/laboratory/genetic information were provided. Descriptive statistical analysis was performed using SPSS program.

Results: Starting with 338 criteria in R1 and following analysis of total 82,677 data entries, MDC were narrowed down to 35, by the end of R9. The graph illustrates the evolution of the criteria over 9 R. A complete list of 35 MDC will be presented at the meeting.

Conclusions: Applying the Delphi methodology to a cohort of t-TMA biopsies in Phase I of the project, nephropathologists from 4 continents generated histopathologic, clinical and laboratory MDC for renal t-TMA. Phase II (Nephrology consensus) and Phase III (consensus of the consensus groups- Combined Phases I & II) will follow Phase I to generate final MDC for t-TMA.

Funding: Commercial Support - Alexion Pharmaceuticals



SU-OR47

Does Screening for Coronary Artery Disease Predict Cardiac Outcomes Following Renal Transplantation?

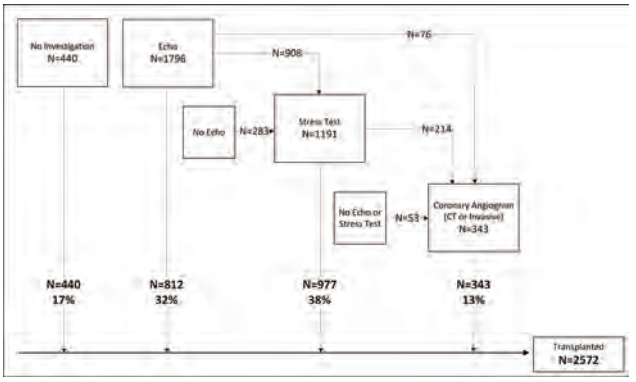
Ailish Nimmo, Dominic M. Taylor, Rommel Ravanan. *Southmead Hospital, Bristol, United Kingdom.*

Background: Screening for asymptomatic coronary artery disease (CAD) prior to transplantation aims to reduce perioperative cardiac events. There is conflicting evidence as to whether this is achieved.

Methods: Individuals recruited to the Access to Transplant and Transplant Outcome Measures (ATTOM) study in England who received a renal transplant between 2011-2017 were studied. Patient demographics and details of screening investigations from ATTOM were linked to outcome data from the Hospital Episode Statistics dataset. Major Adverse Cardiac Events (MACE) comprised unstable angina, myocardial infarction, coronary bypass graft, coronary angioplasty or cardiac death. The effect of screening on MACE was analysed in propensity score-matched groups, using Cox survival analyses, up to 5 years post-transplant.

Results: 2572 individuals received a renal transplant; 51% underwent CAD screening (Figure 1). Age, ethnicity, ischaemic heart disease and diabetes were independently associated with screening. The incidence of MACE at 90 days, 1 and 5 years was 0.9%, 2.1% and 9.4%. After propensity score matching, 1854 individuals were examined. There was no association between screening and MACE at 90 days (HR 0.68, 95% CI 0.28-1.64), 1 year (HR 1.24, 95% CI 0.60–2.54) or 5 years (HR 1.31, 95% CI 0.95–1.79) (Figure 2).

Conclusions: Screening for CAD did not influence the rate of ischaemic cardiac events up to 5 years post-transplant. Units should review protocols with lengthy cardiac workup processes.



Workup patterns. Stress tests: exercise tolerance test, stress echo or myocardial perfusion scan.

		90 day	1 year	5 year
Screening investigation	HR	0.68	1.24	1.31
	(95% CI)	(0.28 – 1.64)	(0.60 – 2.54)	(0.95 – 1.79)
	P	0.39	0.56	0.09
Age (years)	HR	1.02	1.03	1.04
	(95% CI)	(0.99-1.05)	(1.00 – 1.05)	(1.02 – 1.04)
	P	0.09	**0.02**	**<0.001**
Male sex	HR	1.18	1.13	1.47
	(95% CI)	(0.41 – 3.40)	(0.52 – 2.46)	(1.00-2.13)
	P	0.76	0.76	**0.04**
Asian ethnicity (Ref White)	HR	1.76	1.80	1.46
	(95% CI)	(0.54 – 5.71)	(0.60 – 5.37)	(0.76 – 2.83)
	P	0.35	0.29	0.26
Black ethnicity (Ref White)	HR	0.74	1.12	1.02
	(95% CI)	(0.12 – 4.49)	(0.44 – 2.84)	(0.48 – 2.16)
	P	0.74	0.81	0.95
Diabetes	HR	1.17	0.76	1.71
	(95% CI)	(0.28 – 4.81)	(0.25 – 2.31)	(1.02-2.85)
	P	0.83	0.63	**0.04**
Ischaemic heart disease	HR	1.61	6.01	2.32
	(95% CI)	(0.27 – 9.70)	(2.05 – 17.62)	(1.21 – 4.43)
	P	0.61	**0.001**	**0.01**

Factors associated with MACE following propensity score matching

SU-OR48

Albuminuria in Kidney Transplantation Patients Predicts Cardiovascular Morbidity After Two Years

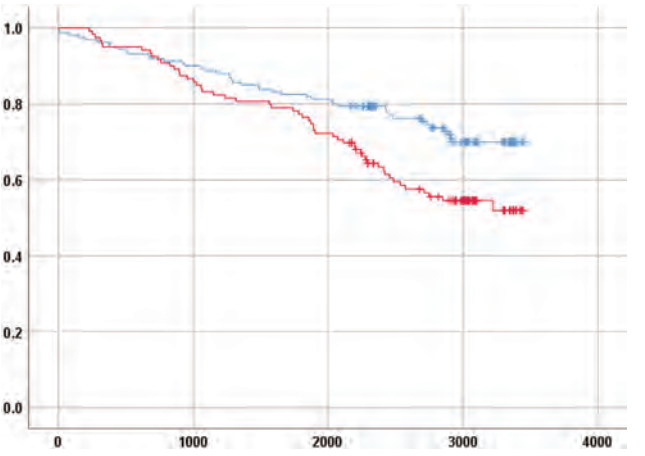
Dana Bielopolski,[1,2] Ruth Rahamimov,[2] Boris Zingerman,[2] Avry Chagnac,[2] Limor Azulay gitter,[2] Benaya Rozen-zvi.[2] *[1]The Rockefeller University, New York, NY; [2]Rabin Medical Center, Petah Tikva, Israel.*

Background: Moderately Increased Albuminuria (MIA) is a well characterized marker of kidney malfunction, both in diabetic and non-diabetic populations, and is used as a prognostic marker for cardiovascular morbidity and mortality. A few studies implied that it has the same value in kidney transplanted patients, but the information relies on spot or dipstick urine protein evaluations, rather than the gold standard of timed urine collection.

Methods: We revisited a cohort of 286 kidney transplanted patients, several years after completing a meticulously timed urine collection and assessed the prevalence of major cardiovascular adverse events (MACE) in relation to albuminuria.

Results: During a median follow up of 8.3 years (IQR 6.4-9.1) 144 outcome events occurred in 101 patients. By Kaplan-Meier analysis MIA was associated with increased rate of CV outcome or death (p=0.03), and this was still significant after stratification according to propensity score quartiles (p=0.048). Time dependent Cox proportional hazard analysis showed independent association between MIA and CV outcomes two years following MIA detection (HR 1.83, 95% CI 1.07-2.96).

Conclusions: Two years after documenting MIA in kidney transplanted patients, their CVD risk was increased, most likely, as a result of endothelial dysfunction. This should prompt the caregiver for strict primary prevention and risk factors modification.



Kaplan-Meier analysis showing rate of CV outcome or death in relation to MIA. X axis shows days since urine collection, Y axis shows cumulative survival. Blue curve – patients without MIA, red curve – patients with MIA.

SU-OR49

Renal Graft Outcomes in Simultaneous Kidney-Heart Transplant Recipients: Analysis of the UNOS Database from 1987-2018

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Background: Simultaneous kidney and heart transplants (SKHT) are employed for patients with both end-stage heart failure and severely impaired kidney function. Renal outcomes in such recipients have been described, albeit in single-center cohorts. We analyzed the United Network for Organ Sharing (UNOS) dataset comprising of 1702 simultaneous kidney-heart transplant recipients since 1987.

Methods: This is a retrospective analysis of SKHT recipients in the UNOS dataset who received transplants between October 1987 and December 2018. We compared the incidence and risk factors of renal allograft loss in SKHT recipients versus deceased donor kidney (DDKT) alone recipients. The Student t-test or Kruskal Wallis tests were used to compare continuous variables, and the Chi2 test for categorical variables between groups. Cox regression hazard model was used to study the factors associated with graft failure.

Results: SKHT recipients were mostly white, males, 5-years older than DDKT recipients. The SKHT donors were younger than DDKT donors, predominantly white males who died from a CVA. Five year patient survival was similar in both the groups (80%) but 1-year mortality was 3 times higher in the SKHT group (12.5%) than DDKT (4.6%). Nearly 20% recipients in both groups died with a functioning graft. Renal graft survival in SKHT group was lower in the first year but equalized with DDKT group over 5 years. Cox regression analysis revealed male gender [HR 2.14], pre-emptive renal transplantation [HR 6.57] and HLA mismatch >4 [5.60] as significant risk factors for renal graft failure in SKHT recipients as compared to DDKT recipients at 4 years. Predominant cause of graft failure in SKHT recipients was primary failure (36%) and in DDKT recipients was acute rejection (26%).

Conclusions: This is the largest analysis of the UNOS database till date to describe risk factors associated with renal graft loss in SKHT recipients. We also showed that 38% of grafts that fail in SKHT recipients, failed in the first year following transplant and primary failure was the predominant cause. Our analysis provides much needed data to policy makers for future combined organ allocation policies.

SU-OR50

Recurrence of IgA Nephropathy After Kidney Transplantation: TANGO Multicenter Study

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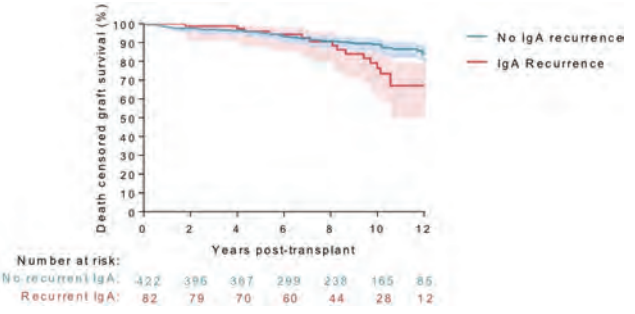
Background: In patients who received a kidney transplantation for end-stage renal disease (ESRD) due to IgA nephropathy, IgA deposits can recur in the transplanted kidney. The incidence, impact and predictors of these recurrent deposits is unclear.

Methods: As part of The Post-Transplant Glomerular Disease (TANGO) project, we performed a multicenter, international, retrospective study to determine the incidence, predictors and treatment response of recurrent IgA deposits after kidney transplantation. Patients with biopsy-proven IgA nephropathy, transplanted in the period 2005-2015 were selected in 16 TANGO centers in Europe, United States and Brazil.

Results: In a total of 504 patients, recurrent IgA deposits were identified by kidney biopsy in 82 patients (16%; 95%CI: 13-19), with a median time to recurrence of 3.4 years (IQR 1.4-5.7 years). Kaplan-Meier analysis showed similar graft survival between patients with and without recurrence in the first years after kidney transplant, though after 8 years, graft failure rates were higher in patients with recurrence (10 year death-censored graft survival 76% and 89%, respectively). Multivariable Cox-regression revealed a higher risk for IgA recurrence

in patients with a pre-emptive kidney transplant (HR 2.56, 95%CI: 1.59-4.17), patients with DSA at time of transplant (HR 2.74, 95%CI: 1.22-6.14) and patients with shorter time from diagnosis to ESRD (HR 0.84 per month, 95%CI: 0.74-0.96). The presence of systemic autoimmune diseases associated with IgA nephropathy did not affect recurrence rates, nor did early steroid withdrawal. In multivariate analysis of post-transplant complications, *de novo* DSA was associated with recurrence of IgA deposits (HR 1.91, 95%CI: 1.04-3.51).

Conclusions: In our international cohort, IgA deposits recurred in 16% of patients and was associated with worse graft outcomes after 8 years of transplant compared to patients without recurrence. A pre-emptive transplant, shorter time from native diagnosis to ESRD, DSA at time of transplant and *de novo* DSA after kidney transplantation were associated with recurrence of IgA deposits



PO2614

Renin Does Not Associate with Mortality or AKI in Acute Respiratory Distress Syndrome

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Background: Renin may be a marker of severity of illness and mortality in critically ill patients. Angiotensin II infusions in patients with lower renin levels may increase the rate of renal recovery from dialysis-requiring AKI. Given that most ACE is found in the lungs and an ACE defect would lead to higher renin levels, we tested associations between renin and clinical outcomes in patients with acute respiratory distress syndrome (ARDS).

Methods: We studied 63 patients with plasma renin measurements enrolled in a phase 1/2 trial of bone marrow-derived human MSCs for moderate-severe ARDS. We estimated associations between renin levels (as a continuous variable) and ARDS severity (assessed by PaO_2/FiO_2), mean arterial pressure (MAP), and serum creatinine at randomization. We then examined if renin was associated with subsequent AKI (defined as ≥ 2x ↑ SCr or new dialysis) or in-hospital mortality.

Results: The median renin was 72 pg/mL (25^{th}-75^{th} percentile 33-181 pg/mL). At randomization, there was no cross-sectional correlation between renin level and PaO_2/FiO_2 (R^2 = 0.03, 95% CI 0.00-0.14, p = 0.21), between renin level and MAP (R^2 = 0.01, 95% CI 0.00-0.12, p = 0.35), or between renin level and serum creatinine (R^2 = 0.003, 95% CI 0.00-0.08, p = 0.68). In longitudinal unadjusted analysis, renin did not significantly associate with AKI (OR 1.006 per 10 pg/mL increase, 95% CI 0.992-1.021, p = 0.41) or 28-day mortality (OR 1.000 per 10 pg/mL, 95% CI 0.987-1.014, p = 0.97). Results were similar in adjusted analyses. Serum creatinine at randomization was associated with AKI (OR 3.27 per mg/dL, 95% CI 1.47-7.30, p = 0.004).

Conclusions: We did not find that renin level is a risk factor for mortality or AKI in moderate-severe ARDS.

Funding: NIDDK Support

ARDS Patient Characteristics

Variables	All Patients (n=63)
Age, yrs	55 (17)
Chronic dialysis	5%
Highest serum creatinine within 24 hours prior to randomization, mg/dL	1.8 (1.5)
PaO2/FiO2 at randomization (mmHg)	139 (34)
MAP at randomization (mmHg)	75 (10)
Vasopressors within 24 hour prior to randomization	73%
Norepinephrine equivalent dose at randomization (ug/kg/min)	0.09 (0.13)
AKI/AKI-D, post-randomization	22%, 18%
28-day mortality	24%

Continuous values given as mean (SD). AKI and AKI-D percentages are reported from among the 55 patients not on dialysis at the time of randomization.

PO2615

Renal Denervation Alleviates Renal Ischemic-Reperfusion Injury-Induced Acute and Chronic Kidney Injury Partly by Modulating MiRNAs in Rats

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Background: Renal denervation (RDN) has been used as a potential medium for kidney injury repair and miRNAs involved in the pathophysiology of renal injury. However, the change of miRNAs after RDN and its proper protective mechanisms has yet to be determined.

Methods: Renal ischemic reperfusion injury (IRI) rat model was established and RDN was applied. Animals were sacrificed at 24 hours and 2 weeks after operation. Tyrosine hydroxylase (TH), renal functions, tubular cell apoptosis and histology staining were examined at 24 hours, and renal fibrosis and capillary vessels were measured at 2 weeks. What is more, the expression of miRNAs in injured kidney was determined by micro-array and the target genes were analyzed. Lastly, human renal biopsy samples with chronic kidney disease were picked for the TH and fibrosis analysis.

Results: TH was eliminated and renal functions were improved in the denervation group at 24 hours. RDN reduce tubular cell apoptosis and mitigate the histological lesion. Meanwhile, the increase of capillary vessel density and reduce of renal fibrosis was observed after 2 weeks. Moreover, numbers of miRNAs were up-regulated after RDN treatment both at 24 hours and 2 weeks, and the miRNA targeted pro-angiogenesis, anti-fibrosis and inflammatory pathways were modulated. Lastly, less fibrosis regions were found in TH high expression regions of human renal biopsy samples.

Conclusions: RDN was a reliable method in alleviating IRI induced acute and chronic kidney injury, and the modulation of miRNA related pro-angiogenesis, anti-fibrosis or inflammatory pathways involved in this process.

PO2616

Obesity Has Opposing Effects on Acute vs. Chronic Kidney Disease

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Background: With an accumulation of lipid droplets, mitochondria become incapable of upregulating the glucose-dependent response to ischemia and the cell becomes dependent upon glycolysis to satisfy metabolic need. This dysregulation has contributed to the exacerbation of ischemic injury in various tissues in diet-induced obese (DIO) mice. However, very little is known in how DIO can contribute to ischemic kidney disease. We hypothesized that obesity may dampen the response to acute kidney injury (AKI) and further exacerbate the development of dysfunction in chronic kidney disease.

Methods: Fat content and lean muscle mass of 20-wk old B6 lean and DIO mice were analyzed via EchoMRI (calculate fat %) and data used to randomize mice between either acute (AKI, 26 mins of bilateral ischemia with 24 hrs of reperfusion) or chronic (CKD, 26 mins of unilateral ischemia with 14 days of reperfusion) models of kidney injury. Kidney injury was assessed by plasma creatinine (PlCr; mg/dL), blood urea nitrogen (BUN; mg/dL), and histological analysis (H&E or MT).

Results: Fat % significantly differed between lean and DIO mice (4.18±0.4 vs 17.49±1.2; p<0.001) along with blood glucose levels (384±27.8 vs 522±16.1; p<0.01). In AKI, DIO mice had worsened kidney function when compared to lean mice as shown by the significant increase in PlCr (1.43±0.23 vs 2.32±0.14; <0.05). However, the degree of injury was not reflected in BUN or acute tubular necrosis (ATN). Interestingly, there was no significant changes in either PlCr or BUN between DIO and lean mice at 14 days.

Conclusions: When compared to lean controls, mice fed HFD and then subjected to IRI expressed significant exacerbation of injury by a heightened expression of clinical chemistry markers. Though this dysregulation has been associated in other tissues with an accumulation of dysfunctional mitochondria secondary to the increased accrual of lipid-droplets, this does not seem to be the case in the kidney as no lipid-deposits were observed in the histological analysis. In addition, no significance existed between DIO and lean mice having undergone unilateral ischemia. With the increasing prevalence of obesity and obesity-related co-morbidities, more studies are warranted to explicitly unravel the effects of DIO in relation to acute and CKD.

Funding: NIDDK Support

PO2617

Protective Effects of Apelin on Contrast-Induced Nephropathy

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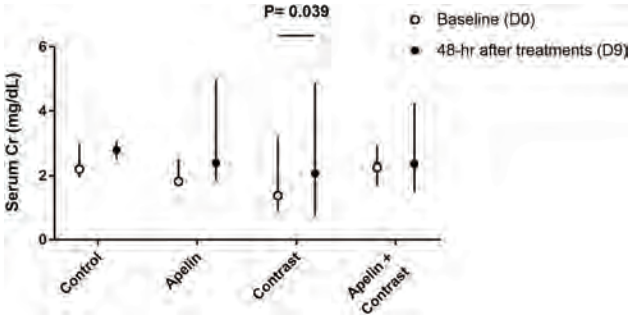
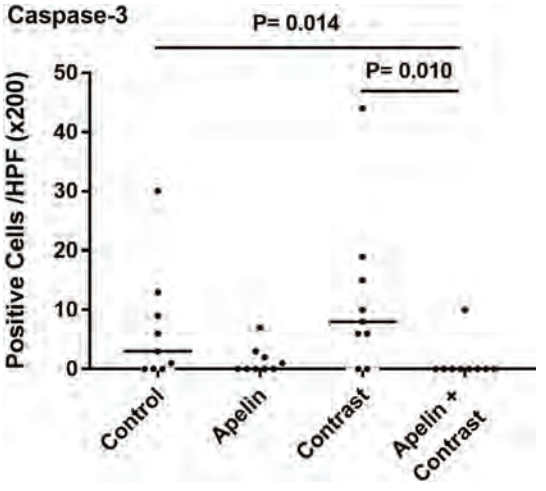
Background: Contrast induced nephropathy (CIN) has no proven preventive measures yet except for saline administration. Apelin is a endogenous ligand to apelin receptor in body, which has physiologic roles such as increasing cardiac output and peripheral vasodilation. This study aims to examine the protective effect of apelin on CIN.

Methods: A total of 22 rats were divided into 4 groups: Control, Apelin, Contrast, and Apelin/Contrast. In order to effectively induce CIN, 50 mg/kg of gentamycin IV was injected daily to all rats from Day-1 to Day-6. On Day-7, the rats were pre-treated as follows; Control and Contrast groups: Saline SQ, Apelin and Apelin/Contrast groups: apelin-13, 300 μg/kg SQ. After 1-hour of pre-treatment, main treatments were followed; Control and Apelin groups: Saline IV, Contrast and Apelin/Contrast groups: Iohexol-350 mg Id/mL, 1.8 g Id/kg IV. We performed serum and 24-hour urine tests on Day-0 and Day-9 which was 48 hours after contrast administration. We collected the kidney with sacrifice on Day-9.

Results: The results showed a significant increase in serum creatinine (Cr) in only Contrast group (p=0.039). In Contrast (p=0.015) and Apelin/Contrast (p=0.007) groups, urinary Cr excretion significantly increased indicating renal tubular injury. The immunohistochemistry for caspase-3 indicated that Contrast group had significant tubular cell damages, while other groups including Apelin/Constrast were less damaged (p=0.014).

Conclusions: We could identify the protective effects of apelin against CIN in the study.





PO2618

Male, but Not Female, Spontaneously Hypertensive Rats (SHR) Have Sustained Renal Injury Following a Single Ischemic Insult Progressing to CKD

Riyaz Mohamed, Jennifer C. Sullivan. *Augusta University, Augusta, GA.*

Background: Renal ischemia-reperfusion (IR) injury is a major cause of acute kidney injury (AKI), which is an independent risk factor for the development of CKD and all-cause mortality. The goal of the current study was to test the hypothesis that hypertensive males will have greater IR injury than hypertensive females resulting in the development of CKD.

Methods: 13-week old male and female SHR were subjected to sham or 30-minute warm bilateral ischemia followed by reperfusion (n=5-6). Systolic blood pressure (BP) measured weekly by tail-cuff.

Results: Plasma creatinine (Pcr) and urine protein creatinine ratio (UPCR) remained elevated at 1-week post IR in male SHR compared to sham (PIR*sex=0.005); Pcr and UPCR returned to baseline in SHR females. Histological examination of SHR kidneys 7 days post-IR showed greater increases in vascular congestion ($P_{sex*IR=}$0.002) and tubular damage (P_{sex*IR}=0.001) in males. However, glomerular filtration rate (GFR) and systolic BP were not altered in both male and female SHR at 1-week post IR. To determine if this was sustained dysfunction or simply delayed recovery, additional 13-week old male and female SHR were subjected to sham or 30-minute warm bilateral ischemia followed by 20 weeks of reperfusion (n=4-5). Male SHR showed progressive increases in UPCR (PIR<0.05) and systolic BP up to 20 weeks post-IR compared to respective shams (PIR=0.001). Whereas in female SHR, UPCR remained at baseline up to 16-week post IR compared to respective sham. However, at 20 weeks of post IR, both male and female SHR exhibit an increase in UPCR compared to respective sham control; although the increase in UPCR was greater in males (P_{sex}=0.01; PIR*sex=0.09). Male SHR also exhibited greater decreases in glomerular filtration rate (GFR: P_{sex}=0.025; P_{sex}=0.12) and increases in systolic BP (P_{sex}=0.0001; P_{IR*sex}=0.27) compared to females.

Conclusions: Our data demonstrated that impaired renal recovery following IR in SHR males results in exaggerated progression towards CKD.

Funding: Other NIH Support - NHLBI

Male SHR		UPCR	GFR (mL/min)	Systolic BP (mmHg)
1 wk post-IR	Sham	1.14±0.23	2.95±0.33	187±8
	IR	3.44±1.37	2.55±0.287	192±6
20 wk post-IR	Sham	1.70±0.26	2.58±0.50	205±10
	IR	4.50±0.85	1.10±0.67	225±4
Female SHR				
1 wk post-IR	Sham	0.77±0.47	3.24 ±0.349	164±10
	IR	0.79±0.349	3.35±0.68	165±3
20 wk post-IR	Sham	1.10±0.54	2.96±1.09	167±9
	IR	2.72±0.46	2.85±0.44	177±9

PO2619

High Serum Strontium May Predict AKI After Cardiac Surgery with Cardiopulmonary Bypass

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Background: The prevalence of acute kidney injury after cardiac surgery under cardiopulmonary bypass (AKI-CPB) is high and it worsens patient prognosis, which renders it a major concern during intensive care. Therefore, a predictable marker of AKI-CPB is required. Because some trace metals have been found to affect renal injury, we investigated their association with AKI-CPB.

Methods: Study 1. We enrolled 30 patients from the Nagoya City University Hospital. Serum concentrations of 19 trace metals were measured before surgery and immediately after CPB withdrawal. We defined AKI according to the KDIGO criteria. Factors associated with AKI-CPB were identified by univariate and multivariate analyses. **Study 2.** We treated male Wistar-ST rats with 1 mg/kg/day of strontium (Sr) or vehicle orally for 3 days, followed by the application of 30 min of ischemia and reperfusion to cause renal injury. Serum creatinine (SCr) and blood urea nitrogen (BUN) levels were evaluated 24 h later. We also incubated human kidney (HK)-2 cells with Sr (0.25 μM, high-Sr or 0.19 μM, normal-Sr) or PBS for 24 h *in vitro*. These Sr concentrations were determined according to the average serum Sr concentrations in patients with and without AKI. The cells were incubated under normoxia (20% O_2) or hypoxia (1% O_2) conditions; then, cell viability and mRNA expression were assessed.

Results: Study 1. The incidence of AKI-CPB was 30% (n = 9). Serum Cr levels before surgery were high in the AKI group. Intraoperative factors did not differ between patients with and without AKI. Univariate analysis revealed significantly higher levels of Sr and arsenic before surgery, and higher Sr, arsenic, and zinc levels after CPB in the AKI group ($p < 0.05$). Multivariate analysis showed that only Sr levels after CPB withdrawal correlated independently with AKI. **Study 2.** The SCr and BUN levels were higher in Sr treated rats than vehicle treated rats. Incubating HK-2 cells with Sr did not affect their viability under normoxia and hypoxia conditions. However, NF-κB mRNA levels increased only under hypoxia conditions following exposure to high Sr levels.

Conclusions: High Sr levels before CPB may be a useful predictor of AKI-CPB. This study suggested that high Sr levels enhance ischemia-induced inflammation following CPB.

PO2620

BAM15 and Mitochondrial DNA Form a Drug-Companion Biomarker Pair Working Through Reactive Oxygen Species in Septic AKI

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Background: Sepsis is multifactorial, so drug-biomarker co-development is likely necessary for developing effective therapeutics. Administration of BAM15, a mitochondrial uncoupler, improved sepsis AKI mortality, kidney function, and mitochondrial function in kidney tubules (ASN, 2019). We now evaluate if BAM15 and mtDNA form a drug companion biomarker pair and are linked mechanistically.

Methods: Mice with sepsis AKI [cecum ligation/puncture (CLP) in CD-1 mice] were treated with BAM15 (5mg/kg IV) at 0h (early) or 6h (delayed) after surgery. Serial plasma and urinary mtDNA was measured by qPCR. This was mimicked *in vitro* by incubating mouse primary cultured proximal tubular cells (PTCs) with serum from CLP mice. Mitochondrial superoxide generation was measured by live cell imaging with MitoSox-Red. Mitophagy detected in Mt-Keima mice [transgenic for pH-sensitive ratiometric fluorescent protein] by measuring mitochondrial pH.

Results: Plasma and urinary mtDNA were increased in CLP mice starting at 3 hr after CLP. Delayed treatment with BAM15 (6 hr) decreased mtDNA at 12 hrs (Fig 1).

CLP serum stimulated superoxide production and release of mtDNA into cultured PCT media; both were proportionately inhibited by BAM15 (Fig 2A-C). Released mtDNA correlated with superoxide production. BAM15 recovered mitochondrial biogenesis through activation of PGC1α pathway and, inhibited CLP reduction of mitophagy.

Conclusions: Sepsis increased kidney mtROS and released mtDNA from PT cells. BAM15 attenuated generation of mtROS and inhibited mtDNA release into urine and also circulating mtDNA even delayed BAM15 treatment. In sepsis AKI, BAM15 changed the trajectory of mitochondrial fate. Our results suggest that BAM15 and mtDNA are mechanistically linked via ROS, and form a drug-companion biomarker pair.

Funding: NIDDK Support

Figure 1 plasma and urine mtDNA from CLP mice treated with BAM15 at 6hr

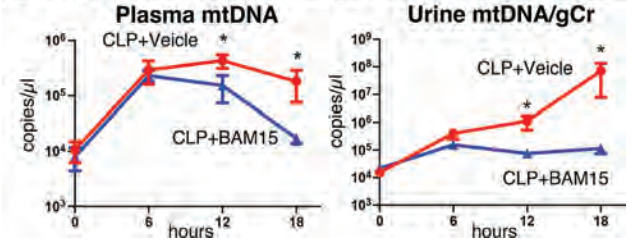
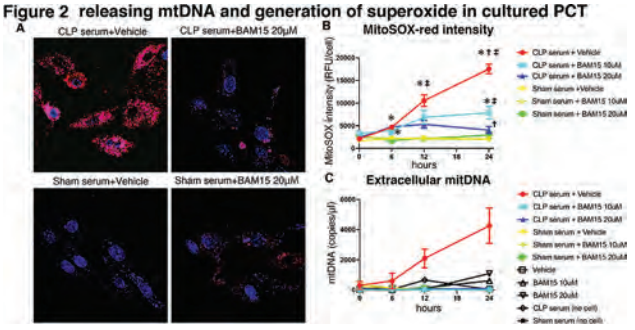


Figure 2 releasing mtDNA and generation of superoxide in cultured PCT



PO2621

Grb2 Promotes Cardiorenal Syndrome Type 3: Roles of Cardiomyocyte Contractile Cytoskeleton, Mitochondria Damage, and Inflammation Response

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Background: Cardiorenal syndrome type-3 (CRS-3) is a damage to heart following acute kidney injury. Although many experiments have found that inflammation, oxidative stress, and cardiomyocyte death are involved in cardiomyocyte pathophysiological alterations during CRS-3, it lacks a non-bias analysis to figure out the primary mediator of cardiac dysfunction. Herein, the aim of our study is to figure out the primary upstream regulator of these intracellular molecular biological events.

Methods: In this study, proteomic analysis was operated in CRS-3 and growth factor receptor-bound protein 2 (Grb2) was identified as a regulator involving AKI-related myocardial damage.

Results: Increased Grb2 was associated with cardiac diastolic dysfunction, mild cardiomyocyte death and prominent myocardial inflammation; these pathological changes could be reversed through administration of Grb2-blocking peptide after AKI. Molecular investigation illustrated that augmented Grb2 promoted cardiomyocytes contractile cytoskeleton degradation through inhibiting the expression of Myosin. In addition, increased Grb2 triggered mitochondrial fission, inactivated mitochondrial autophagy, induced mitochondrial potential reduction, and triggered caspase-9/3 activation. Pro-inflammatory signaling pathways, including NF-κB, MAPK/JNK, and MAPK/p38, were activated by Grb2 in cardiomyocytes following AKI.

Conclusions: Our results identify CRS-3 is caused by Grb2 upregulation which contributes to cardiac dysfunction, cardiomyocyte apoptosis and myocardial inflammation. This finding provides a potential target for the clinical treatment of patients with CRS-3.

PO0001

AKI Identification: Use of Electronic AKI Alerts vs. Electronic Health Records in Hospital Episode Statistics

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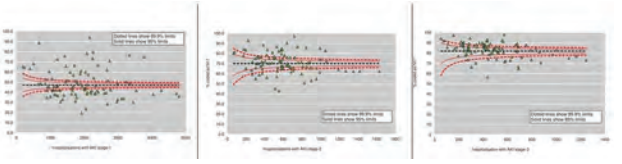
Background: Acute Kidney Injury (AKI) refers to an abrupt decline in the glomerular filtration rate (GFR) potentially associated with significant morbidity and mortality. Since April 2015, an automated real-time electronic (e)-alert system for AKI has been introduced and progressively implemented in England, with alert data being sent to the UK Renal Registry (UKRR) for collection into a master patient index (MPI). Historically, the only way to routinely measure AKI incidence in hospital was to analyse the Hopital Episode Statistics (HES). This project aims to determine whether episodes of AKI identified in the UKRR MPI correspond to coded diagnoses on the discharge record held in HES.

Methods: The UKRR MPI of all AKI e-alerts (stages 1, 2 and 3) in patients aged ≥18 years, between 01/01/2017 and 31/12/2017 were linked to HES data to identify a hospitalised AKI population. Descriptive analyses were conducted to describe the demographics and to investigate whether those with an AKI e-alert also had an International Classification of Diseases (ICD)-10 code for AKI (N17) in HES.

Results: From 01/01/2017 to 31/12/2017, 301,504 hospitalised adults received an AKI e-alert. AKI severity was positively associated with the percentage of AKI alerts coded in HES. There was a significant variation in HES coding between hospitals, most pronounced for AKI stage 1 (mean 48.2% SD 14) versus AKI stage 3 (mean 83.3 % SD 7.3) (figures 1). Younger adults with AKI e-alerts were less often coded in HES for all three AKI stages (33% people aged 18-29 years versus 64% people aged ≥ 85 years).

Conclusions: In 2017, earlier stages of AKI e-alerts were poorly coded in HES. There was also high degree of inter-hospital variability, particularly for AKI stage 1, reflecting potentially poor clinical recognition and documentation in medical records and subsequent clinical coding. AKI e-alerts were poorly captured in HES for younger adults in comparison to those of older age. Use of HES to identify cases of AKI is likely to underestimate the incidence of AKI, especially for AKI stage 1, though a high proportion of the most severe cases will be captured.



PO0002

Assessment of a Modified Renal Angina Index for the Prediction of AKI in Hospitalized Adult Patients

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Background: Risk-stratification tools of incident AKI in hospitalized patients are needed. The renal angina index (RAI) was developed and validated in the pediatric population. The purpose of this study was to evaluate the performance of a modified RAI (mRAI) for the prediction of AKI in hospitalized patients.

Methods: We analyzed data from 55 hospitalized patients admitted to our center. Inclusion criteria consisted of age ≥18, hospital stay ≥3 days, at least 2 serum creatinine (SCr) measures in the first 2 days of hospital stay and one measure at 3-7 days of stay. Exclusion criteria consisted of ESKD, kidney transplant or baseline eGFR <15. At admission, mRAI was calculated using the following formula: **risk level criteria** 1) ICU admission, 2) mechanical ventilation or vasoactive drug support, and 3) diabetes ***X* injury level criteria** of SCr increments of <0.1 mg/dL, ≥0.1 mg/dl, ≥0.3 mg/dL and ≥0.4 mg/dL. AKI was defined as an increase of serum creatinine level ≥ 0.3 mg/dL or ≥ 1.5 times within 48 hours or ≥1.5 times in contrast to baseline creatinine level. We assessed the performance of the mRAI to predict the subsequent development of AKI using KDIGO sCr criteria.

Results: Mean (SD) age was 67.9 (13.3), 47.3% were women and 100% Hispanic. The incidence of AKI at 3-7 days of hospital or ICU stay was 52.7%. Most patients developed AKI stage 1 (61.3%) and 38.7% developed severe AKI (KDIGO-SCr stage ≥2) at 3-7 days. Performance metrics are reported in **Table**. The RAI exhibited a good, AUC of 0.87 (95% confidential interval [CI]: 0.77–0.96; p <0.0001) in ROC analysis, with a cutoff of 8.

Conclusions: The mRAI have robust predictive capacity to identify hospitalized adults patients at high risk of developing AKI. Incorporation of AKI biomarkers into the RAI may potentially improve prediction. The preliminary data of our ongoing study warrants future studies to validate these findings.

Funding: Private Foundation Support

Table: Performance of the mRAI for the prediction of AKI in hospitalized patients

Statistic	Value	95% CI
Sensitivity	89.6%	72.6% to 97.8%
Specificity	76.9%	56.3% to 91.0%
Positive Likelihood Ratio	3.89	1.91 to 7.92
Negative Likelihood Ratio	0.13	0.05 to 0.40
PPV	81.2%	68.0% to 89.8%
NPV	86.9%	69.1% to 95.2%

PO0003

Early Prediction of Hospital-Acquired AKI from Electronic Health Records Using Machine Learning

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Background: Hospital-acquired acute kidney injury (HA-AKI) leads to increased morbidity and mortality. Early prediction of HA-AKI using Electronic Health Records may enable clinicians to modify treatment to minimize risk and AKI severity

Methods: Inpatient admissions from 7/13/2012 – 7/11/2018 who had serum creatinine measured were included. Patients with end-stage renal disease, length of stay <48 hours and AKI at admission were excluded. A validated algorithm was used to determine baseline renal function. AKI was defined according to KDIGO guidelines. Machine learning algorithms were implemented to predict development of HA-AKI beyond the initial 24-hours of admission. 50 input variables to machine learning algorithms (random forest, XGBoost, logistic regression) included demographics, initial laboratory values taken within the first 24-hours of admission, active medications at time of admission, and prevalent comorbidities. Multiple imputation by chained equations (MICE) was used for missing variables. Univariate Feature Selection was utilized where variables were ranked by evaluating contribution to classification outcome. Randomized search strategy was performed to obtain the optimal hyperparameter set for each algorithm. Models were evaluated using a mean area under the receiver operating characteristic curve (AUC) over 5-fold cross-validation

Results: Among 209,300 inpatient admissions, 26,410 (12.6%) developed HA-AKI. For AKI prediction, the AUC of the full model was 0.88 for both random forest and XGBoost, and 0.86 for logistic regression. To balance the tradeoff between model simplicity and performance, 23 variables from univariate feature selection evaluated using random forest were selected in predicting HA-AKI (AUC = 0.87). The probability cut-off point of AKI prediction outcome was determined using Youden's Index based on the balance between false positives and false negatives. A probability cutoff of > 0.23 provided sensitivity and specificity of 78% and 81%, respectively

Conclusions: Our machine learning algorithm applied at 24 hours of admission identifies patients at risk for HA-AKI with excellent accuracy. Significant variables included in this algorithm should be monitored in real-time to allow early identification and preventive interventions in patients at risk for HA-AKI

Funding: Clinical Revenue Support

PO0004

A Meta-Analysis of Clinical Predictors for Renal Recovery and Mortality in AKI Requiring Continuous Renal Replacement Therapy

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Background: Acute kidney injury (AKI) is a common complication in critically ill patients and can result in a broad spectrum of severity. It is well-established that severe AKI requiring continuous renal replacement therapy (CRRT) carries a significant risk for increased mortality compared to non-dialysis AKI. However, there are no concensus guidelines describing the discontinuation criteria from CRRT. Thus, we performed this meta-analysis to determine the clinical predictors for CRRT discontinuation and overall mortality in patients with AKI.

Methods: Ovid MEDLINE, EMBASE, and Cochrane Library were searched without language restrictions up to January 2020. Our inclusion criteria included patients ≥ 18 years of age, non-end-stage kidney disease patients who required CRRT for AKI. Renal recovery was defined by CRRT discontinuation. Intermittent hemodialysis was excluded. Only articles utilizing multivariate analysis were included. We divided our analyses into two cohorts based on the primary outcomes: renal recovery cohort and overall mortality cohort.

Results: For renal recovery cohort (n = 4,497 from 14 studies), the mean effluent dose of CRRT was 24.93 ± 5.87 ml/kg/h with a median duration of CRRT of 3.75 days (IQR 2.45). Increasing urine output at time of CRRT discontinuation (per 100 ml/day), elevated initial SOFA score (per 1 score) and serum creatinine level at CRRT initiation (per 1.0 mg/dl) were predictive of renal recovery with odds ratio of 1.021 (95% CI, 1.012-1.031), 0.890 (95% CI, 0.805-0.984) and 0.995 (95% CI, 0.991-0.999), respectively. For overall mortality cohort (n = 16,948 from 11 studies), The mean effluent dose of CRRT was 26.22 ± 6.47 ml/kg/h with a median CRRT duration of 4.5 days (IQR 3.40). Age (per 1 year) and presence of sepsis were significantly associated with overall mortality with odds ratio of 1.023 (95% CI, 1.006-1.040) and 2.031 (95% CI, 1.267-3.257), respectively. All analyses remained significant through sensitivity analyses. No potential publication bias was identified.

Conclusions: Urine output at CRRT discontinuation, initial SOFA score, and serum creatinine level are predictive of renal recovery and successful CRRT discontinuation. Increasing age and the presence of sepsis are independent risk factors for elevated overall mortality.

PO0005

Regional Variation in Recovery of Kidney Function in Patients Requiring Maintenance Hemodialysis with Acute Tubular Necrosis

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Background: Geographic variations in the likelihood of recovery of kidney function in ESKD attributed to acute tubular necrosis (ATN) has not been well established.

Methods: Using data from United States Renal Data System, we performed a retrospective cohort study of incident maintenance hemodialysis (HD) patients between 1/1/1996-12/31/2015 with ESKD attributed to ATN followed up to 1 year. Recovery of kidney function was defined as discontinuation of HD for at least 90 days and alive without the need for kidney transplantation during this period. We used Fine-Gray models to determine unadjusted and adjusted hazard of recovery while accounting for the competing risk of death.

Results: In 48,771 patients included for analysis, 30% recovered kidney function within 1 year. Most patients received HD within a 10-mile radius of their home. Recovery rates at 1 year were lowest in the northeast and highest in the south; lower in metropolitan compared to micropolitan/rural areas. Recovery of kidney function was less likely to occur with distance between patient and dialysis facilities in adjusted analysis.

Conclusions: Patients living in rural/micropolitan locations and receiving dialysis close to home had higher recovery rates. Studies examining regional differences in practice patterns are warranted.

Funding: NIDDK Support

Predictor		N	% Recovered	Unadjusted SHR [95% CI]	Adjusted* SHR [95% CI]
US region	West	7548	31.0	Ref	Ref
	Midwest	13701	29.3	0.94 [0.89-0.99]	0.98 [0.93-1.04]
	South	16519	33.9	1.07 [1.02-1.13]	1.11 [1.05-1.17]
	Northeast	11003	23.2	0.72 [0.68-0.76]	0.81 [0.77-0.86]
Population	Metropolitan	39108	29.1	Ref	Ref
	Micropolitan/Rural	8730	32.1	1.13 [1.08-1.18]	1.10 [1.05-1.14]
Distance from home to HD facility	0-<10 miles	33859	29.7	Ref	Ref
	10-<25 miles	9776	29.2	0.98 [0.94-1.02]	0.96 [0.92-1.00]
	≥25 miles	5224	30.3	1.02 [0.97-1.10]	0.93 [0.88-0.99]

Abbreviations: SHR = subdistribution hazard ratios, CI = Confidence Interval; * adjusted for age, sex, race, body mass index, initiation calendar period, and medical comorbidities (coronary artery disease, malignancy, heart failure, diabetes, hypertension, peripheral vascular disease, stroke, drug use, and smoking)

PO0006

Development and Validation of a Model to Predict In-Hospital AKI Among Hospitalized US Veterans

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Background: Acute kidney injury (AKI) occurs commonly in hospitalized patients, affects millions of Americans annually, and is recognized as one of the most significant contributors to chronic kidney disease (CKD). As the primary treatment for most AKI is limited to supportive care, improving the health consequences of AKI (most notably CKD) relies on identifying high-risk patients in a timely manner and targeting them for preventive interventions.

Methods: Using data from a random sample of 100,000 hospitalized veterans, we developed and internally validated a gradient-boosted decision tree (GBDT) model for the prediction of in-hospital acute kidney injury. We excluded patients without an available creatinine during their hospitalization (n = 21,165), and randomly divided the remaining patients into a training cohort (n = 39,418), tuning cohort (n = 13,139), and a test cohort (n = 26,278). We divided each patient's hospitalization into 6-hour steps and removed all steps where a patient actively had known AKI. We then used the prior 48 hours of clinical data to predict the onset of AKI during the next 48 hours. After fitting the GBDT model on all steps from the training cohort, we iteratively checked model performance on the tuning cohort to determine optimal parameters for early stopping to prevent overfitting. We then evaluated the model's performance on the test cohort using the maximum predicted score for each patient prior to the onset of AKI.

Results: Our cohort had a mean age of 72, was 96% male, 34% with baseline diabetes mellitus, and 24% with baseline CKD. 11% of patients experienced in-hospital AKI by creatinine-based KDIGO criteria (3.8% in any 6-hour window), and 1.6% of patients experienced AKI stage 2+. The area under the curve (AUC) was 0.76 (95% bootstrap CI 0.75-0.77) for predicting any AKI in the next 48 hours and 0.70 (95% CI: 0.67-0.73) for predicting AKI stage 2+ in the next 48 hours. Patients who met or exceeded a risk threshold of 14.5% had a 33% chance of developing AKI during their hospitalization with a 42% sensitivity.

Conclusions: In a retrospective validation in a large national cohort of veterans, a predictive model for acute kidney injury identifies nearly half of patients who will experience AKI prior to its onset.

Funding: Veterans Affairs Support

PO0007

Adequacy of Kidney Follow-Up Among AKI Survivors After Hospital Discharge

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Background: Acute kidney injury (AKI) affects 20% of hospitalized patients and results in long-term adverse outcomes. To limit its complications, post-discharge follow-up is advised. The objective of the study was to evaluate the frequency of appropriate follow-up after discharge among AKI survivors.

Methods: This was a population-based cohort study of adult Olmsted County residents hospitalized at their local hospital (Mayo Clinic in Rochester, MN) with an episode of stage II or III AKI between 2006 and 2014. Those dismissed from the hospital on dialysis or who died within 30-days after discharge were excluded. The cumulative incidence of adequate kidney follow-up defined by a serum creatinine (SCr) level and/or an in-person healthcare visit within 30-days, 90-days, or 1-year after discharge was described.

Results: There were 563 survivors of AKI studied [Stage II: N=360 (64%); Stage III: N=203 (36%)]. The 30-day cumulative incidence of follow-up with SCr was 78% (95% confidence interval (CI) : 74%, 81%), by provider visit was 80% (95% CI: 77%, 83%), by *both* SCr assessment and provider visit was 70% (95% CI: 65%, 73%). Within 90-days and 1-year, the cumulative incidences of *both* SCr assessment and provider visit rose to 81% and 91%, respectively. Within 30-days after discharge, only 13% (95% CI: 10%, 16%) of these stage II or III AKI survivors saw a nephrologist. The statistically significant predictors of receiving *both* a SCr assessment and provider visit within 30-days included higher body mass index, worse baseline and discharge kidney function, higher comorbidity burden, greater maximum AKI severity, and longer duration of AKI during the hospitalization. Age, sex, race/ethnicity, education status, and socioeconomic status did not predict kidney follow-up.

Conclusions: These data demonstrated that 30% of patients with moderate to severe AKI received insufficient kidney follow-up in the 30-day post-discharge interval. Medical risk factors rather than social/demographic characteristics were the primary determinants of kidney follow-up.

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PO0008

Predicting Intra-ICU Mortality Using Machine Learning Algorithms in Patients Who Require Acute Renal Replacement Therapy in a Critical Care Unit

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Background: The Acute Physiology, Age, Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score(SAPS) are not a fair mortality prediction tools for patients receiving acute renal replacement therapy (RRT) in the ICU. Our objective was to develop a series of machine learning models to predict intra-ICU mortality for patients requiring acute dialysis therapy using data obtained one day prior to RRT initiation.

Methods: We extracted data on patients who commenced acute RRT captured in eICU and MIMIC databases. We trained machine learning models by using the eICU and MIMIC dataset. The validity of those models was then evaluated by using MIMIC and eICU.

Results: The eICU cohort included 2,360 patients and MIMIC included 1,274 patients who met our eligibility criteria. The discrimination power of the model was evaluatedby calculating the area under the receiver operating characteristic curve (AUC). The intra-ICU mortality AUC of the Sequential Organ Failure Assessment (SOFA) score using data collected one day before RRT initiation was 0.803 (95% CI 0.777-0.829) in eICU and 0.683 (95% CI 0.636-0.729) in MIMIC. The intra-ICU mortality AUC of machine learning models using logistic regression (LR), XGBoost, random forest (RF) and multilayer perceptron (MLP) trained in eICU cohort were 0.858 (95% CI 0.850-0.867), 0.858 (95% CI 0.850-0.866), 0.859 (95% CI 0.848-0.870), 0.864 (95% CI 0.851-0.876) and validated in MIMIC were 0.799 (95% CI:0.775-0.824), 0.809 (95% CI:0.786-0.833), 0.814 (95% CI 0.791-0.837), 0.800 (95% CI 0.776-0.825), respectively. When training the models using MIMIC dataset, the intra-ICU mortality AUCof LR, XGBoost, RF and MLP were 0.818 95% CI (0.786-0.852], 0.821 (95% CI 0.787-0.856) 0.822 (95% CI 0.791-0.854), 0.827 (95% CI 0.795-0.858), respectively. Validating these models using eICU dataset, the AUC of LR, XGBoost, RF and MLP were 0.846 95% CI:0.828-0.864, 0.847 (95% CI 0.829-0.865), 0.853 (95% CI 0.835-0.870), 0.846 (95% CI 0.828-0.865), respectively.

Conclusions: In this study, we designed machine learning models to make intra-ICU mortality prediction for patients who required RRT. Our models correlated better than SOFA score in predicting the mortality of patients requiring RRT in ICU. All of the models almost had excellent performance in both databases.

PO0009

Risk Factors for Mortality and Hospital Readmission Following AKI

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Background: Acute kidney injury (AKI) occurs in over 20% of hospitalized patients and is associated with long-term morbidity and mortality. The purpose of this study is to identify risk factors for readmission for renal cause and mortality following a hospitalization with AKI in US Veterans.

Methods: AKI was defined as a creatinine increase of ≥0.3 mg/dL at or after admission to a VA hospital between 2013 and 2018. The primary outcomes were death and readmission for a renal indication. Proportional hazards frailty model was applied. Variables evaluated included demographics, comorbidities, and laboratory data. The final model was chosen based on clinical relevance and parsimony.

Results: From a cohort of 624,822 Veterans with AKI, 218,839 (35%) met inclusion criteria. Reasons for exclusion were <1 year of prior patient data (35%), missing serum creatinine values (14%), palliative status or metastatic cancer (13%), or death during the hospitalization (4%). AKI was present on admission in 71% of patients and developed after admission in 29%. Overall, 48,202 (22%) died within one year. Between 2013 and 2018, 101,170 (46%) died and 21,116 (9%) experienced a renal readmission. The patient characteristics associated with increased hazard of death included age (HR=1.53 per 10 years, CI 1.52-1.54, p<.001), male sex (HR=1.27, CI 1.22-1.32, p<.001), heart failure (HR=1.55, CI 1.53-1.57, p<.001), prior myocardial infarction (HR=1.14, CI 1.11-1.17, p<.001), peripheral vascular disease (HR=1.15, CI 1.13-1.17, p<.001), anemia (HR=1.32, CI 1.30-1.33, p<.001), chronic kidney disease (HR=1.15, CI 1.13-1.17, p<.001), creatinine at time of admission (HR 1.012, CI 1.009-1.015, p<.001) and increase from pre-admission values (HR 1.045, CI 1.041-1.048, p<.001). The same patient characteristics were significant predictors of readmission for a renal indication.

Conclusions: We report factors in AKI survivors that predict long-term mortality and hospital readmission due to renal indication among US Veterans. Cardiovascular diseases were prominent predictors, and AKI follow-up should focus on those with heart disease. Future studies should evaluate the potential benefit in this population from post-hospitalization specialty AKI follow-up.

PO0010

CRRT Is Associated with Improved Kidney Recovery from Dialysis-Requiring AKI in a Multicenter Retrospective Analysis

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Background: AKI requiring dialysis (AKI-D) is common with a high rate of adverse outcomes. Little is known about modifiable factors that promote kidney recovery.

Methods: Five CTSA universities (UAMS, UAB, UKY, MUSC and Emory) formed a consortium to identify modifiable risk factors for kidney recovery in AKI-D patients. We selected all patients that received dialysis while in the hospital, then excluded patients from the cohort with a diagnosis related to ESKD, kidney transplantation or CKD stage V at the time of the first RRT. Modality of dialysis, comorbidities and outcomes were analyzed.

Results: The total number of patients in the four available cohorts was 4537 (range 647-1477). Outcomes were determined at the time of discharge from the hospital. The primary outcomes in the study were death (n=2190, 48.3%), alive and dialysis-dependent at discharge (n=1160, 25.6%) or alive and dialysis-free at discharge (n=1187, 26.2%). We defined dialysis dependence as receiving dialysis within the last four days of hospitalization. We compared patients that were initiated on CRRT to patients that were initiated on intermittent hemodialysis (iHD) while adjusting for confounders: sepsis, age, race, gender, qSOFA, mechanical ventilation, serum bicarbonate and serum potassium at the time of dialysis initiation. We analyzed hospital cohorts separately. There was a higher risk of death in patients initiated on CRRT vs. iHD. The odds ratios and 95% CIs for death were: UAMS 2.8, 1.9-4.2; UAB 3.2, 2.1-4.9; MUSC 3.7, 2.6-5.3 and UKY 3.1, 2.3-4.2. Among survivors, patients started on CRRT generally had a lower risk of being dialysis-dependent at discharge. The odds ratios and 95% CIs for renal recovery were: UAMS 0.1, 0.04-0.2; UAB 0.3, 0.1-0.5; MUSC 0.3, 0.2-0.5 and UKY 0.8, 0.5-1.2.

Conclusions: The odds of kidney recovery were significantly better for patients started on CRRT in three of the four cohorts examined in this study and trended toward favoring CRRT in the fourth. This has important implications for care of patients with AKI in the ICU. We believe the increased mortality in the CRRT group reflects the sicker nature of patients in that group and is not inherent to CRRT as an initial dialysis modality.

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PO0011

Region-wide Implementation of Best Practice in AKI

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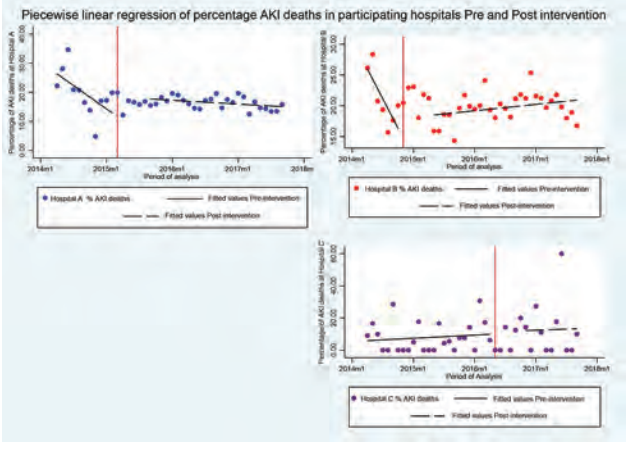
Background: The Cheshire & Merseyside Acute Kidney Injury Network, United Kingdom, rolled out best practice guidelines of13 interventions for Acute Kidney Injury (AKI) in October 2014. The aim was to assess the impact of the guidelines.

Methods: Setting & Population: Hospitals in Cheshire & Merseyside. **Predictor:** Time period before & after introduction, allowing six-month bedding in period. **Outcome: Percentage AKI:** Number of AKI per month, divided by total number of admissions/ month expressed as %. **Percentage AKI deaths:** Number of AKI related deaths per month divided by total deaths/month expressed as %. **Data analysis:** Descriptive & Piecewise Linear Regression.

Results: The region saw a notable increase in the number of admissions/month (31,173 vs 38,443) and AKI episodes (4,871 vs 44,493) in the 8 hospitals in pre and post guideline implementation period. Five hospitals were excluded due to guideline implementation pre-roll out (2), implementation dates not provided (2) & no pre-implementation data (1). The outcomes in the 2 periods are detailed in the Table. The introduction of E-alert saw an increase in AKI detection across the hospitals. The figure shows longitudinal piecewise regression curves. The most significant reduction was noted in hospital A.

Conclusions: The rollout of interventions caused an increased and sustained recognition of AKI, across the hospitals. The % AKI deaths stayed the same except in Hospital A. We theorise that the onsite nephrology team in Hospital A aided implementation of the guidelines and training of wider healthcare staff which made the impact. This study highlights the hurdles faced in implementing AKI improvement strategies across various healthcare settings.

		Pre-intervention	Post-intervention	P-Value
HOSPITAL A	% AKI Median (IQR)	1.1 (1.0-1.9)	4.9 (4.7-5.2)	0.0001
	% AKI deaths Mean (95% CI)	19.6 (16.9-22.4)	16.4 (14.5-18.2)	0.05
HOSPITAL B	% AKI Median (IQR)	5.2 (1.3-5.7)	4.9 (4.6-5.2)	0.85
	% AKI deaths Mean (95% CI)	21.1 (18.9-23.3)	19.7 (18.6-20.8)	0.24
HOSPITAL C	% AKI Median (IQR)	4.2 (2.5-5.3)	3.3 (2.9-4.7)	0.40
	% AKI deaths Mean (95% CI)	7.9 (2.8-12.9)	12.8 (5.1-20.4)	0.30



PO0012

Impact of Impella on Renal Outcomes in High-Risk Percutaneous Coronary Intervention and Cardiogenic Shock: Meta-Analysis

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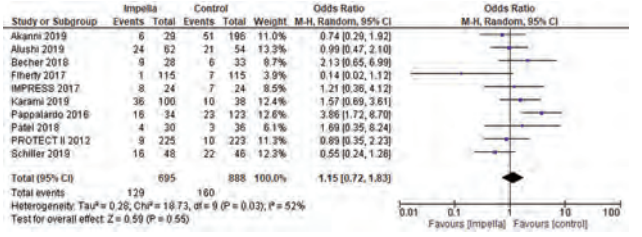
Background: Several studies have examined the impact of Impella on renal outcomes in high-risk PCI and cardiogenic shock (CS). These studies were limited in study sample size and exhibited mixed results. We conducted a meta-analysis of these studies to evaluate the association between the use of Impella and adverse renal outcomes.

Methods: We searched multiple databases up to March 2020 for studies, which evaluated the effect of Impella use on adverse renal outcomes in cardiogenic shock and high-risk PCI. Studies that reported adverse renal outcomes were included. Odds ratios (ORs) with corresponding 95% confidence interval (CI) were synthesized.

Results: A total of ten studies were included in the meta-analysis. The included studies evaluated a total of 1,583 patients with CS or undergoing high-risk percutaneous coronary intervention (PCI), including 695 patients assisted with Impella. The incidence rate of adverse renal outcomes ranged from 0.87% to 47.1% in the Impella group and from 4.48% to 69.6% in the control group. The HRs or ORs ranged from 0.14 to 3.86. Use of Impella was not associated with significant increase in the risk of adverse renal outcomes as compared with controls (OR: 1.15, 95% CI: 0.72-1.83, I^2 = 52%). Subgroup analysis revealed that the risk of adverse renal outcomes was comparable with comparators in patients with refractory CS, myocardial infarction complicated by CS, and patients undergoing high-risk PCI.

Conclusions: Our meta-analysis showed that the use of Impella may not have impact on renal outcomes in CS and high-risk PCI. Further randomized controlled trials are needed to better assess the effects of Impella on renal outcomes.



PO0013

Incidence and Impact of AKI on Patients with Implantable Left Ventricular Assist Devices: A Meta-Analysis

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Background: This systematic review and meta-analysis was performed to evaluate the acute kidney injury (AKI) incidence and its associated risk of mortality in patients with implantable left ventricular assist devices (LVAD).

Methods: A systematic literature search in MEDLINE, EMBASE, and Cochrane Databases was conducted through January 2020 to identify studies that provided data on the AKI incidence, and AKI-associated mortality risk in adult patients with implantable LVADs. Pooled effect estimates were examined using random-effects, generic inverse variance method of DerSimonian-Laird.

Results: 56 cohort studies with 63,663 LVAD patients were enrolled in this meta-analysis of AKI incidence. The pooled incidence of reported AKI was 24.9% (95%CI: 20.1%-30.4%), but rose to 36.9% (95%CI: 31.1%-43.1%) when applying the standard definition of AKI per RIFLE, AKIN, and KDIGO criteria. The pooled incidence of severe AKI requiring renal replacement therapy (RRT) was 12.6% (95%CI: 10.5%-15.0%). AKI incidence did not differ significantly between types of LVAD (p = 0.35) or indication for LVAD use (p = 0.62). While meta-regression analysis did not demonstrate a significant association between study year and overall AKI incidence (P=0.55), the study year was negatively correlated with incidence of severe AKI requiring RRT (slope = -0.068, p <0.001). The pooled odds ratios (ORs) of mortality at 30 days and 1 year in AKI patients were 3.66 (95% CI, 2.00-6.70) and 2.22 (95% CI, 1.62-3.04), respectively. The pooled ORs of mortality at 30 day and 1 year in severe AKI patients requiring RRT were 7.52 (95% CI, 4.58-12.33) and 5.41 (95% CI, 3.63-8.06), respectively.

Conclusions: 37% of LVAD patients developed AKI based on standard definitions and 13% developed severe AKI requiring RRT. There has been potential improvement in the incidence of severe AKI requiring RRT for LVAD patients. AKI in LVAD patients was associated with increased 30-day and 1-year mortality.

PO0014

AKI in the Emergency Department: A Prospective Case-Control Study

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Background: Acute kidney injury (AKI) is an abrubt decline in kidney function that occurs in hours or days. AKI has been throughly studied in the hospital setting, however data on community-aquired AKI are scarce. The aim of this study was to investigate the incidence, causes and prognosis of patients presenting with AKI to the emergency department (ED).

Methods: This was a prospective case-control study in which serum creatinine (SCr) measurements of all patients presenting to the ED of Landspitali–The National University Hospital in Reykjavík were examined for the presence of AKI. The study started on January 1, 2020, and we present data until March 3, 2020. All patients who met the criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex and time of ED admission. Participants signed informed consent and were questioned about their medical history, habits and use of medications, including over-the-counter (OTC) medications and supplements, in the week prior to admission. Medical records were also reviewed with regard to prior diseases and medical prescriptions.

Results: From January 1 to March 3, 124 cases of AKI were identified among patients presenting to the ED, 114 (92%) of whom participated in the study. The mean (±SD) age of the 114 AKI cases and the 228 controls was 68.7±15.2 years and 68,8±15.0 years, respectively; 43% of cases and controls were female. AKI cases were significantly more likely than controls to have been taking non-steroidal anti-inflammatory drugs (NSAIDs) (36,0% vs 20,6%, p<0,01) in the week preceding the ED visit. In both cases and controls, the usage of OTC NSAIDs was more common than prescription NSAIDs (72.2% and 66.0%). No significant difference was observed between AKI cases and controls in use of ACE-inhibitors/angiotensin receptor blockers (45.6% vs 39.9%, p=0.314). The use of proton pump inhibitors was less common among AKI cases than controls (27.2% vs 41.7%, p<0.01) and same was true for statins (22.8% vs 33.3%, p=0.045).

Conclusions: These preliminary results suggest a significant contribution of OTC NSAID use to AKI among patients presenting to the ED. A detailed information on adverse events should be provided when these medications are sold over the counter.

Funding: Government Support - Non-U.S.

PO0015

Prehospital Systolic Blood Pressure and Lactate Are Early Predictors of AKI After Trauma: A Prospective Validation Study

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Background: We have already reported that prehospital systolic blood pressure and lactate can be predictive factors for acute kidney injury (AKI) after trauma. This study is a prospective validation study to determine whether these risk factors are helpful.

Methods: We evaluated all trauma patients who were admitted from January 2019 to December 2019. Patients who were <16 years of age, patients with burns, and patients with chronic kidney disease were excluded from the present study. AKI was defined according to the risk, injury, failure, loss of the kidney function, and end-stage kidney disease (RIFLE) classification from serum creatinine alone.

Results: Four hundred -three patients were included in the analysis. The prevalence of AKI in the overall population was 14.7% including 11.7% of patients with stage R, 2.0% of patients with stage I and 1.0% with stage F. The incidence of stage I and F AKI in the high-risk group (5 of 38 patients, with the positive predictive value of 13.2%) was significantly higher (P<0.001) than that in the low-risk group (7 of 358 patients, with the negative predictive value of 98.1%).

Conclusions: The prehospital systolic blood pressure and early hospital arterial lactate showed good performance in the early prediction of AKI after trauma. These parameters are associated with the early onset of AKI after trauma and may be an early predictor of the effects of treatment to prevent AKI.

PO0016

Association of Race and Risk of Future Scleroderma Renal Crisis at Systemic Sclerosis Diagnosis

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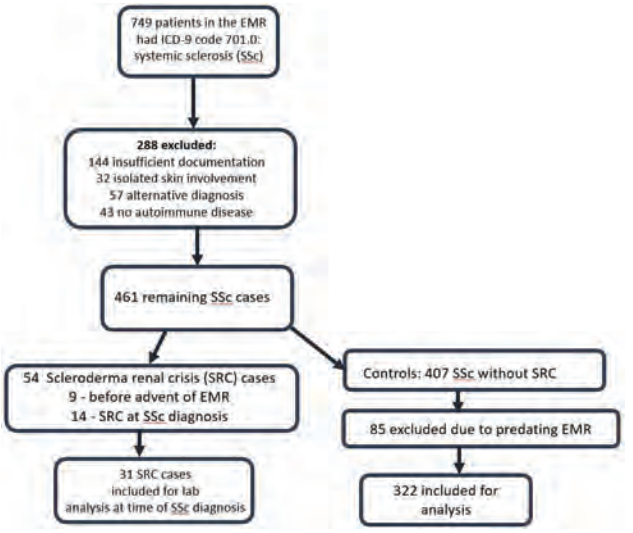
Background: Scleroderma renal crisis (SRC) is a rare and severe manifestation of systemic sclerosis (SSc). Although it is well documented that Blacks with SSc have worse morbidity and mortality than non-Blacks, racial predilection for SRC is underreported. We examine the association of race and future development of SRC in an SSc cohort.

Methods: Using the electronic medical record of the U.S. Military Health System which consisted of 9.6 million beneficiaries worldwide, we conducted a comprehensive chart review of each patient with SSc from 2005 to 2016 (see flowchart). The final study cohort was comprised of 31 SRC cases and 322 SSc without SRC controls. We conducted logistic regression of SRC as the outcome variable and race (Black vs. non-Black) as the primary predictor variable, adjusted for age, estimated glomerular filtration rate (eGFR), hypertension and proteinuria at SSc diagnosis.

Results: Out of 353 patients, 294 had identifiable race (79 Black, 215 non-Black). Thirteen out of 79 Blacks (16.5%) vs. 16/215 (7.4%) non-Blacks developed SRC (p=0.02). Black SRC patients were younger (47 ± 12 vs. 57 ± 13 years, p=0.04) and had a higher eGFR at baseline (93 ± 30 vs. 61 ± 17 ml/min/1.73m2, p=0.003) than their non-Black counterparts. Other baseline clinical and laboratory characteristics were comparable between the 2 racial groups with SRC. On adjusted analysis, Blacks had a significantly higher risk of developing SRC than non-Blacks (odds ratio 6.4, 95% CI 1.3-31.2, p=0.02).

Conclusions: Black race was independently associated with a higher risk of future SRC. Future studies are needed to elucidate the mechanisms that underlie this important association.



Flowchart of study participants. EMR: electronic medical record; ICD-9: International Classification of Diseases, 9th Revision; SRC: scleroderma renal crisis; SSc: systemic sclerosis.

PO0017

Racial Differences in AKI Following Percutaneous Coronary Intervention

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Background: Percutaneous coronary intervention (PCI) is a risk factor for AKI, but few studies have quantified racial differences in AKI incidence following PCI.

Methods: We examined the association of self-reported race – black, white, and other – and baseline eGFR with AKI incidence among patients captured in the Duke Databank for Cardiovascular Disease (DDCD) who underwent PCI at Duke between January 1, 2003 and December 31, 2013. AKI was defined as ≥ 1.5-fold increase in serum creatinine from outpatient reference value before PCI to the peak value within 7 days post-PCI or a 0.3 mg/dl increase from the reference value within 48 hours. We used logistic regression adjusted for demographics, comorbidities, predisposing medications (NSAIDS, RAAS inhibitors, diuretics), PCI indication (presenting with vs without acute coronary syndrome), peri-procedural prophylaxis with IV fluids and n-acetylcysteine, urgency of PCI and BP at time of PCI.

Results: Of 9422 patients (median age 63y [IQR 54 to 72]; 33% female; 75% white, 20% black, 5% other race), 9% developed AKI: 14% of blacks, 8% of whites, 10% in other race groups. After adjustment, black race was associated with greater likelihood of AKI: odds ratio (OR) 1.80 in black (vs white) patients (95% confidence interval (CI) 1.49 to 2.18. Compared to white, other race was not associated with AKI: OR 1.31, 95% CI 0.91 to 1.87. Low baseline eGFR was associated with graded, higher likelihood of AKI: p for trend <0.001. There was no interaction between race and baseline eGFR.

Conclusions: Black patients had nearly twice the likelihood for AKI following PCI than whites despite adjustment for baseline kidney function, prophylaxis and procedural characteristics. Future investigations should identify other factors that predispose black individuals to disparate AKI risk following PCI.

Funding: Private Foundation Support

PO0018

The Spectrum of Biopsy-Proven Kidney Diseases in 2027 Patients with AKI

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Background: Acute kidney injury (AKI) is a group of highly heterogeneous, complicated clinical syndrome. The kidney biopsy plays an irreplaceable role in the evaluation of patients with unexplained AKI and may offer fresh insights into disease heterogeneity. Hence, in this study we aim to analyze the pathological disease spectrum, etiology, and renal recovery of biopsy-proven AKI patients.

Methods: We retrospectively analyzed the clinical and pathological data of AKI patients who went to a kidney biopsy during the hospitalization at our center from January 2013 to December 2018. We classified included patients into pure AKI and ACKD two groups.

Results: The study included 2027 AKI patients who had undertaken renal biopsy, which accounting for 6.8% of the total renal biopsy cases and 31.7% of the total hospitalized AKI cases during the same period. The majority of AKI patients were male (65.1%), with an average age of 42±16.5 years, pure AKI and ACKD account for 21.6% and 78.4%.%. Pure AKI mainly presented as AKI-3 (74.8%), while ACKD mostly presented as AKI-1 (53.5%). The proportion of patients undergoing renal replacement therapy in pure AKI group was significantly higher than ACKD group (29.3% vs 11.9%, P <0.001).) In pure AKI group, acute interstitial nephritis (AIN) was most common (56.1%), followed by acute tubular necrosis (ATN) (34.6%). The main cause of AIN was due to drugs (84.9%) and the main causes of ATN were infections (41.7%) (epidemic hemorrhagic fever) and drugs (38.4%). In ACKD group, primary and secondary glomerular disease accounted for 70.6%.and 26.9%, and the most frequent pathological disease were IgAN, followed by MCD, FSGS, MN, LN, AAV. Among the followed-up patients the proportions of complete, partial and non-renal recovery were 73.2%, 13.3% and 13.5%, respectively.

Conclusions: Among biopsy-proven AKI patients, pure AKI was relatively rare while ACKD accounts for the majority. Pure AKI tend to be more serious than ACKD and more patients required dialysis. ACKD patients had a wide spectrum of pathological diseases, and the prognosis of renal recovery was worse than pure AKI.

Funding: Private Foundation Support

PO0019

Higher Ambient Level of Nitrogen Dioxide Is Associated with an Increased Risk of AKI

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Background: Previous studies have suggested that long-term exposure to air pollution increased the risk of chronic kidney disease and its progression. However, the effect of air pollution on the risk of acute kidney injury (AKI) has not been studied.

Methods: We selected from the Epidemiology of AKI in Chinese Hospitalized patients (EACH2 study) AKI cases of which the onset date could be unambiguously determined. We obtained city-specific daily averages of the ambient level of $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2 and O_3, from the Ministry of Environmental Protection of China. We used the time-stratified case crossover approach to examine the association between the ambient level of air pollutants and the risk of AKI in the selected cases.

Results: A total of 11,293 AKI cases that met the inclusion and exclusion criteria were selected, of which, 3175 (28.1%) were severe AKI (stage 2 or 3). In univariable analysis, the ambient levels of NO_2 and SO_2, were significantly associated with the risk of AKI. In the multivariable analysis that incorporated all six pollutants in the same model, NO_2 was the sole pollutant whose level remained to be associated with the risk of AKI ($p<0.001$). The relationship between level of NO_2 and the risk of AKI appeared to be linear, with an estimated odds ratio of 1.072 (95% CI: 1.033, 1.113) for each increment of one standard deviation in the exposure. The association was consistent across the subgroups stratified by age, gender, baseline eGFR, AKI severity, need for intensive care, and season.

Conclusions: Higher ambient level of NO_2 was associated with an increased risk of AKI in hospitalized adults in China.

PO0020

AKI After Procedures of Orthotopic Liver Transplant: Risk Factors, Renal Outcomes and Survival

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Background: The incidence of acute renal injury (AKI) after orthotopic liver transplantation (OLT) ranges between 40 and 70%. The etiology of this syndrome is multifactorial.

Methods: Medical records of patients undergoing OLT in the period from January 2012 to August 2019 were reviewed. A total of 355 patients were included. 171 patients presented AKI. Baseline characteristics, variables during surgery and variables during their stay in intensive were analyzed. Renal outcomes and survival were also analyzed.

Results: In the group without AKI age mean was 45.8 years and 37% were men, in the group with AKI the age mean was 51.2 years and 54% were men (P = 0.001). Mean baseline creatinine was 0.77 while vs 0.88 mg/dl P = 0.003. Furosemide prior to transplantation was found: 51.6% vs 71.9% P = 0.001. A difference was also found between the incidence of AKI and the number of AKI events in the 3 months prior to transplantation (17.3% vs. 37.4% P = 0.001) and (0.21 vs. 0.53) During surgery. Difference was found in maximum lactate, maximum dose of norepinephrine and vasopressin use during surgery: (5.1 vs. 5.8 P = 0.014), (0.59 vs 0.34 P = 0.001), (36% vs 51% P = 0.003) Differences were also found in drained ascites and anehepatic period: (1508 vs 973 SD vs 1871 P = 0.021) and (52.9 vs 57.4 P = 0.014). In the stay in the ICU, there was a difference in the income of liquids first and second 8 hours after transplant (1319 vs 1984 P = 0.001) and (1208 vs 1606 P = 0.009), norepinephrine dose in the first 24 hours (0.14 vs 0.27 P = 0.001), use of vancomycin and anidulafungin (27.1% vs. 42.1% P = 0.02) and (3.8% vs. 13.4% P = 0.001), transfusion of blood derivatives 33.15% vs 59% (P = 0.001). There was difference in creatinine and GFR at the end of hospitalization (0.67 vs 0.97 P = 0.001) and (104 vs 82.6 P = 0.001). Survival at 7 days after the transplant 100% vs 96.5% P = 0.01. Survival 30 days 99.5% vs 93.6% P = 0.002.

Conclusions: The incidence of AKI in the first 7 days was 48%, which is consistent with that reported in the world literature. The development of AKI seems to be multifactorial influencing baseline characteristics of patients before transplantation and renal insults during surgery and intensive care stay. AKI was associated with higher mortality at 7 and 30 days, in addition to lower GFR at patient discharge and higher risk of CKD.

PO0021

Anemia Following AKI After Non-Cardiac Surgery and Long-Term Outcomes: The NARA-AKI Cohort Study

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Background: The aim of this study was to investigate whether acute kidney injury (AKI) is an independent predictor of anemia and whether anemia following AKI is a mediator of mortality after AKI.

Methods: This is a retrospective cohort study. Adults who underwent non-cardiac surgery from 2007 to 2011 were included. Those with obstetric or urological surgery, missing data for analyses, or preoperative dialysis were excluded. Subjects were followed until the end of 2015 or loss to follow-up. The exposure of interest was postoperative AKI defined by KDIGO criteria. The outcome variables were hematocrit values measured at 3, 6, and 12 months postoperatively and mortality. Associations between AKI and hematocrit or association between AKI and mortality were examined by multivariable linear regression or cox regression analyses, respectively. Data were adjusted for potential confounders.

Results: Among 6692 subjects, 445 (6.6%) developed AKI. Among those with postoperative data, AKI was independently associated with lower hematocrit values at 3, 6, and 12 months postoperatively, with coefficients [95% confidence interval] of −0.79 [−1.47 to −0.11], n=1750, −1.35 [−2.11 to −0.60], n=1558, and −0.91 [−1.59 to −0.22], n=2463, respectively. Higher stages of AKI and longer duration of AKI were associated with more severe anemia. AKI was associated with higher mortality after 3 months postoperatively with hazard ratio [95% confidence interval] of 1.54 [1.12 to 2.12]. Further adjustment with hematocrit values at 3 months attenuated the association (1.45 [1.05 to 2.00]). Mediation effect was significant (p=0.02) by mediation analysis.

Conclusions: AKI was an independent predictor of anemia following AKI. This might be due to permanent interstitial damage and impaired erythropoietin production. Higher mortality associated with AKI was at least partially mediated by anemia following AKI. Whether correction of anemia following AKI improves outcome of AKI requires further research.

Funding: Private Foundation Support

PO0022

The Association of Intraoperative Gross Hematuria on Postoperative AKI After Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy: A Retrospective Study

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Background: Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has been established in the management of peritoneal carcinomatosis (PC). Although it's still necessary to take adequate measures against major postoperative complications including acute kidney injury (AKI), there is no consensus on how to assess and stratify risk for patients with postoperative AKI following CRS+HIPEC. The aim of this retrospective cohort study is to investigate the association of intraoperative gross hematuria as a surrogate marker of ureter injury with post-operative AKI incidence.

Methods: We conducted a retrospective cohort study consisting of patients without impaired pre-operative kidney function who underwent CRS+HIPEC at a single referral center, Center Hospital of the National Center for Global Health and Medicine, and evaluated the relationship between intra-operative gross hematuria and the incidence of post-operative AKI defined by the Kidney Disease Improving Global Outcomes practice guidelines. We estimated the adjusted odds ratio of hematuria for AKI by multivariate logistic regression with linear terms of intra-operative hematuria, PC index score(PCI), sum of the subscores for abdominoperitoneal region 4-8(4:left flank, 5: left lower, 6: pelvis, 7: right lower, 8:right flank) of PCI ,Body Mass Index, estimated blood loss, age, pre-operative estimated glomerular filtration rate and platina-based infusion (cisplatin) without any interaction terms.

Results: We enrolled 185 patients (males, 37%) and 25 patients developed intra-operative gross hematuria. Post-operative AKI occurred in 10 (40%) of 25patients with hematuria and 28 (17.5%) of 160 patients without hematuria. The crude odds ratio for exposed to hematuria was 3.14 (95% confidence interval: 1.30-7.60, p=0.020) for post-operative AKI. Adjusted odds ratio estimated by the multivariate logistic regression was 4.57 (95% confidence interval : 1.55-13.45, p=0.006).

Conclusions: We first disclosed that the intra-operative gross hematuria is significantly associated with post-operative AKI incidence after CRS+HIPEC.

PO0023

Decreased Urinary Uromodulin Is Potentially Associated with AKI: A Systemic Review and Meta-Analysis

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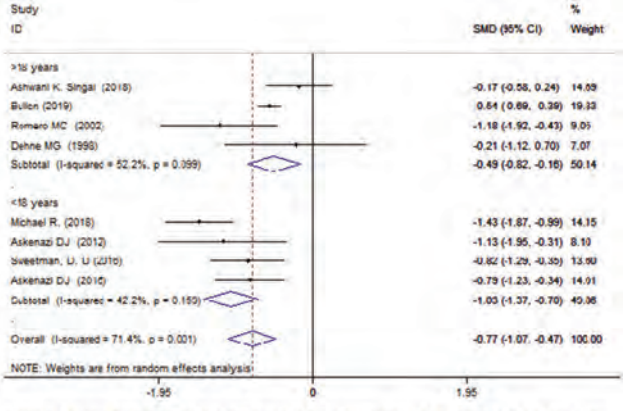
Background: Conventional diagnostic criteria based on the serum creatinine isn't sensitive enough to detect Acute Kidney Injury (AKI) timely. Urinary uromodulin (uUMOD) is one of the novel biomarkers being studied for the value of predicting AKI. However, currently available publications showed inconsistent outcomes. This meta-analysis aimed to evaluate the potential association between uUMOD and AKI.

Methods: We searched research articles in Pubmed-Medline, Web of Science, Cochrane library, Embase, China National Knowledge Infrastructure, and Weipu Database(up to 2020.3). Random-effects models were used to estimate the standardized mean difference (SMD) between AKI and Non-AKI. The sensitivity analysis was conducted using the leave-one-out method. Random-effects meta-regression was performed to evaluate the impact of potential confounders on age and surgery.

Results: The meta-analysis was comprising 2678 subjects of 8 studies, which showed that the uUMOD in the patients with AKI was significantly lower than the Non-AKI patients (SMD:-0.77, P=0.001, 95% confidence interval -1.07,-0.47). Subgroup analysis indicated a significant difference in different ages and surgery group(Figure1-2). Sensitivity analysis displayed the synthetic outcome always in the 95% CI of the pool SMD suggesting a robust result.

Conclusions: The study suggests a potential negative association between uUMOD and AKI. Further studies are needed to investigate the promising diagnostic values and mechanisms in protecting AKI.



Ficure 1.Subgrcup analysis for age difference of urine uromodulin in the patients of AKI and Non-AKI. CI: Confident Interval, SMD: Standardized Mean Difference; AKI: Acute Kidney Injury

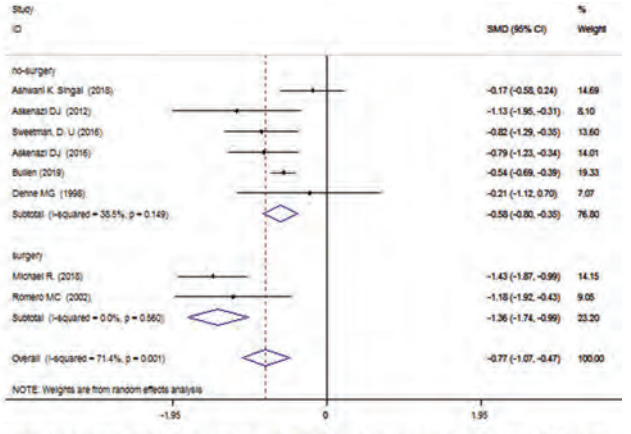


Figure 2. Subgroup analysis for surgery condition of urine uromodulin in the patients of AKI and Non-AKI. CI:Confident Interval,SMD: Standardised Mean Difference,AKI:Acute Kidney Injury.

PO0024

Independent Predictors of Checkpoint Inhibitor-Associated AKI

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Background: Checkpoint inhibitors(CPI)–associated acute renal injury(AKI) is an adverse effect of these therapies and its incidence is 13-29%. Clinical characteristics and risk factors of CPI-associated AKI were investigated

Methods: Clinical and demographic data of patients receiving CPI March2018-May2019 were evaluated. Patients were divided into two groups depending on the development of AKI.

Results: 821 patients received CPIs. Mean age 62.03±12.06 and 486(59.2%) men. Malignancies: lung 249(30.3%), urogenital tract 168(20.5%), melanoma 89(10.8%) and others 315(38.4%). 446(54.3%) anti-PD1, 230(28%) anti-PDL1, 13(1.6%) anti-CTLA4, 36(4.4%) other drug and 96(11.7%) both anti-CTLA4 and anti-PD1 or anti. PDL1. Baseline creatinine(bCr) 0.85±0.30 mg/dL and 188(22.9%) Cr>1mg/dL before starting CPI.125 (15.2%) developed AKI, 85(68%) men and mean age 65.1±10.7. Baseline Cr 0.97±0.45 mg/dL and 44(35.2%) presented bCr>1mg/dL.Cr at AKI diagnosis 2.27±1.34mg/dL and two required haemodialysis. 5 AKI secondary to obstructive uropathy. Time from CPI initiation to AKI 5.6±5.8months. Of those 125 patients, 23(18.4%) referred to Nephrology and 9(7.2%) underwent kidney biopsy. 1 endocapillar non-CPI related glomerulonephritis and 8(6.4%) acute tubule-interstitial nephritis(ATIN). 23(18.4%) were treated with corticosteroids. Cr at 6months after AKI 1.04±0.34 mg/dl and 40 showed complete recovery of kidney function at 6 months. AKI stage 2 or 3 were lower bCr(0.86±0.25 vs 1.06±0.54 mg/dL, p=0.01), increased latency from CPI initiation to AKI(6.9±6vs 4.5±5.5 months, p=0.03) and worse recovery of kidney function at 6 months than AKI patients stage 1(Cr 1.18±0.40 mg/dL, p=0.04 and complete recovery of kidney function 70.5%vs 93.3%,p=0.03). AKI patients were older (65.1±10.7 vs 62.03±12.06years, p=0.01), male (68%vs57.9%), p=0.03) and higher bCr(0.97±0.45 vs 0.85±0.30 mg/dL,p<0.01), bCr>1mg/dL (35.2%vs20.7%,p=0.04). Older age (OR 1.020, CI 95%1.002-1.038) and bCr(OR 3.293, CI 95% 1.678-6.461) were identified as independent predictors of AKI development in CPI

Conclusions: CPI-associated AKI is 15.2%,44% developed severe AKI.18.4% were referred to a nephrologist and kidney biopsy performed in 7.2%. 18.4% received corticosteroids. Older age and higher bCr were identified as independent predictors for AKI development in patients with cancer CPI-treated

PO0025

Relationship of Loop Diuretic with Hospital-Acquired AKI: A Multi-center, Propensity Score-Matching Analysis

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Background: Loop diuretics have been widely used to prevent and treat acute kidney injury (AKI). However, there is no clear consensus on the role of loop diuretics in AKI.

Methods: The Epidemiology of AKI in Chinese Hospitalized patients is a multicenter retrospective cohort included 3,044,024 hospitalized patients from 25 tertiary hospitals across China during 2013-2015. Patient data were obtained from the electronic hospitalization information system. We selected 57589 adult patients who had at least two serum creatinine tests within any 7-day window during their first 30 days of hospitalization and excluded those with end-stage renal disease, community-acquired AKI and without prescription data. AKI was defined using the SCr data by the Kidney Disease Improving Global Outcomes criteria. Exposure to Loop diuretics as any filled prescription within 14 days prior to the detection date of AKI in patients with HA-AKI and within 14 days prior to the last SCr testing date in those without AKI. Propensity scores (PS) were calculated using a logistic regression model with age, gender, hospital, division, baseline SCr, SCr testing times, comorbidities, operation procedures, need for intensive care and exposure to other nephrotoxic drugs. Moreover, the inverse probability of the treatment weighting (IPTW) method and standardized mortality ratio weighting method was also used.

Results: Of 57589 adult analysed, 20599 (35.8%) used diuretics, 17077 (29.7%) used loop diuretics, and 6277 (10.9%) had HA-AKI events during hospitalization. 8,274 pairs matched after nearest-neighbor matching without replacement and within caliper width (0.2*SD of the logit of PS). By IPTW, use of loop diuretics was associated with a significantly increased risk of HA-AKI compared with non-users (OR, 1.39; 95% CI, 1.28-1.52). The associations were consistent across multiple regression models.

Conclusions: Loop diuretics were widely used and associated with an increased risk of HA-AKI in hospitalized adult in China.

Funding: Government Support - Non-U.S.

Table 1. Use of Loop diuretics and the Risk of HA-AKI in the 1:1 propensity score-matched cohorts.

Variable	AKI Events, N	Total patients, N	Crude rate (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)		
					MVT	IPTW	SMRW
Non-users	1,188	8,274	14.4 (13.6, 15.1)	reference	reference	reference	reference
Use of Loop diuretics	890	8,274	9.7 (9.0, 10.3)	1.59 (1.44, 1.75)	1.65 (1.42, 1.92)	1.39 (1.28, 1.52)	1.54 (1.33, 1.77)

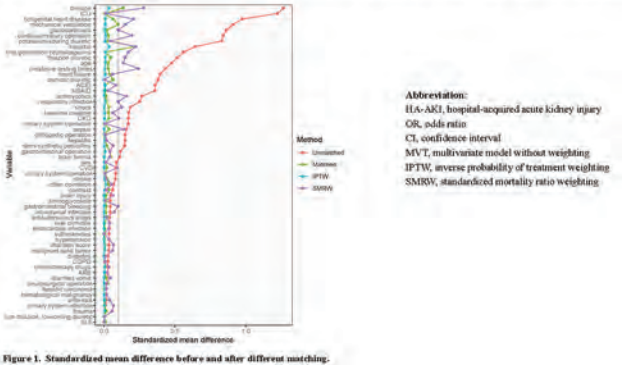

Figure 1. Standardized mean difference before and after different matching.

PO0026

AKI and Bleeding Risks Associated with Vitamin K Antagonists and Antiplatelet Agents in Patients with CKD

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Background: Anticoagulation in patients with chronic kidney disease (CKD) is challenging because of altered pharmacodynamics/pharmacokinetics. Patients prescribed vitamin K antagonists (VKA) are at high risk of bleeding, and possibly also acute kidney injury (AKI). We assessed bleeding and AKI risks associated with VKA and/or antiplatelet agents (AP) prescription in patients with moderate or advanced CKD.

Methods: CKD-REIN is a prospective cohort of 3022 nephrology outpatients with CKD stages 2-5 at inclusion. Drug prescriptions and their duration were collected prospectively. We used cause-specific Cox proportional hazard models to estimate hazard ratios (HR) of bleeding (identified through hospitalizations) and AKI (as defined according to KDIGO 2012) associated with VKA only, AP only, or VKA + AP prescriptions treated as a time dependent variable and adjusted for baseline comorbidities, laboratory data, and medications.

Results: At baseline, 65% of the patients were men, median age was 69 (interquartile range (IQR), 60-76), median eGFR was 32 mL/min/1.73m^2 (IQR, 23-41), 328 (10%) patients were prescribed VKA only, 1196 (40%) AP only, and 100 (3%) both VKA and AP. Over a median follow-up of 3.0 years (IQR, 2.6-3.1), 71 (2%) patients were newly prescribed VKA and 187 (6%) AP; 152 patients experienced a bleeding event requiring hospital visit/stay (crude incidence rate (IR): 1.9% person-years [95%CI,1.6-2.2]) and 414 patients experienced AKI (crude IR: 5.4 % person-years [95%CI, 4.9-5.9]. The adjusted HRs for bleeding associated with prescriptions of AP only, VKA only and AP+VKA were 0.77 [95%CI, 0.48-1.22], 2.29 [95%CI, 1.41-3.73] and 3.77 [95%CI, 2.08-6.83], respectively. Prescription of VKA was associated with increased AKI risk, adjusted HR, 1.79 [95%CI,1.39; 2.32], but not that of AP, 1.19 [95%CI, 0.94; 1.49].

Conclusions: This study confirms the high risk of AKI associated with VKA prescription in CKD patients. It also highlights the potential aggravating effect of combining VKA and AP on the risk of bleeding in this population.

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PO0027

Use of Ibuprofen and the Risk of Hospital-Acquired AKI in Children

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Background: Ibuprofen is widely used in children worldwide, especially in children with cancer, fever or trauma. However, large and high-quality studies on the association between ibuprofen and acute kidney injury (AKI) in children have been lacking.

Methods: The Epidemiology of AKI in Chinese Hospitalized patients (EACH2 study) is a multicenter, retrospective study of 3,044,023 patients admitted from 2013 to 2015 at 25 academic medical centers in China. Patient-level data were obtained from the electronic hospitalization information system. We included 50,420 hospitalized children aged between 1 month to 18 years who had at least one SCr test during the first 3 days and any interval between two continuous SCr testing <14 days during the first 30 days of hospitalization, excluding those with end-stage renal disease, community-acquired AKI, insufficient SCr testing and without prescription. AKI was defined as an increase in SCr by 26.5 μmol/L within 48 hours or a 50% increase in SCr from the baseline. We estimated the effect of exposure to ibuprofen on the risk of HA-AKI using a COX proportional hazard model with adjustment for age, sex, standardized baseline creatinine, comorbidities, clinical procedures, other nephrotoxic drugs use and stratification by hospital and division. We also compared the effect sizes of ibuprofen among subgroups stratified by age, gender, chronic kidney disease, need for intensive care and exposure to other nephrotoxic drugs.

Results: Among 50,420 children who met the inclusion and exclusion criteria, 5,526 (11.0%) were ibuprofen users, and 3,476 (6.9%) had HA-AKI during hospitalization. Ibuprofen use was associated with significantly increased risk of HA-AKI (hazard ratios, 1.23; 95% CI, 1.14-1.34) after adjusting for confounders. The greater nephrotoxicity of ibuprofen was observed in children who had chronic kidney disease, required intensive care, or were of elder age.

Conclusions: Ibuprofen was widely used and associated with an increased risk of HA-AKI in hospitalized children in China.

Use of ibuprofen and the risk of HA-AKI in patients by Cox proportional hazard

	Total, N	No. of AKI	Crude HR (95% CI)	P value	Adjusteda HR (95% CI)	P value
Non-user	44,894	3,049	Reference		Reference	
Ibuprofen	5,526	427	1.36 (1.27-1.46)	<0.001	1.23 (1.14-1.34)	<0.001

a: Adjusted age, sex, standardized baseline creatinine, comorbidities, clinical procedures, other nephrotoxic drugs use and stratified by hospital and division.

PO0028

Nonsteroidal Anti-Inflammatory Drugs and Risk of Acute Adverse Renal Outcomes in Diabetes

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Background: Individuals with diabetes mellitus (DM) may be susceptible to non-steroidal anti-inflammatory drug (NSAID) –induced acute kidney injury (AKI). However, data on their risk of NSAID-related adverse renal events is sparse. We aimed to evaluate the risk and factors for acute kidney injury and/or hyperkalemia after NSAID prescription to individuals with DM.

Methods: Retrospective cohort study of individuals ≥21 years with DM who received prescriptions between 1st July 2015 and 30th December 2017 from the largest tertiary hospital and a major public primary care institution in Singapore. Laboratory, hospitalization and medication data from 6 months before until 30 days after first prescription were retrieved from electronic medical records. Individuals prescribed systemic NSAID >14 days were identified as the "NSAID" group. We excluded those with systemic NSAID in the preceding 6 months, missing laboratory values, or had baseline estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2. The outcome was the incidence of AKI (serum creatinine increased >50%) and/ or hyperkalemia (serum potassium >5.5 mmol/L) within 30 days after prescription.

Results: We studied 3896 individuals (mean age 64.5 ± 13.3 years) with incident prescriptions: 138 in the NSAID group and 3758 in the non-NSAID group. 30-day AKI and/or hyperkalemia occurred in 525 individuals (13.5%). After adjusting for age, gender, ethnicity, baseline CVD, eGFR, serum potassium, NSAID, RAAS blocker and diuretic, baseline CVD (adjusted OR 1.41, 95% CI 1.03-1.93, p=0.03), RAAS blocker (adjusted OR 1.42, 95% CI 1.15-1.75, p=0.001), diuretic (adjusted OR 1.91, 95% CI 1.53-2.38, p<0.001) and higher baseline serum potassium (adjusted OR 1.36, 95% CI 1.19-1.57, p<0.001) were independent predictors for the outcome. NSAID prescription for >14 days was associated with a higher 30-day risk of AKI and/or hyperkalemia (adjusted OR 1.62, 95% CI 0.99 – 2.65, p=0.05). However, the risk of AKI and/or hyperkalemia was markedly increased if NSAID was prescribed concurrently with RAAS blocker (adjusted OR 4.17, 95% CI 1.74–9.98, p=0.001) or diuretic (adjusted OR 3.31, 95% CI 1.09-10.08, p=0.04).

Conclusions: NSAID prescription in individuals with DM may be associated with higher 30-day risk of AKI and/or hyperkalemia, especially with concurrent RAAS blocker or diuretic.

Funding: Private Foundation Support

PO0029

A Retrospective Cohort Study of Chemotherapy-Related AKI

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Background: Chemotherapy-related acute kidney injury (CR-AKI) is increasing with the growing number of cancer patients and the development of chemotherapeutic agents, whereas systemic information about CR-AKI is still limited.

Methods: This is a multicenter retrospective cohort study of cancer patients with CR-AKI screened from a cohort of hospital-acquired adult AKI patients based on a nationwide AKI survey in China. The enrolled CR-AKI patients were divided into three groups according to peak AKI stages (1 to 3) during hospitalization. The primary outcome was all-cause death in hospital, and the secondary outcome was AKI recovery.

Results: Of 3,468 adult inpatients with hospital-acquired AKI identified basing on the China nationwide AKI survey, 258 patients with CR-AKI were enrolled in our study, of which 20.1% (52/258) were ≥ 70 years old. A total of 413 person-time chemotherapeutic agents were related to AKI, of which platinum compounds (24.5%, 101/413) were the most common ones, followed by fluoropyrimidines (13.1%, 54/413), and anthracyclines (9.2%, 38/413). Among the 258 CR-AKI patients, 61 (23.0%) reached AKI stage 3, and 12 (4.7%) received RRT. The in-hospital mortality was 14.7% (38/258). Of the 207 surviving patients with a reliable serum creatinine value at discharge, 48.3% (100/207) failed to renal recovery. AKI stage 3 remained the independent risk factor for in-hospital death (OR 2.930, 95%CI 1.156~7.427) after adjustment for gender, age, comorbidities, and medications. It is surprising to note that, although patients of AKI stage 1 had lower levels of SCr both at peak and at discharge compared to patients with AKI stage 2 or 3, there was a higher proportion of patients of AKI stage 1 not achieving renal function significantly improved at discharge (failure to recover) compared to those of AKI stage 2 or 3 (57.1% vs. 41.4% vs. 36.4%, P = 0.032). More importantly, a lot more AKI episodes were not recognized or diagnosed by physicians in charge in patients of AKI stage 1 compared to the other two groups (82.8% vs. 60.0% vs. 36.1%, P < 0.001).

Conclusions: CR-AKI accounted for a considerable proportion of hospital-acquired AKI. Severe CR-AKI increases in-hospital mortality. Mild CR-AKI that overlooked by physicians yet sustained kidney injury was common in these patients. Recognizing CR-AKI at an early stage and making personalized treatment should be emphasized when offering chemotherapy to patients.

PO0030

Characterizing AKI from Vancomycin-Associated Nephrotoxicity in Adult Non-ICU Patients at an Inner City Hospital: Incidence and Predictors

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Background: Vancomycin is a widely used antibiotic in the in-patient setting. Concerns of vancomycin-associated nephrotoxicity(VAN) were raised due to impurities associated with the first released parenteral formulations in the 1950s. Nephrotoxicity is reported to have markedly declined with a wide variability in the incidence. There is a dearth of information on the current incidence of VAN as a cause of acute kidney injury(AKI) in adult non-ICU populations. The purpose of this study was to estimate the incidence of VAN AKI and identify risk factors of VAN for this population.

Methods: A cohort of patients admitted between January 2015 and December 2017 with the diagnosis of sepsis and who received at least 3 days of parenteral vancomycin were identified through a retrospective chart review. Exclusions were ESRD or CKD history. Our primary outcome was the occurrence of VAN AKI, defined as an increase in serum creatinine by 0.3 mg/dl or 50% above baseline after vancomycin exposure. The incidence of VAN AKI was determined and we estimated risk factors associated with VAN in a logistic regression model.

Results: 587 adult patients received at least 72hours of parenteral vancomycin for the treatment of sepsis during the period. Demographics were: male 350(59.6%), female 237(40.4%) and mean age of 62.3 years. Distribution by ethnicity: non-Hispanic Blacks 71.2%, Hispanics 12.6%, non-Hispanic white 3.4% and 12.4% were other ethnicities. The incidence of VAN AKI was 15.24%. These patients had a longer hospital stay (26.8 versus 21.5 days for no VAN AKI), higher mean vancomycin trough levels, longer duration of exposure to vancomycin and a higher Charlston Comorbidity Index (3.5 versus 2.6). Independent predictors for VAN were: mean vancomycin trough level, hypertension, COPD, congestive heart failure, liver disease, severe obesity and dementia (all p values <0.05). Previous ICU admission and hypotension status did not predict VAN AKI.

Conclusions: We report an incidence of VAN AKI of 15.24% in non-ICU adult patients with no history of ESRD or CKD. Risk factors associated with the development of VAN include mean vancomycin trough level, hypertension, congestive heart failure, COPD, liver disease, severe obesity and dementia.

PO0031

Baseline Urinary Protein Biomarkers as Predictors of eGFR Decline in Cancer Patients Receiving Cisplatin

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Background: Previous data from our group reported significant changes in urinary biomarkers of sub-clinical kidney injury over 10 days after receiving i.v. cisplatin. The current study evaluated the performance of single and a combination of two urinary biomarkers at the time of cisplatin initiation in predicting a reduction in eGFR.

Methods: Patients (n=57) with solid tumors receiving i.v. cisplatin (≥25 mg/m^2) were enrolled in a study to characterize concentrations of 9 urinary proteins (Table). For the outcome of eGFR decline, the eGFR (MDRD equation) after the first dose and prior to the second dose was used. Statistical models used the baseline urinary biomarker concentrations as predictors. Logistic regression was used to assess Maximum Likelihood Estimates for models containing single and a combination of two urinary biomarkers for prediction of the reductions in eGFR outcome, and reported as odds ratios (OR) with 95% confidence intervals (CI). ROC curves for each model were based on the eGFR reduction outcome. Models were adjusted for age, gender, race and BMI.

Results: A single model for KIM-1 was significant (p=0.0421; OR 0.08; 95% CI 0.01, 0.91) for capturing eGFR decline according to ROC analysis (Table). The six combined models with ROC >0.70 are included in the Table. KIM-1 was a significant contributor in two models when combined with B2M or albumin, but ROC analyses demonstrated similar AUC as the single significant KIM-1 model. Although cystatin C was not significant in a single model (ROC AUC of 0.75), when combined with B2M the ROC AUC (0.77) was the best of all combined models.

Conclusions: Urinary biomarkers have emerged as tools to identify overt and sub-clinical kidney injury. However, single and double combinations of urinary proteins are insufficient to reliably predict reductions in eGFR as an ideal model outcome. Future studies must determine an improved outcome benchmark for evaluating urinary protein biomarkers.

Funding: NIDDK Support

Logistic models of eGFR degrease adjusted by age, race, gender, BMI and biomarker or combined biomarkers

Biomarker (baseline)	Models #	Variable	OR estimate	95% CI Lower	95% CI Upper	P value	AUC ROC
Single	S1	KIM-1	0.08	0.01	0.91	0.0421	0.72
	S2	Calbindin	0.99	0.98	1.00	0.08	0.69
	S3	B2M	1.00	1.00	1.00	0.84	0.65
	S4	TFF3	1.00	1.00	1.00	0.45	0.67
	S5	Cystatin C	0.99	0.97	1.00	0.09	0.75
	S6	Albumin	1.00	1.00	1.00	0.78	0.67
	S7	Clusterin	1.00	1.00	1.00	0.36	0.67
	S8	GSTpi	0.98	0.96	1.01	0.14	0.72
	S9	MCP1	0.23	0.04	1.21	0.08	0.72
Combined	C1	KIM-1	0.04	0.00	0.83	0.0384	0.72
		B2M	1.00	1.00	1.01	0.36	
	C2	KIM-1	0.05	0.00	1.06	0.05	0.71
		TFF3	1.00	1.00	1.00	0.62	
	C3	KIM-1	0.02	0.00	0.68	0.0292	0.74
		Albumin	1.00	1.00	1.00	0.23	
	C4	B2M	1.01	1.00	1.01	0.12	0.77
		Cystatin C	0.97	0.94	1.00	0.0378	
	C5	TFF3	1.00	1.00	1.00	0.20	0.73
		Cystatin C	0.97	0.95	1.00	0.05	
	C6	Albumin	1.00	1.00	1.00	0.16	0.75
		GSTpi	0.97	0.93	1.00	0.05	

TFF3: trefoil factor 3; GSTpi: glutathione s-transferase pi; MCP1:monocyte chemoattractant protein-1

PO0032

Urinary Sediment Score Is a Useful Predictor of AKI in Hospitalized Patients

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Background: Risk-stratification tools of incident AKI in hospitalized patients are needed. Early documentation of impaired kidney function through a simple examination like the urinary sediment may provide risk reduction in such patients. The present study aims to explore an association between urinary sediment score described by Perazella et. al. and hospital-acquired AKI.

Methods: This study included 86 patients who underwent urinalysis, including scoring the urinary sediment during the first 24 hour of admission. Inclusion criteria consisted of age ≥ 18, hospital stay ≥ 3 days, at least 2 serum creatinine (SCr) measures in the first 2 days of hospital stay and one measure at 3-7 days of stay. Exclusion criteria consisted of ESKD, kidney transplant or baseline eGFR <15 ml/m/1.73m^2. AKI was defined as an increase of serum creatinine level ≥ 0.3 mg/dL or ≥ 1.5 times in contrast to baseline creatinine level within 48 hours. We evaluated if the microscopic examination of the urine sediment (score ≥2) could be use as a non-invasive detector of renal damage.

Results: Mean (SD) age was 65.1 (17.2), 38.4% were women and 100% Hispanic. The incidence of AKI at 3-7 days of hospital or ICU stay was 34.9%. From the 30 patients that developed AKI, 20 were on stage 1 (66.6%), 8 were on stage 2 (26,6%) and 2 were stage 3 (26.6%). Performance metrics of the urinary score used are reported in **Table**. A urinary sediment score ≥ 2 exhibited a fair, but not good, AUC of 0.681 (95% confidential interval [CI]: 0.554–0.808) in ROC analysis.

Conclusions: Cellular casts and granular casts are occasionally observed in hospitalized adult patients with risk factors for AKI. The urinary sediment score proposed by Perazella el al. could be a potentially useful marker for early documentation of hospital-acquired AKI.

Funding: Private Foundation Support

Statistic	Value	95% CI
Sensitivity	43.33%	25.46% to 62.57%
Specificity	92.86%	82.71% to 98.02%
Positive Likelihood Ratio	6.07	2.17 to 16.98
Negative Likelihood Ratio	0.61	0.44 to 0.84
Disease prevalence (*)	34.88%	24.92% to 45.92%
Positive Predictive Value (*)	76.47%	53.73% to 90.10%
Negative Predictive Value (*)	75.36%	68.93% to 80.83%
Accuracy (*)	75.58%	65.13% to 84.20%

(*) These values are dependent on disease prevalence.

Table: Performance of the urinary sediment score for the prediction of AKI in hospitalized patients

PO0033

Kidney Biopsy Findings in AKI in the Cohort of Patients of Mexico Tertiary Hospital

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Background: The study of the epidemiology of biopsy-confirmed renal disease provides useful information about the prevalence of renal disease and its clinical manifestations. Performing a kidney biopsy is necessary to accurately diagnose diseases such as glomerulonephritis and tubulointerstitial nephritis, among other such conditions Kidney biopsy in acute kidney injury (AKI) of unknown origin provides irreplaceable information for diagnosis, treatment, and prognosis. In this report, we analyze the frequency and clinicopathologic correlations of renal native biopsied AKI in Mexican cohort during the period 2014 through 2019.

Methods: We analyzed the frequency and clinicopathologic correlations of AKI confirmed by native renal biopsy in Mexico tertiary hospital and the distribution of the different clinicopathologic findings. From 2014-2019 period, totally 515 patients first received renal biopsy. AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes criteria.

Results: Of the 515 patients investigated, 200 (38.8%) showed AKI. Of these, 102 (51%), 47 (23.5%), and 51 (25.5%) presented with AKI classified as stages 1, 2, and 3, respectively. The primary indication for performing biopsy was rapidly progressive glomerulonephritis (RPGN) in 70 (35%) and nephrotic syndrome in 47 (23.5%). Dialysis previous kidney biopsy was necessary in 48 patients (24%). Focal segmental glomerulosclerosis was the most prevalent primary disease in 37 (18.5%) and lupus nephritis wast the most prevalent secondary disease in 53 (26.5%). In the early patients the most prevalent disease was pauci-immune rapidly progressive GN Multivariate analysis of risk factors associated with AKI showed hemoglobin levels (OR 0.800, 95% confidence interval [CI] 0.671–0.941, p=0.01), dialysis previous kidney biopsy (OR 3.970, 95% CI 2.949–4.392, p=0.008), and baseline serum creatinine levels (OR 2.402, 95% CI 1.371–4.758, p=0.001) were significantly associated with AKI.

Conclusions: We observed a high prevalence of AKI in patients who underwent kidney biopsy to investigate their renal disease, particularly glomerulonephritis. The prevalence of vasculitis and crescentic GN is high, especially in elderly patients.

PO0034

Risk of Incident Bleeding After AKI: A Retrospective Cohort Study

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Background: End-stage kidney disease (ESKD) causes bleeding diathesis; however, whether these findings are extrapolable to acute kidney injury (AKI) remains uncertain. We assessed whether AKI is associated with an increased risk of de novo bleeding.

Methods: We conducted a one-year single-center retrospective cohort study, excluding readmissions, admissions less than 24 hours, ESKD or kidney transplant patients. The primary outcome was the development of incident bleeding analyzed by multivariate time-dependent Cox models and independently adjudicated by two investigators.

Results: In 1,001 patients, bleeding occurred in 48% of AKI and 57% of non-AKI patients (p=0.007). To identify predictors of incident bleeding, we excluded patients who bled before ICU (n=488). In bleeding-free patients (n=513), we observed a trend toward higher risks of bleeding in AKI (22% vs. 16%,p=0.06), and a higher risk of bleeding in AKI-requiring dialysis (38% vs. 17%, p=0.01). Cirrhosis, AKI-requiring dialysis, anticoagulation, and coronary artery disease were associated with bleeding (HR 3.67, 95%CI:1.33-10.25; HR 2.82, 95%CI:1.26–6.32; HR 2.34, 95%CI:1.45–3.80; and HR 1.84, 95%CI:1.06–3.20, respectively), while SOFA score and sepsis had a protective association (HR 0.92 95%CI:0.84-0.99 and HR 0.55, 95%CI:0.34–0.91, respectively). Incident bleeding was not associated with mortality.

Conclusions: AKI-requiring dialysis was associated with incident bleeding, independent of anticoagulant administration. Studies are needed to better understand how AKI affects coagulation and clinical outcomes.

Funding: Government Support - Non-U.S.

PO0035

Relationship Between Serum Uric Acid Levels and Reduction in Kidney Function Associated with Blockade of the Renin-Angiotensin System

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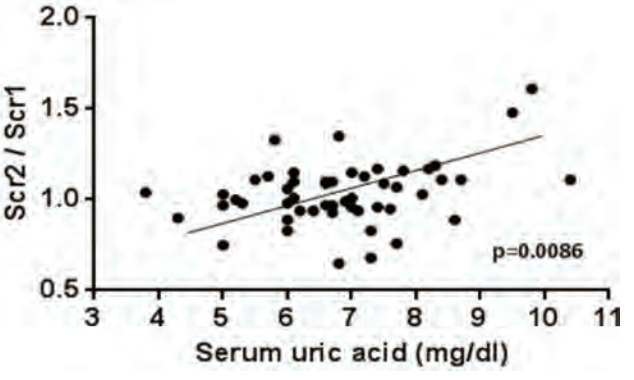
Background: Renin-angiotensin system blockade(RASb) induced by treatment with angiotensin type 2 receptor antagonists and angiotensin converting enzyme inhibitors is frequently associated with a reduction in glomerular filtration rate(GFR). Experimental hyperuricemia is associated with dysregulation of renal hemodynamics and reduced GFR. We studied if serum uric acid(sUA) levels are related to the depression of renal function associated to RASb

Methods: 107 patients(23-77 years, 53 females) when they were first prescribed RASb for primary hypertension(PHT)(n=25), diabetic nephropathy(DN)(n=12), PHT&DN(n=8), congestive heart failure(n=26) and proteinuric nephropathes(n=36). Changes in serum creatinine(Scr), mean sUA levels and systolic(SBP) and diastolic(DBP) blood pressures(mmHg) were obtained from records before and 3,1±0,2 months after RASb

Results: Baseline eGFR(ml/min/1,73m2) was 43,6±2,81 and 64±4,89 in male and female patients, respectively .55% male and 51% female patients increased Scr with RASb but only 8 male and 2 female patients increased baseline Scr more than 0,3mg/dl. RASb reduced significantly SBP (pre130,7±1,67 vs. post124,1±1,57,p=0,004) but not DBP. Reduction in eGFR was found in 87% of the patients in whom SBP was reduced by RASb. Reduction of SBP was unrelated to the increase in Scr. sUA(mg/dl) was 6,9±018(males) and 6,1±0,23(females) (p=0,09). In female there was no relation between UA levels and change in Scr. In male there was a direct relationship between changes in Scr (ScrPre/ScrPost) and the mean serum UA levels(r:0,36, p=0,008) that was unrelated to SBP changes. Relationship was stronger in male patients with sUA ≥7,0(r=0.051)

Conclusions: Since 14% of the male patients treated with RASb increased Scr more than 0,3 mg/dl and deterioration of kidney function was directly related to sUA levels, the potential benefit of reducing sUA in male patients treated with RASb should be investigated further



PO0036

Seizure-Induced Hyperuricemia and Associated Urate Nephropathy: A Prospective Cohort Study

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Background: Urate nephropathy is an uncommon cause of acute kidney injury (AKI). Although most factors are associated with tumor lysis syndrome and rhabdomyolysis, occurrence following severe seizure has also been described. There are effective ways to prevent and treat urate-associated AKI, when adequately identified. However, uric acid measurement following convulsion episodes is rarely performed and therefore, the incidence of hyperuricemia in this context is unknown. Our objective was to quantify these metabolic disturbances following severe generalised tonic-clonic seizures (GTCS).

Methods: We prospectively recruited patients admitted in our hospital for severe GTCS (≥5 min or a series of seizures with an incomplete return to baseline) and described the kinetics of serum uric acid, creatinine, creatine kinase and lactate during a 72h follow-up. Urine urate-to-creatinine ratio was used to monitor urate tubular toxicity.

Results: From August 2018 to September 2019, 13 patients with a median GTCS duration of 5.0 minutes (IQR 2.0-12.5) were included. The median serum uric acid was initially 346.0 μmol/L (IQR 155.0-377.5) and decreased to 178.0 μmol/L (IQR 140.0-297.5), while serum creatinine passed from 73.0 μmol/L (IQR 151.0-80.0) to 57.0 μmol/L (IQR 44.0-70.0) over follow-up (Figure). AKI occurred in 4 patients (KDIGO Stage ≥1).

Conclusions: Serum uric acid levels increase acutely following a severe GTCS than return to baseline within 3 days. During that period, there is an increased risk of AKI that might be associated with urate nephropathy. To quickly identify and manage patients at risk of acute hyperuricemia and related complications, measurement of uric acid following a GTCS might be beneficial.

Funding: Clinical Revenue Support

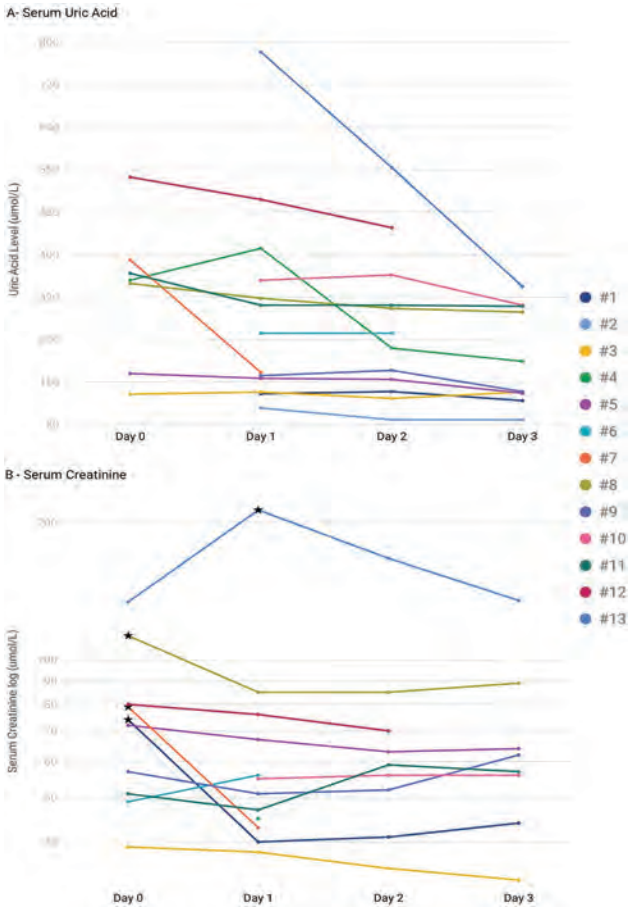

Figure. Post-seizure laboratory values for each participant. Star dots are the maximal value of creatinine where AKI was diagnosed.

PO0037

Late Presentations of Secondary Oxalate Nephropathy

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Introduction: Secondary Oxalate nephropathy is an important differential diagnosis for acute kidney injury (AKI) in chronic malabsorptive disease. Mean presentation is typically within 1-2 years. The following three cases are example of late, abrupt presentations of secondary oxalate nephropathy.

Case Description: Our first case includes a 69-year-old female, with gastric bypass surgery 14 years prior, who presented to emergency room (ER) with AKI. Six months prior her creatinine (Cr) was 1.6 mg/dL, but abruptly increased to 5.99 mg/dL. Serologic work up was negative. Renal biopsy was obtained that revealed deposition of oxalate crystals within renal tubules (Figure 1). Our second case showed a 59-year-old male with history of recurrent pancreatitis due to bulimia that presented to the ER for nausea and vomiting. In the ER, patient had a serum Cr of 5.79 mg/dL. Two months prior, Cr was 1.1 mg/dL. Renal biopsy showed widespread oxalate crystals in the interstitium. The last case was a 48-year-old male with chronic pancreatitis who presented with AKI with suspect acute tubular necrosis. He had been diagnosed with chronic pancreatitis for at least 6 years with Cr 0.9 mg/dL. Patient's Cr remained at 4.00 mg/dL one month later. Renal biopsy revealed interstitial fibrosis and calcium oxalate crystals.

Discussion: Secondary oxalate nephropathy is a side effect of malabsorptive gastrointestinal (GI) disorders. According to prior case series, the mean presentation of oxalate nephropathy is 1-2 years. These cases illustrate that secondary oxalate nephropathy can present at a later course with rapid onset. Patients also likely progress to ESRD after diagnosis. A systemic review of 108 cases, with 13 months follow up, showed 55% of patients required hemodialysis. Currently, there is no treatment and lifestyle changes include a low fat, oxalate diet. Secondary oxalate nephropathy should be considered in the differential of all patients with malabsorptive states presenting with AKI.

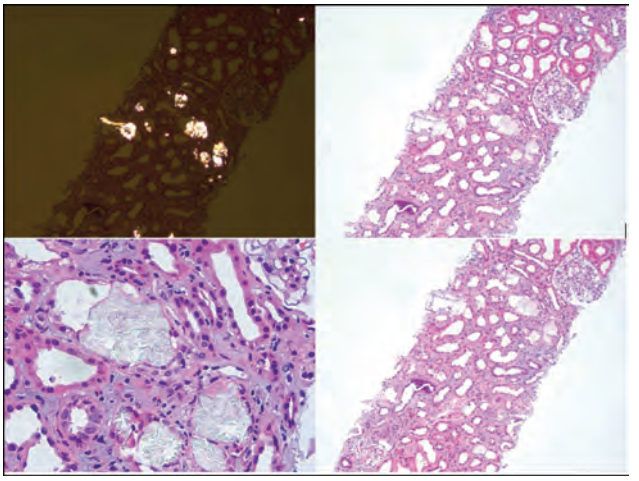

Figure 1

PO0038

Presentation and Outcome of Oxalate Nephropathy Without Known Genetic or Gastrointestinal Cause

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Background: Oxalate nephropathy (ON) is a frequent and often unexpected finding on kidney biopsy. This study aimed to characterize causes and outcomes in biopsy-proven ON not due to known enteric cause or primary hyperoxaluria (PH) in a multisite health system.

Methods: Cases were identified based upon diagnosis of ON on kidney biopsy between 2009 to 2020 without known enteric or primary cause.

Results: Thirty-four cases were identified with a median follow-up of 11.9 months. None had known fat malabsorption. Genetic testing for PH was negative in 11, and there was no clinical suspicion of PH in the rest. Likely causes of ON included documented high dietary oxalate (7, 21%), oral and/or IV vitamin C supplementation (7, 21%), ethylene glycol (3, 9%), and orlistat (1, 3%). No cause could be identified in 16 (47%). Table 1 shows variables across three etiologies: unknown cause, diet-related, and vitamin C. All cases except one had diffuse intratubular calcium oxalate deposition on biopsy. End stage kidney disease (ESKD) was present in 53%. AKI stage III at biopsy was predictive of ESKD at last follow-up ($p<0.05$). Treatments included low oxalate diet (29, 85%), calcium supplementation (18, 53%), pyridoxine (12, 35%), and prednisone taper (12, 35%). Diet-related ON appeared to have lower rates of AKI stage III at diagnosis (5, 67%), ESKD (3, 43%), and mortality (2, 29%) compared to vitamin C-related ON and ON of unknown etiology.

Conclusions: This is the largest study of ON not due to PH or enteric cause. The most common causes were high-oxalate diet and high-dose vitamin C. In 47% of cases no cause was identified. ESKD was common, and AKI severity at presentation predicted ESKD at last follow up. Cases attributed strictly to dietary excess may have better short and long term outcomes.

Funding: Clinical Revenue Support

	Unknown (n=16)	Diet (n=7)	Vitamin C (n=7)	P value
Baseline variables				
Age, yrs (mean, (SD))	64.9 (9.7)	67.1 (11.0)	70.4 (9.86)	0.52
Male	50%	57%	71%	0.63
Diabetes	63%	0	43%	0.02
Hypertension	63%	43%	71%	0.53
CKD III or greater at baseline	44%	43%	29%	0.78
Kidney stones	25%	0	29%	0.31
Characteristics at time of kidney biopsy				
AKI stage III	93%	67%	86%	0.29
Dialysis at diagnosis	33%	43%	71%	0.24
Urine oxalate (median, mg/24hr)	27.7	80.1	37.8	0.79
Plasma oxalate (median, µmol/L)	7.95	15.6	23.4	0.44
ESKD at last follow up	63%	43%	57%	0.68
Alive at last follow up	60%	71%	29%	0.24
Renal histology findings				
Interstitial inflammation	94%	100%	86%	0.56
Moderate-severe tubular injury	69%	57%	57%	0.8
Moderate-severe tubular atrophy	69%	50%	14%	0.04

Table 1

PO0039

The Clinical Impact of Extended-Spectrum Beta-Lactamase-Producing Bacteria in Patients with Community-Acquired Acute Pyelonephritis in a Korean Hospital, 2010-2018

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Background: Acute pyelonephritis (APN) is known to be the most complicated, severe urinary tract infection. It is not uncommon to experience the initial empirical antibiotic treatment failure of APN due to the increasing prevalence of ESBL producing bacteria. In this study, we investigated the microbial etiologies of acute pyelonephritis and resistance to antibiotics in APN.

Methods: We retrospectively reviewed microbial etiologies and resistance among patients who were admitted to Konyang University Hospital with APN from 2010 to 2018. Two blood cultures at different sites, and urine culture were performed at the time of admission. Statistical analysis was performed using R (version 4.0.0).

Results: The total number of patients with APN was 882, and *Escherichia coli* (57.3%) was the most common pathogen followed by *Klebsiella spp.* (2.8%), *Enterococcus spp.*(2%), *Proteus spp.* (0.9%), *Enterobacter spp.* (0.6%) and *Pseudomonas aeruginosa* (0.5%). The rate of ESBL producing bacteria has steadily increased over 9 years from 6.3% to 37.8%. Multivariate analysis showed that male sex (OR 2.395; 95% CI 1.201-4.776), APN occurence after 2015 (OR 1.170; 95% CI 1.057-1.296) and previous antibiotics exposure (OR 2.102; 95% CI 1.014-4.356) were risk factors for acquiring ESBL producing bacteria in urine or blood cultures. ESBL producing bacteria of blood or urine cultures in patients with APN was a significant prognostic factor for recurrence of APN within 1 year and mortality (HR 8.439; 95% CI 2.399-29.694).

Conclusions: Although quinolone and 3rd cephalosporin are recommended for empirical treatment of APN, there is a high risk of treatment failure due to the significant increase of ESBL producing bacteria in the community. Antibiotic therapy with APN should ideally be based on local patient characteristics and their antibiotic susceptibility profiles.

PO0040

Incidence of AKI After IV Vitamin C Treatment for Septic Shock: A Cohort Analysis of Real-World Application

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Background: Septic shock patients exhibit a high prevalence of vitamin C deficiency, and intravenous vitamin C (IVvC) may provide a survival advantage. Preliminary findings from early studies were promising, however, recent studies fail to show a benefit of vitamin C on mortality. Case reports observed that IVvC may be related to acute kidney injury(AKI) through oxalate-nephropathy. While IVvC in sepsis merit further research, clinicians at one institution began the use of IVvC as additional treatment for septic shock. This study is a retrospective analysis of real-world experience to evaluate the effects of IVvC on AKI in patients with septic shock

Methods: Patient-level clinical data of one 525-bed Hospital from 1 February 2016-31 December 2018 was evaluated in the current study. Institutional IRB approval was obtained and data were de-identified. Data included patients between the ages of 18 and 89 who were hospitalized for 48 hours with 2 serum creatinines 48 hours apart or 6 hours of UOP in ICU. Patients with GFR <35ml/min (MDRD formula), creatinine > 4.0mg/dL, or diagnosis of ESRD or kidney transplant (ICD-10 codes) were excluded. Clinical data collected included; admission demographics and past history; UOP; pre-identified medications, laboratory results and order sets; specific consultations; and discharge diagnoses.

Results: A total of 22980 patient visits were evaluated. Of the 2067 patients who were admitted through the ED with a discharge diagnosis of septic shock, 433 (20.9%) received one dose of IVvC 1500mg and were categorized as the IVvC group; 1634 (79.1%) did not receive IVvC. A chi-square analysis can be seen in Table 1.

Conclusions: This retrospective study EMR observed that IVvC in the treatment of septic shock is associated with an increase in the incidence of AKI.

Funding: Clinical Revenue Support

Table 1. Chi-square Analysis Examining the Relationship between IVvC and the Development of AKI among Inpatients with Septic Shock.

	IVvC	IVvC	
AKI	NO	YES	Row Total
NO	876(53.6%)	134(30.9%)	9951010
YES	758(46.4%)	299(69.0%)	1057
Column Totals	1634	433	p≤.0001

Note. A logistic regression revealed that the odds of AKI were 2.57 times higher for IVvC patients compared to non-IVvC patients (95% CI 2.05,3.23)

PO0041

Murine Typhus-Related Thrombotic Microangiopathy, Bilateral Renal Cortical Necrosis, and Acute Disseminated Encephalomyelitis

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Introduction: Thrombotic Microangiopathy (TMA), Bilateral Renal Cortical Necrosis (BRCN) and Acute Disseminated Encephalomyelitis (ADEM) are rare complications of infections. Murine Typhus (MT), a mild rickettsial infection rarely involves kidneys. We present a young male with rash, anuric renal failure, schistocytes, elevated LDH and high IgG and IgM levels for MT. A CT scan and renal biopsy revealed TMA and BRCN. A week after treatment he developed seizures from ADEM. MT should be considered in unexplained TMA, BRCN or ADEM in endemic area.

Case Description: A 22-yr-old male admitted with truncal rash, vomiting and anuria for 5 days. His admission platelet count was141k/ul with 1+ schistocytes. His Sodium was 128, Potassium 5.8, Chloride 82, and HCO3 13 all in mEq/L. His BUN was 200, creatinine 20 and LDH 4232 U/L. Complement levels, ANA and anti DNA, blood cultures, viral serologies for most viruses including SARC-COV-19 IgG were negative. ADAMTS-13 activity was 61%. MT antibodies titers were >1:1024 for both IgG and IgM. A CT scan and renal biopsy revealed severe BRCN. The glomeruli and arterioles contained microthrombi. IF revealed bright staining fibrinogen in the lumen, endothelium and walls of arterioles and arteries. EM revealed endothelial cell injury and necrosis, and fragmented red cells under the endothelium. He was effectively treated with doxycycline but later he developed encephalopathy and seizures.

Discussion: MT is a mild infection caused by *Rickettsia typhi* transmitted by rat and cat fleas and is endemic to Texas, California and Hawaii in the US. MT is mostly self limiting and mild. In severe cases MTpresents with renal, neurologic, hepatic, cardiac and pulmonary symptoms. Renal dysfunction is due to interstitial nephritis or ATN from renal hypoperfusion. RCN is a rare cause of AKI encountered in 1-2 percent of all cases of AKI. ADEM or post infectitious encephalomyelitis is a rare neurologic complication triggered by vaccinations and infections. Recently authors published a case of MT with collapsing glomerulopathy likely a result of TMA. In our patient the only identifiable infection was MT, which usually is a mild infection. We report a case of MT causing BRCN, TMA and ADEM. We suggest that MT should be cosidered in multiorgan involment the endemic area when no other cause is identified.

PO0042

Pembrolizumab and Proton Pump Inhibitor-Induced Nephrotoxicity: A Case Report

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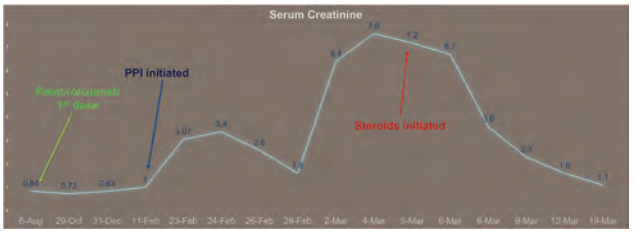
Introduction: Immune checkpoint-blocking antibodies have shown promise in the treatment of a wide-range of malignancies. These medication function by blocking down-regulators of innate immunity, thus augmenting anti-tumor immunity. This upregulation of the immune system can result in immune related adverse events and can affect any organ system. One immune-related adverse event is acute interstitial nephritis. Proton pump inhibitors, themselves, have been implicated in causing acute interstitial nephritis. There is little research regarding synergism of checkpoint inhibitors and proton pump inhibitors and resultant kidney injury. This case report reviews one patient's clinical course in which they experienced acute interstitial nephritis while receiving both pembrolizumab and omeprazole.

Case Description: A 64 year old female with non-small cell lung cancer stage IV with brain metastasis was initiated on pembrolizumab therapy seven months prior to presentation. Three weeks prior to presentation she started omeprazole 20mg daily. At time of presentation the creatinine was found to be 3.07 mg/dL, up from 0.8 mg/dL eleven days prior, improved with cessation of the PPI, however shortly there after the PPI was restarted and creatinine again rose and peaked at 7.6 mg/dL. Renal biopsy was performed and confirmed interstitial nephritis. The patient was started on prednisone 1mg/kg/day with rapid improvement in renal function back to baseline.

Discussion: There has been some research linking both pembrolizumab and pembrolizumab in combination with other chemotherapeutic agents to kidney injury. However, in these trials many patients who suffered kidney injury were also receiving proton pump inhibitors, a class of medications known to provoke acute interstitial nephritis. If synergism can be proven, this combination would be avoided, thus preventing this immune related adverse event. Furthermore, reinitiation of check point inhibitors alone after cessation of the PPI and normalization of kidney function in cases such as these, could be trialed.



PO0043

Zolpidem Mega Dose Resulting in Hemodialysis

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Introduction: Depression and hypoventilation syndromes are factors that may be overlooked when prescribing Zolpidem. Although hypnotics are not directly associated with rhabdomyolysis, they can lead to severe intoxication and prolonged immobilization. This can lead to compartment/ crush syndromes and depressed respiratory drive and may cause seizures. As consequence of the above renal failure ensued and hemodialysis was required.

Case Description: This case portrays a 36-year-old law student who tried to end his life with the ingestion of 90 Zolpidem pills. As consequence of his metabolic derangement he had seizures, rhabdomyolysis and renal failure that required hemodialysis. Due to promt intervention, hemodynamic stability and full recovery were achieved.

Discussion: 36-year-old man with hypertension, insomnia and epilepsy was brought to the emergency room by ambulance. Chief complaint was of disorientation and seizures after the ingestion of 90 Zolpidem pills. He was initially combative, disoriented and with incoherent speech. Once consulted, he presented a Glasgow Coma Scale of 3 for which he was intubated. He was diaphoretic with scattered petechiae and associated subconjunctival hemorrhage. On lab work he had central bicarbonate at 4.6 mEq/ L. Arterial pH was at 6.5 and PaCO2 at 24, which represented severe metabolic acidosis for which initial bicarbonate drip and hyperventilation were provided to correct acidosis. He was admitted to Intensive Care Unit where he was extubated on his second day of admission. He developed progressive renal dysfunction evidenced by rapidly increasing BUN and serum creatinine as well as rapidly increasing CPK from 500 to 44,101 U/ liter for which fluid expansion and observation became the new therapy goals. Even with aggressive hydration, he developed oliguria. BUN and creatinine reached 129.7 and 13.7 mg/dl respectively for which on day 7 of admission, he received 3 session of hemodialysis within 4 days. His recovery was enough to be discharged for follow up as an outpatient. Remarkably after such insult, full renal function was regained. Mental illness is an epidemic, which is often overlooked and as consequence not adequately treated. As physicians, we have the responsibility to individualize therapy. Insomnia may be the symptom of a wide array of etiologies. In this case prescribing a limited amount of medication and/ or treating the underlying depression would have prevented a near fatality.

PO0044

Severe Exertional Rhabdomyolysis with AKI Associated with Sickle Cell Trait

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Introduction: Exertional rhabdomyolysis (ER) is a pathological breakdown of muscle cells which can result in acute kidney injury (AKI) from multiple mechanisms including tubular toxicity from heme pigment, cast formation, and volume depletion. ER has a host of etiologies including drugs, ingestions, infections, electrolyte abnormalities, trauma, venom, and metabolic disorders. Sickle Cell Trait (SCT), a generally asymptomatic condition, has been rarely associated with ER. We present a case of severe ER with AKI in a previously healthy patient who was determined to have SCT as the only risk factor.

Case Description: A 39 y/o previously healthy black police recruit on no medications presented with myalgias and dyspnea following a routine training regimen. He was found to have diffuse tenderness and weakness of arms and legs. Initial labs showed serum creatinine (sCr) 2.0 mg/dL, Na 148 mmol/L, CO2 <5 mmol/L, Creatine Kinase (CK) 1,516 U/L. A peripheral blood smear showed few sickle cells. His urine was dark tea-colored and on urinalysis had large blood and minimal RBCs. Illicit drug panel, autoimmune studies, myophosphorylase deficiency, and myositis panel including anti-SSA, anti-PM/Scl, and anti-U1RNP were normal or negative. A hemoglobin electrophoresis demonstrated 35% Hgb S and 62% Hgb A consistent with SCT. He was oliguric and was started on renal replacement therapy (RRT) with CVVH initially and then iHD. His CK and sCr peaked at 565,000 U/L and 13.9 mg/dL respectively (figure 1). He required 18 days of RRT. His sCr after discharge improved to 1.4 mg/dL.

Discussion: SCT is normally a relatively benign condition as there is enough normal Hgb to prevent significant sickling. However, increased O2 demand with exertion may promote clinically significant sickling and lead to vaso-occlusion and hypoxic muscle injury. ER in SCT is rare and unpredictable and therefore specific recommendations for re-introduction of exercise are not available. However, guidelines for Exercise Collapse Associated with Sickle Cell Trait (ECAST) can be used to guide long term patient management.

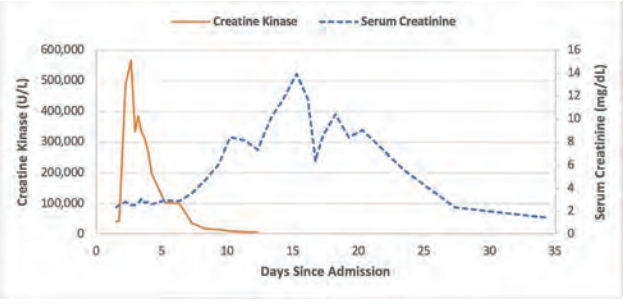

Fig. 1. sCr and CK since admission.

PO0045

A Case of Oxalate Nephropathy in the Setting of Clostridium difficile Infection

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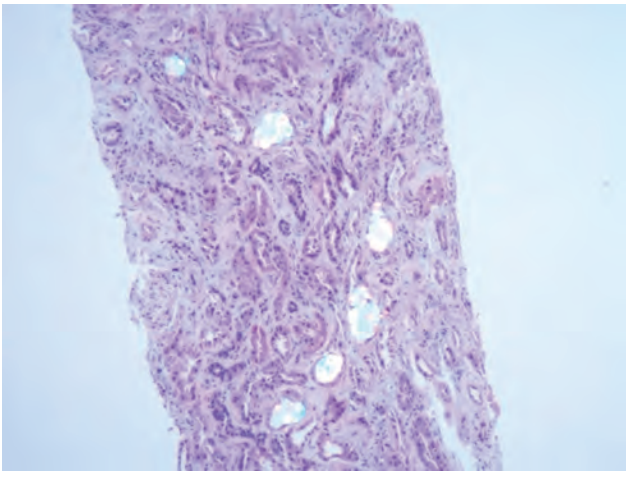
Introduction: While hyperoxaluria is a known complication of inflammatory bowel diseases, it is rarely associated with infectious forms of colitis. We report a case of oxalate nephropathy in the setting of Clostridium difficile colitis in a patient with high dietary oxalate ingestion.

Case Description: A 73 year-old black male with stage 3 CKD, diabetes mellitus, hypertension, and hyperlipidemia presented with a 2-week history of intractable diarrhea after finishing a course of oral antibiotics prescribed for acute diverticulitis. Laboratory data showed serum creatinine 15.4 mg/dL, blood urea nitrogen (BUN) 107 m/dL, potassium 8.7 meq/L, total CO2 8 mmol/L. Urinalysis was unremarkable. Imaging showed no renal obstruction. Stool sample tested positive for C difficile. Emergent dialysis was initiated for hyperkalemia. Despite adequate supportive measures, the patient remained oliguric and dialysis dependent. A kidney biopsy, on day 5, showed extensive tubular deposition of calcium oxalate crystals, and moderate to severe tubulointerstitial fibrosis. Further inquiry elicited dietary intake of 1-2 cups of peanuts daily. 24-hr urine collection showed no hyperoxaluria (urine oxalate 24 mg/24h; ref range: 7-44). The patient remains dialysis dependent.

Discussion: Acute oxalate nephropathy in the setting of Clostridium difficile colitis is rarely reported. The hypothesized etiopathogenesis likely relates to altered gut microbiome, specifically decreased Oxalobacter formigenes, leading to impaired oxalate degradation, increased oxalate absorption, and subsequent hyperoxaluria (potentially transient) leading to calcium oxalate deposition in the kidneys and AKI. Treatment is mainly supportive. For acute kidney injury in the setting of acute or chronic diarrhea illness, oxalate nephropathy should be considered. Recovery rates are low, with over 50% of patients remaining dialysis dependent.



Calcium oxalate crystals in tubules (PAS stain, polarized light)

PO0046

Postrenal AKI due to a Rarely Seen Neoplastic Phenomenon in an Adolescent

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Introduction: AKI is an important cause of morbidity & mortality in adult and pediatric patients. Based on a lit review by Cleto-Yamane, et. al., the pediatric incidence & mortality of AKI in the USA in 2013 was 0.39% and 15.3%, respectively. In general, a patient's presentation may provide clues to the etiology of AKI (i.e. prerenal, intrarenal and postrenal). AKI due to postrenal/obstructive causes is less common in children as compared to adults and is usually associated with congenital abnormalities e.g. posterior urethral valves, or acquired due to stones or tumors. We report the case of a 14 yo previously healthy female with a unique clinical presentation due to lower urinary tract obstruction secondary to a tumor.

Case Description: The patient presented with 3 weeks of back pain, R leg swelling, headaches, urinary frequency, n/v and hematuria. In the ED, her BUN and creatinine were 107 mg/dL and 21.1 mg/dL, respectively. A RUS showed enlarged non-echogenic kidneys with mild bilateral hydronephrosis & a heterogeneous pelvic mass. Further labs revealed anemia, low PTH, normal complement levels, ASO & ANA titers. A LE Doppler study was negative for venous thrombosis. A non-contrast MRI showed a pelvic mass & possible metastasis. Peds Oncology was consulted, and biopsies of bone marrow & pelvic tumor revealed a small round blue cell tumor with immunohistochemical stains diagnostic for rhabdomyosarcoma. She developed oliguria, hyperkalemia & hyperuricemia (24mg/dL). Rasburicase was given & CRRT was initiated. She received emergent chemotherapy with cyclophosphamide, doxorubicin & vincristine. Bilateral percutaneous nephrostomy tubes were placed with improvement in UOP & renal function allowing CRRT to be stopped. Labs showed a downward trend of BUN & creatinine to 14 mg/dL and 0.8 mg/dL, respectively.

Discussion: Our patient's clinical presentation was atypical in that her initial US findings of mild hydronephrosis were not consistent with the severity of her renal injury. Her AKI was likely a combination of obstructive uropathy from the large pelvic tumor compressing her lower urinary tract & uric acid nephropathy. Decompression of the urinary system, management of hyperuricemia & initiation of tumor directed chemotherapy resulted in marked improvement of kidney function. Our case highlights the importance of considering an obstructive etiology in older children presenting with AKI.

PO0047

Profiling AKI Trajectories: Early Results from the Million AKI Project

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Background: Clinical guidelines for risk stratification of acute kidney injury (AKI) patients are based on peak increases in serum creatinine (SC). These definitions do not consider other characteristics of change in SC that may provide information on risk of adverse outcomes. Identification of patient groups that display distinct patterns in trajectory of SC and outcome profiles may lead to more nuanced risk-based definitions of AKI.

Methods: Data from the United States Veterans Health Administration were obtained. A latent class growth model identified patient groups based on similar patterns of trajectory in serum creatinine during a hospitalization with an AKI. Regression models examined associations of trajectory groups with risk factors and in-hospital mortality.

Results: We constructed a cohort of 480,575 veterans with an AKI during an inpatient stay (a subset of the Million AKI Project cohort). Of these, 343,471 (71.5%), 63,665 (13.3%), and 73,439 (15.3%) met KDIGO AKI stages 1, 2, and 3 criteria. 9.4% died during their hospitalization. We identified 9 latent trajectories summarized by 4 phenotypes: a mild increase in SC from low baseline (66%), and varying degrees of increase in SC with no (9%), moderate (17%), and near-full recovery (8%). Higher systolic blood pressure (OR=1.02; 95% CI=1.01-1.02 per 1 mmHg), sepsis (2.24; 2.10-2.39), non-use of ACE/ARB (1.54;1.47-1.61), diuretic use (1.16; 1.12-1.20), albuminuria (1.36; 1.31-1.41), and prior history of AKI (1.27, 1.22-1.32) were associated with trajectories with larger increases in SC, while major surgeries (2.48; 2.37-2.60) were associated with trajectories that recovered. Compared to the mild increase group, those with partial or no recovery had a higher odd of in-hospital mortality (1.64; 1.57-1.71) that increased in magnitude with higher baseline SC and a greater increase in SC (2.73; 2.66-2.80). Groups that experienced near-full recovery showed no evidence of a difference in mortality profile (0.97; 0.90-1.05) despite differences in other aspects of the trajectory.

Conclusions: Leveraging the depth and breadth of a high-quality longitudinal electronic health record system, we characterized nearly half a million cases of AKI; our results suggest that profiling of AKI trajectories informs risk stratification and may guide deployment of post AKI care.

Funding: Veterans Affairs Support, Private Foundation Support

PO0048

Trends in Nephrology Follow-Up After an Episode of AKI in US Veterans

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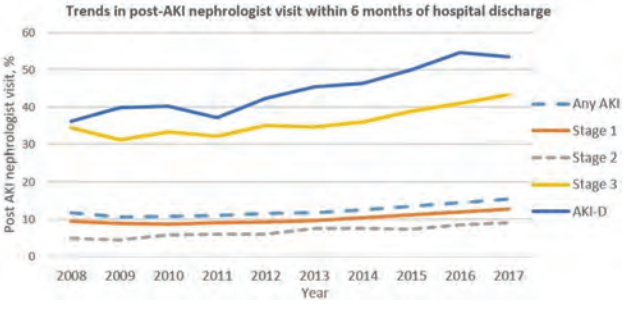
Background: KDIGO guidelines recommend evaluating patients following AKI for new onset or worsening CKD. Yet, historically nephrologist referral post-AKI has been low. We sought to determine recent trends in outpatient nephrologist follow-up after a hospitalization with AKI.

Methods: We assembled a national cohort of US veterans surviving 30-days post hospitalization with KDIGO creatinine-defined AKI from 2008 to 2017, excluding those with ESRD or kidney transplant, those requiring dialysis within 30 days of hospital discharge, or discharged to hospice. The primary outcome was the proportion of AKI survivors completing an outpatient visit with a nephrologist within 6 months of their AKI hospitalization. To assess trends, we assessed the association of year (as a continuous variable) with follow-up in a Cox proportional hazards model adjusting for age, race, sex, AKI stage, hypertension, diabetes, CKD, Charlson Comorbidity Index, ICU utilization, acute myocardial infarction, acute heart failure, and hospital admitting service.

Results: Of the 480,200 survivors of AKI, 12.2% had a visit with a nephrologist within 6 months. The proportion of patients with nephrology follow-up ranged from 10.0% in stage 1 AKI to 43.8% in patients with AKI requiring inpatient dialysis. The proportion of patients receiving post-AKI care increased across the study period, from 11.8% in 2008 to 15.4% in 2017 (figure). Upon adjusting for demographics, comorbid conditions, and hospitalization characteristics, year remained a significant predictor of increasing nephrology follow-up after AKI (per year HR 1.024, 95% CI 1.021-1.027, p<0.01).

Conclusions: From 2008 to 2017, there was a modest increase in post-AKI follow-up that persisted after accounting for changing demographic, comorbid conditions and hospitalization characteristics. However, most patients with severe AKI did not have an outpatient visit with a nephrologist at 6 months, highlighting opportunities to improve processes of post-AKI care.

Funding: Other U.S. Government Support



PO0049

Preoperative Urine Alpha 1 Microglobulin Levels Are Associated with AKI and Mortality After Cardiac Surgery

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Background: Higher urine alpha-1 microglobulin (a1m) levels are a marker of proximal tubule dysfunction and may improve CKD assessment and risk stratification. We hypothesized that a1m levels would be associated with adverse outcomes after cardiac surgery.

Methods: In 1464 adults undergoing cardiac surgery (CABG and/or valve) and prospectively enrolled in the multicenter TRIBE-AKI study, we measured urine a1m pre- and post-operatively. Outcomes were post-operative AKI during index hospitalization (AKIN stage ≥1) and all-cause mortality (median follow-up (IQR) 6.7 (4.0, 7.9) years). Urine a1m was analyzed as a continuous ($\log_2$) predictor in multivariable analyses adjusting for demographics, surgery characteristics, comorbidities, baseline eGFR, urine albumin, and urine creatinine.

Results: There were 230 AKI events and 459 deaths. Higher pre-operative a1m was independently associated with AKI (aOR=1.36, 95% CI 1.14-1.62) and all-cause mortality (aHR=1.19, 95% CI 1.06-1.33) (see table). We observed a significant interaction (p=0.01), whereby a1m had a stronger association with mortality in the subset without CHF (aHR=1.29, 95% CI 1.12-1.47) than among those with CHF (aHR=1.06, 95% CI 0.85-1.32). However, post-operative changes in a1m were not associated with AKI or mortality risk.

Conclusions: Even after adjusting for baseline kidney function and comorbidities, pre-operative a1m was associated with post-operative AKI and all-cause mortality.

Funding: Other NIH Support - NHLBI; study also supported by supported by NIH grant RO1HL085757 (CRP) to fund the TRIBE-AKI Consortium.

	AKI[a]	All-cause mortality[b]
Pre-operative uα1m	***aOR (95% CI)***	***aHR (95% CI)***
per doubling	1.36 (1.14, 1.62)	1.19 (1.06, 1.33)
Tertile 1	1.00 (reference)	1.00 (reference)
Tertile 2	0.64 (0.43, 0.95)	0.93 (0.71, 1.22)
Tertile 3	1.17 (0.78, 1.76)	1.40 (1.07, 1.84)

[a]Adjusted for age, sex, race, cardiopulmonary bypass time >120 minutes, nonelective surgery, CABG vs. valve replacement, diabetes, hypertension, congestive heart failure, myocardial infarction, baseline eGFR, urine albumin, urine creatinine, site.
[b]Adjusted for age, sex, race, cardiopulmonary bypass time >120 minutes, nonelective surgery, diabetes, hypertension, congestive heart failure, myocardial infarction, smoking, BMI, AKI/dialysis during index hospitalization, baseline eGFR, urine albumin, urine creatinine, site.

PO0050

Elevated Serum Tenascin C Predicts All-Cause Mortality in Critically Ill Patients with Multiple Organ Dysfunction

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Background: Tenascin-C (TNC) is a matricellular protein that is rarely expressed in most of adult tissues, but re-induced following injury. This study aimed to evaluate serum TNC in predicting all-cause mortality in critical ill patients with multiple organ dysfunction.

Methods: Adult critical ill patients who met the criteria of at least two organs dysfunction and acute organ injury with an increase of SOFA ≥ 2 points within 7 days were prospectively enrolled in one derivation cohort (Medical ward) and one external validation cohort (Emergency ward). Serum TNC was measured within the first 24 hours after enrollment and the association between serum TNC and 28-day all-cause mortality was analyzed.

Results: A total of 115 patients with median age 56 (38, 66) years and male of 65.2% in derivation cohort and 110 patients with median (quartile) age of 64 (53, 73) and male of 67% in validation cohort were enrolled. Serum TNC was 210.2 (96.8, 469.6) ng/ml in derivation cohort and 229.4 (141.6, 472.5) ng/ml in validation cohort, both significantly higher than that in healthy controls (median 80.9 ng/ml, n=46, p<0.01 for both). The TNC levels were positively associated with the critical illness scores such as SOFA, APACHE II and SPAS II, as well as 28-day mortality (p<0.01 for all). Compared to the patients with TNC<300ng/ml, patients with TNC≥300ng/ml had a remarkably higher 28-day mortality (38.6% vs. 14.1%, p=0.003 in derivation cohort; 57.8% vs. 13.8%, p<0.001 in validation cohort). In multivariate analysis, serum TNC was independently associated with the mortality after adjustment for age, gender and SOFA in both cohorts. The areas under the Receiver Operating Curve of TNC for 28-day mortality was 0.797 in derivation cohort and 0.803 in validation cohort, not inferior to SOFA (0.844 and 0.808), APACHE II (0.86 and 0.762) and SPAS II (0.872 and 0.779).

Conclusions: Serum TNC was significantly increased in critical ill patients with multiple organ dysfunction and was positively associated with the severity of illness and all-cause mortality. It was a useful prognostic tool for predicting all-cause mortality in critical ill patients.

PO0051

Predominance of Mitochondrial Protein Composition in Urinary Sediment Enriched with Muddy Brown Granular Casts During Acute Tubular Necrosis

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Background: Detection of copious number of "muddy" brown granular casts (MBGCs) during microscopic examination of the urinary sediment (MicrExUrSed) is pathognomonic of acute tubular necrosis (ATN). Because hospital laboratories do not properly report MBGCs, nephrologists are required to independently perform MicrExUrSed, a time-consuming and logistically challenging endeavor that requires expertise. Thus, a diagnostic test to identify MBGCs without the performance of MicrExUrSed could prove useful for busy clinicians. We hypothesized that MBGCs-enriched urinary sediment (MBGC-sedi) contains unique proteins that could serve as surrogate and biomarker of ATN.

Methods: MicrExUrSed was performed in specimens from patients with acute kidney injury (AKI) seen for nephrology consultation with a suspected etiology of ATN. Urine specimens from 3 patients containing numerous (>10 casts per low power field) MBGCs were collected and subjected to low-speed centrifugation (100 g) and stored at -80°C. Thawed pellets and urine were proteolytically digested and analyzed by nano-LC tandem mass spectrometry (Orbitrap Fusion Lumos). Proteins were identified by MASCOT and classified by gene ontology.

Results: We identified 1678 proteins (1% false discovery rate) from supernatant and MBGC-sedi combined. Among them, 711 proteins were unique to MBGC-sedi and 27 were unique to the supernatant. Normalized spectral abundance of 242 MBGC-sedi proteins was greater compared to the supernatant (p<0.05) and had proportionally more mitochondrial proteins (17 ± 1% vs. 6 ± 1%, respectively, p=0.0004). Based on spectral counts, the most abundant and unique mitochondrial proteins in all 3 samples included: ATP synthase alpha and beta-subunit, isocitrate dehydrogenase, 60kDa heat shock protein, and aconitate hydratase. Six out of 7 cytochrome proteins identified were unique to MBGC-sedi.

Conclusions: MBGC-sedi contains unique proteins compared to the supernatant. These proteins can serve as a foundation for the search of an ATN biomarker and surrogate for MBGCs detection by MicrExUrSed in patients with AKI. The predominance of mitochondrial proteins in MBGCs-sedi may explain the characteristic brown pigmentation of MBGCs.

PO0052

Treatment of Hepatorenal Syndrome Type 1 with Terlipressin Reduces Need for Renal Replacement Therapy After Liver Transplantation

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Background: Hepatorenal syndrome type 1 (HRS-1) is a severe but reversible acute kidney injury in patients with cirrhosis. The need for renal replacement therapy (RRT) posttransplant is associated with prolonged intensive care unit stays and decreased survival. Recently, a randomized placebo (PBO)-controlled trial (CONFIRM, NCT02770716) demonstrated the efficacy of terlipressin (TERLI) for inducing reversal of HRS-1 and reducing the cumulative need for RRT. This study assessed whether TERLI reduces the rate of RRT following liver transplantation (LT).

Methods: CONFIRM was a North American trial (N=300) that compared HRS-1 reversal rates between patients treated 2:1 with albumin plus TERLI (n=199) or albumin plus PBO (n=101). In a post hoc analysis, we assessed the rate of RRT post-LT by intention-to-treat analysis through 90 days of follow-up. We also conducted a pooled analysis of the 3 TERLI RCTs in HRS-1 (OT-0401 [NCT00089570], REVERSE [NCT01143246], and CONFIRM) to examine 90-day overall and RRT-free survival rates in patients who received LT.

Results: In CONFIRM, 23.1% (46/199) of patients in the TERLI group and 28.7% (29/101) of patients in the PBO group underwent LT. Following LT, the rate of post-LT RRT in patients who received TERLI was significantly lower than that in those who received PBO (19.6% [9/46] vs 44.8% [13/29], respectively; *P*=0.036). The overall 90-day survival rate for those transplanted in the TERLI group was 100% (46/46) compared with 93.1% (27/29) in the PBO group (*P*=not significant). Further, in the pooled analysis of the 3 phase 3 studies, the 90-day survival rates were 98.9% (93/94) and 91.0% (71/78), respectively (*P*=0.014). In the pooled analysis of REVERSE and CONFIRM, for transplant-listed patients, 50.0% (46/92) of patients in the TERLI group were alive without RRT at Day 90 compared with 32.2% (19/59) in the PBO group (*P*=0.032).

Conclusions: Treatment with TERLI added to albumin for patients with HRS-1 significantly decreases the need for RRT following LT.

PO0053

Urinary Waxy Casts Are Associated with Persistence of AKI Requiring Dialysis

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Background: Waxy casts (WxCs) can be identified during microscopic examination of the urinary sediment (MicrExUrSed) and they have been classically linked to chronic kidney disease (CKD). We previously shown that WxCs predict severity of acute kidney injury (AKI). Thus, we hypothesized that WxCs may inform about duration and persistence of AKI and AKI requiring renal replacement therapy (AKI-RRT).

Methods: We conducted a prospective observational study in patients seen in inpatient nephrology consultation with AKI stage ≥ 2 (AKIN) over 2.5 years. On the day of consult, MicrExUrSed was performed to determine the percentage of low power fields with WxCs. The outcome measures were persistence of need for RRT at the time of hospital discharge (AKI-RRT-Persist) and ≥ 50% rise in serum creatinine (sCr) from baseline at the time of hospital discharge (AKI-Persist).

Results: Urine specimens from 286 patients [median age 60 (20 – 88), 37% women] were assessed. The etiology of AKI (de novo AKI 67%, AKI on CKD 33%) was ischemic ATI (47%), toxic ATI (9%), ischemic/toxic ATI (11%) or other (33%). WxCs were found in 85 patients (30%), 61 (72%) of which had de novo AKI. Median sCr for those with WxCs was 3.5 (0.9 – 22.0)mg/dL and 3.1 (0.9 – 12.5) mg/dL for those without WxCs (p=0.12). AKI-RRT at any point during the course of AKI was seen in 45% (38/85) of those with WxCs compared to 32% (54/201) of those without WxCs (p=0.043). There was a greater risk for AKI-RRT-Persist for those withWxCs [15.3% vs 7.5%, odds ratio (OR): 2.2, CI 1.1 – 4.9, p=0.046)]. Presence and abundance of WxCs were also associated with a greater risk for AKI-Persist [62% (94/152), 75% (45/60), 81% (29/36) and 93% (13/14), for those with no WxC, any WxC, >10% WxCs and >50% WxCs, respectively; chi-square for trend, p=0.014].

Conclusions: In patients with AKI, the presence and abundance of WxCs are associated with a greater risk for persistent need for RRT and persistent increase in sCr at the time of hospital discharge. These findings suggest that WxCs inform about the severity of AKI and the timeline of significant AKI recovery.

PO0054

Retrospective Analysis of the Efficiency of Caplacizumab in the Treatment of Acquired Thrombotic Thrombocytopenic Purpura: Results from the REACT-2020 Study Group

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Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare but life-threatening disorder, caused by the formation of inhibitory and occasionally non-inhibitory autoantibodies against ADAMTS13. Despite plasma exchange and immunosuppression, long-term mortality and morbidity associated with acute episodes remain high. Here, caplacizumab – a nanobody approved in Germany in 2018 – has recently expanded the therapeutic options.

Methods: Retrospective analysis of the use of caplacizumab in more than 60 patients from more than 30 different medical centers in Germany during acute disease management.

Results: Caplacizumab led to a rapid normalization of the platelet count (median 3, mean 3.78 days). In 34/60 instances, caplacizumab was stopped prior to day 30 with favorable outcome whenever ADAMTS13 activities were >10%. In contrast, 11/34 patients with ADAMTS13 activities <10% at the time of stopping caplacizumab treatment develop a non-favorable outcome comprising disease exacerbation or relapse. In some cases, prolongation of the treatment interval to every other day was feasible and resulted in a sustained reduction of the vWF activity.

Conclusions: Caplacizumab is efficacious in the treatment of aTTP independent of timing and adjunct treatment modalities. Based on this real-world experience and published literature we propose to administer caplacizumab to all patients with an acute episode of aTTP immediately. ADAMTS13 activity measurements are central for a rapid diagnosis in the acute setting but also to tailor disease management. In addition, vWF activity may serve as biomarker for drug monitoring.

PO0055

Erythropoiesis-Stimulating Agents in AKI Requiring Dialysis

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Background: Erythropoiesis-stimulating agents (ESAs) are used in patients with CKD to treat anemia. AKI may also be a state of erythropoietin deficiency, although data on this is conflicting. Few studies have examined ESA use in AKI, including the most severe AKI cases requiring dialysis (AKI-D). It is unknown whether and to what extent clinicians prescribe ESAs in AKI-D.

Methods: Among the more than 40,000 patients admitted to Beth Israel Deaconess Medical Center ICUs between 2001 and 2012 in the MIMIC-III database, we selected 591 AKI-D patients and 276 ESKD patients based on ICD-9 diagnostic codes. In a cross-sectional analysis, we determined the frequency of ESA usage and estimated associations between ESA usage and age, sex, surgical (vs medical) ICU admission, ICU length of stay, admission hemoglobin, admission serum creatinine, history of CKD, and ESKD (versus AKI-D) status using multivariable logistic regression. We also examined the relationship between ESA use and the number of blood transfusions during the ICU stay.

Results: ESA usage (any time during ICU stay) was 13% in AKI-D (vs 21% in ESKD). Among AKI-D patients (**Table 1**), CKD (adjusted OR 3.59, 95% CI 2.06-6.25, p<0.0001), length of stay (1.06 [1.04-1.08] per day, p<0.0001), sepsis (2.06 [1.08-3.92], p=0.03), and female sex (0.56 [0.31-1.00], p=0.05) were significantly associated with ESA use. Patients treated with ESAs received six more blood transfusions on average than patients who were not treated with ESAs (6.1 more transfusions, 95% CI 2.6-9.7, p=0.0006), but this difference disappeared when adjusted for the variables significantly associated with ESA usage (0.07 more transfusions, 95% CI -3.4 to +3.2, p=0.97).

Conclusions: ESAs usage in patients with AKI-D was not rare. Baseline renal function was the biggest predictor of ESA usage. Use of this costly therapy of unclear risk-benefit ratio in the AKI-D population should be studied further.

Funding: NIDDK Support

Patients with AKI-D

Characteristics	ESA (n = 74)	No ESA (n = 517)
Age, yrs	62 (16)	62 (15)
Female	27%	38%
Baseline chronic kidney disease	45%	23%
Admission serum creatinine, mg/dL	3.1 (2.1)	2.8 (2.4)
Admission hemoglobin, g/dL	10.8 (2.1)	11.3 (2.3)
Surgical ICU	45%	39%
Sepsis during ICU day 1	77%	70%
ICU LOS, days	28 (25)	13 (12)
Blood transfusions during ICU stay	15 (21)	9 (13)

PO0056

Survey of US Critical Care Practitioners on Perspectives Toward Net Ultrafiltration Prescription and Practice

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Background: Previous studies suggest international practice variation in net ultrafiltration (UF_{NET}) among critically ill patients with acute kidney injury treated with kidney replacement therapy. We examined U.S. critical care practitioner attitudes toward UF_{NET} prescription and practice.

Methods: Secondary analysis of a multinational, cross-sectional, internet-assisted, open survey administered to intensivists, nephrologists, advanced practice providers, ICU and dialysis nurses in the U.S.

Results: Of 1,569 international survey respondents, 465 (29.6%) practitioners were from the U.S. Practitioners were mostly nurses and nurse practitioners (58%) and intensivists (38.2%). Median duration of practice was 8.7 (IQR, 4.2-19.4) years and 63.4% practiced in a university- based hospital. Practitioners reported using continuous kidney replacement therapy (CKRT) as the first modality for UF_{NET} in 60% (IQR 20-90%) of their patients with median UF_{NET} rate of 51 mL/h (IQR 25-100 mL/h) for hemodynamically unstable and a maximal rate of 285 mL/h (IQR,200 - 341 mL/h) for hemodynamically stable patients. 58.3% (range 28.7%-79.2%) of practitioners assessed net fluid balance hourly. Hemodynamic instability was reported in 25% (IQR, 10-100%) of the patients, and practitioners decreased the rate of fluid removal (71.2%); started or increased dose of a vasopressor (56.8%); completely stopped fluid removal (44.5%); and administered a fluid bolus (28.7%). Most clinicians (79.8%) reported patient intolerance as a major barrier. Other barriers include frequent interruptions (50.1%), under prescription (17.8%), unavailability of trained staff (17%), inability to titrate fluid removal (10.1%), unavailability of dialysis machines (8.6%) and cost (2.4%) (Figure 1). More than 70% of clinicians agreed with early protocolized fluid removal and expressed desire to enroll their patients in a future clinical trial.

Conclusions: This study provides new knowledge on UF_{NET} in practices in the U.S. We also identified barriers and specific targets for quality improvement initiatives. Our data reflect the need for evidence-based practice guidelines for UF_{NET}.

PO0057

A Pilot Trial to Evaluate the Clinical Usefulness of Contrast-Enhanced Ultrasound in Predicting Renal Outcomes in Patients with AKI

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Background: Contrast-enhanced ultrasound (CEUS) enables the assessment of real-time renal microcirculation. This study investigated CEUS-driven parameters as hemodynamic predictors for renal outcomes in patients with acute kidney injury (AKI).

Methods: Forty-eight patients who were diagnosed with AKI were prospectively enrolled and underwent CEUS at the occurrence of AKI. Parameters measured were the wash-in slope (WIS), time to peak intensity, peak intensity (PI), area under the time–intensity curve (AUC), mean transit time (MTT), time for full width at half maximum, and rise time (RT). The predictive performance of the CEUS-driven parameters for Kidney Disease Improving Global Outcomes (KDIGO) AKI stage, initiation of renal replacement therapy (RRT), AKI recovery, and chronic kidney disease (CKD) progression was

assessed. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of CEUS.

Results: Cortical RT (Odds ratio [OR] = 1.21) predicted the KDIGO stage 3 AKI. Cortical MTT (OR = 1.07) and RT (OR = 1.20) predicted the initiation of RRT. Cortical WIS (OR = 76.23) and medullary PI (OR = 1.25) predicted AKI recovery. Medullary PI (OR = 0.78) and AUC (OR = 1.00) predicted CKD progression. The areas under the ROC curves showed reasonable performance for predicting the initiation of RRT and AKI recovery. The sensitivity and specificity of the quantitative CEUS parameters were 60–83% and 62–77%, respectively, with an area under the curve of 0.69–0.75.

Conclusions: CEUS may be a supplemental tool in diagnosing the severity of AKI and predicting renal prognosis in patients with AKI.

Funding: Government Support - Non-U.S.

PO0058

A Clinical Score to Predict Recovery in ESKD due to AKI

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Background: Acute kidney injury (AKI) is a major contributor to end-stage kidney disease (ESKD). About one-third of patients with ESKD due to AKI recover kidney function. However, there is lack of clinical models to predict kidney recovery in ESKD due to AKI.

Methods: Using data from the United States Renal Data System (2005-2014), we developed a clinical score to predict kidney recovery by 90-days post-dialysis initiation in patients with ESKD due to AKI (N=22,922). We used multivariable logistic regressions to model the effects of patient demographics, comorbidities, and laboratory measures on kidney recovery. The resulting logistic parameter estimates were transformed into integer point totals by doubling and rounding the estimates. The predictive accuracy of the score models was compared to the underlying logistic models by comparing areas under the receiver operating characteristic curves (AUROC) and internal validation was performed.

Results: In ESKD due to AKI, kidney recovery within 90-days occurred in 24% of patients. Median recovery time for patients who recovered was 2 months; 72% recovered within 90-days. In the logistic models of recovery at 90-days, older age, lower body mass index, hemoglobin < 12 gm/dl, Black and Native American race, Hispanic ethnicity, congestive heart failure, amputation, poor functional status, and pre-dialysis nephrology care were associated with a lower likelihood of recovery. Eight patient characteristics were included in the final clinical score- age, body mass index, race, congestive heart failure, amputation, functional status, and prior nephrology care. Recovery scores ranged from zero to 11, with corresponding recovery rates ranging from 6% to 86%. Three risk categories (score range of 0-5, 6-7, and 8-11) exhibited 90-day recovery rates of 11%, 23%, and 45%. The internal validation assessment showed no overfitting of the models. The AUROC of the score was 0.70, similar to the original AUROC of 0.71.

Conclusions: A simple clinical risk score derived from information available at incident dialysis can accurately predict kidney recovery at 90 days in ESKD due to AKI. This predictive tool can be utilized by dialysis providers and policymakers to individualize care, and to improve the quality and processes of care.

Funding: Clinical Revenue Support

PO0059

AKI in Hospitalized Patients with Influenza Is Associated with Worse Outcomes: A Study of National Inpatient Sample from 2012 to 2014 in the United States

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Background: Influenza causes significant morbidity and mortality every year. Physiologically, kidneys receive only 25% of the cardiac output in an average weight adult and therefore often develop acute kidney injury (AKI). Our study determines outcomes of AKI in adults hospitalized with influenza between 2012 and 2014 in the US.

Methods: We analyzed adult patients with a principal diagnosis of influenza from the 2012 to 2014 National Inpatient Sample. ICD-9-CM was used to identify the diagnosis variables. Patients were divided into two cohorts; with and without AKI. Patient characteristics between both groups were compared. Chi-squared analysis for categorical variables and multivariate regression analysis was done using STATA 16.0 to determine the relationship of outcomes. P <0.05 was used as the level of statistical significance.

Results: 120,730 hospitalizations with influenza were sampled. 16,270 (13.5%) of these had AKI (image 1). After adjusting for potential confounders, patients with AKI had higher odds of mortality (adjusted odds ratio (aOR): 3.83; 95% confidence interval (CI) 3.00-4.89, p<0.001), developing severe sepsis (aOR 8.65; 95% CI 6.46-11.57), septic shock (aOR 9.53; 95% CI 6.42-14.16), rhabdomyolysis (aOR 3.03; 95% CI 2.39- 3.84), requiring intubation (aOR 5.57; 95% CI 4.61-6.74, p<0.001), a longer length of stay (1.8 day; 95% CI 1.52-2.08, p<0.001) and higher costs ($5054.4; 95% CI $3918.8-$6190.1, p<0.001).

Conclusions: Influenza complicated with AKI in hospitalized patients is associated with a worse outcome in terms of morbidity and mortality along with increased healthcare costs and a longer length of stay.

Patient characteristics and comorbidities (%)	Without AKI	With AKI	P value
Age groups			<0.001
Age>=18 and <=35	7.5	2.7	
Age >35 and <=50	12.7	7.0	
Age >50 and <=65	22.1	19.4	
Age >65 and <=80	26.3	29.5	
Age >= 80	31.3	41.3	
Female	56.6	46.5	<0.001
Chronic kidney disease	13.9	45.3	<0.001
Hypertension	61.3	74.5	<0.001
Coronary artery disease	22.2	32.6	<0.001
Congestive heart failure	16.9	33.8	<0.001
Diabetes mellitus	28.7	40.6	<0.001
Chronic obstructive pulmonary disease	20.9	21.9	0.187
Obesity	12.1	13.1	0.111
Race			<0.001
White	71.4	71.4	
Black	13.4	15.9	
Hispanic	9.5	7.9	
Asian or Pacific Islander	2.2	2.1	
Native American	0.7	0.3	
Other	2.7	2.3	
Charlson Comorbidity Index score			<0.001
0	28.3	16.0	
1	32.0	18.3	
2	18.1	17.4	
3	10.2	19.2	
≥4	11.5	29.0	

Characteristics of adult patients admitted with influenza

PO0060

Impact of Chloride-Rich Crystalloids on Sepsis-Associated Community-Acquired AKI Recovery in Critically Ill Patients

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Background: The use of chloride-rich crystalloids for resuscitation is associated with developing acute kidney injury (AKI). We aimed to explore the impact of resuscitation with chloride-rich crystalloids compared to balanced crystalloids on the recovery of kidney function in patients presenting with established sepsis-associated community-acquired AKI (SACA-AKI).

Methods: This was a single-center, historical cohort study of patients admitted to the intensive care unit (ICU) who presented to the emergency department (ED) with SACA-AKI at Mayo Clinic, Rochester, MN, from January 2011 to April 2018. We divided the cohort into two groups based on the primary type of crystalloids received in the ED and the first 48-hours of ICU. The first group received primarily normal saline with <20% balanced solutions, and the second group received at least ≥20% balanced crystalloids during the initial volume resuscitation.

Results: We included 736 patients who were resuscitated with crystalloids after SACA-AKI diagnosis (mean age 64±16, n = 463 (63%) males). There were 286 (39%) patients in the second group, found to have higher positive fluid balance during the first 48-hours of admission compared to the first group [median 5.7 (IQR: 3.6; 8) vs. 3.8 (IQR: 2.1; 6.1) L, $P < .001$]. By multivariate logistic regression, the patients in the second group had a higher rate of kidney function recovery after adjustments for known recovery risk factors (OR 1.4; 95% CI: 1.04-2, $P = .027$).

Conclusions: The use of balanced crystalloids during the initial resuscitation is associated with higher odds of kidney function recovery in patients with SACA-AKI.

Funding: Other NIH Support - National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number K23AI143882 (PI; EFB).

PO0061

The Effect of Care Bundles for AKI: A Systematic Review and Meta-Analysis

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Background: Acute kidney injury (AKI) is common and associated with increased morbidity and mortality. Implementation a set of evidence-based AKI care bundles may have some benefits to patient outcomes by reducing variable standards of care. We aimed to systematically review the literature to quantify the effect of AKI care bundles on patient outcomes.

Methods: We searched Pubmed (Medline), EMBASE and Cochrane databases for studies that compare the effect of AKI care bundles with usual standard care in patients with or at risk of AKI from database inception to December 31, 2019. The quality of included studies was assessed using the Newcastle-Ottawa Scale. Heterogeneity was

assessed using Cochrane Q test and I^2 test statistics. Data were analyzed by RevMan 5.3 and Comprehensive meta-analysis (CMA 3.0). The primary outcome was in-hospital or longest follow-up mortality. Secondary outcomes included AKI incidence and AKI severity.

Results: A total of 11 studies (23,491 patients) were included in the meta-analysis. The implementation of AKI care bundles significantly reduced mortality in all patients (odds ratio, 0.87; 95% CI, 0.79–0.94; P =0.001; I^2 = 0%; Fig 1). And in patients at high risk for AKI(identified by novel biomarker, risk prediction score or electronic alert), care bundles significantly reduced AKI incidence(odds ratio, 0.62; 95% CI, 0.44–0.86; P=0.005; I^2 = 70%; Fig 2) and rates of AKI severity (odds ratio, 0.52; 95% CI, 0.35–0.76; P<0.001; I^2= 41%; Fig 3). In addition, there was no evidence of publication bias among the included studies.

Conclusions: The introduction of AKI care bundles can effectively improve outcome in patients with or at risk of AKI, especially when combined with novel biomarker, risk prediction score or electronic alert to manage AKI at early stage. However, the evidence so far is limited and not strong enough to make definite conclusions.

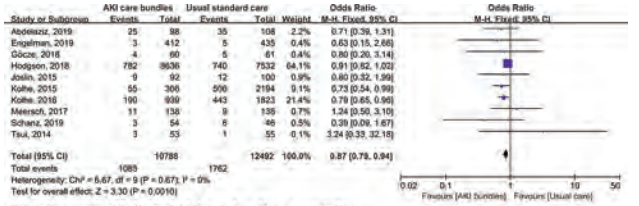

Fig. 1 Forest plot of effect of AKI care bundles on mortality.

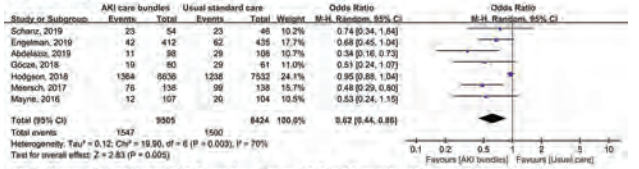

Fig. 2 Forest plot of effect of AKI care bundles on AKI incidence in patients at risk of AKI.

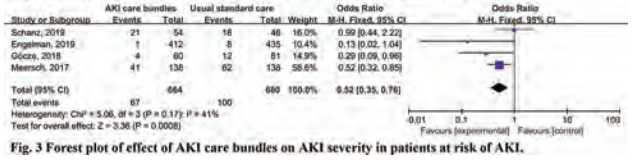

Fig. 3 Forest plot of effect of AKI care bundles on AKI severity in patients at risk of AKI.

PO0062

Block Randomized Implementation of a Decision-Making Algorithm for Renal Replacement Therapy Initiation in AKI Compared with Standard Care on AKI-Related Outcomes

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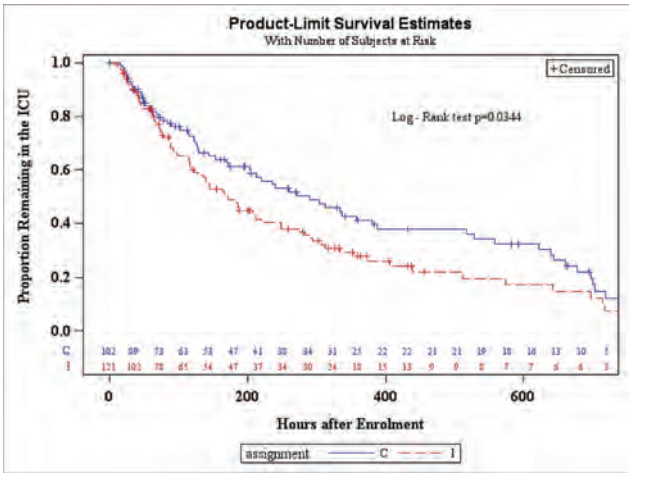
Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high mortality and utilization. Clinical decision-making related to AKI-RRT initiation in the intensive care setting is not standardized.

Methods: We conducted a 12 month single center block randomized controlled trial in the intensive care units (ICUs) of a large academic tertiary medical center; alternating use of an AKI Standardized Clinical Assessment and Management Plan (SCAMP), a decision-making algorithm to guide front-line clinicians, with use of a "sham" control form in 4-6 week randomization blocks. The SCAMP provided recommendations about optimal indications for initiating RRT on the basis of various clinical parameters, whereas the sham control form did not provide any recommendations for management of AKI-RRT.

Results: 122 patients were managed with AKI-SCAMP while 102 patients were managed using the sham control form. There was no significant difference in the primary outcome of odds of inpatient, 30-day or 60-day mortality associated with use of the AKI-SCAMP. With respect to secondary outcomes, use of the AKI-SCAMP resulted in a significantly reduced ICU length of stay (relative risk 0.68; 95% CI 0.66-0.69, p < 0.0001) and hospital length of stay (relative risk 0.75; 95% CI 0.72-0.79, p < 0.0001), as well as a reduced 30-day hospital readmission rate (odds ratio 0.38; 95% CI 0.15-0.99, p = 0.05).

Conclusions: Use of an AKI-SCAMP clinical decision support tool for assessment and management of AKI-RRT led to reduced ICU and hospital length of stay and 30-day hospital readmission rates. We advocate for increased study and use of this clinical decision support tool.



Kaplan-Meier curves for ICU length of stay according to treatment group; censoring for ICU mortality

PO0063

The Effect in Renal Function and Vascular Decongestion in Type 1 Cardiorenal Syndrome Treated with Two Strategies of Diuretics: A Randomized Clinical Trial

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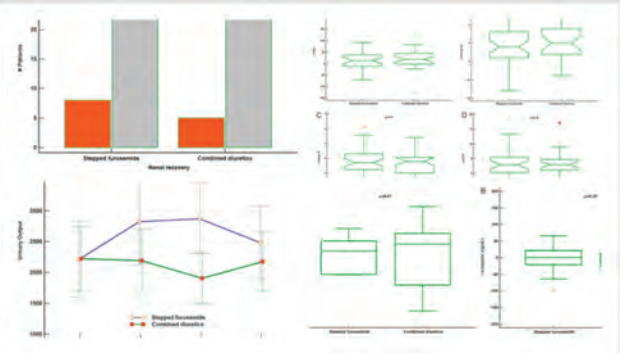
Background: The main treatment strategy in type 1 cardiorenal syndrome (CRS1) is vascular decongestion, it is probable that sequential blockage of the renal tubule with combined diuretics (CD) will obtain similar benefits when compared with stepped furosemide (SF).

Methods: We conducted a double-blind randomized clinical trial in CRS1 consecutive patients, we randomized in a 1:1 fashion to SF group or CD. The SF group received a continuous infusion of furosemide 100mg during the first day, with daily incremental doses to 200mg, 300mg and 400mg during the second, third and fourth day, respectively. The CD group consist in the combination of diuretics trying to block different tubular segments, including 4 consecutive days of oral chlortalidone 50mg, spironolactone 50mg and infusion of furosemide 100mg. The objectives were asses renal function recovery, and variables associated with vascular decongestion.

Results: During July 2017 to February 2020, 80 patients were randomized, 40 to the SF and 40 to the CD group, both groups were similar at baseline and had several very high-risk features. Mean age was 59 ± 14.5 years, male gender was 37 (46.2%), the median follow up was 182 days, Primary endpoint occurred in 20% in the SF group and in 15.2% in the DC group (p= 0.49), all secondary and exploratory endpoints were similar between groups with non-significant differences. Adverse events occurred frequently (85%) with no differences between groups (p = 0.53).

Conclusions: In patients with SCR-1 and high risk of resistance to diuretics, the strategy of CD compared to SF, offers the same frequency of renal recovery, diuresis, vascular decongestion and adverse events, so it can be considered as an alternative, especially in cases where it is not considered advisable to increase furosemide.



PO0064

Renin Levels Are Higher in Patients with AKI and Associate with Mortality and Major Adverse Kidney Events

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Background: Renin is a marker of tissue perfusion and may be useful in predicting mortality in critically ill patients. Renin might also reflect structural kidney damage in heterogeneous AKI settings. We examine if renin levels are different in patients with vs. without AKI and if renin levels associate with adverse outcomes in critically ill patients.

Methods: Multicenter observational study utilizing blood samples of critically ill patients (KLAKI) and patients undergoing cardiac surgery (TRIBE-AKI). Renin was measured by ELISA in serum from 296 critically ill patients at 24-48 h of AKI diagnosis (KDIGO ≥2) or ICU admission (controls), and perioperatively in plasma from 105 patients undergoing cardiac surgery (35 with AKI [≥0.3 mg/dL increase or ≥50% increase in serum creatinine from baseline preoperative level to postoperative level] and 70 controls without AKI). The association of renin levels with hospital mortality and major adverse kidney events at hospital discharge (MAKE: composite of death, need of renal replacement therapy or inability to recover more than 75% of baseline eGFR) was evaluated in the critically ill group.

Results: Renin levels were higher in critically ill patients with AKI vs. ICU controls without AKI (median [IQR], 67.9 [21.7-343.7] vs 22.2 [6.4-73.0] pg/mL, p<0.001). Similarly, patients undergoing cardiac surgery who developed postoperative AKI had pre and postoperative renin levels differentially higher than those without AKI, sustained from POD1 to POD3 (157.9 [80.0-390.8] vs. 68.9 [20.6-149.9] pg/mL at POD1 in AKI vs. no AKI, p=0.003). In adjusted models, higher renin levels independently associated with increased risk of hospital mortality (OR: 1.27, 95%CI: 1.02-1.58 for every 1-unit increase in renin and OR: 3.44, 95%CI: 1.08-11.02 when the highest tertile was compared to the lowest tertile). Further, every 1-unit increase in renin increased the risk of MAKE by 16% (95%CI: 1-33%).

Conclusions: Renin levels are differentially higher in patients with heterogeneous AKI when compared to controls without AKI. Renin levels associate with hospital mortality and MAKE in critically ill patients and therefore its utility in risk-stratification should be further explored in this vulnerable population.

PO0065

Angiotensin 1-7 as a Novel Biomarker of AKI in Pediatric Kidney Transplant Recipients

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Background: While graft survival rates of pediatric kidney transplant recipients have improved dramatically, acute kidney injury (AKI) accounts for up to 21% of graft failure in pediatric patients and prompt diagnosis of AKI is difficult. AKI activates the renin-angiotensin system (RAS), leading to increased angiotensin (Ang) II-induced inflammation and fibrosis. The ACE2/Ang-(1-7) pathway mitigates these effects but may be downregulated in AKI. The objective was to investigate Ang II and Ang-(1-7) as biomarkers to predict AKI in pediatric kidney transplant recipients. We hypothesized that changes in Ang II and Ang-(1-7) over time would predict biopsy-proven AKI in the first 6 months post-transplant.

Methods: This was a prospective cohort study of children recruited from a kidney transplant evaluation clinic. Blood and urine were collected pre-transplant and post-transplant at several time points. Ang II and Ang-(1-7) were measured with radioimmunoassays. Participants underwent for-cause or surveillance biopsies and histologic findings were recorded. We applied directed acyclic graph-informed Cox proportional hazards regression analysis with robust standard errors adjusted for age to estimate the association of time-varying Ang II and Ang-(1-7) with AKI.

Results: Of the 27 participants, mean age was 11.7 ±6.1 years, 63% were male, and 44% were Caucasian. The most common cause of kidney failure was congenital anomalies of the kidney and urinary tract (30%) and 74% received a deceased-donor transplant. Ten patients (37%) had AKI, most commonly due to tacrolimus toxicity (19%). In the urine, a 1-unit increase per day in Ang II (HR 0.97, 95% CI 0.93-1.0), Ang-(1-7) (0.99, 0.98-0.999), and Ang II:Ang-(1-7) (0.56, 0.28-1.11) over time predicted AKI, while blood levels did not.

Conclusions: Among pediatric kidney transplant recipients, changes in urinary Ang II and Ang-(1-7) over time predicted biopsy-proven AKI in the first 6 months post-transplant. Conversely, our findings suggest that for every 1-unit per day decrease in urine Ang-(1-7)[AMSM1], AKI risk increases by 1%. Our findings support the notion that both pathways of the renin-angiotensin system are involved in transplant AKI. Larger studies are needed to confirm the utility of measuring Ang II and Ang-(1-7) as biomarkers to detect transplant AKI and inform its pathophysiology.

PO0066

Biomarker and Safety Results from a Phase 1b Study of RBT-9 in Healthy Volunteers and Subjects with CKD Stage 3/4

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Background: Acute kidney injury (AKI) remains a major unmet medical need without any FDA approved preventive or therapeutic options. Safe administration of pharmacologic agents that can prevent AKI in the hospital setting have great potential given the high rate of AKI-related morbidity and mortality. Organ preconditioning to elicit a state of induced cytoresistance prior to insult, such as cardiac surgery, is a mechanism by which the drug RBT-1 has been shown to be protective in various animal models of AKI including glycerol-induced rhabdomyolysis, maleate-induced hypoxic/ischemic renal injury, and ischemia reperfusion injury. RBT-1 is composed of proprietary formulations of stannous protoporphyrin (RBT-9) and iron sucrose (RBT-3). We conducted three phase 1 clinical trials to study the effect of RBT-1, RBT-3, and RBT-9 on biomarkers of cytoprotection observed in experimental animals and on clinical safety. Herein, we report results from the Phase 1b study of RBT-9 in both healthy volunteers and subjects with CKD Stage 3/4.

Methods: Forty-two subjects were enrolled and received a single dose of RBT-9 at 9 mg (N=6), 27 mg (N=18), and 90 mg (N=18). None of the subjects in the 9 mg group had CKD; 12 subjects (67%) in each of the 27 and 90 mg groups had CKD. Mean age was 59.5 years.

Results: RBT 9 dose-dependently induced cytoprotective biomarker responses (heme oxygenase-1 [HO-1], ferritin, NAD[P]H dehydrogenase [quinone] 1 [NQO1], and interleukin-10 [IL-10]) in both healthy volunteers and CKD subjects. Treatment-emergent adverse events (TEAEs) were reported in 20 subjects (47%), the majority of which were photosensitivity events and largely confined to the 90 mg treatment group. TEAEs were generally mild in severity. Only 3 TEAEs were moderate; no TEAEs were severe. No serious adverse events were reported. All TEAEs resolved during follow-up. There was no evidence of renal injury, as assessed by albuminuria and various biomarkers of renal tubular injury (KIM-1, NGAL, cystatin C, NAG).

Conclusions: We conclude that RBT-9 was safe and well tolerated in healthy volunteers and subjects with CKD. Adverse events were generally mild and related to photosensitivity reactions. Dose-dependent cytoprotective protein responses were observed that have previously corresponded with AKI protection in experimental animals.

Funding: Commercial Support - Renibus Therapeutics

PO0067

Analysis of AKI in Patients with Systemic Lupus Erythematosus

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Background: Renal involvement is commonly seen in systemic lupus erythematosus (SLE). The goal of our study is to analyze the impact and burden of acute kidney injury (AKI) on patients with SLE.

Methods: We analyzed the Healthcare Cost and Utilization Project Nationwide Inpatient Sample from the years 2012 to 2014. We included patients aged 18 years or older with either a primary or secondary diagnosis of SLE. Descriptive analyses were performed with a focus on patient characteristics and comorbidities. We used weighted multivariable survey regression methods to assess outcomes. Statistical analysis was performed using STATA 16.0. We considered a P value of <0.05 as statistically significant.

Results: We identified a total of 101,615 hospitalizations with SLE, of which 9,475 (9.3%) had AKI. Patients with a diagnosis of AKI were younger (mean age 39.3 vs. 45.4), more likely to be male (16.5% vs. 8.9%), black (45.6% vs. 33.3%), discharged from a teaching institution (72.2% vs. 65.4%). Patients with AKI had a higher prevalence of chronic kidney disease (53.2% vs. 10.1%), hypertension (74.5% vs. 47.5%). After adjustment with the patient and hospital level of confounder, the presence of AKI was independently associated with increased overall in-hospital mortality in patients with SLE (adjusted odds ratio [aOR] 12.1, 95% confidence interval [CI] 6.5- 22.4, p < 0.001). Length of stay (LOS) was 5.0 days longer (95% CI 4.5- 5.6, p < 0.001) in patients with AKI, and total hospital costs were $12485.6 more than in patients without AKI (95% CI 10656.1- 14315.2, p < 0.001).

Conclusions: Patients with AKI were more likely to die in the hospital, had a longer length of stay, higher inpatient care costs. Thus, the presence of AKI poses a significant burden on patients with SLE. Close monitoring and early treatment are warranted in this population.

Patient characteristics		SLE without AKI	SLE with AKI	P value
Age, (%)				
	Age >=18 and <=35	29.1	46.6	<0.001
	Age >35 and <=50	32.0	26.9	<0.001
	Age >50 and <=65	26.2	18.3	<0.001
	Age >65 and <=80	10.2	6.4	<0.001
	Age >= 80	2.5	1.7	0.023
Gender, (%)				
	Female	91.1	83.4	<0.001
Race, (%)				<0.001
	White	45.4	24.5	
	Black	33.3	45.6	
	Hispanic	14.8	19.8	
	Asian or Pacific Islander	2.4	5.1	
	Native American	0.49	0.65	
	Other	3.5	4.3	
Median annual income in patient's zip code, US$, (%)				<0.001
	$1-$38,999	33.1	38.5	
	$39,000-$47,999	24.1	25.1	
	$48,000-$62,999	21.7	21.1	
	$63,000 or more	21.1	15.3	
Insurance type, (%)				<0.001
	Medicare	33.4	25.5	
	Medicaid	26.8	34.3	
	Private	33.2	30.5	
	Uninsured	6.5	9.7	
Comorbidities, (%)				
	Chronic kidney disease	10.1	53.2	<0.001
	Hypertension	47.5	74.5	<0.001
	Coronary artery disease	10.4	7.1	<0.001
	Congestive heart failure	5.2	16.9	<0.001
	Diabetes mellitus	14.4	12.5	0.0353
	Atrial fibrillation	3.9	3.7	0.6209
	Cerebral vascular disease	2.6	1.4	0.0011
	Peripheral vascular disease	6.5	6.2	0.5314
	Hyperlipidemia	17.3	17.6	0.7855
	Obesity	12.4	10.6	0.0213

PO0068

AKI After Lung Transplantation: A Retrospective Analysis from a Single Transplantation Center

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Background: Acute kidney injury (AKI) is a common and serious complication after lung transplantation (Ltx). No data from the Swedish Ltx program have been published, and thus we performed a retrospective analysis of AKI after Ltx at our unit.

Methods: After ethical board approval, all patients ≥18 years who underwent Ltx in Gothenburg, Sweden, between 2012–2016 were assessed. Exclusion criteria were: death within 48 hours, multiple organ transplantations or pre-operative dialysis. AKI was defined according to the KDIGO creatinine criteria and the AKI group was compared to the patients without AKI using Mann-Whitney U-tests or Chi²-tests as appropriate. A multivariate logistic regression model for pre- and intraoperative predictors of AKI was built.

Results: In total, 211 patients were transplanted 2012–2016, and 197 patients were analyzed. Of these, 37% developed AKI within 1 week after Ltx (grade 1; 58%, grade 2; 12%, grade 3; 29%). AKI was associated with increased mortality at 30 days (5.5% vs. 0.8%, p=0.044) and at 1 year (26.0 % vs. 8.9%, p=0.001). In the regression model, higher body mass index, diabetes mellitus, measured GFR < 60 ml/min, tricuspid regurgitation and the use of extra-corporeal circulation during Ltx were independent predictors of postoperative AKI ($p<0.001$, $R^2=0.273$).

Conclusions: AKI affected more than 1/3 of the patients after Ltx, and was associated with increased time on mechanical ventilation, longer stay in the intensive care unit and increased mortality. The multivariate regression model had a modest predictive value, suggesting that postoperative factors may be important contributors to the development of AKI efter Ltx.

Funding: Government Support - Non-U.S.

Variable	Non-AKI (n=123)	AKI (n=73)	p-value
Age (years)	54±12	54±13	0.980
Female gender	69 (56)	34 (47)	0.218
Diabetes mellitus	8 (6)	12 (16)	0.025
Preoperative s-creatinine (µg/L)	70±19	78±25	0.026
Measured GFR (ml/min/1.73 m^2)	87.7±21.5	80.0±24.4	0.025
Body mass index (kg/m^2)	23.0±4.1	25.1±5.4	0.006
Tricuspid regurgitation	25 (20)	29 (40)	0.001
Use of Cardiopulmonary bypass	17 (14)	28 (38)	<0.001
Intraoperative bleeding (ml)	515±550	1530±3686	0.024
Postoperative mechanical ventilation (hours)	49±159	193±360	<0.001
Use of RRT within first postoperative week	0 (0)	14 (19)	<0.001
Length of stay in intensive care (days)	4.5±6.5	13.0±15.5	<0.001

Data are mean±SD or n (%)

PO0069

Efficacy Evaluation of Neutrophil Gelatinase-Associated Lipocalin and Cystatin C in Urine as Biomarkers in Early Diagnosis of AKI in Preterm

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Background: To investigate the value of neutrophil gelatinase-associated lipocalin(NGAL) and cystatin C in urine in the early diagnosis of acute kidney injury in preterm and the efficacy of these two biomarkers in urine.

Methods: A prospective study was conducted on 98 preterm admitted to the NICU, including 55 males and 43 females. According to the diagnostic criteria for neonatal AKI published by the Acute Kidney Injury Network and the Kidney Disease Improving Global Outcomes (KDIGO), the serum creatinine is 1.5 times of the basic level or the urine volume is less than 1.5 mL/ (kg*h) ×24 h, 10 cases of AKI and 88 cases of non-AKI were confirmed on the first day of inclusion, 3 cases of AKI and 95 cases of non- AKI were confirmed on the seventh day of inclusion. Urine samples were collected on the day1, day7 of inclusion and the day of urine volume significant decrease (urine volume < 1.5ml/k*h), urine NGAL (uNGAL) and urine cyst-C values were measured by ELISA, meanwhile serum creatinine were measured. The study was approved by the ethical community board and written consent was obtained from the kids' parents.

Results: Among 98 cases, 10 cases were separated in AKI group and 88 in non-AKI group on the admission day, uNGAL and urine cyst-C in the AKI group were significantly higher than those in the non-AKI group ($P < 0.05$). On day 7, 3 cases were diagnosed AKI and 95 cases in non-AKI group. uNGAL and urine cyst-C in the AKI group were significantly higher comparing with those in the non-AKI group ($P < 0.05$). Receiver operating characteristic curves (ROC) for the diagnosis of AKI on day 1 and day 7 were drawn, the area under the curve(AUC) of urine cyst-C on day1 and day7 was 0.922 vs. 0.849, the sensitivity was 0.900 on day1(when set the critical value for AKI as 25.19ng/ml), and the sensitivity on day7 was 1(When the critical value was set 23.16ng/ml), and the specificity of urine cyst-C on day1 vs. day7 was 0.795 and 0.737 separately. The area under the curve(AUC) of uNGAL for AKI diagnosis was 0.860(day1) and 0.867(day7). When the critical value for AKI diagnosis was 100.12 g/L, the sensitivity for uNGAL was 1, and the specificity was 0.695. The positive value for uNGAL on day1 and day7 were 90% and 100% separately.

Conclusions: NGAL and cyst-C in urine can be used as biological indicators for the diagnosis of AKI in premature infants.

Funding: Government Support - Non-U.S.

PO0070

AKI in Sickle Cell Disease

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Background: Sickle cell disease may cause acute injury to the kidney, especially during sickle cell crisis. Which mainly related to underlying stress-induced renal vasculopathy and alterations in glomerular hemodynamics. There is a paucity of national-level evidence showing the effect of acute kidney injury (AKI) on patients hospitalized with sickle cell disease. We aim to quantify the relationship between AKI and mortality and resource utilization in patients with sickle cell disease.

Methods: We analyzed adult patients admitted from 2012 to 2014 with a primary or secondary diagnosis of sickle cell disease using the Nationwide Inpatient Sample (NIS). The NIS is the largest publicly available inpatient database in the United States (U.S.). It contains data from approximately 8 million hospital stays each year, representing a 20% stratified sample of all U.S. non-federal hospitals, and is sponsored by the Agency for Healthcare Research and Quality and the Healthcare Cost and Utilization Project (HCUP). The International Classification of Diseases, Ninth Revision, Clinical Modification Coding System (ICD-9-CM) was used to identify comorbidities. Survey multivariate regression analysis was performed using STATA 16.0.

Results: We included 240,550 admissions with sickle cell disease, majority of them were black patients (93%). 10,825 (4.5%) of sickle cell disease patients had AKI. Patients with AKI were older (mean age 41.3±12.5 vs. 31.1±10.4, p<0.001), more likely to be male (53.1% vs. 44.4%, p<0.001). Sickle cell disease patients had higher prevalence of hypertension (49.9% vs. 16.8%, p<0.001), coronary artery disease (6.3% vs. 2.1%, p<0.001), congestive heart failure (22.5% vs. 4.4%, p<0.001), diabetes mellitus (9.8% vs. 3.5%, p<0.001). After adjusting for patient and hospital-level confounders, patients with AKI had higher odds of mortality (adjusted odds ratio [aOR] 11.3, 95% confidence interval [CI] 7.04- 18.34, p<0.001), a longer length of stay (2.6 days, 95% CI: 2.21- 2.93 days, p<0.001), higher costs ($6707.2; 95% CI: $5816.2-$7598.3, p<0.001).

Conclusions: The demographic characteristics were significantly different between patients with or without AKI. Sickle cell nephropathy imposes a burden on both individual and health care systems. Randomized controlled trials are needed to investigate the role of vaso-occlusive events on AKI development.

PO0071

Combining Renal Arrest and Damage Biomarkers to Predict the Progression of AKI in Patients with Sepsis

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Background: Septic AKI accounts for approximately half of all AKI in ICU, and up to 40% of mild or moderate septic AKI would progress to more severe AKI which is associated with significantly increased risk for in-hospital death and later CKD/ESRD.

Early identifying high risk patients for AKI progression might help physicians to enhance individualized monitoring and personalized management in patients with septic AKI.

Methods: This is a prospective, multicenter cohort study which enrolled adult septic patients who initially developed stage 1 or stage 2 AKI in the ICU from January 2014 to March 2018. Sepsis was diagnosed based on the 2016 Sepsis-3 criteria, and AKI was diagnosed and staged according to 2012 KDIGO-AKI guidelines. Renal arrest biomarkers (urinary TIMP2*IGFBP7 [u TIMP2*IGFBP7])and renal damage biomarkers (urinary KIM-1[uKIM-1] and urinary IL-18 [uIL-18]) were measured at time of AKI clinical diagnosis, and the utility of biomarkers for predicting septic AKI progression alone or in combination were evaluated. The primary outcome was AKI progression defined as worsening of AKI stage. The second outcome was receiving dialysis or death during ICU stay.

Results: A total of 149 septic patients with stage 1 or 2 AKI were included, 63 patient developed progressive AKI, 49 patients received dialysis or died during ICU stay. uTIMP2*IGFBP7, uKIM-1 and uIL-18 independently predicted the progression of septic AKI in which uTIMP2*IGFBP7 showed the greatest AUC (0.745; 95%CI, 0.667-0.823) as compared to uKIM-1 (AUC 0.719; 95%CI 0.638-0.800) and uIL-18 (AUC 0.619; 95%CI 0.525-0.731). Combination of uTIMP2*IGFBP7 with uKIM-1/uIL-18 further improved the performance of predicting septic AKI progression with AUCs of 0.752 (uTIMP2*IGFBP7 with uKIM-1) and 0.747 (uTIMP2*IGFBP7 with uIL-18), respectively. uTIMP2*IGFBP7, alone or combined with uKIM-1/uIL-18, improved the risk reclassification over the clinical risk factor model alone both for the primary and secondary outcomes, as evidenced by significant category-free net reclassification index.

Conclusions: Combination of renal arrest and damage biomarkers enhanced the prediction of AKI progression in patient with sepsis and improved risk reclassification over the clinical risk factor model alone.

Funding: Government Support - Non-U.S.

PO0072

Bicarbonate May Not Be the Best Treatment for Rhabdomyolysis: A Retrospective Cohort Study

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Background: It is controversial whether the use of bicarbonate solution, which has been traditionally attempted to treat rhabdomyolysis, has the beneficial effect of reducing acute kidney injury (AKI) and mortality, compared with the use of non-bicarbonate solution. The purpose of this study is to analyze whether bicarbonate therapy versus non-bicarbonate therapy may be effective in preventing AKI and death in patients with rhabdomyolysis.

Methods: We collected 4077 hospitalized patients with creatinine kinase (CK) > 1000 U/L and divided them into 2 groups: patients who received fluid with bicarbonate and who received fluid without bicarbonate. Patients were subgrouped into low (<2ml/kg/hr), middle (2-4ml/kg/hr) and high (≥4 ml/kg/hr) amounts of fluid to receive in first 72 hours of admission. Cox regression analysis models were used to identify risks for dialysis and mortality. Safety profiles were assessed by volume overload and electrolyte imbalances.

Results: In a total of patients with a mean age of 57.9 years (male 66.7%), bicarbonate-containing solution was used in 61.1% of the participants. The proportion of the subjects were 34.6%, 36.5%, and 28.9% for the low, middle, and high fluid group, respectively. The bicarbonate group showed higher incidence rate of AKI (OR 4.5), higher 1-year mortality (OR 3.1) and longer hospital stay (26.6 ± 54.4 vs. 22.0 ± 22.7 days) than the non-bicarbonate group. Patients given high amount of fluid therapy showed higher incidence rate of AKI (OR 3.1), higher rate of dialysis dependency (OR 2.7) and higher 1-year mortality (OR 1.4), compared with low fluid group, regardless of the use of bicarbonate. The use of bicarbonate (adjusted HR [aHR] 1.55), volume overload (aHR 1.28) were associated with higher mortality while the use of furosemide (aHR 0.8) showed the preventive effect. Baseline CK or peak CK were not related to the risk of dialysis or death. Volume overload was significantly higher in the bicarbonate group compared with the non-bicarbonate group.

Conclusions: We showed bicarbonate therapy or high-volume fluid management in patients with rhabdomyolysis were not beneficial in preventing AKI and death, compared with the non-bicarbonate therapy or low-volume fluid management. It suggests that limited use of bicarbonate and adjustment of fluid volume may improve the short-term and long-term outcome of rhabdomyolysis.

Funding: Clinical Revenue Support

PO0073

Plasma Metabolites Do Not Change Significantly After 48 Hours in Patients on CRRT

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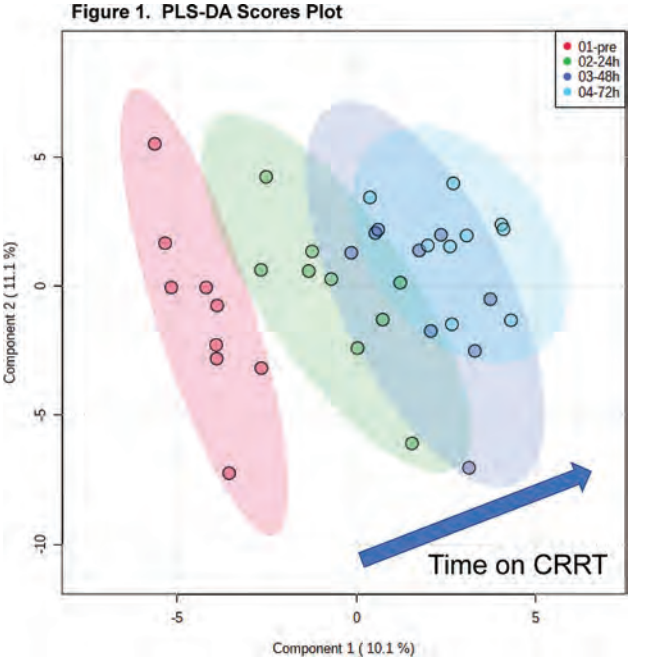
Background: Continuous renal replacement therapy (CRRT) is used in critically ill patients with hemodynamic instability. One of the primary aims of CRRT is to remove solutes that accumulate due to impaired kidney function. Surprisingly, few studies have assessed plasma solute levels during CRRT, and the duration of CRRT necessary to achieve adequate solute removal is unknown.

Methods: To assess the effect of CRRT on plasma solutes, metabolites were determined via untargeted ultra-high pressure liquid chromatography coupled to mass spectrometry (UHPLC-MS) in 13 critically ill patients requiring CRRT. Metabolites were assessed on plasma collected prior to CRRT initiation, and on plasma and effluent collected on days 1, 2, and 3 thereafter.

Results: A total of 101 annotated metabolites were evaluated. Plasma levels of 22 metabolites (21.8%) were significantly reduced by Day 1 of CRRT, and included creatinine, phosphate, lactate, and the amino acids alanine, proline, and cysteine. Only 2 metabolites (2.0%) were significantly reduced between Day 1 and Day 2, and *none* were reduced between Day 2 and Day 3. Figure 1 demonstrates that marginal changes in solute levels decrease as CRRT progresses. All metabolites were detected in the effluent, and the sieving coefficients for metabolites that were reduced versus not reduced after CRRT were not statistically different.

Conclusions: No further reduction in plasma metabolites occurred after 48 hours of CRRT. Since the median CRRT treatment time is 4-7 days nationwide, with some patients treated substantially longer, these data bring into question the utility of prolonged, uninterrupted CRRT therapy, and have major potential implications for the duration of CRRT in the ICU population.

Figure 1. PLS-DA Scores Plot



PO0074

Sustained Low-Efficiency Dialysis with Regional Citrate Anticoagulation and a Standard Hemodialysis Machine in Critically Ill Patients with AKI

Francesca Di Mario,[1] Filippo M. Fani,[2] Paolo Greco,[1] Caterina Maccari,[1] Elisabetta Parenti,[1] Tommaso Di Motta,[1] Maria Teresa Farina,[1] Giuseppe Regolisti,[1] Enrico Fiaccadori.[1] *[1]UO Nefrologia, Azienda Ospedaliera-Universitaria Parma, Parma, Italy., Parma, Italy; [2]UO Nefrologia e Dialisi, Ospedale San Giovanni di Dio, USL Toscana centro, Firenze, Italy.*

Background: Sustained-Low Efficiency Dialysis (SLED) is an increasingly used Kidney Replacement Therapy (KRT) modality in critically patients with Acute Kidney Injury (AKI); in this setting regional citrate anticoagulation (RCA) is a rational approach to avoid extracorporeal circuit clotting. The present study was aimed at evaluating the safety and efficacy of a simplified RCA protocol for SLED with a conventional hemodialysis machine.

Methods: SLED was performed for 8-12 hours (daily or every other day) with a Surdial X Nipro® hemodialysis machine and a cellulose triacetate filter (Sureflux-19L, 1.9 m2, KUF 19 ml/mmHg/h). Blood flow was set at 200 ml/min and dialysis fluid flow at 100 ml/min. Citrate was infused in pre-dilution as ACD-A solution (citrate 2.2%, 112.9 mmol/L) at 200-400 ml/h rates (estimated pre-filter citrate concentration 2-4 mmol/L). Treatment was monitored by serial evaluations of ionized calcium (Ca^{++}) and ACT at the beginning, at the 2nd hour and at the end of SLED session. Blood in the extracorporeal circuit was recalcified by the dialysis fluid itself (Ca^{++} 1.5 mmol/L) through Ca^{++} backfiltration; i.v. calcium supplementation was started only if patient Ca^{++} at the 2nd hour was ≤0.9 mmol/L.

Results: 41 SLED sessions were performed in 12 critically ill patients with AKI (mean age 69 ± 18 SD, mean APACHE II 22). Average pre- and post-SLED urea values were respectively 94 and 32 mg/dL. Most sessions (38/41, 93%) were completed for elapsed prescribed time. No statistically significant differences were observed between systemic ACT values measured during SLED as compared to baseline values. Ca supplementation

(10% Ca gluconate at fixed rate 5 ml/hour) was needed in 10/41 treatments, with rapid normalization of serum Ca^{++}. No new cardiac arrhythmia episode or hemorrhagic events were observed.

Conclusions: Our preliminary data suggests that a simplified RCA protocol for SLED using a conventional dialysis machine is easy and safe, also ensuring a good match between prescribed and actual dialysis dose administered.

PO0075

Prediction of AKI in Inpatient General Medical Ward Units

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Background: Acute kidney injury (AKI) is common in hospitalized patients (A). A few scoring systems have been proposed to predict the risk of developing AKI in certain populations such as cardiac catheterization patients (B, C, D, E, F). However, there is no scoring system for predicting AKI in patients on the general medical wards. Our aim is to predict the development of AKI in acute general medical patients.

Methods: Retrospective single center study of all adult patient admitted to a tertiary care university hospital between July 2016-July 2018. AKI was defined by the KDIGO definition of AKI and all stages of AKI were included. We used chi-squared tests, ANOVA, and Kruskal Wallis to determine statistically significant factors. We calculated odds of AKI using logistic regression models. All analyses were conducted using STATA SE 15.

Results: A total of 10,981 were included in the study, 1573 (14.3%) with AKI and 9408 (85.7%) without AKI. Baseline demographics were significantly different between the two groups including age, race, length of hospital stay (p<0.001). In the univariate analysis, history of cancer and diabetes, proteinuria, admission BUN, hemoglobin (HGB), and hypotension during admission were predictive of AKI. After adjustment for significant univariate factors, age (OR 0.97 [0.96–0.99], P<0.001), admission BUN (OR 1.02 [1.01–1.04], P<0.001), and HGB (OR 0.79 [0.73–0.85], P<0.001) were significant in the multivariate analysis (Table 1).

Conclusions: We found that the age, admission BUN, and HGB were predictive of AKI in inpatient general medical units. These criteria can be used in acute general medicine patients to create a scoring system to determine the likelihood of developing AKI and therefore prevent AKI and its downstream complications in these patients.

Table 1: Risk Predictors of AKI	Univariate Odds Ratio	95% CI	P	Multivariate Odds Ratio	95% CI	P
Age	1.01	1.01 – 1.01	<0.001*	0.97	0.96 – 0.99	<0.001*
Male	0.95	0.85 – 1.05	0.32			
Black	1.48	1.19 – 1.83	<0.001*	1.34	0.74 – 2.42	0.34
Length of hospital stay	1.04	1.03 – 1.05	<0.001*	0.98	0.94 – 1.0	0.20
BMI	1.0	0.99 – 1.01	0.67			
History of Cancer	1.24	1.1 – 1.4	<0.001*	1.31	0.89 – 1.94	0.17
History of Diabetes	2.07	1.82 – 2.36	<0.001*	1.18	0.78 – 1.79	0.42
Proteinuria	1.96	1.76 – 2.19	<0.001*	0.79	0.55 – 1.13	0.21
BUN	1.03	1.02 – 1.03	<0.001*	1.02	1.01 – 1.04	<0.001*
Hemoglobin	0.71	0.69 – 0.73	<0.001*	0.79	0.73 – 0.85	<0.001*
Mean Arterial Pressure	0.99	0.99 – 0.99	<0.001*	0.99	0.98 – 1.0	0.16

PO0076

Is Procalcitonin a Reliable Marker of Bacterial Infection in Patients with AKI?

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Background: Procalcitonin (PCT) is a biomarker that helps to distinguish bacterial infections from other causes of infection or inflammation and can be used as a helpful adjunct to clinical judgment for resolving diagnostic uncertainty. Limited data is available about the diagnostic value of PCT in patients with acute kidney injury (AKI). We aimed to assess the diagnostic usefulness of serum PCT level as a marker of bacterial infection in patients with AKI and assess the correlation of serum creatinine clearance to serum PCT level.

Methods: This retrospective case-control observational study involved patients admitted to the hospital during the study period and had PCT checked. Patients were categorized into proven, possible, and no bacterial infection groups. We compared PCT level in AKI group with proven bacterial infection vs no bacterial infection and PCT level during proven and no bacterial infection groups with AKI vs non-AKI. Patients with end-stage kidney disease and other causes of elevated PCT (pancreatitis, cancer, severe burns) were excluded.

Results: 379 patients were analyzed, 24 patients were excluded from the study. 66 patients classified into the AKI group and 226 into the non-AKI group. 107 patients were in a proven bacterial infection group and 98 Patients in no bacterial infection group. The mean value of PCT was significantly higher with confirmed bacterial infection compared to no bacterial infection in all patients despite their renal function (4.9±8.75 vs 1.66±4.88, p<0.001). PCT level was higher in the AKI group than in the non-AKI group (10.99±12.24 vs 2.39±2.93, p>0.001) in patients with a proven bacterial infection. Patients with no infection had much higher PCT level in the AKI group as compared to the non-AKI group (5.76±14.67 vs 0.7±1.39, p=0.003). PCT level was also significantly higher during confirmed bacterial infection vs no bacterial infection in patients with AKI (9.2±11.05 vs 0.72±1.27, p=0.04). There was a weak positive correlation between creatinine clearance and PCT level (correlation coefficient 0.125, p=0.15).

Conclusions: Higher cutoff level of PCT is needed in patients with AKI to use it as a marker of infection. The specificity of PCT may decrease in patients in AKI if current reference cutoff values are used to guide clinical decisions.

PO0077

Predicting Outcomes After AKI: Are You Better Than a Machine?

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Background: While multiple studies have used statistical models to predict outcomes after AKI, no studies have compared these models to physician intuition at the time of AKI consult. We studied the accuracy of physicians in predicting outcomes after AKI and compared it to the strength of predictive statistical models.

Methods: Our pilot study focuses on the prediction of 3 outcomes after AKI : Recovery, progression to dialysis and mortality. Postgraduate years 4 and 5 level Nephrology providers were asked, at the time of initial renal consult, to forecast outcomes at 3 timepoints : 24hr, 48hr and 7 days. We compared physician prognosis to a gradient boosted trees model trained using retrospective EHR data. Our primary measure of performance was area under the receiver operating characteristic curve (AUROC) at each time point.

Results: Data was captured from 56 patients with stage 2 AKI. Nephrology providers (n=7) were good to excellent at predicting dialysis at all three timepoints and death at 48 hours and 7 days. In contrast, their ability to predict recovery of AKI was relatively poor. The statistical model performed significantly better at predicting death at all timepoints, however was poorer at predicting dialysis (Figure 1.0).

Conclusions: Both physician clinical acumen and our statistical model showed good performance in predicting need for dialysis and death after AKI, however performed poorly when predicting recovery. This highlights the need to conduct further in-depth analysis into this area and implement strategies to enhance prediction of recovery after AKI.

Funding: Other NIH Support - NIH R01DK113191

Outcome after AKI	Recovery		Dialysis		Mortality	
	Physician	Model	Physician	Model	Physician	Model
24 hours	0.51	0.65	0.94	0.79	0.59	0.92
48 hours	0.49	0.47	0.82	0.70	0.78	0.90
7 days	0.64	0.57	0.75	0.65	0.79	0.93

Figure 1.0 : AUCs comparing physician and model performance at predicting outcomes at 24hr, 48hr and 7 days after AKI

PO0078

Short-Term Prognosis of Patients with Cardiorenal Syndrome Type 1-Induced AKI Requiring Continuous Renal Replacement Therapy

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Background: Cardio-renal syndrome (CRS) type 1 is a condition wherein an acute heart failure (AHF) leads to the development of acute kidney injury (AKI). Continuous renal replacement therapy (CRRT) is used to remove excess solutes and fluids in CRS type 1 patients who have diuretic resistance. However, little is known about the outcomes of CRS type 1 patients who undergo CRRT.

Methods: We reviewed the clinical data of 74 consecutive CRS type 1 patients treated with CRRT from 2012 to 2015. Patients who underwent cardiovascular surgery and those who had chronic kidney disease stage 5 prior to admission were excluded. The primary outcome examined was in-hospital mortality.

Results: The mean age of patients was 70.6 ± 13.6 years old. The causes of AHF were ischemic heart disease (54.1%), valvular disease (13.5%), and other diseases. At the time of the CRRT initiation, the mean serum creatinine was 2.8 ± 1.0 mg/dL. The in-hospital mortality rate was 77.0%. Compared with non-survivors, the survivors had fewer number of previous hospitalizations for heart failure (50.9% vs. 23.5 %, $p = 0.046$), higher systolic blood pressure (97.7 ± 22.2 mmHg vs. 112.3 ± 21.1 mmHg, $p = 0.02$), better ejection fraction (31.4 ± 17.9% vs. 42.0 ± 15.7%, $p = 0.03$), smaller inferior vena cava (IVC) diameter (18.0 ± 5.8 mm vs. 14.8 ± 4.4 mm, $p = 0.04$), lesser respiratory variations in the IVC diameter (59.6% vs. 13.3 %, $p = 0.002$), lesser vasopressor requirement (96.5% vs. 31.9%, $p = 0.001$), and lesser respirator support (56.1% vs. 23.5%, $p = 0.02$) at CRRT initiation. The survivors required a shorter CRRT duration over the non-survivors (6.1 ± 6.9 days vs. 11.7 ± 12.4 days, $p = 0.03$). Through the multiple logistic regression analysis, certain factors were associated with a poor short-term prognosis. These factors were history of previous hospitalizations for heart failure, vasopressor requirement upon the start of CRRT, and the need for respirator support at CRRT initiation.

Conclusions: In our single-center experience, the use of CRRT for treating AKI caused by CRS type 1 was associated with a high in-hospital mortality rate. Patients with a history of previous hospitalization for heart failure, those who required vasopressors, and patients needing respirator support at CRRT initiation had an especially poorer prognosis.

PO0079

Roux-en-Y Gastric Bypass Is the Most Common Current Cause of Biopsy-Proven Oxalate Nephropathy

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Background: The objective of this study was to analyze patient characteristics and outcomes of biopsy-proven oxalate nephropathy likely due to an enteric cause at a single large tertiary health system.

Methods: Cases of oxalate nephropathy were identified based on documented kidney biopsy findings between 2009-2019 in patients with an associated enteric process likely to cause fat malabsorption.

Results: A total of 30 cases were identified (mean age of 65.2±8.56 years; 18(60.0%) female) with a median follow-up of 5 months; Risk factors included: hypertension in 21(70%), diabetes in 14 (46.7%), chronic kidney disease (CKD) stage 3A or greater in 16(53.3%) and prior kidney stones in 6(20%). The most common enteric causes were Roux en Y gastric bypass (RYGB) in 17(56.7%), pancreatic insufficiency in 6(20%), inflammatory bowel disease in 4(13.3%), and recurrent *C. difficile* infection in 3(10%). At the time of diagnosis, acute kidney injury (AKI) stage II and stage III were present in 9 (30%) and 15 (50%) respectively, while 11(36.7%) required dialysis. Urinalysis revealed proteinuria in 16(55.2%), oxalate crystals in 10(33.3%), and hematuria in 9(31%). Median plasma oxalate at the time of biopsy was 18.3 [reference <2.0]) µmol/L in 26 patients and median 24 hour urine oxalate excretion was 53 (reference [9.7-40.5]) mg/24 hrs in 17 patients. RYGB patients had a higher plasma oxalate compared to patients with other enteric causes (median 24.6 vs 16.5 µmol/L, p=0.03). Renal biopsy and clinical outcomes are shown in table1 [table1]. Patients with acute tubular injury had greater number of tubules with calcium oxalate crystals by biopsy (median 19 vs 4), as did patients with CKD5 at last follow-up (20 vs 6). Features at the time of biopsy predictive of CKD5 at follow-up included AKI severity (p=0.002), dialysis at diagnosis (p=0.0008), and the presence of moderate to severe tubulointerstitial atrophy (p=0.001).

Conclusions: In this series RYGB was the most common enteric cause of biopsy-proven oxalate nephropathy. Severity of AKI at presentation and degree of tubulointerstitial fibrosis were both associated with worse renal outcome. The amount of renal crystal deposits at diagnosis associated with the short and long term renal injury.

Renal Histology (A) & Outcome (B)

(A) Acute tubular injury	26 (86.6%)
Interstitial inflammation	21 (70%)
Number of tubules with calcium oxalate crystals	Median 19 (range 2, 40)
Moderate to severe tubular atrophy	23 (76.7%)
(B) Renal recovery	1 (3.33%)
CKD Stage 3	5 (16.7%)
CKD Stage 4	8 (26 %)
CKD Stage 5	5 (16.7%)
Dialysis	10 (33.3%)
Kidney transplant	1(3.33%)

PO0080

Impact of AKI on In-Hospital Outcomes in Chinese Patients with Community-Acquired Pneumonia

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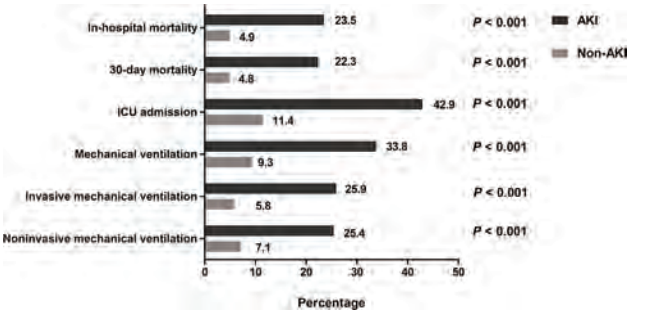
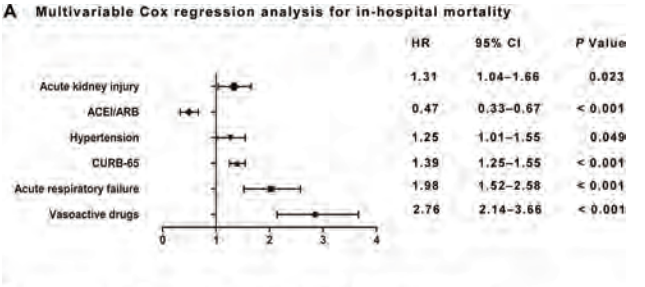
Background: Acute kidney injury (AKI) is common in community acquired pneumonia (CAP). However, the impact of AKI on in-hospital outcomes of patients with CAP in the population of Chinese remains largely unknown.

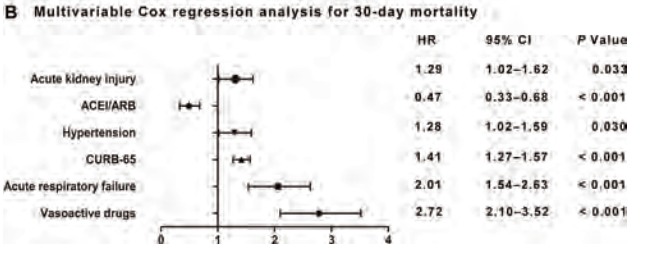
Methods: Multiple Cox regression models were employed to identify the association between AKI and in-hospital mortality and 30-day mortality.

Results: 4213 patients were included, and 950 (22.5%) patients were AKI. The independent risk factors for AKI were age, male, hypertension, cardiac dysfunction, diabetes, chronic kidney disease, acute respiratory failure, diuretic, vasoactive drugs, and CURB-65. After multivariable Cox regression, independent risk factors of in-hospital mortality and 30-day mortality were similar: AKI, ACEI/ARB, hypertension, CURB-65, acute respiratory failure, and using vasoactive drugs. Patients developed AKI had increased 1.31-fold (HR 1.31, 95 % CI, 1.04–1.66, P = 0.023) and 1.29-fold (HR 1.29, 95 % CI, 1.02–1.62, P = 0.033) risk for in-patient mortality and 30-day mortality, respectively. In addition, patients with AKI were more vulnerable to require intensive care unit (ICU) admission (42.9% vs. 11.4%; P < 0.001), mechanical ventilation (33.8% vs. 9.3%; P < 0.001), invasive mechanical ventilation (25.9% vs. 5.8%; P < 0.001), non-invasive mechanical ventilation (25.4% vs. 7.1%; P < 0.001), and had a longer length of hospital stay (14 days vs. 10 days; P < 0.001) than those without AKI.

Conclusions: AKI was common in Chinese patients with CAP. Patients with CAP who developed AKI had worse in-hospital outcomes.







PO0081

Risk of Nephrotoxicity in Patients Receiving Concomitant Vancomycin and Intravenous Contrast Media

Amy Hsu, Helen S. Lee, Benjamin Lee, Kamyar Kalantar-Zadeh, Ramy M. Hanna, Mark A. Baje. *University of California Irvine, Irvine, CA.*

Background: Contrast-induced nephropathy (CIN) has been described as a significant cause of acute kidney injury (AKI). Although the nephrotoxic potential of vancomycin has widely been published, the contributory effect of these two agents towards AKI has not been fully elucidated. We sought to better define this interaction.

Methods: The primary objective of this retrospective cohort study was to compare the incidence of AKI among adult patients receiving vancomycin (VAN) and vancomycin plus IV contrast (VC) within 96 hours of administration. Secondary outcomes included time to AKI development, hospital length of stay (LOS), and 30-day, all-cause mortality. A logistic regression was performed to identify potential risk factors for AKI among vancomycin-treated patients.

Results: A total of 114 patients receiving ≥ 4 consecutive days of vancomycin were included, 50 receiving VAN and 64 receiving VC. An additional 50 patients who received IV contrast alone were independently assessed for CIN, of which only 3 (6%) developed AKI. In the unadjusted analysis, no statistically significant difference in the rate of AKI (10% vs 20.3%; p=0.13), days until AKI (6 days vs 5 days; p=0.37), highest vancomycin trough (16.7 vs 17.8; p=0.62), and hospital LOS (7.5 days vs 8 days; p=0.62) were found between VAN and VC patients. The addition of IV contrast to vancomycin was not an independent risk factor for AKI after adjusting for relevant confounders (aOR 1.65; 95% CI, 0.48-5.65; p=0.42).

Conclusions: The addition of IV contrast was not associated with an increased risk of AKI in vancomycin-treated patients. The incidence of CIN was rare.

	Univariate Analysis [a]			Multivariate Analysis [b]		
Characteristics	OR	95% CI	*P-value*	OR	95% CI	*P-value*
Receipt of contrast	2.29	0.76 - 6.94	0.14	1.65	0.48 - 5.65	0.42
Male	1.07	0.35 - 3.30	0.91			
Age ≥ 65 (year)	2.0	0.72 - 5.53	0.18			
Weight (kg)	0.98	0.96 - 1.01	0.18			
Diabetes mellitus	0.38	0.12 - 1.25	0.11	0.36	0.10 - 1.30	0.12
Heart Failure	2.02	0.70 - 5.81	0.19			
Anemia	3.92	0.49 - 31.43	0.20			
ICU Status	4.3	1.32 - 13.98	0.015			
Sepsis/Bacteremia	1.79	0.60 - 5.33	0.30			
LR Aggressive Hydration	1.85	0.66 - 5.16	0.24			
NS Aggressive Hydration	2.2	0.78 - 6.17	0.13			
ACE inhibitor/ARB therapy	0.87	0.23 - 3.31	0.83			
Diuretics	4.23	1.48 - 12.08	0.007	3.44	1.10 - 10.80	0.034
NSAIDs	1.08	0.28 - 4.19	0.91			
Vasopressors	7.73	2.44 - 24.56	0.001	5.37	1.49 - 19.33	0.010

Abbreviations: ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor blocker; ICU, intensive care unit; kg, kilogram; LR, lactated ringer; NS, normal saline; NSAIDs, non-steroidal anti-inflammatory drug; OR, odds ratio

[a] Significant at $P < 0.2$

[b] Significant at $P < 0.05$

PO0082

Mortality Prediction of Serum Neutrophil Gelatinase-Associated Lipocalin in Patients Requiring Continuous Renal Replacement Therapy

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Background: We investigated whether serum neutrophil gelatinase-associated lipocalin (NGAL) can predict mortality in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: This study enrolled 169 patients who underwent serum NGAL testing at CRRT initiation from June 2017 to January 2019. The predictive power of serum NGAL level for 28-day mortality was compared to the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score and Sequential Organ Failure Assessment (SOFA) score via area under the receiver operating characteristic curve (AuROC) value.

Results: There were 55 survivors and 114 non-survivors at 28 days post-CRRT initiation. Median serum NGAL level was significantly higher in the non-survivor group than in the survivor group (743.0 vs. 504.0 ng/mL, P=0.003). The AuROC value of serum NGAL level was 0.640, which was lower than APACHE-II score and SOFA score values (0.767 and 0.715, respectively). However, in the low APACHE-II score group (<27.5), AuROC value of serum NGAL was significantly increased (0.698), and it was an independent risk factor for 28 day-mortality (hazard ratio 2.405, 95% confidence interval (1.209-4.783), P=0.012).

Conclusions: In patients with AKI requiring CRRT, serum NGAL levels may be useful for predicting short-term mortality in those with low APACHE-II scores.

Funding: Government Support - Non-U.S.

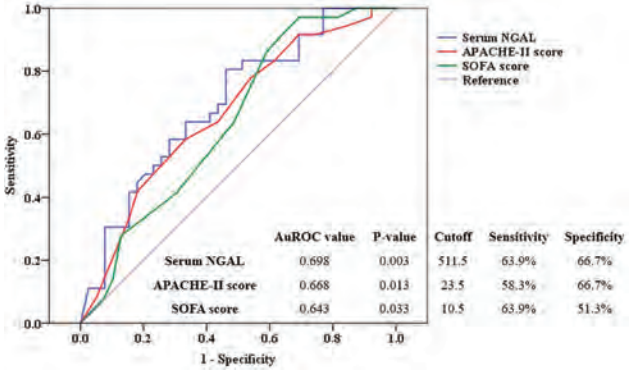

Figure 1. Predictive value for 28-day mortality of serum NGAL level, APACHE-II score, and SOFA score in low APACHE-II score group

PO0083

The Impact of AKI on Patients with Out-of-Hospital Cardiac Arrest Managed with Venoarterial Extracorporeal Membrane Oxygenation at the University of Minnesota

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Background: Since 2015, the Minnesota Resuscitation Consortium (MRC) in conjunction with the University of Minnesota medical center have been treating patients who suffer out of hospital refractory ventricular fibrillation/ventricular tachycardia (VF/VT) with a protocolized treatment strategy utilizing mechanical cardiopulmonary support including venoarterial extra corporeal membrane oxygenation (VA ECMO). In this unique and new group of patients, the incidence and clinical impact of acute kidney injury (AKI) and AKI requiring renal replacement therapy (RRT) is not known. Additionally, we observed electrolyte abnormalities in these patients that have not been previously described.

Methods: We conducted a retrospective chart review of patient data obtained via an electronic database created as part of the MRC's program in conjunction with the health system's electronic health record. Descriptive statistics were utilized to describe baseline characteristics. We restricted analyses to participants without end stage kidney disease on admission and those who survived at least 24 hours to allow for development of AKI. Kaplan-Meier plots were utilized to show death free survival by AKI category. All analyses were conducted using the R Statistical Computing Environment.

Results: We obtained data for 116 patients in the time period since 2015. Among the 116 patients, 55 patients had AKI defined as doubling of creatinine within 7 days but did not require RRT. Of the remaining 61 patients, 28 developed AKI requiring RRT. Patients who developed AKI or AKI requiring RRT had a mortality of 70% at 30 days. The remaining 33 patients who did not develop AKI had a mortality of 52% at 30 days. Regarding electrolyte derangements, cooling was associated with hypokalemia and hypophosphatemia with 64% percent of patients with potassium less than 3 mmol/L and 57% of patients with phosphorus less than 2 mg/dL.

Conclusions: AKI is associated with a high rate of mortality in this unique patient population, and additionally there is marked hypokalemia and hypophosphatemia in the setting of therapeutic cooling. Given the high mortality, this study raises questions regarding optimal treatment strategy for patients who develop AKI, including timing and delivery of RRT and the ideal approach to volume and electrolyte management.

PO0084

Prevalence, Length of Stay, and Hospitalization of AKI in Patients with and Without Sjogren Syndrome

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Background: Acute Kidney Injury (AKI) has emerged as a significant cause of morbidity and mortality in patients with autoimmune diseases. However, this has not been examined in patients with Sjogren's syndrome (SJS). To achieve this, we examined the prevalence, mortality, outcomes, Length of Stay (LOS), and hospital charges in patients with AKI with SJS compared to patients without SJS from a National Inpatient Sample database in the period 2010-2013.

Methods: Data retrieved from the National Inpatient Sample (NIS) for adult patients admitted with a principal diagnosis of acute kidney injury between 2010 and 2013, using the respective ICD-9 codes. The study population divided into two groups, with and without Sjogren's disease. Multivariate and linear regression analysis conducted to adjust for covariates.

Results: The study population represented 97,055 weighted patient discharges with acute kidney injury. Analysis revealed acute kidney injury patients with Sjogren's compared to patients without Sjogren's had statistically significant lower hyperkalemia rates (adjusted Odds ratio (OR)0.65, CI 0.46 to 0.92; p =0.017). There was no statistically significant difference in mortality, length of stay, hospital charges, and other outcomes. Moreover, The charges of hospitalization and length of stay were found to be statistically insignificant by the adjusted linear regression model. In addition, nearly three quarters of patients had Medicare, followed by privately insured patients with the least number being on Medicaid. More than half of the population have received their treatment in a tertiary center hospital. Charlson's index reported more than two-thirds of study subjects to have two or more co-morbidities.

Conclusions: At present, our study is unique as it has examined the prevalence, mortality, and outcomes of Sjogren's in patients with acute kidney injury. Patients with Sjogren's had significantly lower hyperkalemia during the hospitalization. Further research is needed to identify the underlying protective mechanisms associated with Sjogren's that resulted in lower hyperkalemia.

Variables	without Sjogren	with Sjogren	P value
No. of observations, weighted	975,670	1,385	
Age,Mean (SD)	69.18(16.26)	65.71(14.73)	0.001
Ethnicity (%)			0.001
White	841,430(68.84%)	1,065(81.01%)	
Black	174,550(18.73%)	130(9.96%)	
Hispanic	70,765(7.59%)	50(3.83%)	
Asian	18,345(1.97%)	15(1.15%)	
$Median household income (%)			
1st quartile $1-$35,999	31,2956(32.75%)	355(26.01%)	0.0009
2nd quartile $36,000-47,9999	250,915(26.25%)	300(21.98%)	
3rd quartile $48,000-62,9999	219,635(22.98%)	355(26.01%)	
4th quartile $63,000 and more	172,205(18.02%)	355(26.01%)	
Insurance (%)			0.0001
Medicare	694,435(72.1%)	965(72.01%)	
Medicaid	84,710(8.92%)	60(4.48%)	
Private	142,630(15.02%)	300(22.39%)	

PO0085

Clinical Characteristics and In-Hospital Outcomes for 1519 Consecutive Patients with AKI

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Background: Acute kidney injury (AKI) occurs in about 15% of hospitalized patients. Patients who recover from AKI have a higher long-term risk of end-stage kidney disease and death. The aim of this large single center study was to report differences in laboratory findings and short-term hospital outcomes in relation to cause of AKI in consecutive patients in a nephrology department.

Methods: All patients diagnosed with AKI between 2009 and 2018 and admitted to the nephrology department at Danderyd University Hospital, Stockholm, Sweden, were included. Relevant laboratory and physiological measures were registered. Patients on dialysis treatment were excluded. Patients were followed until discharge or death, whichever came first.

Results: In 1519 AKI patients, the majority (n=687) was of prerenal, followed by combined (defined as chronic kidney disease combined with any type of AKI) (n=536), renal (n=166), and postrenal (n=130) etiology. Patients with renal AKI were younger, had longer duration of stay, and had higher bicarbonate levels on admission. 63.2% of patients had a sCr decrease of at least 30% from admission during their stay. Most of these had prerenal followed by postrenal etiology. There was no statistically significant difference in mortality between the four etiologies of AKI.

Conclusions: This study provides data from a large, contemporary AKI patient cohort under nephrology care. We confirm that patient characteristics as well as short-term outcomes differ substantially in patients of variable AKI etiology. Greatest in-hospital reduction of sCr was seen in patients with prerenal and postrenal AKI, whereas patients with renal and combined AKI had poorer renal recovery. These findings have important implications for prognostic evaluation upon admission and further resource planning.

Funding: Private Foundation Support

	Total	Prerenal	Postrenal	Renal	Combined	p-value
Etiology (%)	*100*	45	8.6	11	35	-
AT ADMISSION						
Age (years)	*72.7*	73 (16)	76 (14)	61 (21)	75 (14)	0.062[a]
Female (%)	*40.4*	49.8	23.1	44.6	34.1	<0.001[b]
sCr (µmol/L)	*413*	354 (260)	561 (456)	391 (260)	459 (271)	<0.001[a]
CRP (mg/dL)	*79.3*	82.5 (99.7)	97.2 (97.5)	74.9 (89.3)	71.9 (97.7)	0.047[a]
Hemoglobin (g/L)	*116*	121 (24.9)	113 (23.2)	111 (23.5)	110 (21.5)	<0.001[a]
Potassium (mmol/L)	*4.7*	4.7 (5.6)	4.8 (1.4)	4.4 (1.8)	4.8 (2.4)	0.787[a]
Bicarbonate (mmol/L)	*20.7*	21.1 (4.4)	20.4 (4.1)	23.3 (16)	19.7 (4.6)	<0.001[a]
Systolic BP (mmHg)	*130*	125 (23.9)	141 (26.7)	142 (25.8)	132 (25.4)	<0.001[a]
OUTCOME						
Length of stay (days)	*8.3*	7.3 (5.5)	7.5 (5.2)	10.6 (7.8)	9.0 (7.1)	<0.001[a]
Discharge sCr	*238*	172 (179)	213 (176)	301 (232)	308 (210)	<0.001[a]
Renal recovery (≥30% sCr decrease)	*63.2*	76.1	72.9	40.4	51.4	<0.001[b]
Deaths (%)	*4.4*	4.5	0.9	2.5	5.6	0.114[c]

Values are presented as per cent or mean (SD). a= ANOVA. b= Chi²-test. c= Fisher-test.

Characteristics of study population

PO0086

Traditional and Non-Traditional Risk Factors and Their Influence on In-Hospital Mortality in Community- vs. Hospital-Acquired AKI

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Background: Many studies compare hard outcomes in Community Acquired (CA-AKI) vs. Hospital Acquired AKI (HA-AKI), but few works contrast how various risk factors (RF) impact in-hospital mortality risk in both groups.

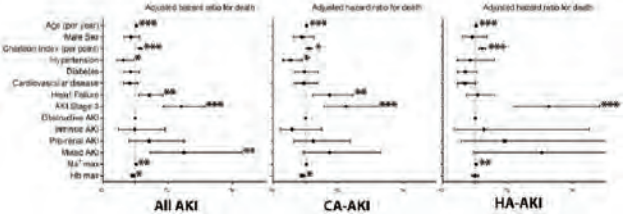
Methods: Retrospective study of in-patients with AKI. AKI was classified by KDIGO-2012 Stages. CA-AKI occurred in the first 48h, and HA-AKI >48h after admission. We compared clinical and epidemiological features, and the traditional RF (age, Charlson's Index (ChI), ICU entrance, and AKI severity). We analyzed hyponatremia Max (Na <134 associated with peak SCr) (HNa Max), anemia Max (Hb <10 with peak SCr), and AKI etiology as non-traditional RF. All RF relationship with mortality was calculated with a multivariate Cox regression.

Results: We included 1269 cases, 69% in the CA-AKI group. The HA-AKI group showed a higher ChI, had longer hospital stay, were less frequently admitted to medical wards, and less HD dependent at discharge. Mortality was significantly higher among HA-AKI vs. CA-AKI (31% vs.18% p<0.001). See Table 1. Traditional RF correlated with higher risk of death in both groups. Hypertension, heart failure and anemia Max were associated with mortality in CA-AKI but not in HA-AKI. On the other side, HA-AKI had a higher risk of death associated with HNa, which was not significant among CA-AKI patients. See Figure 2.

Conclusions: We found that HA-AKI is more deadly than CA-AKI (consistent with previous studies), but shows lesser HD dependence at discharge. The traditional RF: older age, higher ChI, ICU admission, and AKI stage 3 influenced in-hospital mortality in both groups. Non-traditional RF showed an heterogeneous influence on outcomes according to AKI type, probably due to diverse baseline characteristics, evolution time, and AKI etiologies between cohorts. We conclude that these novel associations (e.g. anemia and HNa) should be explored and modifiable factors should be tackled in order to prevent AKI mortality.

	CA-AKI (870)	HA-AKI (399)	P Value
A. Feature			
Age	74 ± 13	75 ± 10	0.30
Female Sex	272 (31)	114 (29)	0.36
HT	778 (89)	347 (87)	0.22
DM	352 (41)	184 (46)	0.07
CKD	539 (62)	239 (60)	0.49
AHF	332 (38)	159 (40)	0.56
Medical Service	617 (71)	191 (48)	<0.001
Charlson's Index	4.8 ± 2.2	5.1 ± 2.3	0.041
ICU	113 (13)	128 (32)	<0.001
KDIGO Stage			
1	338 (40)	157 (39)	0.90
2	106 (12)	61 (15)	0.13
3	426 (49)	181 (45)	0.25
B. Results			
Hospital Stay	15 ± 12	21 ± 17	<0.001
Need for HD	104 (12)	63 (16)	0.73
HD Dependence	41 (5)	6 (1)	0.004
In-hospital Mortality	154 (18)	125 (31)	<0.001

Table 1.



PO0087

One-Year AKI Stage 3 Outcome in Elderly Patients at a Secondary Care Hospital in the United Kingdom

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Background: Elderly patients are prone to Acute Kidney Injury (AKI) 3 due to multiple co-morbidities and frailty. The short term and long term outcome and mortality in this group of patients is unclear.

Methods: We prospectively collected data on patients aged over 70 years with AKI 3 from the daily e-alert sent by the hospital biochemistry lab. 117 patients attended or admitted to secondary care hospital in West Kent, UK over 6.5 months between 13 December 2018 and 26 May 2019 were analysed and followed up for next 12 months. AKI 3 was defined as per KDIGO Criteria. Data was collected for age, co-morbidities, serum creatinine at admission, peak, discharge and 12 months, cause of AKI 3 and mortality. Exclusion criteria: AKI stage 1, stage 2 and patients on regular dialysis.

Results: 57% patients had community acquired and 43% developed AKI 3 while as in-patient. The mean age was 80.1 ± 6.2 years with co-morbidities of Chronic Kidney Disease (>3) 64.7%, Cardiovascular disease (CVD) 50%, Diabetes Mellitus 42.2% and Malignancy 8.7%. The stable baseline, peak and discharge s. creatinine (mean ± std dev) were 127.7 ± 85.6, 420.9 ± 222.7 and 248.5 ± 184.5 umol/L respectively. 59.5% patients were reviewed by nephrologists and 20.7% were transferred under renal care. 30.4% had oliguria at presentation. The reasons for AKI 3 were classified as pre-renal (59.48%), urinary obstruction (11.2%) and renal that included sepsis (13.79%), cardio-renal syndrome (3.45%), drug induced nephrotoxicity (2.6%), other renal including ATN (9.70%). Renal function recovery was complete in 44.8%, Partial in 22.4% whereas 32.8% did not have any recover. 6 (5.17%) patients needed acute haemodialysis, of these 2 died and 4 (66.6%) were discharged off dialysis and were alive at 12 months. 47.4% patients were alive at discharge with s.creatinine of 173.2 ± 143.2 umol/L while only 32% of the overall patients were alive at 12 months with s. creatinine (eGFR) (mean ± std dev.) 161.5 ± 127 umol/L (48 ± 28 ml/min) with mean follow up of 331 ± 112 days. All patients that did not recover from AKI died.

Conclusions: We conclude that short and long term outcome in patients with AKI 3 aged more than 70 years has high mortality at discharge (52%) and 12 months (68%). AKI 3 is common in patients with co-morbidity of CKD, CVD and Diabetes mellitus. Outome of acute haemodialysis is effective in select group of patients.

PO0088

Urinalysis and Urine Electrolytes Among Patients with COVID-19 Infection and AKI

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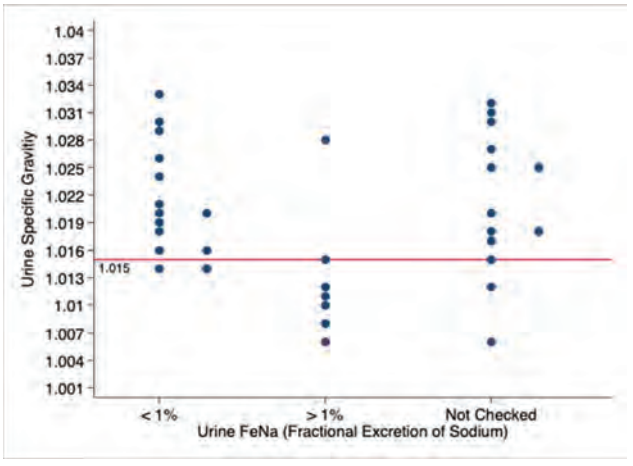
Background: Determining intravascular volume status for patients who have COVID-19 infection and AKI is critical for guiding decisions about fluid management and treating AKI. In this study, we present data on urinalysis and urine electrolytes among patients with COVID-19 infection who developed AKI at our hospital.

Methods: This is a cohort of patients with COVID-19 who were diagnosed with AKI at our center in Spring of 2020 and had a urinalysis performed within 48 hours of diagnosis of AKI. When applicable we used Mann-Whitney test to compare groups.

Results: 34 patients had AKI, 21 (61%) were female, and 21 (61%) were Black race. All patients had a urinalysis, 23 (68%) had a urine sodium (UNa), and a 21 (61%) had a urine FeNa (fractional excretion of sodium). The median urine specific gravity (SG) was 1.019 (IQR 1.04 – 1.026). The median UNa was 39 (IQR 24 - 55). The median FeNa was 0.69% (IQR 0.18% - 1.07%). **Figure 1** shows the distribution of urine SG by FeNa. The median serum creatinine at the time of diagnosis was 2.42 (IQR 1.52 - 3.92). A diagnosis of ATI (acute tubular injury) was made by the treating physician in 17 (50%) patients. The median creatinine at the time of diagnosis for patients who were diagnosed with ATI was 3.35 (IQR 2.29 – 5.16), and for those without ATI was 1.61 (IQR 1.48 - 2.63), p-value 0.0641. The median FeNa for patients who were diagnosed with ATI was 0.85% (IQR 0.56%-1.97%), and for those without ATI was 0.33% (IQR .12%-1.27%), p-value 0.105.

Conclusions: In our cohort, the majority of patients with AKI had urine studies consistent with volume depletion, suggesting that volume depletion is common. Implementation of urine studies in COVID-19 patients as part of regular care might help guide treating physicians deciding about fluid management.



PO0089

Recovery of Renal Function Among Left Ventricular Assist Device Patients with Severe AKI Requiring Renal Replacement Therapy: A Meta-Analysis

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Background: Acute kidney injury (AKI) is a common and severe complication after left ventricular assist devices (LVAD) implantation with an incidence of 37%; 13% of which requiring renal replacement therapy (RRT). Severe AKI requiring RRT in LVAD patients is associated with high short-term and long-term mortality, compared with those without RRT. While recovery of renal function is associated with better outcomes, the rates of recovery of renal function among LVAD patients with severe AKI requiring RRT are unclear.

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Databases were systemically searched from database inceptions through January 2020 to identify studies evaluating the rates of recovery from severe AKI requiring RRT after LVAD placement, which is defined by regained kidney function resulting in the discontinuation of RRT. Random-effects and generic inverse variance method of DerSimonian-Laird were used to combine the effect estimates obtained from individual studies.

Results: A total of 268 patients from 14 cohort studies with severe AKI requiring RRT after LVAD were enrolled. Follow-up time ranges from hospital discharge up to 12 months. 78.5% of renal recovery occurred at the time of hospital discharge or within 30 days. Majority (85%) of patients used continuous-flow LVAD. Overall, the pooled estimated rates of AKI recovery among patients with severe AKI requiring RRT was 50.5% (95%CI: 34.0%-67.0%), respectively. While the data on pulsatile-flow LVAD were limited, subgroup analysis of continuous-flow LVAD demonstrated the pooled estimated rates of AKI recovery among patients with severe AKI requiring RRT of 52.1% (95%CI: 36.8%-67.0%). Meta-regression analysis did not demonstrate a significant association between study year and AKI recovery rate (p = 0.08). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test in all analyses.

Conclusions: Recovery from severe AKI requiring RRT after LVAD occurs approximately 50.5%, and it has not significantly changed over the years despite advances in medicine.

PO0090

Early Nephrologist Interventions to Avoid Kidney Replacement Therapy in AKI

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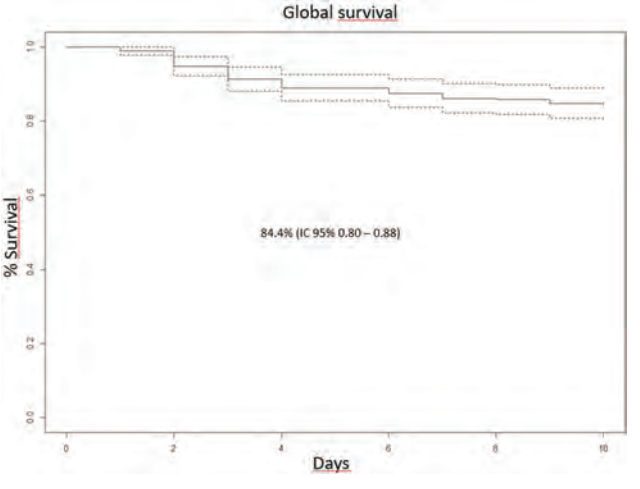
Background: Is well know that early nephrologist involvement in patients with AKI improve outcomes. Determine which intervention has a greater impact on avoiding the need for KRT will be an important advance.

Methods: Our objective was to Identify which nephrologist intervention decrease the need of KRT. We analyze age, gender, comorbid conditions, cause of AKI, pharmacology therapy, cause of KRT, **early interventions: fluid, antibiotic and nutritional adjustment, nephrotoxic withdrawal and removal of hyperchloremic solutions** and death. Kaplan Meier survival analysis. Multivariable logistic regression model was performed. P< 0.05 which is significant.

Results: From 2017 to 2020 288 patients with AKI where analyzed prospectively with a 10 days follow-up, 45 (15%) patients die, overall survival of 84.4% (IC 95% 0.80 – 0.88) (Figure1). Only fluid adjustment decreases the risk of KRT (OR 0.74, 95% CI 0.68-0.81, p < 0.001) while having AKI KDIGO 3 increases the risk (OR 1.12, 95% CI 1.05-1.20, p<0.001) being the fluid overload the main cause of KRT (OR 1.67, 95% CI 1.53-1.82, p<0.001). Between all interventions, just fluid adjustment avoid progression to AKI KDIGO 3 (OR 0.76, 95% CI 0.65-0.89, p < 0.001). (Table1)

Conclusions: In AKI, fluid adjustment was the most important nephrologist intervention to avoid KRT.

Variable	OR	95% CI		p
KDIGO 3	1.12	1.05	1.20	<0.001
KDIGO 1	1.03	0.95	1.12	0.35
Age	0.99	0.99	1.00	0.06
DM	0.99	0.93	1.07	0.98
HAS	0.96	0.89	1.02	0.24
CKD	0.97	0.90	1.03	0.36
NSAIDs	0.98	0.93	1.04	0.60
Vasopressors	0.94	0.87	1.02	0.17
Sepsis	1.02	0.96	1.09	0.43
Hypovolemia	0.97	0.91	1.04	0.54
Cardiorenal syndrome	0.94	0.85	1.04	0.31
Nephrotoxic drugs	1.00	0.92	1.08	0.95
Shock	1.05	0.97	1.13	0.21
Nephrotoxic withdrawal	0.94	0.88	1.01	0.12
Liquid adjustment	0.74	0.68	0.81	<0.001
Antibiotic adjustment	1.02	0.95	1.11	0.45
Nutritional adjustment	0.97	0.82	1.15	0.79
Removal of hyperchloremic solutions	0.91	0.80	1.04	0.19
RRT due to Hyperkalemia	1.36	1.21	1.54	<0.001
RRT due to acid base disorders	1.13	1.01	1.27	<0.001
RRT due to fluid overload	1.67	1.52	1.82	<0.001
RRT due to Uremia	1.31	1.19	1.45	<0.001



PO0091

Usefulness of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Community-Acquired AKI

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Background: The neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios have been identified as markers of inflammation and endothelial dysfunction. To date, its usefulness as prognostic markers in community-acquired acute kidney injury (CA-AKI) has not been evaluated.

Methods: We established a cohort of patients with CA-AKI admitted to our Nephrology service from January 2010 to February 2015. NLR and PLR ratios were obtained with the first analysis performed.

Results: We studied 308 patients with CA-AKI, 58 % were men, mean age 73.22. Etiology of CA-AKI: prerenal 69.5%; renal 23.1%; obstructive 7,5%. AKI KDIGO stages: I, 14.6%; II, 11%; III 74.4%. CKD was detected in 68.8%.17,15% of cases required hemodialysis and 12,3 % died. Mean NLR was 9.14 ± 8,47. Mean PLR was 236,99 ± 228,41. NLR according to etiology was: prerenal 8,55±6,8*;* renal 9,37±9,8; obstructive 13,99±14,82 (significant differences between obstructive and prerenal). PLR according to etiology: prerenal 228,31±216,34*;* renal 236,15±233,77*;* obstructive 320,37±304,89 (non-significant differences). Within the group prerenal, 79 cases were complicated by acute tubular necrosis (ATN). These cases presented a higher NLR (10,7±10,28 vs NLR 7,8±5,6; p=0,026). There were no significant differences between the PLR of both grups. The NLR showed a significant correlation with the peak creatinine (r= 0,186; p = 0,001) and with serum albumin (r= -0,237; p < 0,001). The PLR also showed the same correlations (r= 0,134, p = 0,018 and r = 0,165, p= 0,07).The NLR, but not the PLR, was associated with the length of hospital stay (multiple linear regression analysis). Through a multivariate binary logistic regression analysis, the variables that were independently associated with mortality during admission were the Liaño individual severity index and the NLR (OR 1,060; IC 95 % 1.014 – 1,108). The best cut-off point of the NLR to predict mortality was 6,68 (AUC 0,584; sensitivity 0.60; specificity 0.58; Youden index 0.178)

Conclusions: In our CA-AKI patients cohort, the NLR was associated with the morbidity and the mortality. More studies are need to confirm this finding, but the easiness of obtaining it and its economic cost make it cost-effective, giving the NLR a leading role in assessing the risk of CA-AKI.

PO0092

Clinical Characteristics and Histologic Descriptions of Acute Tubular Injury: A Systematic Review

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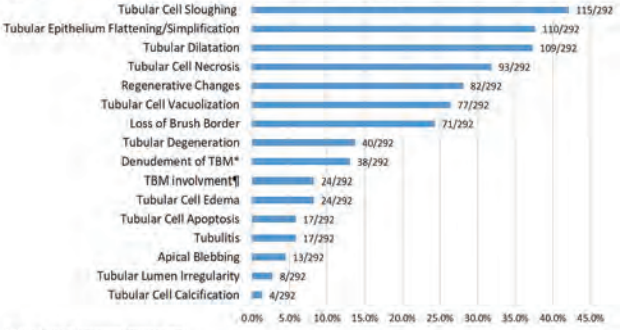
Background: The term acute tubular injury (ATI) represents histopathologic renal tubular injury and often manifests clinically as acute kidney injury (AKI). Studies systematically summarizing the clinical presentation and histologic changes in human ATI are limited.

Methods: We comprehensively searched human studies of ATI from 1936 to July 2019. We extracted study characteristics, clinical characterstics and histologic descriptions of ATI by bright field, immunofluorescence or electron microscopy (EM) and by immunohistochemistry. We also compared histology of tubular cell injury as a function of tissue procurement timing and etiologies.

Results: We included 292 studies comprising of 1987 patients. The majority of studies (76%) were single center case reports. The mean age of patients included was 47 years old. 39.3% of patients had hypertension and 24.9% of them had diabetes mellitus. Baseline, peak and latest creatinine were 1.29 mg/dL, 7.04 mg/dL and 1.86 mg/dL respectively. 48.9% of studies were native kidney biopsy cases, of which 86.7% were performed after serum creatnine peaked. There were significant amount of missing data in these clinical characteristics reported across studies. We identified 16 histologic descriptions used to report tubular injury (shown in Figure 1), including tubular cell sloughing (39.4%), tubular epithelial flattening/simplification (37.7%), tubular dilatation (37.3%), tubular cell necrosis (31.9%), regenerative changes (28.1%) and tubular cell vacuolization (26.4%). There was no difference in tubular injury histology either before or after creatinine peaked or between etiologies. EM and immunohistochemistry were used in minority of studies.

Conclusions: Tubular injury manifests with diverse histological changes. Efforts to establish protocols to harmonize biopsy practices, handle kidney biopsy and report results across clinical practice are needed to improve our understanding of this complex disease.

Figure 1. Overall reporting of histology descriptors of tubular injury.



*TBM: tubular basement membrane

¶ TBM involvement: tubular basement membrane rupture, duplication, thickening or thinning

PO0093

AKI and CKD Distribution in the Novel Clinical Phenotypes for Sepsis

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Background: Sepsis is the most common cause of Acute Kidney Injury (AKI) in critically ill patients. Four clinical phenotypes (alpha, beta, gamma, delta) of sepsis have been recently described. Our objective was to investigate which of these sepsis phenotypes were associated with severe AKI, chronic kidney disease (CKD), AKI with CKD, and acute kidney disease (AKD).

Methods: We examined the 4 phenotypes using patient data from a previously published multicenter sepsis trial. After excluding patients with end-stage kidney disease and missing data, we analyzed 1243 patients with septic shock. We described the presence of severe AKI within the first 24 hours defined as KDIGO stage 2 or 3 or stage 1 with [TIMP-2]●[IGFBP7] at 6 hours >2.0. AKD was defined for patients with severe AKI as the presence of any AKI on day 7 or, if death occurred before 7 days, death without AKI recovery. The Chi-square test was used to compare distributions between groups, if $p<0.05$ then a pairwise comparison between groups was made using the Chi-square test adjusted with Bonferroni correction.

Results: We found a total of 633 patients with severe AKI (53.6%) within 24h. The rate of severe AKI at 24h was different across phenotypes being highest in the delta and beta phenotypes (80.8% and 73.6% respectively), and lowest in the alpha phenotype (30.1%, overall $p<0.0001$). CKD was most common in the beta phenotype (52.0%, overall $p<0.0001$) while in the others was lower (31.4% in alpha, 28.6% in gamma, and 35.0% in delta). The highest prevalence of AKI with CKD was again in the beta phenotype (52.8%), compared to alpha (25.0%), gamma (26.6%), or delta (34.8%, $p<0.0001$). AKD occurred more often in the delta (57.4%) and beta (50.0%) phenotypes compared to alpha (32.7%) and gamma (40.1%, $p=0.0002$).

Conclusions: Severe AKI was significantly more common among patients with beta and delta phenotypes. However, the beta phenotype had a higher level of underlying CKD that predisposed to new AKI. Alpha and gamma phenotypes not only had lower rates of AKI, but these cases were less likely to progress to AKD.

Funding: NIDDK Support, Other NIH Support - The data of the abstract refer to: ProCESS trial (NCT00510835) funded by NIH/National Institute of General Medical Sciences grand P50GM076659; ProGReSS-AKI study funded by NIH/National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK083961; SENECA project funded by NIH grants R35GM119519, R34GM102696, R01GM101197, GM107231, R01LM012095, K08GM117310-01A1, and GM61992.

	Total	Alpha	Beta	Gamma	Delta	P-value
Severe AKI	633/1180 (53.6%)	116/386$_a$ (30.1%)	195/265$_b$ (73.6%)	158/326$_c$ (48.5%)	164/203$_b$ (80.8%)	<0.0001
CKD	445/1243 (35.8%)	131/417$_a$ (31.4%)	144/277$_b$ (52.0%)	98/343$_a$ (28.6%)	72/206$_a$ (35.0%)	<0.0001
AKI* with CKD	231/633 (36.5%)	29/116$_a$ (25.0%)	103/195$_b$ (52.8%)	42/158$_a$ (26.6%)	57/164$_a$ (34.8%)	<0.0001
AKD*	290/626 (46.3%)	37/113$_a$ (32.7%)	97/194$_{b,c}$ (50.0%)	63/157$_{a,b}$ (40.1%)	93/162$_c$ (57.4%)	0.0002

Values in the same row not sharing the same subscript letter are significantly different for the pairwise comparisons within a row. *Includes only patients with severe AKI.

PO0094

Comparison of Clinical Characteristics of AKI in Patients with Glyphosate and Glufosinate Herbicide Poisoning

In O Sun, A young Cho. *Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea.*

Background: This study aimed to investigate the clinical characteristics of acute kidney injury in patients with glyphosate and glufosinate herbicide poisoning.

Methods: From 2008 to 2019, 230 patients admitted to our hospital after glyphosate or glufosinate herbicide poisoning. We compared the clinical characteristics of acute kidney injury in patients with glyphosate (n=173) and glufosinate (n=57) herbicide poisoning.

Results: The patinets included 155 men and 75 women with a mean age of 59 years (range, 22-101 years). There were no differences in the clinical characteristics between glyphosate and glufosinate poisoning except for serum bicarbonate and intensive care unit admission. The serum bicarbonate level was lower in glufosinate intoxication than in glyphosate intoxication (19.8 ± 4.5 vs. 21.5 ± 3.9, p<0.01). In comparison with patients of glyphosate poisoning, patients with glufosinate poisoning experienced intubation (59.6% vs. 19.7%, P<0.01) and intensive care unit admission (68.4% vs. 38.2%, p<0.01) more frequently. The overall incidence of acute kidney injury was 38.3% in this study, and there was no difference between two groups (35.8% vs. 45.6%, p=0.123).

Conclusions: Patients with glufosinate intoxication showed more severe type of clinical manifestation and intensive care unit admission rates than glyphosate intoxication.

PO0095

Clinical Significance of Hypoalbuminemia for AKI in Patients with Scrub Typhus

In O Sun, A young Cho. *Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea.*

Background: The aim of this study is to investigate the clinical significance of hypoalguminemia for acute kidney injury in patients with scrub typhus.

Methods: From 2009 to 2018, 611 patients were diagnosed with scrub typhus. We divided the patients into two groups (normoalbuminemia vs. hypoalbuminemia) based on the serum albumin level of 3.0 g/dL, and compared the incidence, clinical characteristics, and severity of acute kidney injury based on RIFLE classification between two groups.

Results: Of the total 611 patients, 78 (12.8%) were categorized as hypoalbuminemia group. Compared with patients in normoalbuminemia group, patients in hypoalbuminemia group were older (73 ± 9 vs. 62 ± 14, p<0.01) and had higher total leukocyte counts (10.2×10^3/mL vs. 6.7×10^3/mL, p<0.01). Hypoalbuminemia group showed significantly longer hospital stay (9.6 ± 6.1 vs. 6.1 ± 3.0, p<0.01) and higher incidence of complications in respiratory system (50% vs. 14%, p<0.01), cardiovascular system (28% vs. 11%, p<0.01), neurologic system. Furthermore, acute kidney injury (58% vs. 18%, p<0.01) was also developed in hypoalbuminemia group. The overall incidence of acute kidney injury was 23.1%; of which, 14.9%, 7.0% and 1.2% were classified as Risk, Injury and Failure, respectively. The serum albumin level correlated with acute kidney injury severity (3.4 ± 0.5 vs. 3.0 ± 0.5 vs. 2.6 ± 0.3, p<0.05). In a multivariate logistic regression analysis for predicting acute kidney injury, age, presence of co-morbidities such as chronic kidney disease, diabetes, or hypertension, total bilirubin, leukocytosis and hypoalbuminemia were significant predictors of acute kidney injury.

Conclusions: Hypoalbuminemia was closely associated with scrub typhus associated with acute kidney injury.

PO0096

Risk Factors for Patient Subgroups with Distinct Health Utility Profiles Following AKI

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Background: Health-related quality of life (HRQOL) after dialysis initiation for acute kidney injury (AKI) is low. We sought to determine patient subgroups with distinct health utility profiles at 60 days after diagnosis of AKI and evaluated the potential risk factors for these profiles.

Methods: The Biologic Markers of Renal Recovery for the Kidney (BioMaRK) study is an observational cohort of patients nested within the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network study. Clinical characteristics and biomarkers of inflammation were collected from 817 patients with AKI around the time of dialysis initiation. Of these patients, 402 were alive at 60 days and 328 completed the Health Utility Index, which measures 8 health attributes and calculates an overall HRQOL score. Using latent class analysis (LCA) of these 8 attributes, we identified patient subgroups with distinct health utility profiles and risk factors associated with subgroup membership.

Results: Two subgroups were identified with 47% of patients being included in the low healthy utility subgroup (i.e. Low HU subgroup). This subgroup was characterized as having higher median ambulation, emotion, cognition, and pain scores. The remaining (i.e., 53%) were labeled as belonging in the subgroup with higher health utility (i.e. High HU subgroup). No significant differences were found between the two subgroups in terms of age, gender, or race. However, patients in the Low HU subgroup were more likely to have diabetes, lower albumin levels, and higher SOFA score. In addition, patients in the Low HU subgroup had more dialysis days, hospital days, and ICU days. No between groups differences were found in the assignment of high versus normal dialysis intensity. Day 1 biomarkers of GM-CSF, IL1, IL6, IL8, TNF-alpha, IL10, TNFR1, TNFR2, MIF, IL18 and DR5 were not statistically different between the two subgroups. However, patients in the Low HU subgroup had higher IL8, TNFR1, TNFR2, and DR5 levels at day 8.

Conclusions: Using a person-centered analytic technique (i.e., LCA), we found two subgroups of patients with distinct health utility profiles among 60 day survivors following acute kidney injury. Demographic, clinical, and biomarker characteristics associated with each subgroup may be used to identify patients at high risk of poor HRQOL.

Funding: NIDDK Support

PO0097

Safety and Efficacy of a New Simplified Regional Citrate Anticoagulation Protocol for Continuous Venovenous Hemodiafiltration and Sustained Low-Efficiency Dialysis Focused on Acid-Base Balance Optimization and Prevention of Kidney Replacement Therapy-Induced Hypophosphatemia

Francesca Di Mario,[1] Paolo Greco,[1] Caterina Maccari,[1] Elisabetta Parenti,[1] Giovanni maria Rossi,[1] Valentina Pistolesi,[2] Santo Morabito,[2] Enrico Fiaccadori.[1] Nephrology Unit, Parma University Hospital, Parma, Italy *[1]UO Nefrologia, Azienda Ospedaliera-Universitaria Parma, Parma, Italy; [2]Umberto I Policlinico di Roma, Roma, Italy.*

Background: Regional citrate anticoagulation (RCA) is the first-line anticoagulation strategy for Kidney Replacement Therapy (KRT) in Acute Kidney Injury (AKI). Hypophosphatemia is a common electrolyte disorder in the ICU, especially in course of prolonged and highly efficient KRTs. This pilot study is aimed at evaluating a simplified RCA protocol for Continuous Venovenous Hemodiafiltration (CVVHDF) and Sustained Low Efficiency Dialysis (SLED), based on the combination of a low-concentration citrate solution with a phosphate-containing solution.

Methods: KRT was performed in ICU patients with AKI by the Prismax system (Baxter) and polyacrylonitrile AN69 filters (ST 150, 1.5 m2, Baxter), combining a 18 mmol/l pre-dilution trisodium citrate solution (Regiocit 18/0, Baxter) with a phosphate-containing solution used as both dialysate and post-dilution replacement (Ca^{2+} 0, HPO_4^{2-} 1, Mg^{2+} 0.75, HCO_3^- 22 mmol/l; Biphozyl, Baxter). Calcium chloride (CaCl 10%) was infused in a central venous line to maintain the systemic Ca^{2+} within a normal range. In each patient three consecutive daily 8-h SLED sessions or 72-h CVVHDF were evaluated. Phosphorus (P) losses were replaced, when needed, with sodium glycerophosphate pentahydrate (Glycophos™ 20 mmol/20 ml, Fresenius Kabi Norge AS, Halden, Norvegia).

Results: 20 patients with AKI on SLED and 10 on CVVHDF were studied (mean APACHE II score 23.8). No premature interruptions for irreversible filter clotting occurred; prescribed dialysis dose was delivered in 95% of cases. No statistically significant differences were observed between systemic ACT measured at KRT start and at different times during KRT. No major hemorrhagic events nor clinically relevant episodes of hypo- or hypercalcemia were observed. Acid-base status and serum phosphorus levels were effectively maintained.

Conclusions: Our simplified RCA protocol is safe and efficacious both for SLED and CVVHDF, allowing to optimizing acid-base balance and to preventing KRT-related hypophosphatemia.

PO0098

Relationship Between the Presence of Infectious Disease and Clinical Outcomes of Patients with Cardiorenal Syndrome Type 1

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Background: Cardiorenal Syndrome type 1 (CRS-1) can be triggered by an infection. The pathophysiological basis is vascular congestion, which is why it has been treated with different strategies of diuretics, but in the presence of infection, the inflammatory, neurohormonal and hemodynamic effects can compromise the efficacy of the diuretic therapy and potentially worsen clinical evolution. Here we compare the clinical evolution during the hospitalization of CRS-1 patients with and without infection.

Methods: This is a retrospective cohort study conducted in the Hospital Civil of Guadalajara "Fray Antonio Alcalde", from January 2015 to September 2018. Conducted in CRS-1 patients, we showed the clinical evolution and diuretic strategies analyzed according to the presence or absence of infection.

Results: We identified 63 patients classified as having CRS-1, 28 (44.4%) were classified as having an infectious disease. The mean age was 62 years (±14.6) and 58 (±12.4) in the group with infection and no infection, respectively. There were no statistically significant differences between the clinical outcomes of both groups. The median length of hospital stay was 8 days in the group with infection and 7 days in the group without infection (p=0.065). Three patients (10.7%) of the group with infection received renal replacement therapy and 1 patient (2.9%) in the group without infection (p=0.315). In the group with infection, 2 patients died (7.1%), whereas in the uninfected group there were no deaths (p=0.194). sCr values tend to diminish in a similar manner in both groups. We found that all patients received furosemide at least during the first five days of hospitalization and the strategy of the diuretic chosen was similar between groups.

Conclusions: We showed that the clinical evolution of patients with CRS-1 is similar in the presence or absence of infection. We anticipate that this study may be a reason to expand knowledge in patients with CRS-1 and the presence of infection.

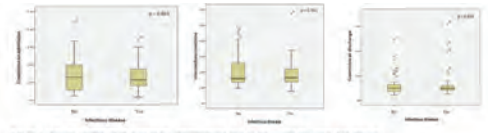

Figure 1- serum creatinine at admission, intermediate and at discharge between two groups.

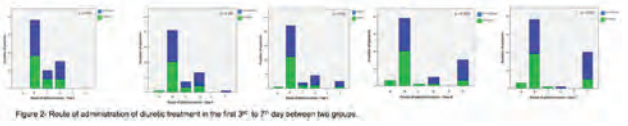

Figure 2- Route of administration of diuretic treatment in the first 3rd to 7th day between two groups.

PO0099

Design of START: A Phase 2 Study Evaluating the Safety and Efficacy of RBT-1 on Preconditioning Response Biomarkers in Subjects Undergoing Cardiac Surgery

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Background: Cardiac surgery is associated with an increased risk of acute kidney injury (AKI). RBT-1 induces non-ischemic tissue preconditioning that has shown organ protective effects in several animal models of AKI. Markers of cytoprotection observed with RBT-1 treatment in animals were also found to be upregulated in a Phase 1 study of RBT-1 in healthy volunteers and subjects with Stages 3 and 4 chronic kidney disease (CKD). Based on these data, we have designed a Phase 2, placebo-controlled, double-blind, randomized, multicenter study that will assess the effect of RBT-1 on preconditioning response biomarkers in subjects scheduled to undergo cardiac surgery

Methods: Study Design: This study will enroll 126 subjects scheduled to undergo coronary artery bypass graft (CABG) and/or cardiac valve surgery. Eligible subjects will be randomized to receive a single dose of RBT-1 or placebo via intravenous infusion between 24 and 48 hours prior to scheduled cardiac surgery. Subjects will be followed through Day 90. **Inclusion/Exclusion Criteria:** Subjects eligible for enrollment include adults who are scheduled to undergo non-emergent, on-pump coronary artery and/or cardiac valve surgery. Major exclusion criteria include CKD with eGFR ≤20 ml/min/1.73m^2 or need for dialysis.

Results: Objectives: The primary objective of this study is to evaluate the efficacy of RBT-1 on preconditioning response biomarkers from baseline through Day 3 post-cardiac surgery. Based on preclinical data, plasma heme oxygenase-1 [HO-1], ferritin, and interleukin-10 [IL-10]) have been identified as the relevant biomarkers for this study. Secondary objectives include change in tubular injury biomarkers and incidence of AKI based on KDIGO classification. Exploratory objectives include the occurrence of major adverse kidney events (MAKE) through Days 30 and 90.

Conclusions: The multinational START study will assess the cytoprotective preconditioning response to RBT-1 in subjects undergoing cardiac surgery.

Funding: Commercial Support - Renibus Therapeutics

PO0100

Acute Peritoneal Dialysis During the COVID-19 Pandemic in New York City

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Introduction: The dramatic spread of COVID-19 in March 2020 threatened to overwhelm ICU capacity. At the peak we had more than 120 patients in the ICU. About 40% of the ICU patients required RRT due to AKI. Our ability to provide RRT with CVVH and IHD was severely limited by critical shortages of equipment and personnel. We rapidly established an acute PD program at Bellevue hospital for AKI patients. The acute PD program turned out to be instrumental in the BH response to COVID AKI.

Case Description: Patients All patients who needed RRT in the ICU were eligible to receive PD catheters except for those with prior abdominal surgery. 36/38 patients who received catheters were Covid (+). Proning was not always planned; we did not use this as a contraindication. We were able to successfully perform adequate PD on patients who were proned with minimal complications. **Surgical Support** Catheters were placed using a limited cut down to the peritoneal membrane through the rectus muscle at bedside; most of the patients were intubated and sedated. **Training and Initial Experience** A nurse affiliated with Bellevue's outpatient dialysis unit helped make videos and trained the lead nephrologist on how to perform PD and how to use a Cycler. 25 people were on the PD team and we were able to provide exchanges 24 hours per day. Exchanges were initially performed manually every 1-2 hours. Eventually we acquired 18 cyclers which greatly eased the workload. **Outcomes** As of May 8, 2020 63 patients were evaluated, 38 PD catheters were placed with 35 used for exchanges. 2 patients had catheters placed but recovered renal function prior to starting PD. 1/38 was nonfunctioning and changed to IHD. 15/35 survived >30 days; 8 recovered renal function; 20 expired <30 days.

Discussion: Because of the shortage of our typically used dialysis modalities we were compelled to start an acute PD program. No patient on PD required additional dialytic support with IHD or CVVH. PD was well tolerated by ventilated patients with hemodynamic instability. Acute PD more than adequately filled the gap in treatment options during this unprecedented crisis

PO0101

Novel Prescription of Continuous Venovenous Hemodialysis Dialysate Na^+ in a Patient with Cerebral Edema and Severe Hypernatremia

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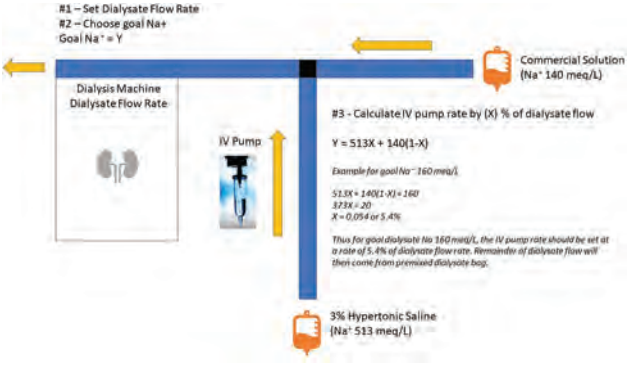
Introduction: AKI necessitating dialysis is difficult in patients with traumatic brain injury. Slow clearance and increased dialysate Na^+ are recommended. Yet, barriers in adjusting dialysate Na^+ may occur with premixed commercial dialysate. We present a unique method of prescribing CVVHD to prevent Na^+ overcorrection in a patient with cerebral edema and severe hypernatremia.

Case Description: An 18 year old male presented with polytrauma after a motor vehicle accident. His injuries included multiple intracranial bleeds. On day 13, nephrology was consulted for AKI, BUN > 150 mg/dl, and refractory hyperkalemia. Head CT scan showed known bleeds and diffuse cerebral edema. At consult, IV 3% saline had already resulted in plasma Na^+ ranging 161-166 meq/L for > 3 days. Our hospital performs CVVHD via NxStage with commercial dialysate bags with Na^+ fixed at 140 meq/L. To avoid Na^+ overcorrection, we combined commercial bags and 3% saline in-circuit. Initially, clearance goals were set by dialysate flow rate. Then, separate IV pump for 3% saline was Y connected to the pre-pump dialysate line, and IV pump rate was calculated to adjust final dialysate Na^+ (Figure). Final dialysate flow equated to IV pump flow plus residual drawn from commercial bags. Our initial goal dialysate Na^+ was 160 meq/L. Dialysis solution labs steadily showed adjusted dialysate Na^+ of about 158$^+$ meq/L at initiation. Changes to other dialysate factors (i.e. K^+, $HCO3^-$) were negligible. CVVHD was started with titration of the dialysis-attached 3% saline IV pump to control of dialysate Na^+. All other 3% saline was discontinued. Though the patient ultimately died from overall injuries, change in plasma Na^+ was slow and controlled (10 meq in 7 days).

Discussion: We present a new method for adjusting dialysate Na^+ using in-circuit mixing of commercial dialysate and 3% saline. Our method used readily available solutions, was easy to titrate, depended solely on dialysis, and did not require manipulation of commercial bags. We suggest consideration of our method in CVVHD, brain trauma, and hypernatremia.



PO0102

Use of Azathioprine in Treating Severe Corticosteroid-Resistant Acute Interstitial Nephritis

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Introduction: Acute interstitial nephritis (AIN) is a pattern of renal injury characterized by inflammatory infiltrate in renal interstitium leading to decline in renal function. It is commonly caused by drugs such as penicillin, diuretics and proton pump inhibitors. Other causes include autoimmune diseases or systemic infections. Treatment involves removing the offending agent and steroids in severe cases. We describe a case of drug induced severe AIN refractory to steroids that is treated with azathioprine, an immunosuppressant drug that inhibits purine synthesis.

Case Description: A 20 year old Caucasian female with past medical history of gastroesophageal reflux disease (GERD) presented to the emergency with severe nausea, vomiting and oliguria. She had been taking omeprazole for 2 weeks prior to presentation. Initial labs indicated eosinophilia, raised creatinine levels of 3.5 mg/dl and Blood Urea Nitrogen of 27 mg/dl. Renal biopsy was done which showed severe acute interstitial nephritis with raised eosinophils. The diagnosis of Acute Kidney Injury secondary to drug induced AIN was made and patient was given pulse dose steroids for 3 days. She was discharged on 60 mg of prednisolone daily. A month later, the patient's creatinine improved to 1.75 from a peak of 6.27 mg/dl. The steroid dose was tapered to 40 mg. However, the creatinine raised to 2.7 mg/dl again due to which prednisolone dose was

increased to 60 mg/dl. Kidney function did not improve even after 2 months and re-biopsy revealed ongoing interstitial nephritis. Consequently, the patient was given a trial of azathioprine 200 mg daily with reduced prednisolone dose (40 mg/dl). Creatinine levels decreased moderately after 2 weeks to 1.70 mg/dl due to which the prednisolone dose was further tapered to 20 mg/dl.

Discussion: In past, azathioprine has shown promise in treatment of lupus nephritis and IgA nephropathy. To our knowledge, this is the first reported case of successful treatment of steroid resistant severe drug induced AIN with azathioprine. As it has lesser side effects and better compliance than steroids, it is suggested that azathioprine may be considered in future as an adjuvant or alternative first line of treatment for AIN. Larger, randomized clinical trials need to be conducted in order to establish optimal dosing and long term effectiveness of azathioprine in treating AIN.

PO0103

The Successful Treatment of Bile Cast Nephropathy with Plasma Exchange

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Introduction: Bile cast nephropathy is a condition of renal dysfunction in the setting of hyperbilirubinemia. There are very few cases of this condition reported in literature, and there is a lack of established treatment guidelines. We report the successful management of three patients with bile cast nephropathy using therapeutic plasma exchange (TPE).

Case Description: CASE 1: A 59 year old man with stage 3 colon carcinoma on Capecitabine developed chemotherapy-induced liver toxicity resulting in severe cholestasis and biopsy-proven bile cast nephropathy. He underwent TPE. CASE 2: A 69 year old man with history of colon cancer status post remote hemicolectomy was admitted with pruritus and acute kidney injury (AKI). CT abdomen without contrast showed a 6 cm liver mass with bile duct dilatation, a biopsy proven metastasis from his previous colon cancer. A kidney biopsy confirmed bile cast nephropathy. The patient was started on hemodialysis (HD), and a biliary stent was placed. He was treated with TPE. He opted for hospice due to cancer CASE 3: A 38 year old man was admitted with severe acute alcoholic hepatitis and AKI. A kidney biopsy confirmed bile cast nephropathy. He underwent TPE and a total of four sessions of HD. The clinical course in our patients with biopsy proven bile cast nephropathy prior to and after TPE therapy is noted in Table 1.

Discussion: Our patients had acute liver and kidney failure with no underlying chronic liver disease. 1-1.2 plasma volume exchange was performed with each procedure with a combination of plasma and 5% albumin. A good response to TPE in decreased total bilirubin level and improvement in renal function was noted. There were no serious apheresis adverse events, and all procedures were tolerated well by the patients. Medical management of bile cast nephropathy such as steroids and cholestyramine have shown limited or no benefit. Renal replacement therapy has also been shown to be of limited benefit and should be mainly instituted for the treatment of AKI. In bile cast nephropathy, TPE may help in the clearance of bile acid crystals and reduction of proinflammatory molecules which contribute to acute liver and kidney injury. In this small case series, institution of TPE appeared to improve the clinical course of patients with bile cast nephropathy.

Case Number	AKI Stage on admission	Number of TPE sessions	Creatinine (mg/dl) At Baseline	Creatinine (mg/dl) Admission	Creatinine (mg/dl) At last TPE	Creatinine (mg/dl) 3 weeks post TPE	Direct Bilirubin (mg/dl) Admission	Direct Bilirubin (mg/dl) After last TPE	Complications from TPE
Case 1	3	12	0.9	3.5	1.3	0.8	16.3	7.7	None
Case 2	3	7	1.1	7.1	2.8	Hospice	31.8	3.6	Mild Hypocalcemia
Case 3	3	7	0.8	3.76	1.8	1.3	46.4	7.1	None

PO0104

An Unusual Case of IgA Nephropathy Associated with Parvovirus B19

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Introduction: Parvovirus is known to cause upper respiratory infections in children and the immunosuppressed. It's association with kidney disease has been sporadically reported in literature, mostly causing lupus like glomerulonephritis with endocapillary proliferation. We describe a unique case of IgA Nephropathy (IgAN) in an African American patient associated with Parvovirus B19.

Case Description: A 23 year old African American female with a history of Hemoglobin C disease presented with one week of generalized malaise, abdominal pain and nausea, found to have non-oliguric AKI with Creatinine 2.5 mg/dL (baseline Cr: 0.6 mg/dL). Within one week, her Creatinine peaked at 7.4 mg/dL. Urinalysis showed 3+ protein, 5 white cells and 9 red cells. Urine microscopy was bland. Spot urine protein to creatinine ratio was 3.84g. Serologies were notable for normal Complements, negative ANA, ANCA, Hepatitis B, Hepatitis C and HIV along with unremarkable serum and urine electrophoresis. Renal ultrasound ruled out hydronephrosis. Labs were also notable for worsening hemolytic anemia. A renal biopsy was pursued, that showed diffuse proliferative glomerulonephritis with dominant IgA deposits. Mesangial and endocapillary proliferation was noted without any crescents. The oxford classification was: M1, E1, S0, T0, C0. Given this atypical IgA phenotype, infectious work was pursued, that came back positive for Parvovirus IgM and detectable Parvovirus DNA. She was started on Pulse dose steroids; immunosuppressives were held off given the absence of crescents. Her proteinuria partially responded to steroids along with an improvement in AKI (Cr: 1.1 mg/dL), after which steroids were tapered.

Discussion: This case provides an example of AKI associated with Parvovirus infection. Since IgAN is predominantly seen in Caucasians, it is not surprising that only 3% African Americans were included in the cohort on which the Oxford Classification was coined. The improvement in acute kidney injury with a short course of steroids is suggestive of Parvovirus related process more than the typical endocapillary proliferation related to IgAN. The extension of Oxford Classification in the African American population can thus be challenging and potentially misleading as seen in this case. A repeat renal biopsy may be warranted to assess the underlying diagnosis of IgA Nephropathy and should be treated based on findings.

PO0105

Angioimmunoblast T-Cell Lymphoma Masquerading as Type II Cryoglobulinemia and AKI: A Case Report

Li Xiangyang, Haiyan He. *University of Hong Kong-Shenzhen Hospital, Shenzhen, China.*

Introduction: Angioimmunoblastic T cell lymphoma (AITL), which belongs to the non-Hodgkin's lymphoma (NHL), is an infrequent hematological malignancy yet with variable and often atypical presentations. The presence of dysproteinemia, autoantibodies and systemic involvement in AITL have often led to a delay in diagnosis and/or misdiagnosis in practice.

Case Description: A 67-year old previously healthy housewife presented with 2-month history of intermittent joint pain affecting the right wrist and right hand, and a 3-day history bilateral lower limb edema. Her serum creatinine rose from 67 to 197 μmol/L and leg swelling appeared after a moderate fever prior to admission. The physical examinations at presentation were insignificant except for bilateral lower-leg pitting edema. Laboratory investigations after admission were notable for ascending serum creatinine levels, moderate anemia, marked hypocomplementemia with multiple autoantibodies of ANA, anti-cardiolipin-IgM and direct antiglobulin. The serum and urinary Immunofixation and serum cryoglobulinemia tests were all negative, while the serum κ to λ light chain ratio was depressed to 0.231. A renal biopsy conducted on day 9 revealed a diffuse proliferative glomerulonephritis with intracapillary pseudo-thrombi formation with orderly arranged microtubular structures of 20-35 nm in diameter in the subendothelial and mesangial area on electron microscopy. The patient developed on day 13 symmetrical finger-tip numbness and tingling with weaknesses in her hands and legs. A diagnosis of cryoglobulinemia complicated with cryoglobulinemic glomerulonephritis and polyneuropathy was made. She responded well with methylprednisolone (1500mg in divided pulse, maintained on 40 mg daily afterwards), intermittent hemodialysis, 5 alternate-day plasma exchange and 600mg rituximab (375mg/m^2). 3 months later, however, generalized pruritic rash, weight loss, and significant groin lymphadenopathy emerged and progressed. An inguinal excisional lymph node biopsy performed at month 8 revealed AITL as the underlying disease.

Discussion: AITL and associated dysimmunity can give rise to multiorgan involvement, while the presence of autoantibodies, monoclonal gammopathy and cryoglobulinemia might conceal it as the underlying disorder. In various auto-immune diseases, it is advisable the clinicians take into consideration the multi-faceted lymphoma.

PO0106

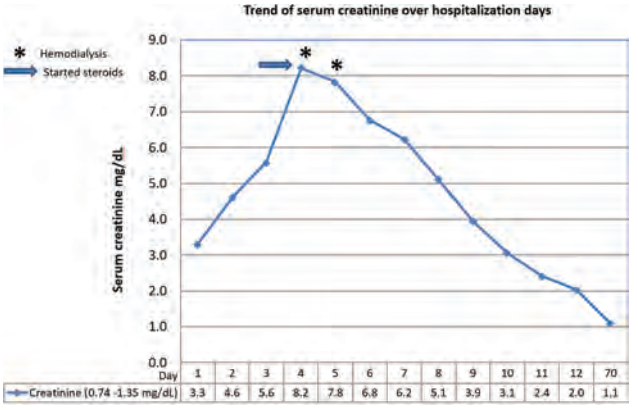
Weil Disease Causing Kidney Failure Responsive to Steroids

Lagu A. Androga. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Introduction: Weil's disease is a life-threatening form of leptospirosis with a potential mortality >22%. Multi-organ dysfunction, acute interstitial nephritis (AIN) and/or acute tubular necrosis (ATN) can occur. We present a patient with Weil's disease who developed acute kidney injury requiring hemodialysis. Treatment with steroids resulted in return to baseline renal function.

Case Description: A 61 year old Caucasian male presented with fevers, lower extremity myalgias, non-bloody emesis, and abdominal pain that began 11 days after swimming in Jamaica. On admission, he was febrile, tachycardic but normotensive with jaundice and leg edema. Admission labs revealed BUN 37, serum creatinine (SCr) 3.3mg/dL (baseline SCr 1), Hemoglobin 14.6g/dL, platelets 25,000, CRP 171.5mg/dL, ESR 41mm/h, serum albumin 3g/dL, AST 153, ALT 75, and direct bilirubin 7.8mg/dL. Urinalysis showed proteinuria 545mg/dL, sterile pyuria of 4-10 WBC, and positive hemoglobin. Creatinine kinase was 5143. Given his history and presentation, leptospira IgM testing was performed and found to be positive. He received supportive therapy and a 10 day course of IV ceftriaxone. His kidney function deteriorated with SCr peak of 8.22mg/L on day 4 (Figure 1). Given anuria and fluid overload, hemodialysis was started. A kidney biopsy was contemplated to assess for AIN, podocytopathy, pigment nephropathy, ATN or a combination, but contraindicated due to thrombocytopenia. Empiric treatment with steroids was started on day 4 (Figure 1) with 250mg IV Solumedrol for 3 days, followed by 40mg daily of oral prednisone tapered by 10mg every 2 weeks over 8 weeks. Urine output improved gradually on day 6 and day 7 to 1.5 and 5.7 L/day, respectively. SCr also started to decrease. At 2 months post hospital discharge, SCr was 1mg/dL on 4mg of prednisone.

Discussion: Renal failure in Weil's disease can be severe, requiring dialysis. Treatment with steroids for presumed AIN can be beneficial when initiated early.



PO0107

Renal Artery Thrombosis in a Patient Homozygous for Plasminogen Activator Inhibitor-1 4G Allele

Frank S. Santana Martinez, Siddharth Mehta, Shyam K. Poudel, Parth R. Shah. *American College of Physicians, Philadelphia, PA.*

Introduction: Renal artery thrombosis is a serious, uncommon, and often undiagnosed condition. Physicians need to consider this diagnosis in unexplained flank pain, especially in the presence of risk factors. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of tissue-type plasminogen activator. Fibrinolysis is impaired due to increased plasma PAI-1 levels which play an important role in the pathogenesis of thrombotic disorders. Homozygous for the 4G allele had increased plasma PAI-1 concentrations.

Case Description: A 53 years old male smoker with hypertension, presented to the emergency room complaining of abdominal pain and pink urine for 3 days. His BP was 186/120 mmHg and pulse 100/min. Physical exam was consistent with right flank tenderness. Urinalysis showed high gravity, high amount of protein, glucose, and blood. Creatinine was 1.6 and the baseline was unknown. CTA showed right renal artery occlusion. The patient was transferred to CCU and started on clevidipine and heparin drip. Arteriogram and directed thrombolysis were performed. Despite these interventions, his creatinine trend peaked at 2.85, whereas hemoglobin started dropping substantially. High rate IV fluids, a workup for malignancy, and hypercoagulable were started with subsequent stent placement for reperfusion. After 3 days of directed thrombolysis, he was transferred to wards. Urine output decreased and a Foley catheter was placed. the patient was started on clonidine, amlodipine, and labetalol. After 10 days of hospitalization, all workup was unremarkable. PAI-1 4G/5G study was homozygous for 4G allele. The patient's medical condition improved. He was discharged and advised to follow up as an outpatient.

Discussion: Studies have proven the link between PAI-1 4G and thrombotic events, however, most of the evidence shows a link between PAI-1 4G and venous thrombosis. In this patient, the fact of him being homozygous for PAI-1 4G allele led to arterial thrombosis. Therefore, it might be prudent to include a PAI-1 workup in prothrombotic studies. In renal artery thrombosis, a cause must be established. Although there are other common causes of arterial thrombosis, PAI-1 4G should be considered as a potential cause in patients with few or no risk factors. This case report glimpses the relationship between an uncommon genetic mutation and a rare diagnosis.

PO0108

Ganja Kidney: Acute Tubular Injury Associated with Synthetic Marijuana, A Rising Incidence

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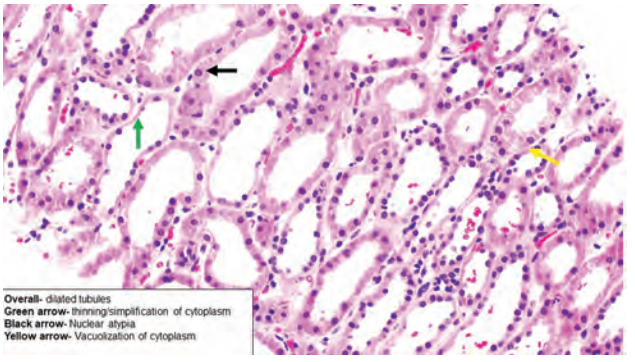
Introduction: Synthetic cannabinoids (SC), "Ganja", have been used as recreational drugs with increasing popularity among young adults but have significant toxicity. We present a case of acute kidney failure in a relatively healthy young male individual after using marijuana pills.

Case Description: 31-year-old hispanic male with no known past medical history presented to the emergency room with nausea and vomiting for 2 days. He stated that he has recently started taking "Ganja" pills to help with relaxation after losing work due to the Covid -19 pandemic. Vital signs were within normal limits and physical findings were unremarkable. Laboratory data were significant for serum creatinine of 10.14 mg/dl, blood urea nitrogen of 91 mg/dl, estimated glomerular filtration rate of 8 ml/min, and serum potassium of 7 meq/l. Urine toxicology was positive for cannabinoids. Complements and serologies were all negative. Renal ultrasound was unremarkable. A renal biopsy showed acute tubular injury with tubular dilatation, cytoplasmic simplification and vacuolization (image). Intermittent hemodialysis was initiated but later discontinued after renal recovery. On discharge, serum creatinine was 1.2 mg/dl.

Discussion: Cannabinoids are found in natural marijuana and contain many active compounds, but delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are of most interest. THC is the primary ingredient in marijuana that makes people "high". Synthetic cannabinoids are analogs of natural occurring cannabinoids that are chemically synthetized. This synthetic compound is added to the natural marijuana or other herbs to appear as a natural product. The clinical effects can be like natural marijuana which include tachycardia, conjunctival injection, slurred speech, and increase appetite due to the partial or full agonistic effect at the cannabinoid receptors. Compared to cannabis, synthetic cannabinoids have a greater risk for serious neuropsychiatric toxicity and severe acute kidney injury. We need more clinical research to identify the specific nephrotoxic agents.



PO0109

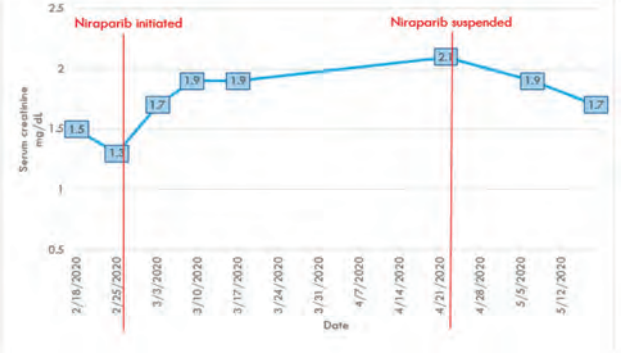
A Case of AKI Secondary to Niraparib, a Poly ADP Ribose Polymerase Inhibitor

Krishna S. Ravipati, Prathima Gopinath, Pramodh Chanumolu, Siddhartha Kattamanchi. *Marshfield Clinic, Marshfield, WI.*

Introduction: Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance therapy of recurrent ovarian and other gynecological cancers in patients who have complete or partial response to platinum-based chemotherapy. We present a unique case of Niraparib resulting in AKI.

Case Description: 73/F with past H/o HTN, hyperlipidemia, persistent ovarian cancer after Cisplatin treatment, currently on Niraparib therapy was evaluated for worsening creatinine. Her baseline creatinine was 0.9-1.0 mg/dL and eGFR was 54.4 - 61.4 mL/min. She initially developed AKI (creatinine 1.8 mg/dL) with cisplatin which subsequently improved to 1.3 mg/dL with eGFR of 40.2 mL/min, upon completion of cycle. Following the initiation of Niraparib, creatinine gradually trended up to 2.1 mg/dL and calculated eGFR was 23.1 mL/min. No obvious etiology for AKI was identified. Urinalysis revealed muddy brown casts w/ protein of 100 mg/dl without any evidence of UTI. Cystatin C was measured (1.72 mg/L) and Cystatin C based eGFR was 33 mL/min which indicates true AKI as opposed to elevated creatinine without renal injury. Niraparib was suspended following which creatinine started to improve (1.7 mg/dL) along with an improvement in eGFR (29.5 mL/min).

Discussion: Niraparib is a PARP inhibitor which functions by causing DNA damage resulting in apoptotic cell death. PARP inhibition in animal models has shown to be reno-protective from ischemia and it has been shown to elevate serum creatinine in drug trials without causing AKI. In our case though, patient developed AKI 2/2 ATN from niraparib. Mechanism for this is unclear as this is one of the earliest reported cases. One possible mechanism could be Apoptotic cell death of renal tubular cells.



Creatinine trend in our patient

PO0110

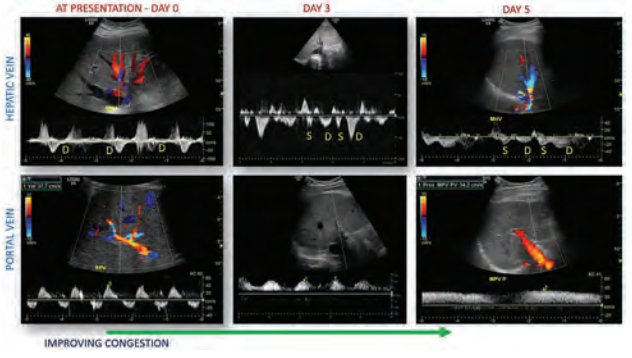
The Emerging Role of Bedside Doppler Ultrasound for Precise Assessment of Venous Congestion in Cardiorenal Syndrome

Abhilash Koratala,[1] Saqib Mahmud,[1] Olanrewaju A. Olaoye,[2] Amir Kazory.[2] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]University of Florida, Gainesville, FL.*

Introduction: Congestion is an integral component of cardiorenal syndrome and the primary reason for hospitalization in patients with heart failure (HF), making it a key target in the management of these patients. Routinely used parameters to monitor response to decongestive therapy such as physical examination, B-type natriuretic peptide, changes in weight and net fluid balance, even inferior vena cava ultrasound (IVC US) are all error prone. Doppler ultrasonography (DUS) of the portal, hepatic and when possible, intrarenal veins is an attractive alternative that can be used at bedside to accurately assess the degree of congestion and guide management strategies.

Case Description: A 55-year-old man with a history of HF with reduced ejection fraction of ~25%, hypertension and chronic kidney disease stage 3 presented with acute kidney injury of uncertain etiology. Serum creatinine (Scr) was 3.5 mg/dL for a baseline of 1.6 mg/dL. He had no symptoms except for his usual dyspnea on exertion. Physical examination was significant for crackles at lung bases and mild pitting pedal edema. Bedside US revealed increased extravascular lung water and a dilated but collapsible IVC. DUS revealed stigmata of severe congestion with a pulsatile portal vein and systolic flow reversal, and a hepatic vein with only diastolic (D) component below the baseline. Therefore, the diagnosis of congestive renal failure due to acute cardiorenal syndrome was made and high dose intravenous diuretics were initiated. The follow up DUS on days 3 and 5 showed remarkable improvement (reversal of waveforms to normal pattern) indicating progressive decongestion [Figure]. His diuretic therapy was titrated based on these findings and Scr improved to 2 mg/dL at discharge.

Discussion: Bedside DUS assessment of hepatic and portal veins aids in management of patients with HF by non-invasively monitoring the efficacy of decongestive therapy, and serves as a valuable adjunct to conventional clinical evaluation.



PO0111

Furosemide: An Unusual Cause of Acute Interstitial Nephritis Requiring Hemodialysis: First Case Report

Hassan Alhalabi. *Dallas Nephrology Associates, Irving, TX.*

Introduction: Furosemide, a loop diuretic, is widely used for volume control and is a known cause of acute interstitial nephritis. However, AIN due to furosemide is not typically associated with abrupt and severe acute kidney injury (AKI). Here we report a patient who developed severe AKI requiring hemodialysis shortly after receiving furosemide.

Case Description: A 65 year old male with a history of hypertension was started on oral furosemide 20 mg daily for edema in his legs. One week later he presented to the emergency room complaining of oliguria and worsening edema. Laboratory findings were significant for a serum creatinine of 37.8 mg/dL and potassium 7.8 mmol/L. Patient required emergent hemodialysis for volume control, clearance and hyperkalemia, and continued to require HD every other day. Serologic work-up included a normal C3, C4, ANA, ANCA, anti-GBM, and SPEP/UPEP. Urinalysis showed small blood, no protein, 12-15 RBC's, 10 WBC's. Renal ultrasound was normal. A kidney biopsy was performed which demonstrated interstitial edema with patchy inflammatory cell infiltrates with eosinophils. The tubules were dilated and showed significant degenerative changes in tubular epithelial cells. The patient was started on treatment for acute interstitial nephritis with oral prednisone 60 mg daily with a subsequent slow taper. Kidneys did not recover and he was placed on hemodialysis three times a week with close monitoring of kidney functions.

Discussion: Furosemide, a loop diuretic, is widely used for volume control. To our knowledge, this is the first report of AIN associated with loop diuretics that resulted in severe AKI requiring hemodialysis. Unfortunately, our patient did not respond to high dose steroids and he continued to require hemodialysis three times a week. Our report highlights the importance of close monitoring of any potential toxicities that may be associated with such medications.

PO0112

Hypothyroidism-Induced AKI: A Case Series

Spoorthi Ramineni, Varun kumar Bandi. *Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & RF, Gannavaram, India.*

Introduction: Thyroid hormones affect the development and various functions of the kidney. Such effects are partly mediated by direct renal action and partly by cardiovascular and systemic effects

Case Description: We present a series of 3 patients who presented with unexplained acute kidney injury (AKI). All patients were male, and one was hypertensive on amlodipine. Investigations showed blood urea levels ranging from 20 to 88 mg/dl, serum creatinine between 1.3 to 3.65 mg/dL with estimated glomerular filtration rate (eGFR) of 17.88 to 63.18 ml/min/1.73m2. Urine routine and ultrasound abdomen did not reveal any abnormalities. The patients had features suggestive of hypothyroidism and thyroid evaluation was done. Thyroid stimulating hormone (TSH) was elevated in all patients and T3 and T4 were decreased. The TSH levels ranged between 88.4 to 100 mIU/l. Creatine phosphokinase (CPK) level was modestly elevated in only one case, with absent urine myoglobin in all cases. A possibility of hypothyroidism induced AKI was considered and renal biopsy was deferred. After starting levothyroxine, complete renal recovery was seen in 2 patients and partial recovery in one within 8 weeks (Table 1).

Discussion: AKI has been reported in patients with severe hypothyroidism, and most cases were suspected to be due to rhabdomyolysis and had rapid normalization. Few cases of slower and incomplete recovery have been noted in cases with prolonged periods of severe hypothyroidism. In our series, normal urinalysis, absence of myoglobin, and normal or modest elevation of CPK makes rhabdomyolysis unlikely. The AKI could be due to hypothyroidism induced changes in renal hemodynamics. Our study relies on eGFR for renal function, and extent to which this reflects true changes in GFR is unclear. Hypothyroidism is a reversible cause of AKI and should be evaluated in cases with unexplained AKI. These patients can attain normal renal function with prompt initiation of levothyroxine therapy.

Characteristics of patients

Case No	Age (years)	Urea-0 weeks (mg/dl)	Urea-8 weeks (mg/dl)	Creatinine-0 weeks (mg/dl)	Creatinine-8 weeks (mg/dl)	eGFR (ml/min/1.73m2)-0 weeks	eGFR (ml/min/1.73m2)-8 weeks	TSH (mIU/l)-0 weeks	TSH (mIU/l)-8 weeks
1	53	88	40	3.65	1.5	17.88	49	100	0.92
2	51	20	17	1.3	1.0	69.62	86.76	94.83	1.28
3	37	45	30	1.7	1.0	50.40	95.72	88.4	16.10

PO0113

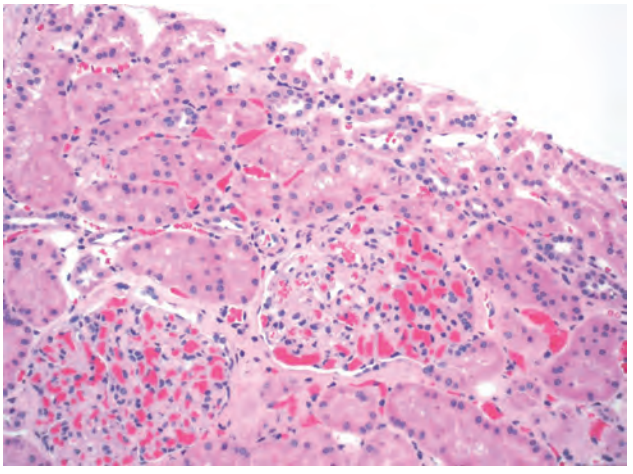
Glomerular Congestion Secondary to Renal Vein Stenosis After Kidney Transplant

Muna Alnimri. *University of California Davis Department of Internal Medicine, Sacramento, CA.*

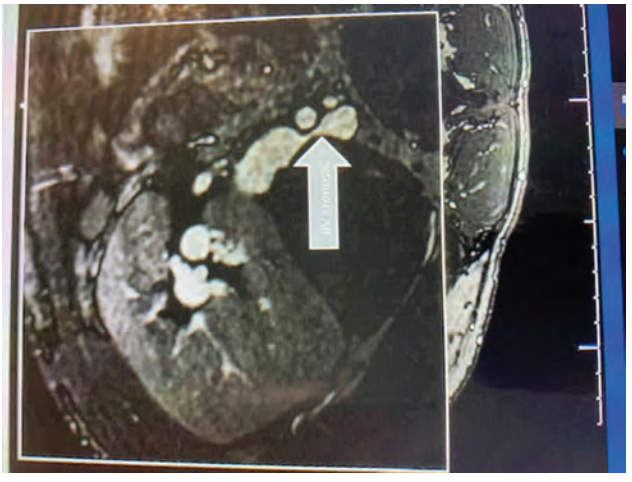
Introduction: Renal vein stenosis (RVS) post kidney transplant is uncommon complication, especially when it causes severe glomerular congestion, and AKI We present a case of RVS 3 months post kidney transplant with kidney biopsy showing severe glomerular congestion

Case Description: 33 y old male CKD secondary to HTN underwent LKT, smooth post op course discharged with a creatinine of 1.1mg/dl presented for 3 months protocol biopsy with creatinine of 1.5mg/dl, kidney biopsy showed severe glomerular congestion No rejection figure1, Doppler US showed suspicion for renal vein stenosis. Renal venogram demonstrated narrowing of the transplant renal vein at the anastomosis with the right common iliac vein figure 2 Successful 10 mm angioplasty balloon was inflated along the narrowed segment follow up creatinine back to 1.1mg/dl

Discussion: Transplant RVS is a rare vascular complication after renal transplantation that may cause graft dysfunction. Correction of RVS with either angioplasty or stent placement is safe and effective approach. Our patient presneted with AKI and severe glomerular congestion that warranted doppler US, the finding of RVS and glomerular congestion from back pressure warranted urgent venogram and angioplasty with excellent results. Conclusion : in evaluating AKI post kidney transplant ureteral obstruction, rejection, CNI toxicity and renal artery stenosis should be ruled out if all negative RVS should be evaluated



Glomerular congestion on kidney biopsy



Renal vein stenosis with post stenosis dilation

PO0114

Brain Got Spongy at Angry Kidneys

Ubaldo R. Madera Sanchez,[1,2] Christian Rodriguez Cintron.[3] *[1]Hospital Universitario Ramon Ruiz Arnau, Bayamon, PR; [2]Universidad Central Del Caribe, Bayamon, Puerto Rico; [3]Doctors Center Carolina, Carolina, PR.*

Introduction: Brain edema is a rare complication of acute kidney injury in patients who have not received renal replacement therapy. Immunologic and pro-inflammatory cascades mediate brain edema that is not dependent on the uremia, and instead, it is due to crosstalk between the kidneys and brain in the so-called reno-cerebral reflex. We are presenting an 88-year-old female with a history of hypertension and hypothyroidism with acute colitis that developed acute kidney injury and cerebral edema. We want to raise awareness of the need for early diagnosis and treatment to prevent severe clinical outcomes.

Case Description: 88-year-old woman with a past medical history of hypertension, hypothyroidism came to the ER complaining of green-colored non-bloody diarrhea with associated epigastric pain for 2 days. Examination remarkable for left lower quadrant tenderness, tachycardia, alerted, awake, oriented to person only, cooperative and following commands. Labs were remarkable for leukocytosis with neutrophilia, fecal leukocyte positive, and metabolic alkalosis. Abdominal CT showed acute colitis localized to descending colon and sigmoid. The patient was admitted with acute colitis. On day 2 of admission creatinine went up to 2.35 from 1.07. On urine, sediment was evident with renal tubular epithelial cells and oxalate crystal. Renal sonogram with no renal abnormality. On day 3 the creatinine continued increasing doubled to 4.4. The patient's mental status started declining, and metabolic acidosis was present. Renal replacement therapy was advised, but the patient's family member refused it and signed off DNR. The creatinine keeps trending up to 9.37. Brain CT without contrast was done and showed diffuse cerebral edema with no acute hemorrhage or ischemic changes. On day 11, the patient passed away.

Discussion: The brain edema seen in this patient was a byproduct of oxidative stress, activation of the immunologic pathway, and activation of the Reno-cerebral reflex occurring in acute kidney injury that is entirely independent of the mechanism seen in uremia. Not every functional or structural brain alteration in acute kidney injury is caused by uremic encephalopathy. Many pathways are activated in acute kidney injury that contributes to the effects of the kidneys in distant organs being the brain one of them. This case will serve to raise awareness to study the crosstalk between organs to prevent complications and improve outcomes.

PO0115

Renal Cortical Necrosis: An Atypical Case from Presentation to Recovery

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Introduction: Renal cortical necrosis (RCN) is a rare cause of acute kidney injury (AKI) accounting for 1-2% of cases. It is most often associated with obstetric emergencies in developing countries. The most common non-obstetric etiology is hemolytic uremic syndrome, but it has also been described in renal allograft rejection, sepsis, and in rare cases pancreatitis where ten cases have been reported. We describe a case of severe renal cortical necrosis in a previously healthy young man with acute pancreatitis.

Case Description: A 29-year-old man with no significant medical history presented with severe epigastric pain and anuria for three days. He was diagnosed with alcohol-induced pancreatitis with a lipase level of 35,534U/L and AKI with a creatinine of 5.8mg/dL (baseline 1.2mg/dL). The anuria did not improve with fluid resuscitation, the AKI progressed and he was initiated on hemodialysis. Evaluation of AKI with hepatitis B and C serologies, HIV, complement levels and ANA was unremarkable. Kidney ultrasound showed increased echogenicity without hydronephrosis. An abdominal CT scan with IV contrast done for worsening fever and leukocytosis showed diffuse areas of non-enhancement involving bilateral renal cortices consistent with acute renal cortical necrosis. To note, throughout his presentation and admission, the patient was not hypotensive. He remained dialysis dependent for three months with oliguria that eventually improved and dialysis was discontinued with a stable eGFR of 20ml/min/1.73m^2. He has remained off dialysis for the past five months and is undergoing transplant evaluation.

Discussion: RCN is thought to be an irreversible cause of AKI secondary to decreased perfusion, vasospasm and endothelial injury resulting in ischemia. It is frequently associated with hypotension but in our case the patient was normotensive. The mechanism leading to RCN associated with pancreatitis remains poorly understood. Acute pancreatitis, on the other hand, has been associated with other vasoocclusive ischemic complications (e.g. Purtscher's retinopathy). RCN is a devastating complication that often leads to dialysis dependence. Despite our patient showing signs of recovery, his prognosis remains poor. Further study is needed to understand its pathophysiology and potentially mitigate its consequences.

PO0116

Severe Vancomycin Nephrotoxicity

Jefferson L. Triozzi, Layth Al Attar, Maryam K. Saeed, Jingyin Yan, Bryan M. Tucker. *Baylor College of Medicine, Houston, TX.*

Introduction: We report a case of acute kidney injury with biopsy-proven changes related to a vancomycin level of 136.6 mg/L. From our review of the literature, this is the highest vancomycin level ever recorded.

Case Description: A 60-year-old female with type two diabetes mellitus, hypertension, Sjogren's disease not requiring immunosuppression, baseline normal kidney function, and left ankle osteomyelitis on home intravenous vancomycin presented with vertigo. Workup revealed oliguric acute kidney injury with sub-nephrotic range proteinuria (blood urea nitrogen 56 mg/dL, creatinine 6.70 mg/dL, urine protein to creatinine ratio 0.98) and an elevated random vancomycin level (136.6 mg/L). A comprehensive evaluation including physical examination, serologic testing, and renal imaging was unremarkable. Due to high vancomycin levels and minimal improvement in renal function despite resuscitation with intravenous crystalloids, hemodialysis was initiated via a tunneled dialysis catheter. A renal biopsy was then obtained, which demonstrated acute tubuloepithelial injury, morphologically consistent with acute tubular necrosis. There was also mild arterial sclerosis, minimal interstitial fibrosis and tubular atrophy, and no immune-mediated glomerulonephritis.

Discussion: Vancomycin is renally-eliminated by glomerular filtration and, to a lesser degree, excretion in the proximal tubule. Various mechanisms of renal injury are reported, including acute tubular necrosis and interstitial nephritis. Accrual of vancomycin-uromodulin complexes lead to inflammation. In this case, a comprehensive workup and kidney biopsy was important to rule out other causes of renal failure and support the diagnosis of vancomycin-induced nephrotoxicity. Renal recovery often occurs with discontinuation of vancomycin therapy. Severe cases, however, are frequently exacerbated by oliguria and require high-flux hemodialysis for effective drug removal by approximately thirty percent. Prolonged exposure to high levels of vancomycin increases the risk of permanent renal failure. This patient developed vancomycin nephrotoxicity despite drug monitoring, dosing based on creatinine clearance, and using the minimum inhibitory concentration required. Further research to establish precise mechanisms of vancomycin-induced nephrotoxicity is needed.

PO0117

DRESS Syndrome and Acute Interstitial Nephritis Relapse: A Case for Caution

Janina Paula T. Sy-Go, James R. Gregoire. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: The syndrome of drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but potentially life-threatening drug-induced type IV hypersensitivity reaction that usually occurs 2-6 weeks after drug initiation. Typical findings include skin eruption, fever, hematologic abnormalities, and visceral organ involvement. Prolonged corticosteroid treatment is often required as relapse after initial improvement is not uncommon.

Case Description: A 62-year old woman with a history significant for right total hip arthroplasty complicated by a prosthetic joint infection requiring hardware explantation and antibiotic spacer placement initially presented to the ED with fever, rash, and pruritus. She was treated with cefepime and vancomycin for positive intra-operative bacterial cultures. Urinalysis showed pyuria (51-100/hpf) and eosinophils (1-5%). Skin biopsy showed a drug reaction. She was diagnosed with DRESS syndrome and acute interstitial nephritis (AIN) secondary to the antibiotics, which were then changed to aztreonam and daptomycin. She was treated with systemic and topical steroids and was discharged on oral prednisone 40 mg daily with plan to taper by 10 mg every week over 1 month. Serum creatinine peaked at 3.36 mg/dL and improved to 0.62 mg/dL on discharge. Patient was seen again the ED 5 days after discharge with fever and worsening rash and pruritus. Physical examination was notable for mild facial swelling and scattered pink macules coalescing into patches on both upper and lower extremities and on the groin. Laboratory studies revealed leukocytosis with peripheral eosinophilia [7.35x10(9)/L] (on discharge: 0.87), elevated serum creatinine of 4.8 mg/dL, and elevated LFTs, ESR, and CRP. She was diagnosed with DRESS syndrome and AIN relapse secondary to rapid steroid taper. She was started on a higher dose of oral prednisone (80 mg daily) and had clinical improvement. She was then discharged with plan to taper by 10 mg every 2 weeks over 4 months.

Discussion: Long-term supra-physiologic doses of steroids are necessary to treat DRESS syndrome even after patients appear to have improved. Relapses do occur and frequently follow treatment discontinuation or rapid steroid taper, leading to increased morbidity and mortality. In such cases, a more prolonged steroid treatment is needed, which can cause well-known adverse events and complications. Close monitoring is thus required.

PO0118

Rivaroxaban-Induced Anticoagulant-Related Nephropathy

Bharat Neelam Raju, Birmaji Ali, Vahid Namdarizandi, Cesar E. Abdul-Massih, Amit K. Rajput. *TriHealth, Cincinnati, OH.*

Introduction: Anticoagulant-related nephropathy (ARN) is a rare and newly recognized cause of acute renal failure (ARF). A lack of serologic studies and hesitancy to perform high risk biopsies due to concerns for thrombosis or hemorrhage, make ARN a challenging diagnosis. The pathophysiology is believed to be from diffuse glomerular hemorrhage which manifests as numerous RBC casts. These RBC casts obstruct and damage tubular epithelial cells resulting in renal failure. We will examine a case of ARN.

Case Description: An 83-year-old Caucasian female presented with complaints of lower extremity weakness and was found to have ARF on laboratory investigation (Cr 5.18mg/dL from 1.1mg/dL one month prior). The patient was recently started on rivaroxaban after being diagnosed with a stroke caused by atrial fibrillation. The patient was admitted for evaluation and management of oliguric ARF, requiring the initiation of HD. Initial evaluation was significant for uncontrolled hypertension, 1+ pitting bilateral lower extremity edema, hypoalbuminemia (Alb 1.8 mg/dL), UA with 3+ blood but no casts on microscopy, and non-nephrotic range proteinuria (UPCR 2.9g), raising concern for rapidly progressive glomerulonephritis. Serologic work up was only remarkable for a mildly positive rheumatoid factor. A renal biopsy was performed after holding rivaroxaban for 5 days. Preliminary results showed IgA nephropathy with oxford classification score of M1E0S1T1C0, prompting initiation of steroid therapy. With no crescentic glomerular lesions to explain the degree of renal failure upon further investigation, the prominent RBC casts provided the diagnosis of ARN with underlying non-proliferative IgA nephropathy. Steroids were tapered and the patient is slowly recovering renal function.

Discussion: The use of novel oral anticoagulants (NOAC), has become prevalent in the medical community as a treatment strategy for various diseases. While previous cases have been mostly described in patients on warfarin, this case illustrates the importance of recognizing the new phenomenon of ARN as a risk factor for patients on NOACs. Due to limited data and no prospective studies, expert opinion has recommended switching one oral anticoagulant to another or reducing the dose of the offending agent. Further research is needed to understand this disease process to help design prevention and treatment strategies.

PO0119

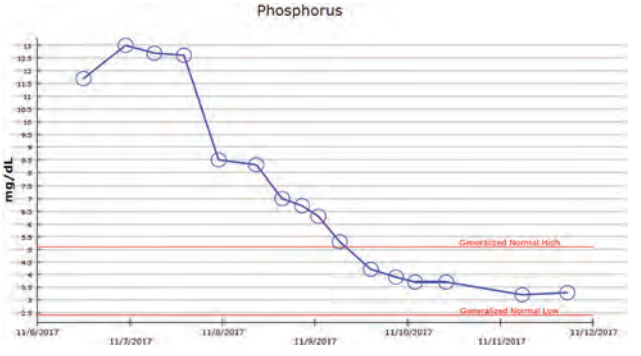
Continuous Venovenous Hemofiltration for Hypouricemic Tumor Lysis Syndrome and Extreme Hyperphosphatemia Complicated by AKI

Muhammad O. Saleem,[1] Ambreen Chughtai.[2] *[1]Augusta University Medical College of Georgia, Augusta, GA; [2]FMH College of Medicine and Dentistry, Lahore, Pakistan.*

Introduction: Tumor lysis syndrome (TLS) is an oncological emergency and can cause Acute Kidney Injury (AKI) mostly by acute urate nephropathy. We present a case of hypouricemic TLS and severe hyperphosphatemia leading to AKI, effectively managed by Continuous Veno-Venous Hemofiltration (CVVH).

Case Description: 44-year male with newly diagnosed Burkitt's lymphoma and currently receiving first cycle of da-EPOCH chemotherapy, was found to have clinical TLS per Cairo-Bishop definition. Laboratory studies were significant for hyperkalemia (K 6.4 mEq/L), hyperphosphatemia (Phosphate 13.0 mg/dL), hypocalcemia (Ca 6.9 mg/dL) and high LDH in addition to oliguric AKI with elevated serum creatinine (2.5 mg/dL, baseline 0.8 mg/dL). Surprisingly Uric acid level was low (1.8mg/dL) as patient had been on prophylactic Allopurinol. Patient did not have any signs of hypovolemia or post renal obstruction. Urine microscopy was bland. Urgent Hemodialysis (HD) session was provided for malignant hyperkalemia. AKI was assumed to be hyperphosphatemia-induced rather than urate nephropathy in TLS. Renal biopsy was considered but deferred due to high risk of bleeding. Hyperkalemia resolved with one session of HD, but hyperphosphatemia rebounded with worsening of creatinine. So CVVH was initiated and carried out for 72 hours. It lowered serum phosphate level to normal range with resolution of AKI.

Discussion: With the broad use of hypouricemic agents, calcium phosphate deposition, rather than hyperuricemia is becoming the leading cause of AKI in TLS. Choosing an appropriate dialysis modality is crucial to prevent further phosphate nephrotoxicity. Intermittent HD followed by CVVH may be an effective approach. CVVH should be considered as a preferred modality to achieve a sustained lowering of phosphate level and prevent rebound hyperphosphatemia. Our case is an excellent example when HD followed by CVVH helped in early renal recovery by effectively lowering serum phosphate levels.



PO0120

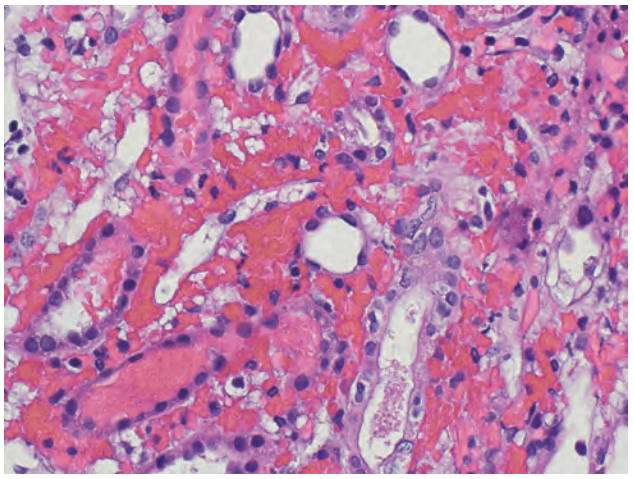
Gross Hematuria, Intense Interstitial Hemorrhages, Red Blood Cell Casts: An Atypical Triad of Amoxicillin-Clavulanate-Induced Acute Tubulointerstitial Nephritis

Ramzi A. Rahiman, Farooq Ahmad, Mohammed Akhtar, Muhammad Asim. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: Drug induced tubulointerstitial nephritis (TIN) usually presents with acute kidney injury, pyuria, white cell casts and micro-hematuria. We report this case to highlight a unique pattern of presentation.

Case Description: A 33-years-old man presented with gross hematuria and acute kidney injury three weeks after a throat infection treated with Amoxicillin-Clavulanate. He denied any previous episodes of hematuria, family history of renal disease or use of any other medication. Physical examination was normal other than mild cervical and axillary lymphadenopathy. Laboratory tests revealed serum Creatinine of 5.3mg/dl, hematuria, sterile pyuria and minimal proteinuria. Immunology screen and renal ultrasound were normal. Peripheral blood smear demonstrated eosinophilia and 7% blast cells. Flow cytometry and bone marrow studies confirmed Acute T-cell Lymphoblastic Leukemia. Kidney biopsy showed acute interstitial nephritis but normal glomeruli. The most striking features were multifocal intense interstitial hemorrhages, abundant red blood cells (RBC) in several tubules [Figure] and RBC casts in some. Direct immunofluorescence, SV40 staining and immunohistochemical studies for leukemic infiltration were negative. Treatment with systemic steroids was initiated. Serum creatinine started to decrease within 3 days. Steroids were continued as a part of induction chemotherapy instituted subsequently for leukemia. Renal function normalized and hematuria subsided within 2 months.

Discussion: Drug induced TIN can present with atypical features masquerading as glomerulonephritis, vasculitis or infectious interstitial nephritis. It is plausible that severe inflammation led to a major breach in the integrity of interstitial vascular walls resulting in interstitial hemorrhages that extended into the tubules through ruptured basement membrane producing gross hematuria and RBC casts.



PO0121

Use of Continuous Venovenous Hemodialysis and Plasmapheresis to Treat Simultaneous Iron and Acetaminophen Overdose

Tripti Singh, Rebecca Nye. *University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Introduction: Iron may fatally exacerbate toxicity in polypharmacy overdoses, including acetaminophen overdose. We present a case of intentional acetaminophen and iron overdose and treatment with continuous veno-venous hemofiltration (CVVH) and plasmapheresis.

Case Description: 31-year-old male with history of schizophrenia and previous suicide attempts presented to an outside hospital with abdominal pain and emesis 1.5 hours after ingestion of 100 tablets each of 325 mg acetaminophen and 325 mg ferrous sulfate. Vitals on admission were BP 121/83 mmHg, pulse 93 bpm, RR 18/min, O2 saturation 98% on RA. Labs showed bicarbonate 23 mEq/L, anion gap (AG) of 14, BUN 16 mg/dL, creatinine 1 mg/dL, total bilirubin 0.7 mg/dL, AST 24 units/L, ALT 16 units/L, iron 356 ug/dL, and acetaminophen 269.8 ug/mL. Patient was started on IV acetylcysteine. Repeat labs 12 hours later revealed iron level 4326 ug/dL, total bilirubin 4.8 mg/dL, AST 476 units/L, and ALT 855 units/L. IV deferoxamine was initiated. Patient became lethargic and hypotensive and required intubation. He was transferred to our hospital for further management. Labs upon arrival showed AG of 16, bicarbonate of 12 mEq/L, creatinine 1.98 mg/dL, ALT 13129 units/L, AST 7351 units/L, total bilirubin 3.6 mg/dL, ammonia 882 umol/L, acetaminophen 179 ug/mL, iron >900 ug/dL. On physical exam, patient was unresponsive, euvolemic, and NG tube drain was bloody. CVVH was started via left femoral dialysis catheter with blood flow rate of 250 ml/min and replacement fluid rate of 3500 ml/hour. 6 hours after CVVH, labs revealed an iron level of 362 ug/dL and an acetaminophen level of 100 ug/mL. Due to continued deterioration including hemodynamic instability and persistent acidosis, plasmapheresis was initiated. Labs 2 hours later showed iron level of 20 ug/dL and acetaminophen level of 91 ug/mL. The patient's clinical status continued to decline despite removal of iron and acetaminophen and he died after 24 hours due to fulminant liver failure.

Discussion: In this case of simultaneous massive iron and acetaminophen overdose, CVVH was effective in removal of iron (60%) and acetaminophen (44%) over 6 hours. Plasmapheresis may be considered as an additional modality to remove excess free iron from the blood.

PO0122

Severe AKI Associated to Acquired Autoimmune Hemolytic Anemia and Hemophagocytic Syndrome: A Case Report

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Introduction: Autoimmune hemolytic anemia (AIHA) is a rare entity with an annual incidence of 1-3/100.000. Secondary AIHA is associated to lymphoproliferative disorders (LD), autoimmune diseases, drugs, and less frequently to infections, being an unusual cause of AKI. Hemophagocytic lymphohistiocytosis (HLH) is an uncommon syndrome of excessive immune activation that can be triggered by infection that disrupts immune homeostasis. Herein, we present a very rare case of a patient with AKI requiring RRT associated to severe AIHA and HLH.

Case Description: A 46-year-old caucasian man was admitted with fever, anuria and severe anemia. Three days prior to admission he had vomiting, diarrhoea and oliguria. Physical examination revealed normal BP, fever and pale skin. Blood tests showed SCr 8.8mg/dL (baseline 0.9mg/dL), metabolic acidosis and urine dipstick Hb3+.He had AIHA with Hb 6.7g/dL, LDH 1194U/L; haptoglobin<30mg/dL; total bilirubin 1.35mg/dL; and positive Coombs test. Blood smear revealed atypical lymphocytes and rare blasts; platelet count was normal. HLH was diagnosed based on clinical (fever, splenomegaly) and laboratorial criteria, with high ferritin (46833ng/mL); triglycerides 308mg/dL, high levels of IL2 receptor (13547pg/mL). Sedimentation rate was 85mm/h and CRP 19mg/dL.LD were ruled out through bone marrow biopsy, lymphocyte immunophenotyping test and full-body CT scan. Viral serology revealed EBV infection. Early treatment was initiated with corticosteroids associated to IV immunoglobulin (IVIG). Kidney recovery started after 10d and haematological recovery started after 3d of IVIG with remission after 15d. The patient remains in complete kidney and hematological remission at 6mo FU.

Discussion: Secondary HLH occurs in response to an inciting stimulus and has been associated to malignancy and infection, particularly with EBV. AIHA is a condition characterized by autoantibodies directed against erythrocytes and can be secondary to EBV infection. Intravascular hemolysis can lead to AKI due to erythrocyte destruction and release of free Hb causing tubular injury by heme proteins' toxicity. This case illustrates the severe presentation of a rare complex entity of AIHA associated to HLH, both caused by EBV infection, and complicated with severe AKI. Early diagnosis was challenging and determined the good outcome.

PO0123

IgG4-Related Disease with Renal Involvement in a Patient with HIV Infection

Karen Flores, Samir V. Parikh, Ganesh B. Shidham. *The Ohio State University, Columbus, OH.*

Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disease that can affect multiple organs. It is characterized by lymphadenopathy and diffuse enlargement of one or multiple organs. Pathologic features include tissue infiltration by IgG4-positive plasma cells, storiform fibrosis, and increased tissue eosinophils. Tubulointerstitial nephritis is the most common renal manifestation. We describe a case of IgG4-RD in a patient with co-existing HIV infection.

Case Description: A 65-year old male with CKD 3, hypertension, hepatitis B, and HIV was hospitalized due to malaise and acute kidney injury with serum creatinine of 4.2 mg/dL and 1.5 g/d proteinuria. HIV was controlled with undetectable viral load on treatment. Infectious work up was negative. CT scan revealed diffuse retroperitoneal lymphadenopathy. PET scan showed diffuse lymphadenopathy and increased uptake in bilateral kidneys and parotid glands. Right inguinal lymph node biopsy showed atypical interfollicular T-cell infiltrate and dense polytypic plasmacytic infiltrate with a kappa/lambda ratio of 3:1 by ISH. TCR gene rearrangement and IGH studies were negative for a monoclonal population. Testing for HHV8 and EBV was negative. SPEP showed a small IgG lambda clone (0.3 g/dL). UPEP showed a small amount of lambda free light chains. Bone marrow biopsy showed no evidence of T cell lymphoma but revealed hypocellular marrow. Total IgG (5048 mg/dL) and IgG4 (572 mg/dL) were elevated and both C3 and C4 were low. Kidney biopsy revealed dense interstitial infiltration of plasma cells strongly positive for IgG4 (>50/hpf) and no electron dense deposits. The patient was diagnosed with IgG4-RD with renal involvement. He was treated with high dose prednisone and mycophenolate mofetil. Renal function improved from 4.6 mg/dL to a 1.9mg/dL after 3 months of treatment. IgG4 levels improved 70mg/dL and C3/C4 normalized suggesting disease control had been achieved.

Discussion: We describe a case of IgG4-RD with renal involvement in a patient with HIV infection. There are only a few reports in the literature. Differential diagnosis of kidney disease during HIV infection is broad. IgG4-RD is a severe systemic disorder that can be mistaken for infection or malignancy. IgG4-RD should be considered in the differential for acute kidney injury in the setting of HIV.

PO0124

Renal Replacement Therapy in Pheochromocytoma

Jennifer Griffiths, Hay Me Me, Aromma Kapoor. *Westchester Medical Center, Valhalla, NY.*

Introduction: Pheochromocytoma is a rare tumor derived from chromaffin cells of the sympathetic nervous system. The triad of headache, palpitations and diaphoresis is often present, but catecholamine excess can present in various contexts. Tumors secreting epinephrine can present with episodic hypotension; rapid cycling fluctuations of hypotension and hypertension also occur. Most acute kidney injury (AKI) in the setting of pheochromocytoma crisis is due to ischemic acute tubular necrosis (ATN). For cases requiring renal replacement therapy, there are no studies supporting one form over another. We describe a patient with Pheochromocytoma who developed AKI requiring renal replacement therapy (RRT).

Case Description: 29 year old woman with history of migraines presented to outside hospital with headache and chest pain, and found to be in hypertensive emergency with mild elevation of troponins. Patient was transferred to our hospital for evaluation of possible myocardial infarction. Cardiac catheterization showed clear coronaries. Patient became hypotensive during the procedure and Intra-Aortic Balloon Pump was placed. Imaging showed high density mass in the left adrenal gland. Patient was started on Phenoxybenzamine. Biochemical tests confirmed Pheochromocytoma. Labs showed creatinine of 5.38. Patient became anuric and RRT was initiated with intermittent hemodialysis(iHD). On the third dialysis session, patient had wide blood pressure fluctuations and became hypotensive with decreased responsiveness. Imaging was negative for acute bleed but concerning for cerebral edema. RRT was switched to continuous renal replacement therapy(CRRT) which was better tolerated.

Discussion: Our patient experienced an acute hypertensive crisis followed by cardiovascular collapse likely precipitated by intravenous glucocorticoids given for presumed myocarditis. Glucocorticoids increase catecholamines ; the excess causes cardiotoxicity which in turn leads to ischemic ATN. Patient was able to tolerate iHD initially. However, as the Phenoxybenzamine was up titrated, the fluctuations included hypotensive episodes and was worsened on dialysis. Given the unpredictable fluctuations in blood pressure and the possibility of associated hypertensive encephalopathy and/or

cerebral edema in the setting of Pheochromocytoma, it may be prudent to choose CRRT when RRT is warranted, though there are no guidelines regarding which modality is superior in these patients.

PO0125

Blast from the Past: A Rare Case of AKI from Sulfadiazine-Induced Nephrolithiasis

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Introduction: Sulfadiazine has been used for the treatment of neurotoxoplasmosis in patients with HIV infection. Nephrolithiasis is a known complication of high dose sulfadiazine therapy. However, this complication is rarely seen in HIV patients due to improved antiretroviral therapy. We present a rare case of sulfadiazine-induced nephrolithiasis in a patient with AIDS.

Case Description: 55-year-old female with DM and HTN was hospitalized for worsening mental status and CT scan finding of frontal lobe mass. During hospital stay, pt. also found to have HIV infection and a very low CD4 count. Antiretroviral therapy and high-dose intravenous sulfadiazine 1,500 mg every 6 hours was initiated for presumed neurotoxoplasmosis. On admission, serum creatinine (Scr) was 0.68. Seventeen days after initiation of sulfadiazine therapy, Scr increased to 2.42. Urinalysis revealed microscopic hematuria. Kidney sonogram showed left hydronephrosis and echogenic foci in both kidneys concerning for kidney stones. Sulfadiazine was discontinued and patient was started on sodium bicarbonate infusion to alkalinize her urine but Scr continued to worsen, peaking at 4.73 within few days. Serial kidney sonograms revealed alternating fullness of the collecting systems of both kidneys. Urology team was consulted and patient underwent cystoscopy with bilateral ureteral stent placement. Scr subsequently returned to normal limits within one week of ureteral stent placement.

Discussion: Our patient developed severe but reversible post-obstructive AKI secondary to high-dose sulfadiazine-induced nephrolithiasis. In the modern era of antiretroviral therapy**,** sulfadiazine-induced nephrolithiasis is a very rare occurrence in clinical practice. Hence, clinicians and nephrology care providers should be aware of this rare cause of AKI in patients with HIV infection.

PO0126

Rhabdomyolysis as Initial Presentation of COVID-19

Hugo Andrade paz, Mala Sachdeva, Nupur N. Uppal. *Northwell Health, Great Neck, NY.*

Introduction: Rhabdomyolysis has infectious etiology including Mycoplasma pneumoniae infection, *Legionella*, and Influenza. To date, there has been one case report from Wuhan China of a patient who developed rhabdomyolysis from COVID-19 during their hospitalization. We report a case where acute kidney injury and rhabdomyolysis was the initial presentation.

Case Description: A 57 year old African American male with history of HTN for more than 10 years, presented with complaints of decreased urine output for 3 days associated with dark urine that progressed to anuria, fever for 11 days, decreased appetite and oral intake and generalized muscle weakness. Labs on admission were notable for acute kidney injury (creatinine 1.77mg/dL) which progressed rapidly to a peak creatinine of 11.10mg/dL within 72 hours, and other electrolyte abnormalities including mild hyperkalemia and acidosis. His CPK was >92,000U/L on admission and COVID-19 PCR was positive. Other labs included: peak AST 1692 U/L and ALT 291U/L, ferritin 1436 ng/mL, 4.86mg/dL, DDimer 2330 DDU, urinalysis specific gravity 1.030 with large blood, 10RBCs, 20WBCs, urine spot protein/creatinine 2.1 and random urine sodium 65. Serologic workup was negative for glomerular etiology. He was presumed to have acute tubular necrosis from rhabdomyolysis. He was started on hemodialysis on day 3 of admission for anuria and worsening of renal function. He was maintained on hemodialysis with minimal ultrafiltration three times a week, intravenous fluid resuscitation along with intermittent doses of bumex. He received total of five hemodialysis treatments until he became non-oliguric and started showing signs of recovery. He was taken off dialysis approximately three weeks after his initial presentation. His creatinine decreased and is 1.4 mg/dL one month after being taken off of hemodialysis.

Discussion: COVID-19 has its usual presentation of fevers, shortness of breath, dry cough and myalgias. This case highlights the importance that rhabdomyolysis can be one of the only presenting features of COVID-19. Checking CPK levels should be an integral part of not only an acute kidney injury workup in the COVID-19 patient but also for any COVID-19 newly diagnosed case as this diagnosis requires prompt and specific treatment.

PO0127

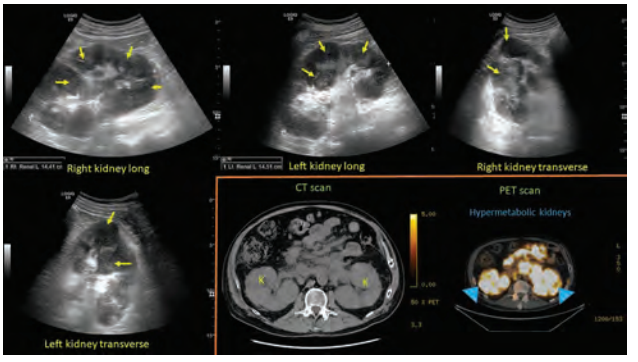
Lymphomatous Infiltration of the Kidney: A Sonographic Diagnosis

Bhavna Bhasin, Abhilash Koratala. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: The purpose of this case study is to illustrate the sonographic findings seen in kidney infiltration by lymphoma.

Case Description: A 56-year-old man with a history of hypertension, diabetes mellitus type 2 and follicular lymphoma with transformation to diffuse large B-cell lymphoma presented with worsening fatigue, headache and diplopia. MRI of the brain demonstrated central nervous system involvement by the lymphoma. He was also found to have worsening renal function with a serum creatinine of 4.5 mg/dL (baseline: 1.6-2 mg/dL). A renal sonogram (RUS) was performed, which demonstrated bilateral enlarged kidneys (~14.5 cm each) with irregular outlines and multiple parenchymal hypoechoic to heterogeneous lesions. No internal vascularity was noted on color Doppler. These findings are consistent with lymphomatous infiltration of the kidneys, confirmed later by PET (positron emission tomography) scan [Figure]. The renal function continued to worsen despite supportive care, and he required initiation of hemodialysis. Acute kidney injury was initially attributed to poor oral intake and mild hypercalcemia, but lymphomatous infiltration likely contributed to his renal impairment as well. Renal biopsy was not undertaken due to progression of the lymphoma and limited life expectancy.

Discussion: Kidney is the most common extra-reticular site of leukemic and lymphomatous infiltration, and tumor-cell infiltrates in the kidney are seen in up to 30% of patients with lymphoma. Rarely, renal involvement may be the first manifestation of lymphoma. The kidneys may appear normal on RUS because of the small size of the nodular infiltrates or with the typical findings described above. Unilateral and perirenal infiltration with lymphoma has also been described. Hydronephrosis may be noted on RUS if there is compression of the renal hilum or ureters by the lymphomatous tissue. Nephrologists performing point of care ultrasonography should be aware of these findings. These patients will require a prompt referral to the Hematology & Oncology team when renal ultrasonography leads to a new diagnosis of lymphoma.



PO0128

Minimal Change Nephrotic Syndrome Superimposed on Anti-Glomerular Basement Membrane Antibody Glomerulonephritis: A Case Report

Yuko Shibata, Kazuhito Fukuoka, Shinya Kaname. Kyorin university school of medicine *Kyorin Daigaku, Mitaka, Japan.*

Introduction: Background : The renal prognosis of anti-GBM glomerulonephritis (anti-GBM GN) is extremely poor as renal dysfunction often progresses acutely before the initiation of treatment. It is also known that once the disease activities are controlled by aggressive treatment, its recurrence is rare. Here we experienced a case of anti-GBM GN that improved from severe renal dysfunction but later relapsed. A possible cause was thought to be a rare complication of minimal change nephrotic syndrome (MCNS).

Case Description: A 30-year-old man was admitted to our hospital because of general malaise, fever, oliguria and renal dysfunction. The patient's laboratory data showed serum creatinine as high as 6.6 mg/dl and severe inflammation (C-reactive protein 20.6mg/dl). Anti-glomerular basement membrane antibody (anti-GBM Ab) was detected in his serum, leading to a diagnosis of anti-GBM GN. Treatment was initiated with high-dose glucocorticoid (GC) and plasma exchange therapy (PE), and the patient's renal function and oliguria improved rapidly and he was discharged 40 days after admission. Renal biopsy findings showed cellular crescents associated with linear IgG depositions along the glomerular tufts compatible with anti-GBM GN, but only about one-third of the glomeruli was involved, suggesting that it still remained an early stage of the disease. However, two months after discharge, he had a relapse and was readmitted due to severe proteinuria associated with positive anti-GBM Ab. On the second admission, he was treated with high-dose GC and PE combined by intravenous cyclophosphamide, and completed remission was achieved a few weeks later. Electron microscopy of the renal biopsy that returned later showed significant foot process effacement on podocytes in the apparently normal glomeruli without electron dense deposits.

Discussion: Considering clinical course and renal pathology findings, it is suggested that the present case was a rare complication of an early stage of anti-GBM GN and MCNS. Although the cause of concurrent development of anti-GBM GN and MCNS associated with anti-GBM antibody titers is unclear, it might have been precipitated by influenza infection or some unknown factor.

PO0129

Thrombotic Microangiopathy with Acute Interstitial Nephritis Secondary to Trimethoprim-Sulfamethoxazole

Armando T. Cardenas, Tiffany Prachachalerm, Grace Mcnutt, Julio P. Zavala Georffino. *University of the Incarnate Word, San Antonio, TX.*

Introduction: Thrombotic Microangiopathy (TMA) and Acute Interstitial Nephritis (AIN) are well recognized entities that individually cause significant morbidity and mortality. The relationships with several medications have been described, but the two conditions coexisting are rare.

Case Description: 28-year-old man with no significant past medical history presented with bilateral lower extremity edema, excoriations, discharge, and weakness for one week. He initially presented to an outpatient clinic and was discharged on trimethoprim-sulfamethoxazole (TMP/SMX). His symptoms progressed leading to admission. Physical

examination revealed an obese man with bilateral lower extremity edema, eczematous rashes, and excoriations on both feet. Initial laboratory results were significant for a creatinine of 5.2 mg/dL and oliguria. Urinalysis revealed proteinuria, hematuria, and pyuria. He then developed thrombocytopenia and anemia. Haptoglobin and lactate dehydrogenase were elevated, and schistocytes were identified on peripheral smear consistent with microangiopathic hemolytic anemia. He also had eosinophilia. Work-up for autoimmune, infectious, and connective tissue diseases was ordered and results were unrevealing. ADAMTS13 activity was decreased at 42%. The patient started hemodialysis and a kidney biopsy was performed with findings of acute tubular necrosis, thrombotic microangiopathy, and acute interstitial nephritis. TMP/SMX was discontinued and he was started on steroids. His renal function improved, and he was discharged home without need for further dialysis.

Discussion: TMA is characterized by endothelial damage causing microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage. TMA can be attributed to genetic, external, autoimmune causes, or may emerge secondary to medical diseases. AIN is a common cause of kidney injury and is associated with multiple drugs. This case demonstrates the unique coexistence of TMA and AIN in a patient receiving TMP/SMX, which has been related to decreased creatinine clearance, bone marrow suppression, hyperkalemia, and hypersensitivity reactions. This case supports the cessation of the offending drug and the use of steroid treatment as an option for TMA and AIN. In conclusion, TMA and AIN may occur simultaneously as an adverse drug reaction.

PO0130

Rhabdomyolysis in SARS-CoV-2 Infection

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Introduction: Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection. Multiple mechanisms have been proposed including acute tubular necrosis (ATN) due to shock, cytokine release syndrome, hypoxia or vascular injury and thrombosis. Direct viral injury to tubular epithelial cells and podocytes has also been described. Rhabdomyolysis has been reported in infection with SARS-CoV, Respiratory Syncytial Virus and Influenza A. Although mild CK elevation was reported in cohorts of patients with COVID-19 and there is a single case report of late onset rhabdomyolysis, overt rhabdomyolysis on presentation has not been described. To our knowledge this is the first patient who presented with signs and symptoms of severe rhabdomyolysis and AKI that was likely secondary to SARS-CoV-2 infection.

Case Description: A 51 year-old male with hypertension and diabetes, presented with 2 days of diffuse myalgia and mild dry cough without shortness of breath. He denied trauma, new medications, changes in diet, strenuous exercise or illicit drug use. Physical exam notable for fever and mild tachypnea, but no hypoxia. Lungs were clear and all muscles groups were soft and non-tender. Polymerase chain reaction was positive for SARS-CoV-2. Serum creatinine was 2.4 mg/dL (baseline 1.3 mg/dL), Urinalysis showed 3+ blood, 2+protein and 1-2 RBC per high power field. Initial serum creatinine kinase was 340,000 U/L and peaked at 464,000 U/L on day 4. Serum and urine myoglobin levels were elevated at 15,175 mg/L and >5000 mcg/L respectively on day 5. He received isotonic intravascular (IV) fluids but developed oliguria on day 2, requiring diuresis to maintain urine output. BUN and creatinine increased to 130 and 19 mg/dL respectively by day 8 and hemodialysis was initiated. Renal clearance and urine output then slowly improved, and dialysis was discontinued by day 15.

Discussion: Myalgia and fatigue are common symptoms of COVID-19 infection. In addition, dipstick hematuria is reported in up to 10% of patients. Thus diagnosis of rhabdomyolysis and myoglobinuria requires a high index of suspicion. Early consideration and timely diagnosis of rhabdomyolysis and the treatment of myoglobinuria with intravenous fluids is critically important to prevent ATN. However, administration of IV fluids may be challenging in COVID-19 patients at risk of hypoxia and acute respiratory distress syndrome.

PO0131

Using a Peritoneal Dialysis Catheter as a Tool for AKI Prevention in a Patient with Refractory Cardiac Ascites: A Case Report

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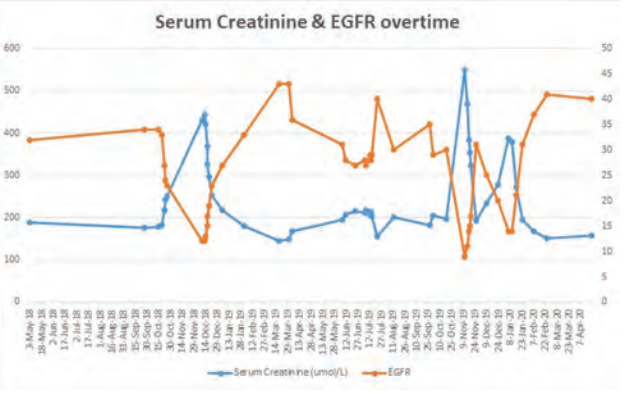
Introduction: Recurrent large volume paracentesis (LVP) is currently the followed management option for refractory cardiac ascites. We are presenting a case where placement of tunneled peritoneal catheter (PD) for such a patient resulted in prevention of repeated AKI, reduced hospitalization, dramatic improvement in quality of life and stabilization of renal function.

Case Description: 59 year old male patient of CKD ¾ secondary to Cardio-Renal syndrome was admitted in Apr 2019 with worsening heart failure, massive ascites and AKI on CKD (Serum Creatinine (cr) worsening from 150 to 210 umol/L). His last echo showed severely impaired biventricular dysfunction with LVEF of 24%. Ascites was sterile and transudative. Kidneys were of normal size and urine PCR was only 20. Owing to poor diuretic response, he underwent LVP (30 Litres) with resolution of AKI. He presented similarly in Nov 2019 (Cr worsened from 197 to 550umol/l) and underwent LVP. 6 weeks later, he presented again with AKI (Cr rose from 190 to 380 umol/l). PD catheter was medically inserted in Jan 2020. 8 litre of ascites was drained and patient was trained to aseptically drain the ascites regularly. He drained the fluid himself 2 to 3 L twice a week. His Cr improved and stabilized around 157 umol/l. His serum albumin (29to 40 g/l), Hb (77 to 135 g/l), quality of life, blood pressure and diuretic response has improved significantly with body weight maintained at 83 kg. He has not been admitted once in past 5 months.

Discussion: Our patient was having repetitive AKI (known cause of CKD progression) due to worsening congestion and possibly raised intra-abdominal pressure (IAP). Increased systemic venous pressure can cause a decline in GFR by increasing renal interstitial pressure. Venous congestion also causes an inflammatory response within the renal parenchyma. Clinical parameters improved once the gentle PD catheter drainage was instituted at home. No further AKI episode was observed and eGFR was stabilized.



PO0132

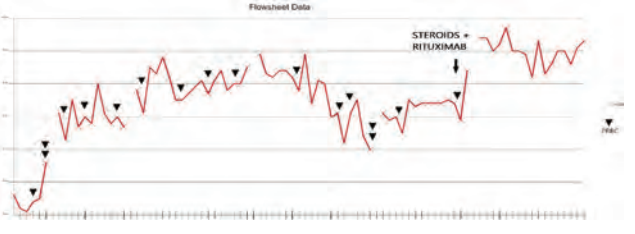
A Rare Case of a 27-Year-Old Man with IgG4-Related Disease

Sai Shalini Pillarisetty, Sumedha Sonde, Winston Lee. *New York City Health and Hospitals Coney Island, Brooklyn, NY.*

Introduction: IgG4-related disease(IgG4-RD) is a rare multisystem autoimmune disease that was first reported in 2010. We present an unusual case of IgG4-RD in a young man demonstrating the heterogeneity of IgG4-RD with multisystem involvement and irreversible organ damage.

Case Description: A 27 year old obese male who presented with 3 month history of vomiting, diarrhea, epigastric pain, left lower extremity edema and severe fatigue. On admission patient appeared toxic, tachycardic and hypertensive with left leg elephantiasis nostras verrucosa. Lab work was significant for: Hgb 4 mg/dl, BUN/Cr 247/33.04, lipase 1100 U/L (13-60),TPO antibodies 43.6 IU/mL (<=34.9), TSH 8.71uIU/mL (0.35-5.50). CT scan confirmed acute pancreatitis with diffuse lymphadenopathy. Hemodialysis was initiated and the patient received multiple blood transfusions (17 units of PRBC) while on Aranesp with no significant improvement in hemoglobin. Blood antibody screening showed IgG4 warm antibodies and elevated serum IgG4 229 mg/dl (2.4- 24), IgG 2305 mg/dl (610-1660) and IgE 4303KU/L (<100). Renal biopsy showed chronic tubulointerstitial nephritis with global and focal segmental glomerulosclerosis and arterial sclerosis. Immunofluorescence stained for IgG, IgA, IgM, C3, C1q, kappa and lamda. Electron microscopy showed plasma cells staining IgG4 and 80% interstitial fibrosis.

Discussion: IgG4-RD is a fibroinflammatory condition characterized by lymphoplasmacytic infiltrates rich in IgG4 and plasma cells with storiform fibrosis and elevated serum IgG4. Our patient presented with interstitial nephritis, pancreatitis, lymphadenopathy, thyroiditis, lower extremity lymphedema and anemia with elevated serum IgG4 levels and histopathology findings of IgG4-RD. The diagnosis was made based on the Japanese comprehensive diagnostic criteria for IgG4-RD. He responded to rituximab and steroids with decreased transfusion requirements. Severe anemia has not been reported with IgG4-RD. In our case the transfusion requirement decreased after initiation of therapy which suggests the anemia may have been secondary to anti-EPO IgG4 or poor response to EPO in the setting of an underlying inflammatory process.



PO0133

Zosyn Induced Neutrophil-Rich Allergic Interstitial Nephritis: A Rare Case

Aulio E. Bustos, Sanjeev Gupta, Savneek S. Chugh, Viviam I. Becerra rivera, Amol Mittal, Xiaotong Wang. *Westchester Medical Center Health Network, Valhalla, NY.*

Introduction: Acute interstitial nephritis (AIN) is a clinico-pathological syndrome associated with infections or drugs. AIN is responsible for 1-3% acute kidney injury (AKI) cases. Drug induced-AIN (DI-AIN) rarely presents with the classic triad of rash,

fever and eosinophilia, and is usually a diagnosis of exclusion. On renal biopsy (Bx), DI-AIN usually presents with interstitial inflammation rich with eosinophils and plasma cells and, in rare occasions, with neutrophils. Here, we report a Zosyn induce neutrophil-rich AIN case

Case Description: A 40-year-old female with medical history breast cancer came with fever, pain and induration over her left breast. On admission she got Zosyn for suspect breast abscess. Next day, AKI noted, creatinine (Cr) increased from 0.6 to 3.3mg/dL. She remained hemodynamically stable. Laboratories showed no anemia, leukocytosis or peripheral eosinophilia. BUN/Cr of 38/4.7. Urinalysis negative for protein, blood, crystals, casts, white blood cells, red blood cells, nitrites, urine sodium and chloride <20mmol/L, positive urine eosinophils. Negative autoimmune and hepatitis B/C work up. Blood and urine cultures were negative. Renal bladder ultrasound (US) showed normal kidney size with no sign of infection. Breast US findings were concerning for neoplasm. Zosyn was held and prednisone (1mg/kg) was given for suspicious of DI-AIN. Renal Bx was done showing interstitial inflammation rich with neutrophils and neutrophilic cast without glomerular injury. Immunofluorescence with negative IgG, IgA, IgM, C3, C1q, fibrinogen, albumin, kappa and lambda light chains. Electron microscopy was unremarkable. Cr at 3rd day peaked at 4.7mg/dL, then trended down. Upon discharge BUN/Cr39/2.36. One week after at renal clinic visit her kidney function came back to her baseline. We continued steroids for 3 weeks due to suspicion of AIN as repeated renal imaging and urine culture remained negative

Discussion: This is a rare case where Zosyn was promptly stopped and prednisone was initiated early in the course of AIN despite neutrophilic infiltration on renal Bx. DI-AIN can present with predominant neutrophilic infiltration; however, this makes the diagnosis more challenging. High suspicion, prompt antibiotic discontinuation and early institution of steroid can prevent further kidney injury or potential chronic kidney disease

PO0134

A Case of BK Polyomavirus-Associated Nephropathy of Native Kidneys in a 19-Year-Old Woman with a History of Orthotopic Cardiac Allotransplantation

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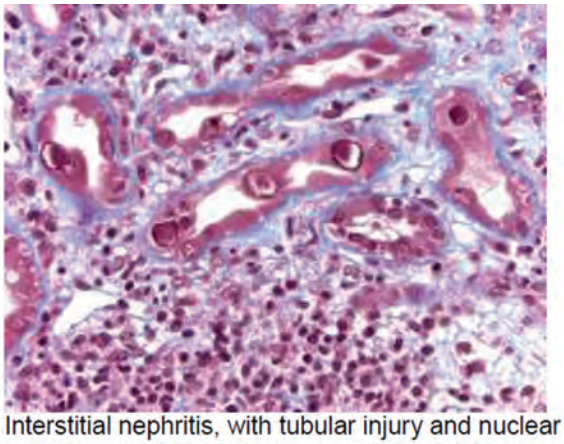
Introduction: BK polyoma virus associated nephropathy (BKPyVAN) is common among kidney transplant recipients. Approximately one to ten percent of kidney transplant recipients will develop BKPyVAN. BKPyVAN can lead to failure of the transplanted kidney allograft.

Case Description: A 20-year-old woman who had orthotopic cardiac allotransplantation in November of 2016 presented to the hospital in January of 2020 with upper respiratory tract infection like symptoms. Her baseline serum creatinine was 1.4 mg/dL three months prior to presentation. Her maintenance immunosuppression included tacrolimus and siroliumus. On admission her serum creatinine was 4.4 mg/dL. Nephrology was consulted and they recommended investigating for BK nephropathy. BK virus DNA quantification was positive for 352,364 BK virus copies/mL. On hospital day nine. The left native kidney biopsy revealed active BK-virus nephritis, patchy interstitial fibrosis and tubular atrophy.

Discussion: BK polyoma virus associated nephropathy of native kidneys is relatively rare. Upon our research we have only found a few case reports.



Interstitial nephritis, with tubular injury and nuclear inclusions typical of BK-virus nephritis (trichrome stain)

PO0135

A Case of Secondary IgA Nephropathy and Response to Steroids

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Introduction: Secondary IgA nephropathy a lesser known variant of primary IgA, has been reported to occur after a bacterial illness. These have led to rapid progression towards kidney failure. Victims of the disease are likely to become dialysis dependent shortly after acquiring the disease process.

Case Description: Patient is an 87 year old male with past medical history of DMT2, CKD IIIb, Prostrate Ca, Bladder Ca and a recent admission for sepsis due to MSSA bacteremia, was admitted to an elevated Cr to 3. His symptoms comprised only of fatigue and confusion with no decrease in urine output. Admission labs showed BUN of 78 and Cr of 4.13 and >300 protein on UA. Urine studies showed FEUrea of 59.3% and 24 hour Urine protein of 5g. Renal U/S and CT abdomen and pelvis did not reveal any obstructive process. Patient was placed on IV fluids while a GN workup was in progress followed by a biopsy and was discharged to be followed up on outpatient. Biopsy demonstrated IgA nephropathy with diffuse proliferative glomerulonephritis with acute tubular injury without crescenteric involvement. There was also evidence of mild chronic tubulointerstial injury and global glomerulosclerosis. His Cr had up trended to 7.4 and BUN 146 without any signs of azothemia. Decision was made to start 500mg methylprednisone once daily for 3 days followed by 0.5mg/kg of oral steroids on discharge and 1 month follow up. 1 month later, Cr was found to have down trended to 5 with no electrolytes disturbances with improvement activities of daily living with adequate urine output. Decision was made to continue oral steroids in an attempt to delay dialysis.

Discussion: Post infectious IgA nephropathy is rare but continues to be responsible for progression towards ESRD. The infections responsible include E Coli Sepsis and Osteomyelitis. Variable approaches have been made which revolve around the inflammatory infiltrates. Immuno-suppressive therapies like cyclophosphamide and rituximab have been typically used for crescenteric glumerolonephritis but have shown limited response. Their use in secondary IGA nephropathy has been limited to transplant recipents. Our case demonstrated one of the rare instances in which there was presence of active inflammatory infiltrate in absence of any crescent formation which guided our decision to initiate steroids. In this process, dialysis was delayed as the patient continued to have adequate renal function.

PO0136

Case of Paraneoplastic Pauci-Immune Glomerulonephritis

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Introduction: This case highlights the importance of complete systemic evaluation for patients presenting with rapidly progressive glomerulonephritis (RPGN).

Case Description: 58 year old male with history of DM type 2 and hypothyroidism presents with acute kidney injury (AKI). Notable findings include a rash which was biopsied and due to leukocytoclastic vascullitis. Baseline Cr 0.59 mg/dl and continued to increase rapidly leading to patient becoming hemodialysis dependent. Urine showed an active sediment; serology including ANCA and anti-GBM were all negative. Patient was empirically started on steroids for possible Immunoglobulin A glomerulonephritis and also due to diagnosis of adrenal insufficiency. Renal biopsy subsequently showed pauci-immune crescentic glomerulonephritis with 89% og glomeruli with crescents, 74% of which are active and negative immunefluorescence. Patient was started on cytoxan. However further work up revealed a inguinal mass which was biopsied and found to be Hodgkin's lymphoma. Patient was started on chemotherapy however did not make any renal recovery and remains dialysis dependent.

Discussion: This case illustrates the importance of thorough evaluation in patients presenting with rapidly progressive glomeronephritis. Although ofent times it is due to a primary renal or renal/pulmonary disorder, paraneoplastic conditions should not be overlooked and need further investigation.

PO0137

Renal Abnormalities in Patients with e-Cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI)

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Background: The use of electronic cigarettes is linked to the development of lung injury. There are no reports to date of renal injury secondary to vaping. Animal studies suggest that vaping could be associated with renal injury (1,2).

Methods: A retrospective chart review of the first twenty cases of patients with EVALI was performed. We present the urinary abnormalities noted in patients with EVALI.

Results: Twenty patients admitted for EVALI underwent urinalysis as part of their laboratory workup. None of these patients had known pre-existing renal disease. All patients except for one had normal creatinine on admission. Proteinuria was seen in thirteen patients (65%) and microscopic hematuria (>4 RBC/hpf) was seen in five patients (20%). All patients with microscopic hematuria also had proteinuria.

Conclusions: EVALI can be associated with hematuria and proteinuria. In animal studies, E cigarette vapor is hypothesized to diminish airway barrier function, release inflammatory protein into the circulation creating systemic inflammation leading to distant organ injury and dysfunction (2). There are several limitations to this study. This is a retrospective chart review and long term outcome is unknown as data is lacking. Nevertheless the high prevalence of urinary abnormalities on admission in patient with EVALI calls for further investigation. While the pathogenesis of vaping-associated renal injury is unclear, urine analysis should be considered in all patients presenting with EVALI. Ref 1. Impact of e cigarette refill liquid exposure on rat kidney Golli NE et al. Regul Toxicol Pharmacol 2016 Jun;77:109-16 2. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces inflammation and multiorgan fibrosis in mice Crotty Alexander et al Am J Physiol Regul Integr Comp Physiol. 2018 Jun 1;314(6):R834-R847

Urinary abnormalities in 20 patients with EVALI

PROTEINURIA	13	65%
1+proteinuria(30mg/dL)	8	40%
2+proteinuria(100mg/dL)	4	20%
3+proteinuria(>300mg/dL)	1	5%
HEMATURIA	5	25%
Hematuria and 1+proteinuria	4	20%
Hematuria and 3+proteinuria	1	5%

PO0138

Kidney Biomarkers and Major Adverse Kidney Events in Critically Ill Patients

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Background: Several biomarkers of acute kidney injury (AKI) have been examined for their ability to predict AKI earlier than serum creatinine. Few studies have focused on using kidney biomarkers to better predict major adverse kidney events (MAKE), an increasingly used composite outcome in critical care nephrology research.

Methods: Single-center prospective study collecting blood and urine samples from critically ill patients with AKI KDIGO stage 2 or above, and matched controls from a single, tertiary care intensive care unit. Samples were collected at 24-48 hours after AKI diagnosis (cases) or ICU admission (controls), 5-7 days later, and 4-6 weeks following discharge for AKI patients. The primary outcome of interest was MAKE at hospital discharge.

Results: Serum/urinary neutrophil gelatinase-associated lipocalin, serum/urinary cystatin C, and urinary kidney injury molecule-1 early in the AKI or ICU course were all significantly higher in patients with MAKE compared to those not experiencing MAKE. Serum cystatin C, and to a lesser extent serum NGAL, significantly improved upon a clinical prediction model of MAKE as assessed by the area under the receiver operating characteristic curve. Patients without MAKE experienced a greater decline in serum NGAL from initial measurement to second measurement than those patients experiencing MAKE.

Conclusions: Early values of kidney biomarkers in critically ill patients are associated with MAKE. This relationship appears to be greatest with serum NGAL and cystatin C, which display additive utility to a clinical prediction model. Trending serum NGAL may also have utility in predicting MAKE.

Funding: NIDDK Support, Private Foundation Support

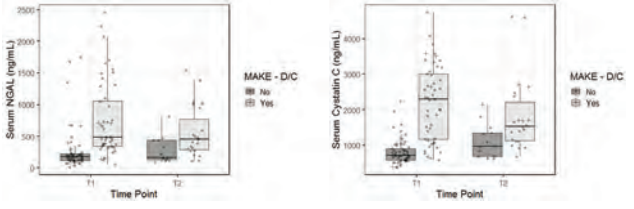

Figure 1. Kidney Biomarker Trends from Time 1 (24-48 hours) to Time 2 (5-7 Days)

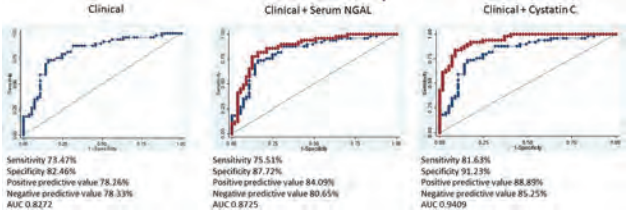

Figure 2. Receiver operating characteristic curves for MAKE-Discharge

PO0139

Urine Biomarkers and Risk of Long-Term Kidney Outcomes After Cardiac Surgery: the TRIBE-AKI Study

Steven Menez,[1] Dennis G. Moledina,[2] Amit X. Garg,[3,4] Heather Thiessen Philbrook,[1] Eric McArthur,[4] Yaqi Jia,[1] Wassim Obeid,[1] Sherry Mansour,[2] Michael Shlipak,[5] Steven G. Coca,[6] Chirag R. Parikh.[1] TRIBE-AKI Consortium *[1]Johns Hopkins University School of Medicine, Baltimore, MD; [2]Yale University School of Medicine, New Haven, CT; [3]Western University Schulich School of Medicine and Dentistry, London, ON, Canada; [4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [5]University of California San Francisco, San Francisco, CA; [6]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The urine biomarkers epidermal growth factor (EGF) and monocyte chemoattractant protein-1 (MCP-1) show promise as biomarkers of chronic kidney disease (CKD) progression in settings such as diabetes mellitus, but their role in the transition from AKI to CKD remains unclear. EGF is produced specifically by renal tubular epithelium of the thick ascending limb and MCP-1 is extensively studied as a marker of kidney inflammation. We evaluated the associations of urine EGF and MCP-1 with CKD incidence or progression after cardiac surgery.

Methods: In this sub-study of the prospective TRIBE-AKI cohort, we evaluated 865 adult patients who underwent cardiac surgery from 2007–2010 at two sites in Canada and the US. We tested the association of first post-operative urine EGF and MCP-1, and the ratio EGF/MCP-1, with the composite outcome of CKD incidence or progression. We assessed for interaction by peri-operative AKI status.

Results: Over a median (IQR) follow-up of 5.8 (4.2-7.1) years, 266 (30.8%) patients developed the composite outcome at an event rate (95% CI) of 55.4 (49.2-62.5) per 1,000 person-years. Elevated levels of first post-operative urinary EGF and MCP-1 were each independently associated with the composite outcome, in opposing directions (**Table 1**), and the ratio (EGF/MCP-1) was strongly associated with decreased risk of CKD incidence or progression in both continuous and categorical analysis (aHR 0.50 [0.33-0.74] for T3 compared to T1). There was no interaction by AKI status.

Conclusions: Urine EGF and MCP-1 measured post-cardiac surgery were independently associated with CKD incidence and progression. The ratio of urine EGF/MCP-1 may be useful for risk prediction of future CKD outcomes after peri-operative injury in cardiac surgery.

Funding: NIDDK Support

Table 1: Risk of CKD Incidence or Progression by Urine Biomarker Level

Biomarker	Level/Tertile	Unadjusted HR (95% CI)	Adjusted HR for Urine Creatinine (95% CI)	Fully Adjusted* HR (95% CI)
Urine EGF (pg/mL)	Continuous‡	0.93 (0.85-1.00)†	0.78 (0.69-0.89)†	0.83 (0.73-0.95)†
	Tertile 1 (83.5-417.8)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Tertile 2 (420.5-1031)	0.99 (0.75-1.31)	0.84 (0.62-1.16)	0.91 (0.66-1.25)
	Tertile 3 (1033-19242)	0.80 (0.59-1.10)	0.59 (0.39-0.91)†	0.68 (0.43-1.07)
Urine MCP-1 (pg/mL)	Continuous‡	1.10 (1.03-1.18)†	1.12 (1.04-1.21)†	1.10 (1.00-1.21)†
	Tertile 1 (4.7-143)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Tertile 2 (144-345)	1.47 (1.09-1.97)†	1.59 (1.15-1.22)†	1.46 (1.03-2.07)†
	Tertile 3 (346-11683)	1.52 (1.12-2.07)†	1.68 (1.18-2.38)†	1.48 (0.99-2.22)
Urine EGF/MCP-1	Continuous‡	0.87 (0.82-0.93)†	0.86 (0.81-0.92)†	0.86 (0.79-0.94)†
	Tertile 1 (0.01-1.77)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Tertile 2 (1.78-5.42)	0.97 (0.73-1.27)	0.96 (0.72-1.26)	0.95 (0.70-1.29)
	Tertile 3 (5.44-108.73)	0.49 (0.35-0.68)†	0.48 (0.34-0.67)†	0.50 (0.33-0.74)†

† p<0.05
‡ continuous analysis following log-2 transformation
* adjusted for age, sex, race, elective surgery, type of surgery, pre-operative eGFR, diabetes, hypertension, congestive heart failure (CHF), myocardial infarction (MI), post-operative albuminuria, post-operative urine creatinine, AKI stage, cardiopulmonary bypass time, and study site

PO0140

Higher Plasma KIM-1 Is Associated with Increased Mortality and Decreased Renal Recovery in Patients with AKI Requiring Renal Replacement Therapy

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Background: Plasma kidney injury molecule-1 (KIM-1), a protein synthesized by renal proximal tubular cells, increases during periods of ischemia and thereby acts as a sensitive marker for AKI severity. We hypothesized that higher plasma KIM-1 levels assessed prior to commencing renal replacement therapy (RRT) would associate with higher mortality and RRT dependence in critically ill patients with severe AKI.

Methods: We measured plasma KIM-1 levels in 806 Day 0 samples from participants in Acute renal failure Trial Network (ATN) trial, a randomized controlled trial of intensive versus less-intensive RRT. For our primary analysis we used a logistic regression model to assess the risk of 28-day mortality and an inverse probability weighted logistic regression model to assess the odds of 28-day renal recovery, per doubling in log-transformed Day 0 KIM-1. Both models were adjusted for components of the ATN trial mortality risk score (age, chronic hypoxemia, CVS disease, malignancy, immunosuppressive therapy, ischemic AKI, post open surgery and vital signs at RRT initiation).

Results: Higher levels of plasma KIM-1 were associated with an increased risk of death within 28 days (adjusted odds ratio 1.15; 95% CI 1.03-1.29; $p = 0.02$) per doubling in log-transformed plasma KIM-1. Higher levels of Day 0 plasma KIM-1 were also associated with an increased risk of persistent RRT dependence at 28 days (adjusted odds ratio 0.76; 95% CI 0.66-0.87; $p < 0.0001$) per doubling in log-transformed plasma KIM-1.

Conclusions: Higher plasma KIM-1 levels measured prior to initiation of RRT are independently associated with higher 28-day mortality and lower probability of 28-day renal recovery in critically ill patients with severe AKI.

Day 0 KIM-1 (pg/ml)	Quartile 1 (0-1393.8)	Quartile 2 (1393.8-2890.3)	Quartile 3 (2890.3-5993)	Quartile 4 (5993-181509.6)	P-value
Age	64 +/- 15	61.3 +/- 13.8	59.6 +/- 15.4	54.8 +/- 16.1	< 0.0001
Sex (no./no. with data)					
Male	105/153 (68.6%)	109/152 (71.7%)	101/152 (66.5%)	101/152 (66.5%)	0.73
Female	48/153 (31.4%)	43/152 (28.3%)	51/152 (33.6%)	51/152 (33.6%)	
Race (no./no. with data)					
White	118/153 (77.1%)	120/152 (79%)	115/152 (75.7%)	118/152 (77.6%)	0.87
Black	24/153 (15.7%)	20/152 (13.2%)	25/152 (16.5%)	24/152 (15.8%)	
Hispanic	7/153 (4.6%)	10/152 (6.6%)	10/152 (6.6%)	8/152 (5.3%)	
Other	4/153 (2.6%)	2/152 (1.3%)	2/152 (1.3%)	2/152 (1.3%)	
Length of stay before randomization - days					
Hospital	8.5 +/- 7.7	10.4 +/- 17.6	12.7 +/- 27.4	13.8 +/- 18.6	0.06
ICU	6.1 +/- 5.7	8.3 +/- 13.4	6.6 +/- 5.8	5.9 +/- 6.1	0.06
Illness severity scores					
Total SOFA score	13.6 +/- 3.7	13.6 +/- 3.7	15.5 +/- 3.6	15.3 +/- 3.4	< 0.0001
Cleveland Clinic ICU Acute Renal Failure Score	10.9 +/- 3.5	11.5 +/- 3.4	12.6 +/- 3.1	12.6 +/- 3.3	< 0.0001

Baseline demographic and illness severity data according to Day 0 KIM-1 quartile

PO0141

Estimated vs. Measured Glomerular Filtration Rate in Acute Decompensated Heart Failure

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Background: Kidney function is closely monitored in patients with acute decompensated heart failure (ADHF). Recent studies indicate that rise in endogenous filtration markers (serum creatinine (SCr) or cystatin c (Cys)), is neither associated with tubular injury nor with adverse outcomes when accompanied by efficient decongestion. The imperfections of SCr or Cys to estimate GFR in non-steady state could contribute to misjudgment of renal function in ADHF. In this study we measured GFR (mGFR) in patients treated for ADHF and correlated them with estimated GFR dynamics.

Methods: In a prospective cohort study in 50 hospitalized subjects treated for ADHF, GFR was measured using a two-component intravenous visible fluorescent injectate (VFI) at two timepoints 48h apart. Serum concentrations of a high molecular weight dextran component of VFI were measured 15 and 60 min after injection to quantify plasma volume (PV) using indicator-dilution principle. Concentrations of a low molecular weight component were measured to determine mGFR based on PV-normalized plasma pharmacokinetics. Pearson's r, Bland-Altman plots, precision, accuracy and bias were calculated for 4 established equations (CKD EPI_{Scr}, CKD EPI_{Cys}, CKD $EPI_{Scr\ Cys}$, sMDRD) and kinetic GFR (kGFR, Chen et al., JASN 2013). 38 subjects had complete serial mGFR data.

Results: eGFR calculated by any estimating equation correlated significantly with measured GFR (CKD EPI_{Scr}, r=0.81; CKD EPI_{Cys}, r=0.81.; CKD $EPI_{Scr\ Cys}$, r=0.84.; sMDRD, r=0.81; kGFR r=0.81, p<0.0001). CKD $EPI_{Scr\ Cys}$ had the best overall performance with an accuracy (P30) of 75%. However, changes in mGFR during 48h of ADHF treatment were not adequately reflected in corresponding changes of eGFR. KDIGO SCr-based AKI criteria frequently failed to detect relevant decreases of mGFR (Sensitivity 55%).

Conclusions: In patients hospitalized for ADHF undergoing decongestion, GFR estimates based on SCr and CC display substantial deficits in estimating GFR. In particular, changes of SCr- and CC- based GFR displayed a remarkable disconnect from mGFR dynamics. KDIGO SCr criteria displayed a poor sensitivity in detecting relevant decreases of mGFR, indicating a need for improved diagnostic approaches to identify true worsening renal function in ADHF.

Funding: Commercial Support - FAST Biomedical

PO0142

Multiple Beneficial Effects of Renal Exosomes on Ischemic Injury

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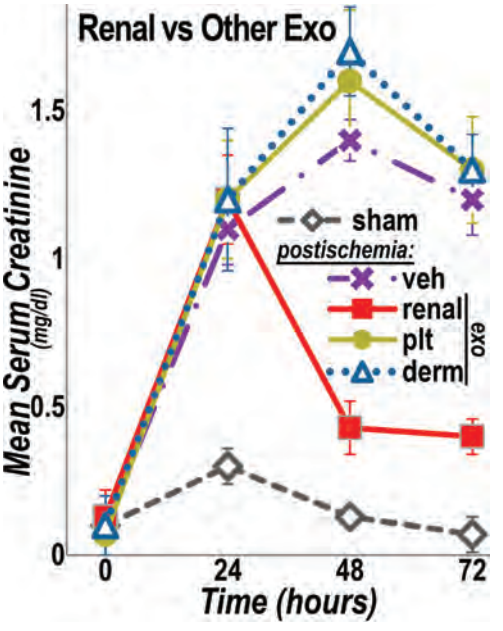
Background: Ischemic injury to the kidney and other organs is deadly and expensive. We have demonstrated the effectiveness of adult cell-based therapies in multiple models of renal failure. Given the large benefits of relatively few cells, we hypothesized that exosomes from transplanted cells were the therapeutic effector. We and others have shown beneft with exosomes in renal injury models. To define the mechanisms of benefit from renal exosomes, the effects of exosomes from platelets and dermal epithelia were compared to those of renal exosomes.

Methods: The hypothesis that renal exosomes improve multiple pathways of injury postischemia and contain anti-oxidant and anti-inflammatory cargo was tested in a renal ischemia model. Exosomes from post-ischemic kidneys, platelets or skin were isolated by serial centrifugation. Renal function was estimated from serum creatinine. Oxidative stress and inflammation were assessed by immunostaining for 4-hydroxynoneal and neutrophils, respectively. Anti-inflammatory cytokine levels were measured by enzyme-linked immunoassay.

Results: We found significant improvements in renal function (figure) and structure with renal exosomes, given 24 hours postischemia, when renal failure was present. Exosomes from skin epithelia or platelets were not effective. Renal, but not skin or platelet, exosomes decreased evidence of oxidative stress in post-ischemic kidneys by 67%, with preservation of catalase and superoxide dismutase. Significantly less renal neutrophil infiltration was found in the renal exosome group as compared to postischemia groups that received vehicle or skin or platelet exosomes. Anti-inflammatory IL-10 levels were significantly higher in post-ischemic kidneys in the renal exosome group.

Conclusions: Exosomes derived from kidney cells effect multiple pathways of injury to improve postischemic kidney function.

Funding: Private Foundation Support



PO0143

Although Human Mesenchymal Stem Cells Effectively Treat AKI in Rats, They Elicit an Immune Response, Abolishing Their Subsequent Protective Activity

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Background: Preclinical and clinical studies have shown renoprotective effects of allogeneic Mesenchymal Stem Cell Therapy (MSC) in preventing AKI, obtained without eliciting an antibody response, confirming MSCs' immune privileged/immune-modulating properties. Many groups have attempted to enhance MSCs' potency by introducing beneficial genes via xenogeneic expression vectors. Whether such alterations conserve MSCs' immune privileged characteristics is unknown. We here tested whether (1) the expression of human antigens by MSCs from Fischer344 (F344) rats transgenic for human Alkaline Phosphatase (hPAP-rMSC), human MSCs (hMSC) or human Adipose-derived Stem Cells (hASC) alters the cells' renoprotective function in female F344 rats with IRI-induced AKI; (2) whether the administration of these cells elicits an antibody response; (3) whether such a response affects the reno-protective efficacy of the cells in subsequent treatments.

Methods: IRI AKI (42 min. bilateral pedicle clamp) was induced (n=6/group). Post reflow, groups were infused via the suprarenal aorta (s.a.) with hPAP-rMSC, hASCs or hMSC, 0.5-2x10e6 cells), or vehicle. Ten days post-AKI, serum samples were obtained and analyzed by FACS to assess for antigenic responses (IgG antibodies) to (1) MSC-specific genes, or (2) to hPAP. Two more groups of F344 rats (n=6 each) were inoculated i.p. with hASC (5x10e5). Immune response to hASCs was assessed 14 days post inoculation, and IRI AKI was induced as above, followed upon reflow by an identical s.a. infusion of hASCs or vehicle.

Results: Versus controls, all 3 cell types significantly protected renal function and hastened recovery from AKI (SCr levels, tissue injury scores); but within 14 days, each treatment elicited a significant IgG antibody response (57-99%) against the infused cell type. Rats inoculated i.p. with hASCs and confirmed to have positive immunity to hASCs were no longer renoprotected by hASCs when treated with them for IRI AKI.

Conclusions: While xenogeneic use of MSCs/ASCs is renoprotective, the demonstrated induction of an immune response makes such applications unsafe/ineffective in pre-clinical studies. Caution is advised in interpreting results of studies using cell lines containing xenogeneic expression vectors for genes meant to enhance MSCs' clinical efficacy. (Not U of Utah work)

Funding: Commercial Support - SymbioCellTech, LLC

PO0144

Point-of-Care Prevention and Treatment of AKI with Adipose-Derived Stem Cells: Efficacy and Cost Advance over Culture-Expanded Bone Marrow-Derived Mesenchymal Stem Cells

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Background: Our pre-clinical studies (AJP 2005) and a Phase I Clinical Trial (Nat Rev Neph 2010) show that administration of bone marrow-derived, culture expanded, allogeneic Marrow Stromal Cells (MSC) is effective in the prevention and hastened recovery from experimental AKI; and safe and renoprotective in on-pump cardiac surgery patients at high risk for post-op AKI. Significantly, MSC treated unlike historical control on-pump cardiac surgery patients did not develop Chronic Kidney Disease (CKD) long term (>7 years). Expansion and banking of MSCs is expensive and time consuming. To address these limitations, we compared treatment with syngeneic, culture-expanded MSCs or vehicle to treatment with either syngeneic, minimally manipulated abdominal Adipose Derived Stem Cells (ASCs) or autologous Stromal Vascular Fraction (SVF, immediately isolated from fat, containing ASCs, endothelial precursor and other cells) for efficacy in preventing AKI. ASCs share therapeutically critical activities with MSCs and are found in sufficiently high numbers/gram fat to present an alternative to culture-expanded MSCs.

Methods: ASCs and SVFs were isolated by minimal processing from abdominal fat harvested from male Fisher344 (F344) rats. IRI AKI was induced (bilateral renal pedicle clamping x 40 min) in 5 groups of male F344 rats (~200 g b.wt.; n=7 each). Upon reflow, groups were infused (suprarenal aorta) with either (1) $1x10^6$ ASCs, (2) $1x10^6$ autologous SVF cells, (3) $1x10^6$ syngeneic, cultured MSCs, (4 and 5) vehicle in animals with or without fat harvest.

Results: Outcomes were compared to those of sham treated animals (n=7). Renal function assessed by serum Cr (SCr) in ASC or SVF treated animals was significantly better protected, and recovery more rapidly achieved compared to vehicle and MSC treated rats.

Conclusions: Our data suggest therefore that autologous ASCs and the SVF, obtained by minimal manipulation from a patient's lipoaspirate, have the potential to treat that same patient with an efficient, inexpensive and safe point-of-care protocol to prevent or treat AKI and prevent subsequent progression to CKD. (No University of Utah resources were used for this work.)

Funding: Commercial Support - SymbioCellTech, LLC

PO0145

Administration of Exosomes from Mesenchymal Stem Cells Provides Effective Survival Benefits and Functional Rescue from Severe, Progressive Ischemia-Reperfusion Injury-Induced AKI in Rats

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Background: While administration of Mesenchymal Stem Cells (MSCs) has been demonstrated clinically to prevent Acute Kidney Injury (AKI) such as that caused by cardiac bypass surgery, administration 48 hrs post-insult was found to be ineffective or potentially damaging, likely because the introduction of large cells (~50μm) into the compromised microvasculature may impair renal function. MSCs' renoprotection is mediated by their paracrine release of anti-inflammatory and trophic cytokines and their exosomes. Exosomes signal, post uptake by target cells, through the lateral transfer of mRNAs, miRNAs, DNA, proteins, and lipids. Since MSC-derived exosomes can prevent AKI we tested whether their small size and ability to move through the compromised renal microvasculature might allow them to provide effective rescue therapy for late stage AKI.

Methods: Exosomes from Sprague Dawley (SD) rat MSCs were isolated post 24 hr culture, purified using the ExoQuick-TC kit, and characterized for size (nanosight), protein and gene expression of relevant markers. I/R AKI (52 min bilateral renal pedicle clamp) was induced in female SD rats. If the SCr value on Day 2 was greater than that on Day 1, demonstrating progressive AKI, then rats were administered via left carotid artery either 1 ml of Vehicle (PBS; n=8), Exosomes (200 μg protein-equivalent; ~4x10e10 exosomes; n=6), or MSCs (2x10e6; n=6) on Day 3.

Results: 1x10e6 MSCs secrete ~ 4.9x10e10 exosomes and other microvesicles (mode 136.7 nm) and >95% express CD44 and CD29, and carry mRNAs of renoprotective genes expressed in MSCs. While both MSC and exosome administration improved survival over PBS, renal function only showed significant and sustained improvement in exosome-treated rats.

Conclusions: MSC-derived exosome therapy 3 days post progressive AKI, when renal blood flow is significantly impaired and when most clinical AKI is diagnosed, is superior to MSC therapy, likely due to their ability to deliver their renoproetective cargo into the compromised renal microcirculation. These data have, we posit, significant translational promise for the development of an effective rescue therapy for advanced AKI. (No University of Utah resources were used for this work.)

Funding: Commercial Support - SymbioCellTech, LLC

PO0146

Microparticles Released in Response to AKI May Influence Glucose and Salt Metabolism

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Background: Renal epithelial injury due to ischemia or toxic/inflammatory insults is the primary cause of acute kidney injury (AKI). Due to their high metabolic activity renal tubular epithelial cells (RPTEC) are especially vulnerable to damage leading to a clinical syndrome of disruption in salt, water and glucose homeostasis. We have previously shown that microparticles (MP) derived from renal epithelial cells are released in the setting of kidney injury and can be detected in vitro as well as in human plasma, and can carry the biological activity.

Methods: In this study, we evaluated the release of MP carrying SGLT2, and SLC12A3 (NCC) in response to kidney injury. Immortalized RPTEC lines were treated with Oxidative stress (H_2O_2) or inflammatory stress (TNFα) agents by the validated methodology to study in vitro models of AKI. Human samples were derived from a prospectively collected repository (31 cases of AKI in critically ill patients compared to 22 living kidney donor healthy controls). Samples were prepared to measure MP (standard methods), and flow cytometric analysis was evaluated using antibodies against SGLT2, and SLC12A3 (NCC). FlowJo software was used for analysis. Mann-Whitney test was used for comparisons.

Results: RPTEC models of injury (H_2O_2) resulted in a significant increase in the release of MP positive for SGLT2 MP 5.49×10^{10}/ml vs 0.41×10^{10}/ml for control cells (p=0.05) and NCC (SLC12A3) 4.2×10^5 vs 0.63×10^5 for control cells (p=0.05). Similar changes were observed when cells were treated with TNFα (p=0.05) for SGLT2 and NCC. We also confirmed the presence of MP containing SGLT2 and NCC in AKI (104.60 $X10^5$ /ml and 1.77×10^5 /ml, respectively). However, when compared to controls, the difference was statistically similar.

Conclusions: This is one of the first reports to confirm that key transporters from renal epithelium can be released and detected as MP in both in vitro and clinical settings of AKI. These findings may provide novel insights into the mechanisms of glucose, salt and water dysregulation during kidney injury and repair.

PO0147

Sex as a Biological Variable in Cardiac Outcomes after AKI in Mice

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Background: Acute kidney injury (AKI) is common in patients, and predisposes patients to cardiovascular disease. Estrogen is known to protect against ischemic AKI, however it is unknown whether it also protects against the cardiac sequelae of AKI. We report a 1 year study evaluating the cardiac and metabolic effects of bilateral renal ischemia-reperfusion injury in male and female C57BL/6 mice.

Methods: Males received 25 minutes of ischemia, while females received 34 minutes. Serial glomerular filtration rate (GFR), echocardiograms and blood pressure assessments were performed with sacrifice at 1 year. Plasma and cardiac metabolomics were measured. Mead's resource calculation was utilized to calculate sample size of n = 5-11. Comparison between two groups was performed using unpaired t tests assuming Gaussian distribution with Welch's correction, $P < 0.05$ for statistical significance.

Results: Serial measurements of GFR showed that the AKI model was matched between males and females throughout the 1 year study. Males with AKI developed diastolic dysfunction (quantified on echocardiogram data by E'/A' <1), hypertension, reduced cardiac adenosine triphosphate (ATP) levels; females with AKI developed hypertension but not diastolic dysfunction and had normal cardiac ATP levels.

Conclusions: This is the first study to show chronic diastolic dysfunction after AKI and variations in cardiorenal outcomes with regards to sex. Diminished cardiac ATP is a known cause of diastolic dysfunction.

Funding: NIDDK Support

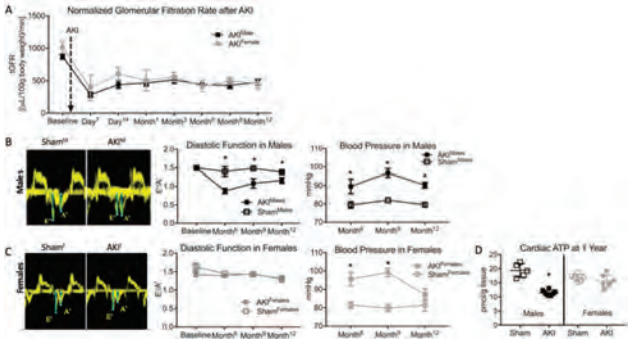

Figure 1. (A) 25 minutes of ischemia in males (AKIMales) and 34 minutes of ischemia in females (AKIFemales) results in a matched model of kidney injury with no statistically significant difference in normalized glomerular filtration rate measured over the 1 year study. (B) Males developed impaired diastolic function (E' < A') and hypertension after AKI. (C) Females maintained normal diastolic function after AKI, but did develop hypertension that resolved by 1 year. (D) 1 year after AKI, males had reduced levels of cardiac ATP whereas females did not.

PO0148

Glomerular Filtration Fails to Increase During Pregnancy After Recovery from Ischemia-Reperfusion Injury

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Background: Renal demands are increased during normal pregnancy due to the large increase in plasma volume and cardiac output, with a corresponding increase glomerular filtration rate and decreased blood pressure (BP). Recent studies in our laboratory have reported that pregnancy after recovery from ischemia reperfusion (IR) injury results in poor maternal and fetal outcomes, including decreased fetal weight, increased fetal demise, and mild uremia in the dams. In the current study, we hypothesized that glomerular filtration fails to increase during pregnancy in these dams after recovery from IR.

Methods: Female Sprague Dawley rats (10 weeks of age, n=3) were implanted with telemeters into the femoral artery for continuous BP measurements. Following 10 days of recovery, rats were randomized to receive either 45 minutes of warm, bilateral renal ischemia or sham surgery. Rats were then given 1 month to recover. Full recovery from IR was confirmed by return of plasma creatinine and urinary protein excretion to baseline prior to mating. Vaginal smears were performed daily once mating began, to identify gestational day 1. Glomerular filtration rate was calculated using creatinine clearance (using 24 hour urine collection from gestational days 19-20 and plasma creatinine on gestational day 20).

Results: BP decreased to a similar extent (7±1.2mmHg in control vs 8±1.2mmHg in IR dams) by gestational day 20, however the decrease in BP was delayed in the IR dams, resulting in an overall higher pressure load as determined by area under the curve analysis (2080±33 vs 2184±16, $p<0.05$, t-test). Glomerular filtration rate was significantly higher in control dams compared to IR dams (3.1±0.7mL/min vs 1.6±0.1mL/min, $p<0.05$).

Conclusions: These data suggest that after recovery from IR, the kidneys are unable to appropriately increase glomerular filtration rate during pregnancy. Ongoing studies in the laboratory are focused on alterations in plasma volume expansion during pregnancy after IR. We propose that plasma volume expansion, characteristic of normal pregnancy, is absent in this model, leading to decreased placental perfusion and poor fetal growth.

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PO0149

Polymorphisms in HAVCR1 Alter KIM-1-Mediated Phagocytosis

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Background: During renal ischemia reperfusion injury (IRI), necrotic cells, and apoptotic tubular epithelial cells (TECs) undergoing secondary necrosis, release their immunogenic contents into the extracellular milieu, exacerbating inflammation. Kidney Injury Molecule -1 (KIM-1) is a cell-surface glycoprotein upregulated on TECs during acute kidney injury (AKI). We previously uncovered that KIM-1 protects against renal IRI by enabling TECs to bind and engulf dying neighbouring cells, limiting inflammation and tissue damage. The gene encoding KIM-1 *(HAVCR1)* is highly polymorphic, but the relevance of human KIM-1 polymorphisms in renal IRI has not been studied. We hypothesized that *HAVCR1* variant expressing TECs would have decreased phagocytic activity *in vitro*.

Methods: Using site-directed mutagenesis, we generated constructs for 3 high-frequency *HAVCR1* coding variants in addition to an expression plasmid-encoding wild-type KIM-1 (pcDNA3-KIM-1). We then expressed the pcDNA3 vector, or *HAVCR1* variants in HEK-293 cells using stable transfection.

Results: We report that all 3 variants had altered cell surface KIM-1 expression compared to the wild-type. Importantly, the phagocytic uptake of apoptotic cells was significantly reduced in HEK-293 cells expressing each of the KIM-1 variants compared to those expressing wild-type KIM-1, indicating that mutations in these coding regions contribute to a functional impairment of KIM-1 activity.

Conclusions: This is the first study suggesting that human polymorphic variants in *HAVCR1* may have consequences on the functional role of the KIM-1 protein in the kidney. This work strengthens the plausibility of a biological role for KIM-1 during AKI.

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PO0150

Sympathetic Signaling in Macrophages Mitigates Systemic Inflammatory Response and Renal Ischemia-Reperfusion Injury

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Background: The sympathetic nervous system is known to control immune cell dynamics. However, the detailed role of sympathetic signaling in inflammatory diseases is still unclear. Here, we focused on sympathetic signaling in macrophages and aimed to determine whether its activation attenuates lipopolysaccharide (LPS)-induced sepsis and renal ischemia/reperfusion injury (rIRI).

Methods: <*In vitro*> Three types of macrophages (RAW 264.7 cells [murine macrophage cell line], murine peritoneal cells, and differentiated U937 cells [human monocyte cell line]) were used to determine the effects of sympathetic signaling, especially β_2 adrenergic receptor (ADRB2) signaling, on LPS-induced proinflammatory cytokine (TNF-α) production. <*In vivo*> We examined the effects of salbutamol (β_2 selective agonist) on LPS-induced sepsis and rIRI models. Macrophage-specific ADRB2 conditional knockout (ADRB2 cKO) mice were used to elucidate the contribution of ADRB2 signaling in macrophages.

Results: <*In vitro*> Norepinephrine, a main sympathetic neurotransmitter, reduced LPS-induced TNF-α production in the three types of macrophages. This anti-inflammatory effect was also induced by salbutamol and reversed by butoxamine (β_2 selective antagonist) in a dose-dependent manner, indicating the importance of ADRB2 in this process. Furthermore, T-cell immunoglobulin and mucin-3 (TIM-3) expression was upregulated in macrophages by ADRB2 signaling and partially mediated the anti-inflammatory phenotypic alteration. <*In vivo*> Salbutamol administration immediately before LPS treatment significantly reduced plasma TNF-α levels in mice, which was mitigated in macrophage-specific ADRB2 cKO mice. Salbutamol administration 24 h before rIRI also attenuated acute kidney injury, which was relieved in macrophage-specific ADRB2 cKO mice. The protection against rIRI was abolished in the mice in which splenectomy was performed 10 days before salbutamol administration, which suggests the contribution of splenic macrophages to the protective effects. In fact, adoptive transfer of salbutamol-treated splenic macrophages conferred protection to the recipient mice subjected to rIRI.

Conclusions: Sympathetic signaling via ADRB2 in macrophages attenuates systemic inflammatory response and rIRI. Phenotypic alterations in splenic macrophages might play critical roles in the protection against rIRI.

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PO0151

Myeloid Lactate Dehydrogenase A (LDHA) Regulates Macrophage Polarization and Promotes Fibrosis in AKI

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Background: Renal ischemia/reperfusion injury (IRI), a major cause of AKI, is characterized by an initial decrease of blood flow, followed by its subsequent restoration. IRI facilitates infiltration of proinflammatory macrophages as well as proliferation of intrarenal resident macrophages that, upon activation, undergo glycolytic switch, and can further exacerbate injury by inducing excessive inflammation. LDHA, a key enzyme involved in the glycolytic switch, catalyzes the conversion of pyruvate to lactate, regenerating NAD+ from NADH. Here we investigate the role of LDHA in myeloid cells and its effect on AKI.

Methods: To test the hypothesis that myeloid LDHA expression regulates macrophage polarization, RNA-Seq studies were performed in bone marrow derived macrophages (BMDM) from wild-type and LysM-Cre LDHA knockout (LDHA KO) mice grown in M-CSF for 7 days and then polarized with IFN-γ for 24 h. To test the effect of myeloid deletion on AKI, in vivo studies were performed using wild-type and LDHA KO mice using a bilateral IRI model (20 min ischemia at 37°C).

Results: RNA-seq analysis of BMDMs lacking LDHA showed significant decrease in HIF-1α and GLUT1, which are essential for the glycolytic switch. NOS2 was increased indicating diminished oxidative phosphorylation. Pro-inflammatory genes, Ccl5, IL-18, and IL-1β were downregulated. Over-representation pathway analysis (ORA) and notable altered genes are shown below (Table). While serum creatinine and GFR were similar between wild-type and LDHA KO mice, renal cortical fibrosis was significantly diminished ($p<0.014$) in myeloid LDHA KO mice, 7 days post IRI.

Conclusions: LDHA deficient BMDMs exhibited significant decrease in essential glycolytic switch machinery in addition to the decrease in the efficiency of oxidative phosphorylation. As a result, LDHA deficient BMDMs showed a diminished pro-inflammatory and fibrotic profile ensuing lesser renal fibrosis despite similar functional injury in both genotypes. These results suggest that LDHA is a potential target to manipulate immunometabolism in the pathogenesis of AKI.

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ORA Pathways and notable genes in BMDM of LDHA KO vs WT

Pathways affected by LDHA deletion	Up-regulated genes		Down-regulated genes	
Regulation of leukocyte activation	IL-7r	Tnfrsf1b	IL-1β	IL-18
Adaptive immune response	IL-12β	Tnfsf4	IL-27	Tnfsf18
Myeloid cell differentiation	Itgb3	Cdkn1c	Hif-1α	Irf8
Cytokine-cytokine receptor interaction	Csf3	Ccl22	Ccl5	Ccl6

PO0152

PD-1 Regulates Metabolic Fitness of Tregs in Protection from Kidney Ischemia-Reperfusion Injury

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Background: Regulatory T cells (Tregs) protect the kidney in models of ischemia reperfusion injury (IRI) induced acute kidney injury (AKI). Previous studies suggested programmed cell death protein 1 (PD-1) expression by Tregs is required for their protective function in AKI. However downstream mechanisms of PD-1 signaling in Tregs in AKI is not clear. We aimed to investigate the role of PD-1 in Tregs with respect to mitochondrial function in AKI.

Methods: We induced AKI in male C57Bl/6 mice with 26 min bilateral renal IRI. $CD4^+$ $CD25^+$ Tregs were isolated from PD-$1^{+/+}$ and PD-$1^{-/-}$ Foxp3-GFP mice and then injected (100,000 cells/200ul) via tail vein into recipient mice 24h prior to ischemia reperfusion surgery. Kidney function was determined by measuring creatinine and tissue KIM-1 and NGAL mRNA expression levels. Histological damage was assessed by light microscopic analysis of H&E stained kidney sections. In different set of experiments, to understand the metabolic fitness of Tregs, we treated isolated T-cells from PD-$1^{+/+}$ and PD-$1^{-/-}$ mice and incubated them overnight with anti-CD3-Ab to mimic antigenic stimulation or with high concentration of IL-2, which is critical for Treg survival and function. Mitochondrial membrane potential of Tregs was measured with TMRE to monitor the mitochondrial fitness. FACS-sorted Tregs from PD-$1^{+/+}$ and PD-$1^{-/-}$ mice were also analyzed for the expression of genes involved in mitochondrial dynamics and biogenesis.

Results: In the mouse kidney IRI, PD-$1^{-/-}$ Tregs offered no protection from AKI. Compared to PD-$1^{+/+}$, PD-$1^{-/-}$ Tregs had reduced mitochondrial mass and mitochondrial membrane potential. In FACS-sorted Tregs, expression of markers of mitochondrial function, antioxidant pathways as well as those for mitochondrial dynamics were remarkably attenuated in the Tregs from PD-$1^{-/-}$ mice as compared to PD-$1^{+/+}$ mice.

Conclusions: Ability of Tregs to protect kidney from IRI-induced AKI is dependent on PD-1 expression by Tregs. Mitotracker green and TMRE experiments suggest that in the absence of PD-1, Tregs have reduced mitochondrial number and/or function. Tregs require mitochondrial fitness for their development and optimal function. Additionally, these genes may regulate cytoskeleton rearrangement and microtubule movement related to cell motility, granule release and cell division.

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PO0153

ST2/IL33 Signaling Axis in Tregs Critical for Restoring Kidney Tissues Homeostasis on Injury

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Background: Renal diseases are a major cause of morbidity and mortality worldwide. Thus, leading to a great financial burden on health care systems. Inflammation elicited by a variety of cytokines and chemokines is a major player in the initiation and progression of the disease. Interleukin 33 (IL-33) acts as an 'alarmin' that regulates the immune response during injury. IL-33 acts in an autocrine/paracrine manner through membrane receptor (ST2) aka IL33R or IL-1 receptor-like 1 (IL1RL1), triggering an innate and adaptive immune response. There is no evidence determining the importance of the ST2/IL33 axis in Tregs during kidney injury. In this study, we attempt to delineate the role of the ST2/IL33 pathway in Tregs cells using murine renal injury models and kidney organoids.

Methods: Murine ischemia-reperfusion injury (IRI) model was used to investigate the importance of cell-specific ST2/IL-33 signaling using IL1RL1^{tm1a} and Foxp3 cre mice to delete ST2 expression in Tregs. RNA sequencing analysis, flow cytometry, histology, immunohistochemistry, quantitative gene expression, and biochemical analysis were applied to dissect the role of ST2/IL33 signaling. Kidney organoid based 3D cell culture platform was used to setup co-culture experiments with ST2-/- and ST2+/+ Tregs for *invitro* evaluation.

Results: The RNA sequencing analysis of ST2-High Tregs indicated higher expression of regenerative factors such as amphiregulin (AREG) and Growth/differentiation factor (GDF15). The *in vivo* renal injury experimental data indicated that elimination of ST2/IL33 signaling from Tregs resulted in exacerbation of renal injury leading to worsening of renal function as determined by plasma creatinine, blood urea nitrogen, kidney injury markers (kim1 and Ngal) and fibrosis markers (Col1a1, Col3a1, SMA, and vimentin). Co-culture of kidney organoids with ST2+/+ expressing Tregs protected organoids from cellular apoptosis under *invitro* ischemia-reoxygenation conditions compared to ST2-/- Tregs.

Conclusions: Impairment of ST2/IL33 signaling in Tregs leads to worsening of renal function following ischemic injury. This indicating that activation of ST2/IL33 signaling in Tregs mediate in the regulation of inflammation, apoptosis, and repair in renal tissue during inflammation and injury.

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PO0154

Toll-Like Receptor 4 Blockade Ameliorates Kidney Ischemia-Reperfusion Injury

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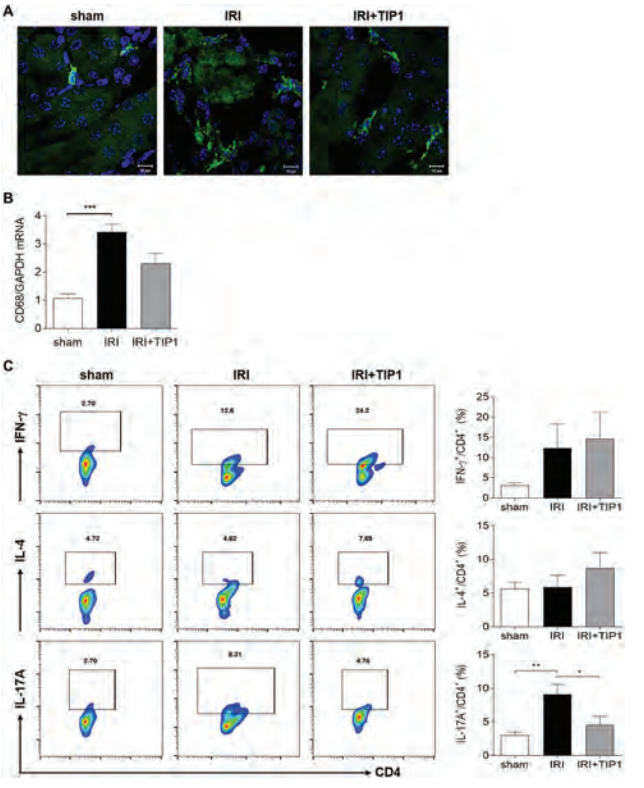
Background: Renal ischemia-reperfusion injury (IRI) is a key mechanism in various clinical conditions including sepsis and transplantation, and animal studies have demonstrated that toll-like receptor 4 (TLR4) is a key mediator of IRI. Since few study have tried the pharmacolgic inhibition of TLR4 in renal IRI, we investigated the effect of TLR4 blockade on this condition with the goal of persuing better therapeutic options.

Methods: We subjected C57BL/6 mice to 23 minutes of renal pedicle clamping following an intraperitoneal injection of TLR inhibitory peptide (TIP1), a TLR4 inhibitor, or vehicle. Sham mice underwent only a flank incision. Then, the kidneys were harvested after 24 hours of reperfusion for histology, western blot, RT-PCR, and flow cytometry. We also performed primary mouse renal tubular cell culture to assess the effects of TLR4 inhibition on tubular epithelial cells under hypoxia and subsequent reoxygenation.

Results: TIP1 pretreatment lowered the magnitude of an increase in serum creatinine levels and attenuated tubular injury. In addition, TIP1 administration decreased mRNA expressions of inflammatory cytokines, and apoptotic cells, and lowered oxidative stress in postischemic kidneys. The kidneys pretreated with TIP1 also showed less infiltration of macrophages and T helper 17 cells. In primary mouse tubular cells subjected to hypoxia and reoxygenation, the addition of TIP1 into culture media ameliorated the magnitude of an increase in mRNA levels of KIM1 and inflammatory cytokines.

Conclusions: Our data demonstrated that inhibition of TLR4 with TIP1 reduced tubular injury and an inflammatory and immune response in a mouse model of IRI.

Funding: Government Support - Non-U.S.



PO0155

Six1 Activation Is Involved in Cell Proliferation and Migration and Anti-Inflammation of Acute Ischemia-Reperfusion Injury in Mice

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Background: Nephrogenic proteins are re-expressed during the regeneration process after ischemia reperfusion (IR) injury, while the role of these proteins in the repair of kidney injury is still unknown. We found that Six1, a developmentally regulated homeoprotein is reactivated in tubular epithelial cells (TECs) after IR injury.

Methods: We established Six1 overexpresstion cell lines to confirm its effect on kidney repair in vitro. Cell proliferation and cell migration was detected by flow cytometry and cell migration assays respectively. Luciferase reporter assay was used to measure the anti-inflammation capacity of Six1 overexpressing cells, and chromatin immunoprecipitation (ChIP)-qPCR was used to analyze Six1 protein occupancy of the indicated genes. In vivo,

we injected adeno-associated viral vector serotype 9 (AAV9)-Six1 into uninjured renal pelvis before IR injury, then assessed morphologic and functional parameters and gene expression in IR injury kidney.

Results: We demonstrated that Six1 promoted cell proliferation by upregulating cyclin and glycolytic genes, and that cell migration through increasing the expression of matrix metalloproteinases (MMPs) in the cell model. Notably, the overexpression of Six1 could suppress inflammation through NF-κB-mediated pathway. Six1 target the promoters of amino-terminal enhancer of split (AES) and translocated in liposarcoma (TLS), which are cofactors of NF-κB subunit RelA, and then inhibit the transactivation function of RelA in a negative feedback circuit. Six1 overexpression resulted in inhibiting inflammation and promoting cell proliferation to reduce kidney damage of mice from IR injury in vivo.

Conclusions: Our studies suggested that Six1 promoted kidney recovery and regeneration through cell proliferation/migration and anti-inflammation which might be a potential therapeutic target that can be used to improve kidney repair after IR injury.

Funding: Government Support - Non-U.S.

PO0156

IRF8-Dependent Regulation of Kidney Dendritic Cells in Ischemic AKI

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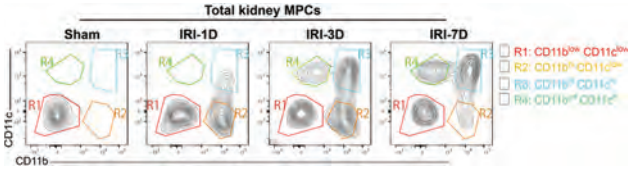
Background: Ischemic acute tubular necrosis is a common cause of acute kidney injury (AKI), which involves a greater functional diversity of mononuclear phagocytes (MPCs) such as dendritic cells (DCs). The deletion of DCs induce more kidney injury and impair the recovery of AKI. The hematopoietic transcription factor IRF8 mediates the phenotype of DC. However, the role of IRF8 dependent mechanism during AKI is not well known. Hence, we hypothesized that the dynamically altered expression of IRF8 in DCs could contribute to AKI.

Methods: AKI was induced by transient renal pedicle clamping in C57BL6/J. Kidneys, lymph nodes and spleens were collected on D1, D3 and D7. MPCs were identified by Flow cytometry. Expression of IRF8 and MHC II were quantified by IHC. The knockdown of IRF8 was performed by transfecting siRNA in bone marrow-derived DCs (BMDCs). BMDCs were stimulated with necrotic supernatant from tubular epithelial cells or histones and analyzed by phagocytosis assay, T cell differentiation assay, RT-PCR or flow cytometry.

Results: *In vivo*, we identified four distinct phenotypically MPCs with diverse expression patterns of CD11b/CD11c during post-ischemic AKI. During the late injury and repair phase (D3 and D7), $CD11b^{low}CD11c^{hi}$ R4 subsets significantly increased (Figure), which were identified as $CD103^{+}$ $CD11b^{-}$ DCs with significantly upregulated expression of IRF8. This pattern was consistent in spleen and lymph nodes. In kidney, more $IRF8^{+}$ cells distributed among the tubulointerstitium and the expression of IRF8 increased significantly during D3 and D7. Further, $IRF8^{+}$ cells showed co-staining with MHCII. *In vitro*, IRF8 knockdown in BMDCs induced a significant downregulated $CD8a^{+}$ $CD11b^{-}$ cells and expression of IL-22 upon necrotic supernatant or histone stimulation. Furthermore, IRF8 knockdown significantly reduced DCs maturation, phagocytosis capacity and naïve T cells polarization.

Conclusions: DC-like MPCs appear in the recovery phase of AKI in a IRF8-dependent mechanism. Selective deletion of IRF8 profoundly alters the phenotype of DCs in response to injury. It implies that selective targeting of $IRF8^{hi}$ DCs may provide an effective strategy to induce immune-modulation of the progression of AKI.

Funding: Government Support - Non-U.S.



PO0157

VNN1 Mediates Renal Maladaptive Repair After AKI by Inducing Premature Senescence of Renal Tubular Cells

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Background: Renal maladaptive repair can promote lead to the transition of acute kidney injury (AKI) to chronic kidney disease. Sustained renal interstitial damage caused by accelerated senescence of renal tubular cells leads to renal fibrosis after AKI. Vanin-1 (VNN1) is an extracellular enzyme with panthenylmethylaminease activity that indirectly reduces the synthesis of glutathione, causing oxidative stress. This study aimed at investigating the role of VNN1 in senescence of renal tubular cells after renal ischemia reperfusion (I/R) injury.

Methods: Thirty male wild BALB/c mice were randomly divided into control group, sham group and I/R group. In the I/R group, bilateral renal pedicles were clamped for 35 min and reperfusion was performed. The expression of VNN1 were detected. Furthermore, the degree of renal damage and the senescence of renal tubular cells were compared in wild type mice and VNN1 knockout mice after I/R injury.

Results: Scr, BUN and renal injury score increased significantly at the early stage (3d) of renal injury after I/R. Renal fibrosis was observed in the advanced stage (28-42d). The expression of VNN1 in renal tubular cells of I/R group increased after I/R injury. The SCr, BUN levels in VNN1 KO mice were significantly lower than those in wild type mice at 7-28 d after renal reperfusion. The renal interstitial fibrosis level was significantly higher in VNN1 KO mice than that of wild type mice at 42d after reperfusion. The results suggest that VNN1 KO promotes renal repair of AKI. It is found that 50% of the VNN1 up-regulated genes after IR renal injury were stress-related genes through mRNA microarray analysis. The ratio of P16 positive tubule cells in VNN1 KO mice was significantly higher than that in wild-type mice at 7d after renal reperfusion. The expression levels of phosphorylated RB1 in VNN1 KO renal tubular cells were significantly higher than those in the wild type renal tubular cells after hypoxia/reoxygenation, suggesting that VNN1 could promote the senescence of renal tubule cells through P16- RB1 pathway during AKI repair

Conclusions: VNN1 mediates renal maladaptive repair after AKI by inducing premature senescence of renal tubular cells through P16-RB1 pathway.

Funding: Government Support - Non-U.S.

PO0158

CDK4-Related Tubular Epithelial Cell Proliferation Was Regulated by Pax2 in Renal Ischemia-Reperfusion Injury

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Background: Pax2 is a transcription factor necessary for kidney development. It has been reported that Pax2 is reactivated in tubular epithelial cells at the recovery phase of kidney injury. However, the roles of Pax2 in the regeneration of kidney injury is unknown. Here in we hypothesized that Pax2 reactivation is involved in the regeneration of impaired tubular cells.

Methods: To determine the function of Pax2 reactivation in mouse proximal tubules, we generated kidney proximal tubule-specific Pax2 conditional knockout (KO) mice. The conditional KO mice were established by KAP (kidney androgen regulated protein) Cre mice and Pax2 flox mice. Six to eight-week old male mice were used for ischemia-reperfusion (I/R) injury (left kidney, 60 minutes). The intensity of cell proliferation and fibrosis of injured kidney was evaluated. A Pax2 inhibitor (EG1) was used to evaluate the roles of Pax2 in the hypoxia condition of cultured tubular epithelial cells (O_2 5%, 24 hour).

Results: The number of Pax2-positive cells and Pax2 mRNA increased after I/R injury. However, the reactivation of Pax2 was significantly suppressed in conditional KO mice ($p<0.05$). In analysis of interstitial fibrosis, the area of Sirius red staining and the content of hydroxyproline (chemical marker of collagen) were higher those observed in conditional KO mice 14 days after I/R injury ($p<0.05$). Moreover, the expression of CTGF was significantly increased in conditional KO mice ($p<0.05$). Furthermore, the number of Ki-67 and BrdU positive cells was significantly decreased in the conditional KO mice 14 days after I/R injury ($p<0.001$). In the cell cycle, the number of CDK4-positive cells (G1 phase marker) and the expression of CDK4 were significantly decreased in conditional KO mice ($p<0.001$). *In vitro* study revealed that CDK4 mRNA and protein expression were decreased by administration of Pax2 inhibitor, however Cyclin D mRNA and protein expression were not decreased by the inhibitor.

Conclusions: Pax2 reactivation may be involved in CDK4 related tubular epithelial cell proliferation. Inadequate Pax2 reactivation (or suppression of Pax2 expression) may be related in exacerbation of kidney fibrosis.

PO0159

Protein Deacetylase SIRT2 Regulates Exosome Release of GPRC5B for Epithelial Tubule Growth

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Background: Exosomes, small membrane vesicles, are formed intracellularly within multivesicular bodies (MVBs) and are released extracellularly upon fusion with the plasma membrane. Previously we have shown that exosomal release of GPRC5B, an orphan G protein-coupled receptor (GPCR) promotes epithelial tubule growth, and the L-type lectin LMAN2 limits trans-Golgi Network-to-endosomes traffic of GPRC5B.

Methods: Using mass spectrometry, CRISPR/Cas9 genetic manipulation, and imaging, we studied how LMAN2 regulates exosomal release of GPRC5B.

Results: Here, we report the protein deacetylase sirtuin 2 (SIRT2) as a novel interactor of LMAN2. Loss of SIRT2 expression resulted in exosomal release of LMAN2, a Golgi resident protein, together with increased exosomal release of GPRC5B. Furthermore, loss of SIRT2 increased total number of extracellular vesicles (EVs) including exosomes, indicating increased MVB-to-EV flux. While knockout of SIRT1 increased EV release with enlarged late endolysosome, knockout of SIRT2 did not exhibit endolysosome enlargement for increased EV release.

Conclusions: Taken together, our study suggests that SIRT2 regulates cargo loading to MVBs and MVB-to-EV flux through a mechanism distinct from that of SIRT1.

Funding: NIDDK Support

PO0160

The Proximal Tubule Is a Source of De Novo NAD$^+$ Synthesis, the Metabolites of Which Are a Valuable Predictor of AKI

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Background: Reduced NAD+ is reported to increase the susceptibility of AKI. De novo synthesis pathway from tryptophan is an important source of NAD+ in the liver and probably kidney. In the present study, we characterized the expression of the enzymes of de novo NAD+ synthesis pathway in the human kidney. We then examined the association of the urine metabolites in this pathway and AKI development in patients who received high-dose methotrexate(HDMTX) chemotherapy or liver transplantation(LT) and analyzed their predictive value for AKI.

Methods: The expression of the enzymes of de novo NAD+ synthesis pathway was examined by immunohistochemistry. To examine the predictive value of urine tryptophan metabolites in AKI, 71 patients who received a total of 191 HDMTX treatments were prospectively enrolled as a discovery cohort and 49 patients receiving LT were enrolled as a validation cohort. Urine samples were collected within 72 hours before chemotherapy/surgery. AKI was defined by KDIGO criteria. Urine tryptophan metabolites were measured by LC-MS and adjusted by creatinine. The performance of these metabolites to predict AKI after HDMTX/LT was analyzed.

Results: Enzymes of de novo NAD+ synthesis pathway including KMO, KYNU, HAAO, QPRT, and ACMSD were detected in renal tubules that were positive for LTL, but not labeled by AQP2, NCCT, nor THP, consistent with proximal tubule expression. A total of 191 HDMTX treatments were included in the discovery cohort and AKI developed after 35 HDMTX treatments (18.3%). In those who developed AKI, the urine level of 3-hydroxyanthranilic acid (3-OH AA) was significantly higher while the level of quinolinic acid (QA) was significantly lower compared with those who did not develop AKI (3-OH AA: 4.42[2.74-9.52] vs 3.57[1.86-5.73], p=0.023; QA: 13.43[9.69-22.34] vs 20.64[14.80-32.05], p=0.004). The area under the receiver operating characteristic curve (AUC) of urine QA/3-OH AA for AKI prediction was 0.748. The discrimination ability of the urine QA/3-OH AA on AKI susceptibility was validated in LT cohort, with the AUC as 0.729.

Conclusions: The proximal tubules are an important source of de novo NAD synthesis. Reduced urine QA / 3-OH AA ratio is associated with development of AKI. The present study suggests that urine QA / 3-OH AA ratio is a potential biomarker to predict AKI and NAD+ synthesis pathway is a potential therapeutic target.

PO0161

Sphingolipid Transporter 2 (Spns2) Expression, Localization, and Role in AKI

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Background: The sphingosine 1-phosphate (S1P) transporter Spns2 exports S1P from the cell and regulates the gradient of high circulating S1P levels to low tissue levels. Activation of S1P receptors can protect kidneys from acute injury, but little is known of the role of Spns2 in kidney. In these studies, we investigated the expression, localization, and role of Spns2 in the kidney after ischemia-reperfusion injury (IRI).

Methods: ***In vivo***. Expression of Spns2 mRNA and protein in the kidneys and urine of C57BL/6 mice was analyzed 24 hours after sham surgery or IRI. Spns2 protein was assessed by western blot (WB) of membrane-enriched fractions of kidney. Renal function was evaluated by measurement of plasma creatinine. Spns2 localization and its co-localization with tubular markers in kidney (lens culinaris agglutinin, marker of brush border of S1-S3 segment of proximal tubules (PT) and wheat germ agglutinin a marker of brush border of S3 segment and cytosol of distal nephron) was by immunofluorescence (IF). To study the role of Spns2 after kidney injury, we pretreated mice 24h before IRI with Spns2 inhibitor (10 and 30 mg/kg, ip). ***In vitro.*** We generated clone with the highest Spns2 expression by the method of limited dilutions in TKPTS; Spns2 expression was validated by WB, quantitative real time PCR and IF.

Results: We demonstrated that the kidney has the highest mRNA expression of Spns2 when compared to other organs (liver, lung, spleen, heart, thymus). We determined that Spns2 is localized to the brush border of S1-S2 segment of PT and its expression is reduced 24h after IRI, while levels of Spns2 protein increased in urine. Pretreatment of mice with Spns2 inhibitor produced dose dependent protection against AKI, as judged by plasma creatinine and Kim1 mRNA expression at 24h after IRI and also induced dose dependent lymphopenia in mice. Spns2-overexpressing cells had increased TGFβ1 mRNA expression.

Conclusions: Spns2 is expressed in high abundance in kidney and is localized to the brush border of S1-S2 segments of the PT. Following IRI, PT Spns2 expression is reduced and appears in the urine. SPNS2 can serve as a potential target to prevent AKI, however further studies are needed to determine whether the protective effect of Spns2 inhibitor was due to lymphopenia or to a direct effect of Spns2 expressed in PT.

Funding: NIDDK Support

PO0162

Dietary Omega-3 Fatty Acids Alter the Lipid Mediator Profile and the Fatty Acid Composition of Membrane Phospholipids but Is Not Enough to Improve Renal Insufficiency

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Background: The efficacy of omega-3 fatty acids on ischemia-induced AKI has been reported, but the underlying mechanisms remain poorly understood. There have been no reports that demonstrated how dietary omega-3 fatty acids influenced the components of membrane phospholipids in the kidney. In this study, we focused on the effect of dietary omega-3 fatty acids on the membrane phospholipids components in the kidney, and examined the disease course of ischemia-induced AKI in the presence of the lipid mediator alterable by dietary omega-3 fatty acids.

Methods: Male 4-week-old wild-type Sprague-Dawley rats were fed for 2 months on AIN-93M, which contains 4% soy oil, or modified AIN-93M, which contains 4% perilla oil instead of soy oil. AKI was induced by unilateral ischemic reperfusion with right nephrectomy. Left renal ischemia was induced by using non-traumatic vascular clamps for 30 min. At 24h after reperfusion, left kidneys and serum were collected. The fatty acid composition of membrane phospholipids and lipid mediators were quantified by HPLC-tandem mass spectrometry (HPLC/MS/MS).

Results: In the kidney of omega-3 diet fed rats, the levels of arachidonic acid-derived proinflammatory lipid mediators, except for 5-HETE, were not reduced compared with omega-6 fed rats. Eicosapentaenoic acid (EPA) and EPA-derived lipid mediators were significantly increased in the kidney of omega-3 diet fed rats. Furthermore, membrane phospholipids which contained EPA and docosahexaenoic acid (DHA) were significantly increased in the kidney of omega-3 diet fed rats. However, there was no significant difference in serum creatinine, blood urea nitrogen or histological damage between omega-3 diet fed rats and omega-6 diet fed rats.

Conclusions: Dietary omega-3 fatty acids altered the lipid mediatorsthe and the fatty acid composition of membrane phospholipids, but was not enough to improve renal insufficiency or histological damage.

PO0163

A Vago-Sympathetic Reflex Mediates Kidney Protection from Ischemia-Reperfusion Injury

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Background: We recently showed that electrical stimulation of the cervical vagus nerve (VNS) protected mouse kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway (PMID: 27088805). Whether the protection is caused by the activation of vagal efferent or afferent fibers needs clarification.

Methods: We generated choline acetyltransferase-channelrhodopsin-2 (*Chat-ChR2*) mice and vesicular glutamate transporter 2 (*Vglut2*)-*ChR2* mice, which express ChR2 in vagal efferent and afferent neurons, respectively. Selective optogenetic stimulation of vagal sensory afferent fibers (*Vglut2-ChR2* mice) or efferent fibers (*Chat-ChR2* mice) was performed 24 h before bilateral renal IRI, and mice were euthanized 24 h after IRI.

Results: Optogenetic VNS protected kidneys from IRI in both *Chat-ChR2* and *Vglut2-ChR2* mice as shown by decreased plasma creatinine, reduced renal Kim-1 expression and improved kidney histology. Next, we sought to identify the circuitry responsible for the renal protection elicited by vagal sensory afferent stimulation (afferent VNS). The protective effect of afferent VNS persisted after blocking the rise in corticosterone with mifepristone or after subdiaphragmatic vagotomy, but was abolished by the sympathetic/parasympathetic ganglionic blocker hexamethonium. Moreover, ablation of the splenic nerve (predominantly sympathetic nerve) and splenectomy abolished the protective effect of afferent VNS. Finally, adoptive transfer of splenocytes from mice subjected to afferent VNS, as opposed to sham stimulation, protected recipient mice from kidney IRI, suggesting that splenocytes activated through the splenic nerve mediate the kidney protection.

Conclusions: Stimulation of either vagal efferent or afferent neurons protected the kidneys from IRI. The beneficial effect of afferent VNS requires the spleen and is mediated via a vago-sympathetic reflex.

Funding: NIDDK Support

PO0164

Kidney Functional Improvements by a Novel Potent and Selective Vasopressin V1a Antagonist After Ischemia/Reperfusion Injury (I/RI) in Rats

Karoline Droebner, Hana Cernecka, Chantal Fuerstner, Marie-Pierre L. Collin, Mira Pavkovic, Peter Hein, Frank Eitner, Peter Kolkhof. *Bayer AG, Wuppertal, Germany*.

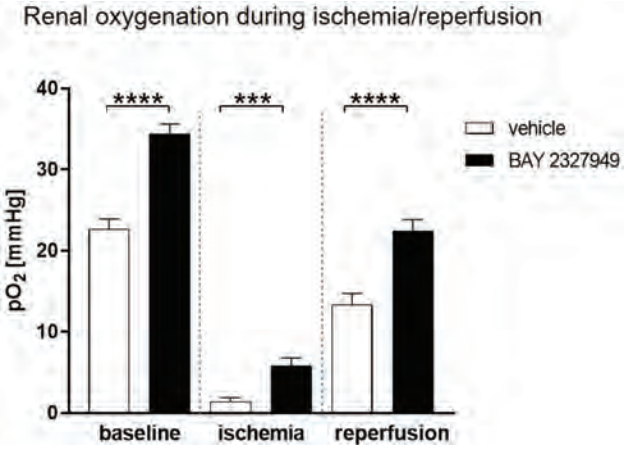
Background: Alteration in renal perfusion is a key pathologic mechanism implicated in the development of ischemic acute kidney injury (AKI). We have reported that activation of V1a receptor decreases renal blood flow (RBF) and oxygenation in settings of increased vasopressin (AVP) levels. Here we studied the role of BAY 2327949, a recently identified potent and selective V1a antagonist, in a rat renal I/RI model.

Methods: In a first setting, rats were infused with BAY 2327949 (100 µg/min/kg i.v.) or vehicle and baseline measurements were determined for 20 min. Unilateral ischemia was induced by clamping of left kidneys for 15 min, followed by 20 min of reperfusion. RBF and intrarenal oxygenation (pO_2) were continuously measured via Laser Doppler Flowmetry. In a second setting, kidney function (creatinine, cystatin C, urea) was studied 24h after 45 minutes of ischemia in uninephrectomised male rats treated with BAY 2327949 (0.5, 1 and 3 mg/kg BID, i.v.).

Results: Unilateral clamping resulted in an immediate drop of RBF and pO_2 that partially recovered during reperfusion (figure). Treatment with BAY 2327949 significantly ameliorated the severity of ischemic hypoxia and resulted in an improved and almost complete restoration of RBF and pO_2 during reperfusion (figure). In the second setting, preventive treatment with BAY 2327949 resulted in dose-dependent, significant improvements of kidney function parameters 24h post I/RI as compared to placebo treated rats.

Conclusions: BAY 2327949 is a novel potent and selective vasopressin V1a receptor antagonist blocking the detrimental effects of elevated vasopressin levels on renal perfusion and oxygenation. For these reasons, BAY 2327949 could become a viable treatment option in conditions of increased AVP levels, such as AKI and CKD.

Funding: Commercial Support - Bayer AG



PO0165

Augmenter of Liver Regeneration Protects Kidney from Ischemia-Reperfusion Injury via Regulation of TLR4/MAPKs Signaling Pathway

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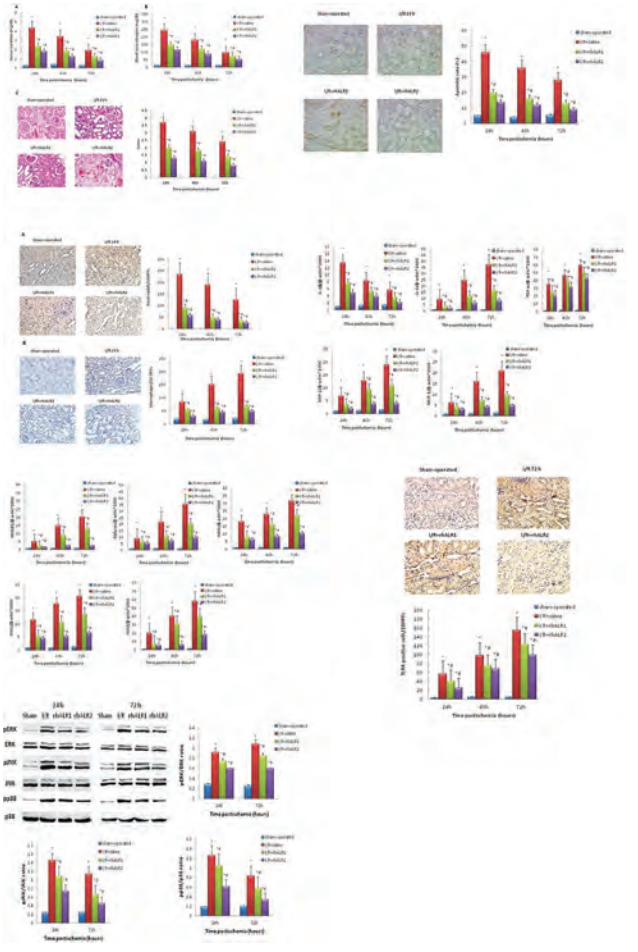
Background: Toll-like receptor 4 (TLR4) expressed within the ischemic kidney is a crucial mediator of innate activation and inflammation. The augmenter of liver regeneration (ALR) is an immunoregulator which is highly expressed in kidney upon induction of renal I/R injury. It has been shown that exogenous ALR can protect kidney against I/R injury. However, whether ALR's protective effect results from its immune regulatory function has yet to be determined. In this study, we show that treating renal I/R induced-rats with recombinant human ALR (rhALR) protects them from kidney I/R.

Methods: Rats were randomized into 4 groups as follows: sham-operated group; I/R group; I/R+rhALR1 group; I/R+rhALR2 group. TLR4, neutrophils and macrophages were detected by immunochemistry. ERK, JNK, and p38 proteins were tested by WB. mRNA of HMGB-1, Biglycan, HAS1, HAS2 and HAS3 was detected by real-time PCR. The cytokines and chemokines were measured by ELISA.

Results: This result is corroborated by less tubular damage on rhALR treated rats than those on untreated rats. rhALR treated rats have significantly less apoptosis in tubular epithelial cells, less tubulointerstitial infiltration by neutrophils (24 h) and macrophages (72 h), as well as lower levels of inflammatory cytokines compared to the untreated control rats. Furthermore, rhALR downregulate mRNA expression of endogenous liagands for TLR4 and restrain activation of TLR4 and downstream signaling molecules (ERK, JNK and p38) on rats with renal I/R injury.

Conclusions: rhALR protects kidney from I/R injury by relieving the inflammatory responses via regulation of TLR4 signaling pathway. These results suggest that ALR might be used in the development of novel immune therapy for the renal IRI

Funding: Government Support - Non-U.S.



rhALR protects kidney from I/R injury by regulation of TLR4 signaling pathway

PO0166

DPP-4 Inhibitor Attenuated Renal Vasoconstriction Following Ischemia-Reperfusion Injury in Cirrhotic Rats

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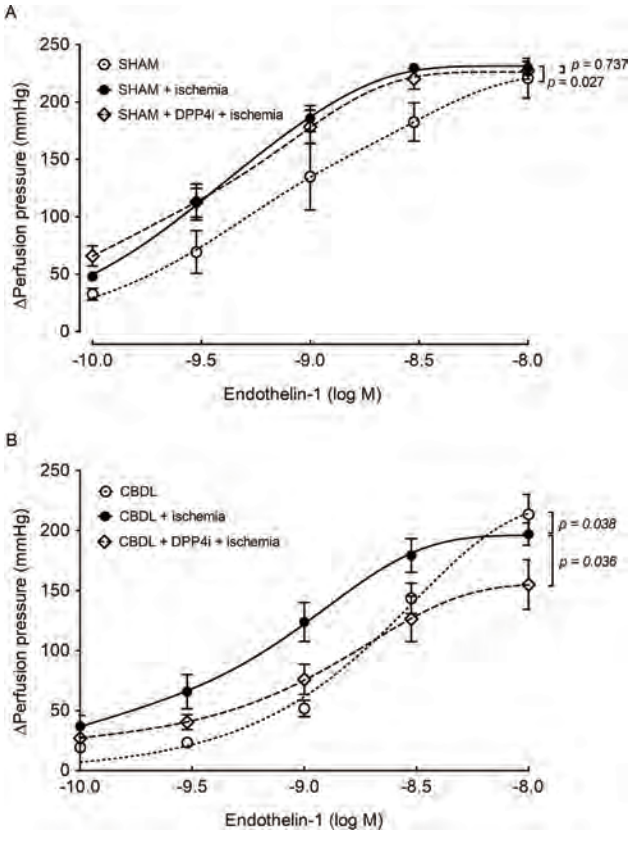
Background: Cirrhotic patients may develop esophageal varices to cope with portal hypertension. Variceal bleeding is usually associated with hypotension and ischemia-reperfusion injury (IRI) which may activate endogenous vasoconstrictors, leading to severe renal vasoconstriction and renal failure (so called hepatorenal syndrome). Previous studies reported that dipeptidyl peptidase-4 inhibitor (DPP4i) could attenuate the endothelin-1 (ET-1) induced vasocontraction and increase vasodilation. The aim of this study is to delineate the effect of DPP4i in renal vascular reactivity of cirrhotic rats following IRI.

Methods: Male S-D rats were used for experiments. Biliary cirrhosis was created by common bile duct ligation (CBDL). Control group received sham surgery (SHAM). After surgery, Linagliptin (3 mg/kg/d) or distilled water (DW) was administered for 28 days. On the 29th day, bilateral renal pedicles were clamped with microvascular clamps for 45 minutes in IRI group. The clamps were then removed followed with 60 minutes of reperfusion. Kidneys were perfused in situ via right renal artery for continuous monitoring of renal perfusion pressure.

Results: There was no difference in mean arterial pressure, heart rate, portal pressure, and blood sugar between DW and DPP4i treated rats. IRI enhanced renal vascular response to ET-1 in both SHAM (p=0.027) and CBDL (p=0.025) rats, implying renal vasoconstriction. Compared with corresponding DW-treated rats, DPP4i treatment abrogated renal hyperreactivity following IRI in CBDL rats (p=0.036), but not in SHAM rats (p=0.737).

Conclusions: We concluded that DPP4i may attenuate the development of renal vasoconstriction following IRI in cirrhotic rats. The potentially mechanisms remained to be elucidated.



Concentration-response curves to ET-1 in perfused kidneys of SHAM (A) and BDL (B) rats.

PO0167

PTEN Protects Against Ischemia Reperfusion-Induced AKI via Regulating TNF-α Mediated Apoptosis

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Background: Recently, PTEN, a vital tumor suppressor, has been raised its role in kidney homeostasis. We previous demonstrated that podocyte-specific knock-in of PTEN alleviated albuminuria and glomerulosclerosis in diabetic kidney disease. However, whether PTEN involves in acute kidney injury (AKI) remains unclear.

Methods: The levels of PTEN in renal tissue and serum were detected in ischemia-reperfusion (IR)-induced AKI mice with different ischemia time. Expression of PTEN was also detected in IR-induced cultured HK-2 injury with different ischemia and reperfusion time using ATP/glucose depletion that concentration of antimycin A mimicked the severity of ischemia. Immunoprecipitation and mass spectrometry were combined to analyze differential PTEN-interacting proteins among control, IRI+LV-NC and IRI+LV-PTEN groups. PTEN intervention including knock-down (si-PTEN) and knock-in (lentivirus-PTEN) was performed in HK-2 to reveal the role and mechanism of PTEN in IRI-AKI.

Results: PTEN was significantly reduced in renal tissue and serum in AKI mice at bilateral renal artery occlusion for 28 min and 35 min, and reperfusion for 1 day compared with sham group (P<0.05). Concentration of serum PTEN was negatively correlated with level of serum creatinine (r=-0.87, 95% CI: -0.94 to -0.71). PTEN was also downregulated in IR-induced HK-2 injury in an antimycin A concentration dependent manner (P<0.05). There were 23 upregulated (ACO2, BRCA1, USP30), and 20 downregulated (BIN1, pericentrin, SLC12A5) PTEN-interacting proteins in IRI+LV-PTEN group compared with IRI+LV-NC group. Gene Ontology enrichment analysis showed that overrepresentation of differential PTEN-interacting proteins functionally related to cytoskeleton, and ATPase activity. Pathway analysis showed a great role of differential PTEN-interacting proteins in apoptosis, and necroptosis. Knockdown of PTEN increased the expression of NGAL, CTGF and TNF-α in IR-induced HK-2 injury (P<0.05), while overexpression of PTEN alleviated IR-induced injury (P<0.05).

Conclusions: PTEN was decreased in renal tissue and serum associated with severity of renal injury in IRI-AKI mice, suggesting that PTEN is promising to be a serum biomarker for early prediction and evaluation of AKI. PTEN protected HK-2 from IR-induced injury possibly via regulating cytoskeleton and TNF-α mediated apoptosis signal.

PO0168

Endothelial Prolyl-Hydroxylase Domain Proteins Regulate Capillary Rarefaction Following Ischemic AKI and Reprogram Endothelial Metabolism

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Background: Endothelial cell (EC) metabolism has emerged as a new regulator of EC behaviour, but its role in capillary rarefaction, a common feature of progressive renal disease, remains unknown. Because EC sense oxygen and metabolic alterations through Prolyl hydroxylases 1 to 3 (PHD1-3), here we wished to define the impact of PHD inactivation on post-ischemic kidney injury outcomes, while in vitro studies focused on metabolic consequences.

Methods: Following the induction of renal ischemia-reperfusion injury (IRI), concurrent deletion of PHD1,2,3 was achieved by the Cdh5(PAC)CreER inducible system. Analysis was performed at day 14 post-IRI. Furthermore, we examined the impact of DMOG, a PHD inhibitor on angiogenic capabilities and global metabolic profiles of endothelial cells.

Results: Post-ischemic kidneys of PHD1,2,3^{ECKO} showed more fibrosis, as indicated by 68% increase in collagen area (P=0.005) and significant upregulation of profibrotic genes *Loxl2*, *Tgf-β and Acta2* (n=6-8, P<0.5) compared to controls. Quantitative analysis of endomucin staining showed 50% decrease in peritubular capillary density, associated with reduced endothelial proliferation as indicated by Ki-67 immunostaining (n=4, p=0.005). Notably, biochemical inactivation of PHDs by DMOG reduced EC proliferation in MTT assay (P= 0.0001) while cell cycle analysis showed decrease of cells in S (~39%, n=3, p=0.0007) and G2/M phase (~24%, n=3, p=0.04). Furthermore, DMOG reduced EC migration (50%, n=3, p=0.005) and tube formation. LC-MS analysis showed a profound effect of DMOG in glycolytic, TCA cycle, lipid and, nucleotide metabolites. Specifically, EC treated with DMOG showed an increase in lactate (1.46-fold, p<0.05) and significant reductions in citrate (2.2 fold, p<0.001), alpha-ketoglutarate (2.5 fold, p<0.001), fumarate (1.4-fold, p<0.05) and malate (1.3 fold, p<0.01). Supplementation with citrate partially rescued the proliferation defect induced by DMOG, suggesting that PHDs may affect angiogenic responses through alterations in mitochondrial metabolism.

Conclusions: Post-ischemic endothelial inactivation of PHDs promotes peritubular capillary rarefaction and fibrosis following AKI, a response which could involve alterations in mitochondrial metabolism.

Funding: NIDDK Support

PO0169

Treprostinil Inhibits Mitochondria-Mediated Apoptosis During Renal Ischemia-Reperfusion Injury in Rats

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Background: Renal ischemia-reperfusion (I/R) injury is a major factor that contributes to acute kidney injury, which is associated with high morbidity and mortality. Renal I/R injury compromises mitochondrial structure and function, further exacerbating renal tubular injury. Currently, there is no treatment for I/R injury available. We recently demonstrated the efficacy of treprostinil (Remodulin®), an FDA-approved prostacyclin analog, in reducing acute kidney injury during bilateral rat renal I/R injury. This study investigates the role of treprostinil in reducing mitochondria-mediated apoptosis during rat renal I/R injury.

Methods: Male Sprague Dawley rats were randomly assigned to groups: control, sham, I/R-placebo or I/R-treprostinil and subjected to 45 minutes of bilateral renal ischemia followed by 1-72 hours reperfusion. Placebo or treprostinil (100 ng/kg/min) was administered subcutaneously via an osmic minipump. Blood and kidney tissue were collected for analysis.

Results: Treprostinil significantly reduced peak elevated SCr vs. placebo (0.6 ± 0.05 vs. 2.1 ± 0.2 mg/dl, p<0.001) at 24-hour post-reperfusion. Treprostinil also prevented I/R-mediated renal apoptosis at 6-hour post-reperfusion vs. placebo (1.0 ± 0.01 vs. 1.4 ± 0.01, p<0.001) relative to control, determined by TUNEL assay. Mitochondrial DNA (mtDNA) copy number was reduced by 23% in I/R-placebo group (p=0.067) from control, starting by 1-hour post-reperfusion. In contrast, treprostinil preserved mtDNA content to control levels (p<0.01). In addition, placebo increased cytochrome c release into cytosol by 2.4-fold vs.control (p<0.05) at 1-hour post-reperfusion, which treprostinil prevented. Non-targeted semi-quantitative proteomics data using SWATH-MS show decreased renal ATP levels in placebo, which were restored by treprostinil to that of control at 6-hour post-reperfusion (p<0.05).

Conclusions: Our results demonstrate that treprostinil reduces mitochondrial-mediated renal apoptosis, evidenced by reduced cytochrome C release, restored mtDNA copy number and ATP protein concentration to that of control kidney levels, thereby accelerating mitochondrial recovery and protecting renal tubules from I/R-induced apoptosis. These results suggest that treprostinil is a viable therapy to reduce renal I/R injury.

Funding: Other NIH Support - The material presented herein is in part supported by Institutional Development Award (IDeA) #U54GM115677 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds Advance-CTR (Brown University), and University of Rhode Island Core Lab (P20GM103430). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

PO0170

DNA Repair Factor KAT5 Acts Against Ischemia-Reperfusion Injury Through Promoted DNA Repair and KCC3-Dependent TGF Regulation in Proximal Tubular Cells

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Background: It is known that an episode of ischemia-reperfusion (IR) results in tolerance to subsequent IR, which is so-called "pre-conditioning (PC) effect". However, the molecular mechanisms of the pre-conditioning effect have not been adequately elucidated. We have recently discovered that DNA double strand break (DSB) repair factor KAT5 is essential for maintenance of podocyte integrity (Cell Rep. 2019). Here we investigated the role of KAT5 in PC effect.

Methods: Wild-type (WT) mice and proximal tubular epithelial cell (PTEC)-specific KAT5 knockout (KO) mice underwent IR injury by clamping bilateral renal arteries for 30 minutes followed by reperfusion. Ischemic pre-conditioning was performed 1 week prior to IR injury. In vitro studies using cultured human PTECs (HK2 cells) were conducted with ATP depletion by Antymicin A (AMA), an in vitro model of acute tubular cell damage.

Results: Serum UN, Cr, urine NGAL, DNA DSB marker γH2AX and KAT5 expression of the PTECs were increased and chloride transoporter KCC3 expression was decreased at 24 hours after IR. IR with PC showed an attenuated increase in serum UN, Cr, urine NGAL and DNA DSBs with accelerated KAT5 and KCC3 expression. Mass spectrometry imaging of the kidney cortex following the first IR demonstrated elevated glomerular adenosine, which is used as a marker of accelerated tubule-glomerular feedback (TGF), whereas it was decreased after the second IR with PC in WT mice, suggesting attenuated TGF in the second IR. Therefore, increased chloride uptake through KCC3 in PTECs may contribute to the suppression of TGF, which maintained GFR. In KAT5 KO mice, PC effect was attenuated with increased DNA damage and decreased KCC3 expression. In vitro ATP depletion studies showed elevated KAT5 and KCC3 expression following second treatment with AMA. Chromatin accessibility assay showed promoted chromatin accessibility of the KCC3 promoter region after the second treatment with AMA. ChIP analysis revealed that KAT5-binding KCC3 promoter region was significantly increased after the second injury compared with the first injury, indicating that elevated KCC3 expression was caused by increased binding of KAT5 to the KCC3 promoter region.

Conclusions: PTEC KAT5 may act against IR injury through promoted DNA repair and regulation of TGF via KCC3 expression.

PO0171

Kidney Proximal Tubular NFκB Essential Modulator Exacerbates Ischemic AKI

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Background: Ischemic acute kidney injury (AKI) is a major clinical problem. We previously showed that renal tubular peptidylarginine deiminase 4 exacerbates ischemic AKI by promoting pro-inflammatory NFκB activation pathway via selective citrullination of NFκB Essential MOdulator (NEMO). Since NEMO plays important and diverse physiological roles in almost all cell types, here, we tested whether renal proximal tubular (PT) NEMO plays a critical role in ischemic AKI utilizing mice lacking PT NEMO and by targeted PT NEMO inhibition with mesoscale nanoparticle encapsulated NEMO binding peptide (NBP MNP) delivery.

Methods: We subjected PT NEMO deficient mice, wild type (WT) mice and C57BL/6 mice to 30 min renal ischemia and 24 hours reperfusion (RIR). C57BL/6 mice received NBP MNP before RIR injury to test whether selective PT NEMO inhibition attenuates ischemic AKI. Separate cohorts of PT NEMO deficient mice or WT mice were injected with recombinant PAD4 (rPAD4) before 20 min renal ischemia to test whether PAD4-mediated exacerbation of ischemic AKI is PT NEMO dependent. In addition, isolated PT from PT NEMO deficient mice and WT mice were treated with rPAD4 or human PT cells were treated rPAD4 after pretreatment of NBP MNP to determine whether PAD4 activates renal proximal tubular pro-inflammatory signaling via NEMO activation.

Results: PT NEMO deficient mice and C57BL/6 mice treated with NBP MNP were protected against ischemic AKI with decreased plasma creatinine (1±0.2, 1.7±0.2 mg/dL), NGAL mRNA (153.6±31.8, 433.2±54.7 fold increase over sham, N=5-7), renal tubular necrosis, inflammation and apoptosis compared to WT or control MNP treated mice (Cr=2.1±0.03, 2.7±0.2 mg/dL, NGAL=752.8±176.3, 840.8±74.7 fold increase over sham, N=5-7). Exogenous rPAD4 exacerbated RIR injury in WT mice but not in PT NEMO deficient mice. Furthermore, rPAD4 upregulated pro-inflammatory cytokine and NFκB activation in freshly isolated PT cells from WT mice but not from PT NEMO deficient mice. Treatment of NBP MNP also protected rPAD4-mediated pro-inflammatory cytokine induction in cultured human PT cells.

Conclusions: Taken together, our studies suggest that renal PT NEMO plays a critical role in ischemic AKI by promoting renal tubular inflammation, apoptosis as well as necrosis. Our studies provide novel insight to the pathophysiology of PT NEMO in ischemic AKI, suggesting a potential therapy for ischemic AKI.

Funding: NIDDK Support

PO0172

Blocking the Histone Lysine 79 Methyltransferase DOT1L Ameliorates AKI

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Background: The Disruptor of telomeric silencing 1-like (DOT1L) gene encodes a histone methyltransferase that methylates lysine-79 of histone H3 (H3K79). DOT1L-dependent H3K79 methylation plays an important role in various physiological and pathological processes, including transcriptional regulation, embryonic development and renal fibrosis. However, its role in acute kidney injury (AKI) tissue injury remains unknown.

Methods: AKI was induced in Male C57/B6 mice by bilateral ischemia-reperfusion (IR) injury or intraperitoneally injection with folic acid (FA). EPZ5676, a highly selective inhibitor of DOT1L (20 mg/kg) or an equal volume of vehicle was administered immediately after IRI or FA injection and then daily for two days. Renal function and histology were assessed by serum creatinine and HE staining. Immunohistochemistry and Western blotting were performed to identify tubule injury (NGAL), apoptosis (TUNEL and cleaved Caspase 3), proliferation (PCNA and Cyclin D) and Wnt signaling activation (active β-catenin and β-catenin).

Results: Mice developed AKI at 48 h after IR injury or FA administration as shown by the upregulation of serum creatinine and NGAL expression levels. Pharmacologic inhibition of DOT1L with EPZ5676 resulted in less severe tubular injury as evidenced by reduced renal dysfunction, diminished NGAL expression. Furthermore, the administration of EPZ5676 significantly reduced the number of TUNEL-positive and cleaved caspases-3 positive tubular cells in kidney tissues. Conversely, renal tubular cell proliferation was enhanced as indicated by increased expression of PCNA and cyclin D. Moreover, DOT1L inhibition by EPZ5676 up-regulated the expression of active β-catenin form and β -catenin.

Conclusions: Our data reveals that blocking DOT1L with EPZ5676 may protect against AKI in mice through inhibition of apoptosis and enhancement of kidney repair by a mechanism involved in the modulation of the canonical Wnt signaling pathway.

Funding: Private Foundation Support

PO0173

Triptolide Treats Renal Tubular Injury Induced by Renal Ischemia-Reperfusion Through Specific Delivery of Kidney-Targeting Nanoplatform

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Background: Triptolide (TP) has been proved to be effective in the treatment of a variety of kidney diseases. Unfortunately, its clinical application is limited because of its high toxicity and low specificity. Here, we report a novel and safe kidney-targeting nanoplatform for specific delivery of TP.

Methods: Nano-polymer MNPs-TP was synthesized by encapsulating TP in a mesoscale nanoparticles (MNPs) with kidney targeting ability. MNPs-TP was injected into mice via tail vein to evaluate its toxicity to organs and immune system, and compared with free TP. The targeting and mechanisms of MNPs-TP treatment were explored by organ imaging, Transwell and other experimental methods. Finally, the model of renal ischemia-reperfusion injury (IRI) in mice was established, and the protective effects and mechanisms of TP and MNPs-TP on renal tubules in different concentrations were compared.

Results: Toxicity test showed serious pathological changes in liver, testes and the proportion of CD4+/cd8+ in blood of mice in TP group, while MNPs-TP showed no obvious toxic effect on these organs and immune system. The organ imaging and pharmacokinetic experiments indicated that free TP showed a fast metabolism and no specificity in the distribution of free TP in various organs, while the MNPs-TP showed longer metabolic cycle and clear kidney targeting. Immunofluorescence assay of kidney sections showed that MNP-TP was mainly concentrated in the cytoplasm of renal tubular cells. After administration of TP at the dose of 0.1mg/kg body weight to the IRI mice, the renal function represented by BUN and SCr of IRI mice was alleviated. Down-regulation of p-ERK and NGAL suggested that TP could help protect the renal tubules by down-regulating MEK-ERK pathway and alleviated apoptosis of renal tubules. Free TP at the dose of 0.01mg/kg lacked these protective effects, and surprisingly, MNPs-TP kept the protection, which demonstrated that the effective therapeutic dose of MNPs-TP was significantly lower relative to free TP.

Conclusions: MNPs-TP showed superior therapeutic effect on renal ischemia-reperfusion injury in comparison with TP. Furthermore, MNPs-TP conjugate presented much lower hepatotoxicity and no adverse effect on the immune and genital system. The kidney-targeting MNPs may provide a promising drug delivery platform of hydrophobic drugs for treatment of renal diseases.

PO0174

Fractional Excretion of NGAL Is Useful to Distinguish Prerenal Azotemia (PRA) from Acute Tubular Injury (ATI) in Mice

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Background: NGAL (*Lcn2*) is one of the most widely studied biomarkers of acute kidney injury (AKI). Our previous studies demonstrated that the primary source of plasma and urine NGAL after AKI is the liver and it is IL-6 dependent. Since the primary source

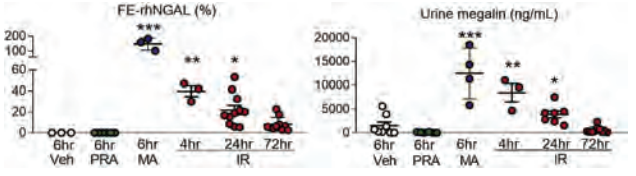
of urine NGAL is from the plasma, our next step was to examine the renal handling of plasma NGAL.

Methods: Mice: C57Bl/6J. Interventions: bilateral kidney ischemia reperfusion (IR) - 27 minutes; maleic acid (MA) (400mg/kg pH7.4 in saline, IP); furosemide (4mg, IP); uninjured vehicle animals served as a control. Recombinant human (rh) NGAL (5µg, IV) was injected to determine the fate of circulating NGAL. Measurements: transcutaneous glomerular filtration rate (tGFR), rhNGAL and mouse (m) NGAL in the plasma and urine, megalin in the urine. To link proximal tubular (PT) function with plasma and urine NGAL levels, we calculated the fractional excretion of rhNGAL (FE-rhNGAL): FE-rhNGAL = ([urine {rhNGAL} x plasma creatinine]/ [plasma {rhNGAL} x urine creatinine]) x 100.

Results: Uninjured vehicle: mice had 100% tGFR and low levels of plasma and urine (rh)NGAL. IR (ATI model) and MA (PT injury model): 1% and 29% tGFR respectively, increased plasma and urine rhNGAL in both models. Furosemide (PRA model): tGFR – 30%, plasma rhNGAL was slightly elevated, urine rhNGAL was similar to control. FE-rhNGAL was less than 1% in normal and PRA mice, and it was greater than 20% in IR and MA treated mice. mNGAL plasma and urine levels, and FE-mNGAL were similar to rhNGAL levels and FE-rhNGAL respectively. Urine concentration of megalin correlated with FE-rhNGAL in every intervention (see Figure). Megalin is expressed on the brush border of PT and is responsible for the resorption of most filtered proteins, including NGAL.

Conclusions: Our data suggest that normal PT function is required for the clearance of plasma NGAL. Consideration of plasma NGAL with FE-NGAL is important to interpret urine NGAL levels and PT function and effectively distinguishes PRA from ATI.

Funding: Veterans Affairs Support



PO0175

A Case Report of Vaping-Related Renal Thrombotic Microangiopathy

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Introduction: Acute kidney injury (AKI) and hematuria have been reported in patients with E-cigarette use (vaping)-associated lung injury (EVALI) but exact renal pathology is not well understood. We report a case of biopsy proven renal thrombotic microangiopathy (TMA) in a patient with EVALI.

Case Description: A 40-year-old woman with history of vaping tetrahydrocannabinol (THC) and depression presented to emergency room with 2 days of fatigue, body aches, non-productive cough, and dyspnea on exertion. On admission, BP was 157/85 mmHg, hemoglobin 6.9, platelet count 239, serum creatinine (SCr) 1.76 with 10-30/hpf non-dysmorphic RBC and 2+ proteinuria on urinalysis. Patient failed initial treatment with diuretics and on day 3, was intubated for respiratory distress. By this time, SCr had increased to 4.68 and LDH was quite elevated (1456) but platelet count was normal (194), haptoglobin high (551) and peripheral schistocytes only occasional. Her EVALI improved with standard cares in the next week but renal function further worsened, and hemodialysis was started on day 13. Renal biopsy revealed acute TMA with diffuse endothelial swelling, focal segmental glomerular and arteriolar thrombi and acute tubular injury. Patient was not taking any medications known to cause TMA. Serologic and infection work up were negative including pneumococcus, HIV, antinuclear, anti-Scl70 and antiphospholipid antibodies. The ADAMTS-13 activity was 48% and serum homocysteine was low (3.8). Imaging studies showed no evidence of malignancy. Functional complement work-up did not reveal increased alternative complement pathway activity or autoantibodies. On day 20, patient was started on plasma exchange (PLEX) for 5 sessions followed by a slow renal recovery - last hemodialysis on day 22 and now, more than 1 month after last PLEX and after approximately 2 months of vaping cessation, most recent SCr is 2.57

Discussion: There is no clear association of kidney disease with marijuana use in large population studies but there are case reports of AKI with synthetic cannabinoid use including one report of biopsy proven TMA. Drug-induced TMA is usually a diagnosis of exclusion and temporal correlation. Given the lack of other evident cause of TMA, our case suggests a potential association between THC and/or vaping and renal TMA.

PO0176

A Rare Case of Obstructive Nephropathy with Intratubular Tamm-Horsfall Polyps Secondary to Acquired Hemophilia

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Introduction: Acquired hemophilia has been rarely implicated in obstructive nephropathy. We present a case of gross hematuria, bilateral hydronephrosis, and biopsy-confirmed tubulointerstitial nephritis with intratubular Tamm-Horsfall Protein (THP) polyps. These atypical pathological aggregations of urinary glycoproteins were previously described to be located in renal veins or lymphatics. Our case represents a rare etiology of obstructive nephropathy, with unique pathological findings, secondary to an acquired hemophilia.

Case Description: A 64-year-old man with hypertension and tobacco use presented with bilateral flank pain and gross hematuria. Urinalysis showed hematuria, pyuria, and proteinuria. He had oliguric acute kidney injury (AKI) with creatinine (Cr) of 3.2 mg/dL. Renal ultrasound showed bilateral hydronephrosis. Renal function deteriorated over 3 days to Cr of 7.4 mg/dL with proteinuria of 10 g/day. Serologic markers revealed mildly elevated PR3-ANCA. Pulse steroid therapy was begun and kidney biopsy was performed. Pathology report described acute tubulointerstitial nephritis with THP polyps and interstitial non-caseating granulomas. Immunohistochemistry assay showed THP polyps within markedly dilated renal tubules, consistent with obstructive nephropathy. No glomerulitis or vasculitis was seen. After biopsy, the patient developed retroperitoneal hemorrhage requiring embolization. Further studies indicated the presence of a factor VIII inhibitor. He improved with transition from steroids to mycophenolate mofetil. A few months later, his renal function returned to normal with a bland urinalysis, proteinuria less than 100mg/day and resolution of hydronephrosis.

Discussion: We encountered a rare presentation of acquired hemophilia with macroscopic hematuria and AKI. We suspect that bladder clots and associated intraluminal clots resulted in elevated tubular pressures causing obstructive nephropathy and the formation of intratubular THP polyps. Administration of immunosuppressive therapy decreased tubulointerstitial inflammation as well as factor VIII inhibitor production, reinforcing our hypothesis. Anti-factor VIII antibodies are a rare complication of solid tumors and urologic malignancy work-up is ongoing.

PO0177

Reflex Anuria: A Forgotten Urologic Etiology of AKI

Hassan Mahmoud, Jasvinder S. Bhatia. *Boston Medical Center, Boston, MA.*

Introduction: Reflex anuria (RA) is a rare entity that can lead to severe acute kidney injury (AKI). It was defined by Hull and colleagues in 1980 as "cessation of urine output from both kidneys in response to irritation or trauma to one kidney or its ureter or severe painful stimuli to other pelvic organs". RA represents a gray area between nephrology and urology that should be considered in the differential diagnosis of AKI. We present a case of AKI and anuria where the prompt recognition and management of RA resulted in full recovery of kidney function and avoidance of renal replacement therapy and unnecessary testing.

Case Description: A 40-year-old male with Crohn's disease status post prior right and left hemicolectomy was admitted with worsening abdominal pain and hematochezia consistent with Crohn's flare. He underwent open abdominoperineal resection. Pre-operatively, urology performed cystoscopy and prophylactic bilateral ureteral stent placement. Stents were removed without complication at the end of the case. On post-op day 1, he developed oliguria that progressed to complete anuria. This was associated with rapid rise in serum creatinine up to 5.5 from baseline of 0.6 (Figure 1). The differential diagnosis was broad, including acute tubular necrosis, vascular thrombosis and obstruction, but because of the temporal relationship with recent procedures, RA was suspected as the etiology of AKI. Patient underwent urgent bilateral ureteral stent placement which was followed by brisk urine output (~11 L/24 hours) and normalization of serum creatinine.

Discussion: RA is a rare diagnosis that requires high index of clinical suspicion. It is a functional rather than parenchymal disease that can cause dramatic cessation of urine output and AKI. Neurovascular reflex leading to arteriolar vasoconstriction and ureteric spasm is a proposed mechanism. This case illustrates that acute anuria and AKI after surgical procedures should prompt nephrology consultants to consider this uncommon diagnosis.

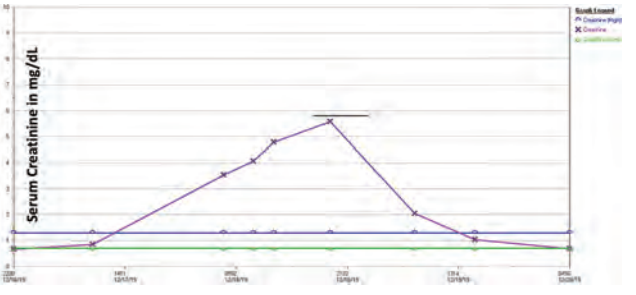

Figure 1. Acute rise in serum creatinine on post-op day 1 followed by rapid resolution of AKI after bilateral ureteral stent placement.

PO0178

AKI in a Patient with COVID-19, G6PD Deficiency, Acetaminophen Overdose, and Methemoglobinemia: What a Broad Differential!

M. Catalina Morales-Alvarez, Benjamin Benhuri, Michelle Shah, Boram Kim. *Mount Sinai Beth Israel Hospital, New York, NY.*

Introduction: Acute kidney injury (AKI) is a common complication in hospitalized and critically-ill patients. Prompt evaluation and subsequent management is warranted to avoid long term kidney dysfunction. However, a clear diagnostic pathway is not always possible. We present a case and the diagnostic analysis of intrinsic AKI in an unusual confluence of comorbidities.

Case Description: 39 year-old man with no past medical history referred from another institution with COVID-19 pneumonia, for which he completed 4 days of hydroxychloroquine. On admission, patient was found to have SCr of 2.0 mg/dL, which increased to 10.8 mg/dL during a 3-day period. Urinalysis showed dysmorphic RBCs but no casts. Total albumin/cr ratio in urine was 3.2 mg/g and FeNa >1%. Renal ultrasound showed no obstruction or masses. Other laboratory results showed methemoglobinemia (14 mg/dL), acute liver failure, schistocytes in the peripheral smear and a G6PD assay with marked deficiency. Other serologies were negative. Patient reported prior ingestion of 1 gr acetaminophen (APAP) every 4 hrs for several days; treated with 48 hrs of N-acetylcysteine infusion. The AKI was complicated by hyperkalemia, severe anion gap metabolic acidosis and volume overload requiring long term renal replacement therapy after failure of resuscitation with crystalloid, albumin, and vasopressors.

Discussion: Our patient presented with significant abnormalities in multiple organ systems, including AKI. An analysis of comorbid conditions and typical AKI diagnostics allowed an expansive differential diagnosis (fig 1). One remaining interrogate was the value of a kidney biopsy. Although the etiology of his AKI would remain uncertain and presumably multifactorial, the lack of a clear therapeutic option and both hemodynamic instability and high risk of complications impeded a kidney biopsy. This case exemplifies the challenging but common scenarios and dilemmas that nephrologists face every day. AKI is a well-described entity, yet its diagnosis is complex and dynamic.

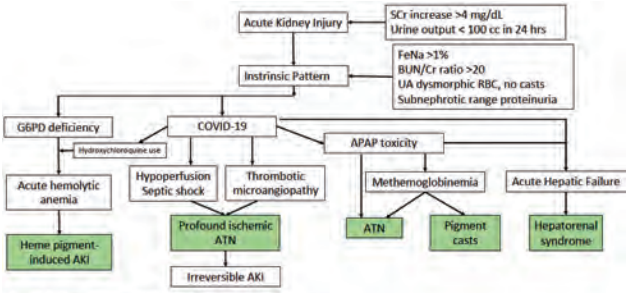

Figure 1. Diagnostic approach and differential diagnosis

PO0179

Catch 22: The Vicious Cycle of Malignant Hypertension and Worsening Renal Thrombotic Microangiopathy

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Introduction: Renal Thrombotic microangiopathy (TMA) may arise from multiple distinct etiologies. Malignant hypertension is one of these conditions that can precipitate and worsen Renal TMA. The detection of C5B-9 on endothelial cells may help determine the timing and selection of treatment to break the vicious cycle of malignant hypertension and worsening renal TMA.

Case Description: 34-year-old woman with a history of gestational hypertension, presented to the ED with complaints of a viral URI and was found to be in hypertensive emergency with an SBP in the 260's. She was a non-smoker and did not use drugs or alcohol. She denied having any other symptoms or any recent medication use. Her labs were notable for hemolytic anemia and acute kidney injury with a creatinine of 4.0 mg/dL. A peripheral smear confirmed schistocytes, along with a normal serum ADAMTS 13 activity at 89. Extensive work-up for atypical hemolytic uremic syndrome was negative and complement levels were normal. Renal ultrasound showed diffusely increased renal cortical echogenicity. Renal biopsy confirmed the diagnosis of acute on chronic thrombotic microangiopathy with severe endothelial swelling and onion-skin lesions of the arterioles and small arteries. Her creatinine peaked at 5.49 mg/dL, but urine output was stable, and she never required dialysis. She was treated with aggressive antihypertensives with consideration of eculizumab therapy.

Discussion: Eculizumab was approved to inhibit complement-mediated TMA in atypical HUS in 2011. The literature describes complement-amplifying conditions including malignant hypertension, complications of pregnancy, and autoimmune diseases being associated with the onset of TMA as they activate the alternative complement pathway in up to 69% of cases with atypical HUS. Standard therapies for malignant hypertension do not address underlying complement dysregulation and TMA may persist despite blood pressure management. The 'domino effect' created by this inflammatory cascade is difficult to reverse and may benefit from eculizumab therapy, whether they have a genetic predisposition or not. The detection of C5B-9 formation on the endothelial cells may reflect complement defects among patients with TMA and severe hypertension, which can be a valuable tool in sub-stratifying whether these patients may benefit from terminal complement inhibitor therapy.

PO0180

Acute Interstitial Nephritis and Diffuse Pulmonary Infiltrates in Recreational Drug User

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Introduction: Synthetic cannabinoids are designer drugs smoked as an alternative to marijuana with lower cost and greater potency. Here we describe a patient who presented with acute kidney injury and diffuse pulmonary infiltrates with recent inhaled synthetic cannabinoids use.

Case Description: A 26-year-old man with history of alcohol and recreational drug abuse including marijuana, tobacco and vaping, presented with acute kidney injury and diffuse pulmonary infiltrates. He recalled attending a party a week ago where he smoked someone else's marijuana. On presentation, he was hypertensive to 170/115 mmHg with benign physical examination. Laboratory values were significant for serum creatinine of 17 mg/dL and BUN of 162 mg/dL. Urine sediment showed no cellular casts, but some monomorphic red blood cells, rare dysmorphic red blood cells and white blood cells. He had a spot protein/creatinine ratio of 230 mg/g, Chest X-ray showed bilateral pulmonary infiltrates. Renal ultrasound showed normal kidneys. Laboratory studies were all negative including CK, ANCA, anti-GBM, ANA, dsDNA, SPEP and legionella urinary antigen. His urine toxicology screen was positive for opiates and cannabinoids. Renal biopsy revealed widespread edema of the interstitium and a mild to focally moderate inflammatory infiltrate involving approximately 80% of the cortical area. Tubular dilation, cytoplasmic vacuolization, and rare mitoses were seen in the tubules. He required 2 sessions of hemodialysis, but he had a rapid resolution of his kidney failure with steroid initiation. A repeat chest CT showed resolution of bibasilar opacities, although with persistent upper lobe ground glass opacities consistent with smoking and vaping-related injury.

Discussion: Synthetic cannabinoids use should be considered in young healthy patients who present with unexplained AKI, as there are more case reports suggesting its direct nephrotoxicity. The etiology of tubulointerstitial injury from synthetic cannabinoids remains elusive, but a dysregulation of the endocannabinoid system in kidneys via endogenous cannabinoid receptors, CB1 and CB2, may be part of the mechanisms of injury. The cannabinoid receptors are now recognized to play potential roles in diabetic nephropathy and chronic kidney disease progression, and our case highlights the need of future research on their possible role in immunue activation.

PO0181

Renal Limited Lupus-Like Nephritis in an Elderly Male

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Introduction: Lupus nephritis is a major cause of morbidity in Systemic Lupus Erythematosus (SLE). 60% of SLE patients develop renal impairment, which is more common in age < 55 years old. SLE has a female predominance with a female-to-male ratio of 8:1. We report a case of an elderly male, who has negative serology and absence of extra-renal manifestations of SLE, diagnosed with renal limited lupus-like nephritis (RLLLN).

Case Description: A 76-year-old Caucasian male with no previous history of renal or autoimmune diseases was admitted because of acute kidney injury (AKI). Patient had no history of joint pain and swelling, rash, or oral ulcers. He was not taking NSAID or Hydralazine. Laboratory test showed creatinine 2.7 mg/dL, serum albumin 2.1 g/dL, urine protein creatinine ratio 725mg/g, and urinalysis with dysmorphic RBC of >5 RBC/HPF. Serology showed negative anti-dsDNA, ANA titer <1:40 and undetectable complements C3 and C4. Hepatitis B and C, Human immunodeficiency virus, and rapid plasma reagin were also negative. Patient's renal function continued to worsen that he eventually required hemodialysis. A renal biopsy was performed. Light microscopy revealed diffuse endocapillary hypercellularity and no crescent lesion. There was a full house with global granular mesangial and basement membrane staining for IgG, IgA, IgM, C1q, C3, free kappa and lambda light chains under immunofluorescence microscopy. Electron microscopy revealed mesangial and subendothelial dense deposit and segmental duplication. All these findings are consistent with RLLLN.

Discussion: This is a case of an elderly male patient who developed AKI with kidney biopsy that showed lupus nephritis; however, ANA and anti-dsDNA antibody were negative and there were no clinical manifestations of SLE. The patient was treated with Methylprednisolone, which was followed by Prednisone and Mycophenolate Mofetil (MMF). On 1-month follow-up, there was improvement in C3 and C4, and 24-hour CrCl estimated the GFR of 35 ml/min; hence, hemodialysis was discontinued. On 6-month follow-up, serum creatinine 1 mg/dL, BUN 14 mg/dL, and GFR >60 ml/min. Our patient's kidney function recovered; however, there is no definite prediction of RLLLN prognosis due to limited data. 47% had a poor outcome with a permanent decrease of renal function and 62 % of patients with poor outcome had glomerular crescents involving 43–75% of the glomeruli.

PO0182

Postpartum Thrombotic Microangiopathy of Unknown Etiology: Is It Too Late to Save the Kidneys?

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Introduction: Thrombotic microangiopathy (TMA) is a rare (0.004%) but life threatening complication in pregnancy. Differentials include uncontrolled hypertension, Hemolysis elevated liver enzymes low platelet count (HELLP) syndrome, atypical Hemolytic Uremic Syndrome (HUS), Thrombotic Thrombocytopenic Purpura (TTP) among others. Lack of randomized trials and absence of gold standard laboratory tests can make diagnosis and treatment challenging. We present a patient with post-partum TMA confirmed on renal biopsy with no conclusive etiology identified.

Case Description: A 36 years old African American patient, G7P5 with history of Hypertension (HTN) and preeclampsia was noted to have blood pressure elevated to 180/103 mmHg during an antenatal care visit at 36 weeks of gestation. Serum Creatinine (sCr) was 0.5mg/dl with urine protein/Cr ratio (UPCR) of 0.75 g/g. She had an induced labor with persistent HTN postpartum. She left against medical advice and was readmitted 10 days later with acute kidney injury (AKI) with sCr of 6 mg/dl and UPCR was 4g/g, urinalysis showed positive protein but no RBCs. BP was elevated to 143/97 mmHg/ Laboratory data showed AST 33 U/L, ALT 24 U/L, Hb 9.5 g/dL, platelet counts 211 $X10^9$/L, C3 of 74 mg/dL, C4<2 mg/dL, negative ANA, ADAMTS 13 >94, Cryo results was inconclusive although RF was elevated at 160 IU/mL. Blood smear showed no schistocytes. She was started on pulse steroids for clinical suspicion of eclampsia related TMA. While awaiting biopsy therapeutic plasma exchange (TPE) was initiated, it was stopped after 3 sessions. Kidney biopsy on day 12 of delivery showed TMA, with negative immune-florescence (IF), minimal interstitial fibrosis/tubular atrophy, focal 2/15 glomerular crescents and minimal arterial intimal thickening. Patient became progressively oliguric, requiring hemodialysis. At the time of writing this report, there has been no recovery at 4 weeks as patient remains oliguric on thrice weekly dialysis.

Discussion: Peri-partum care is crucial in early detection and prompt management of TMA in patients with pre-eclampsia/Eclampsia. Benefit of TPE in post-partum period is not well established. A kidneybiopsy was obtained but the diagnosis remained elusive with negative IF in setting of reduced complement levels. Further studies should evaluate treatment strategies in the late-presenting patient to avoid irreversible kidney injury.

PO0183

Thrombotic Microangiopathy as a Complication of Malignant Hypertension

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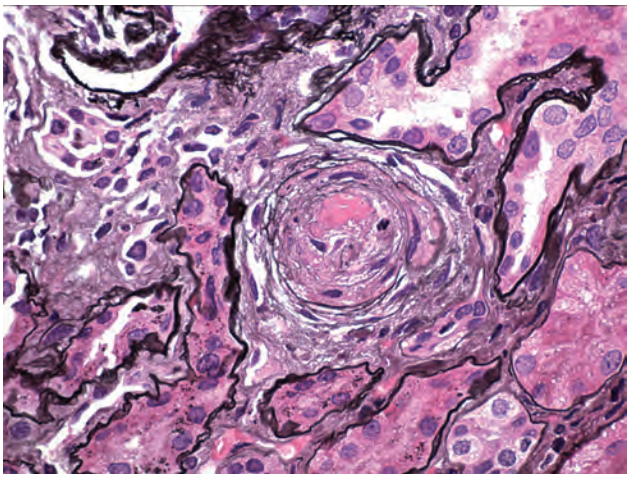
Introduction: Thrombotic microangiopathies (TMA) are defined as disorders characterized by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and microthrombi. Of all the known causes of TMAs, malignant hypertension is one of the most underreported ones.

Case Description: A 23-year-old African American male patient presented to the emergency department with a 2-week history of nausea, vomiting, diarrhea, and abdominal pain. His past medical history is significant for hypertension treated with lisinopril, but the patient is noncompliant with his medication. He had a blood pressure of 245/176 mmHg. Laboratory tests revealed hemoglobin of 10.7g/dl, platelet count of 88,000/microliter, white blood count of 14,300/microliter, blood urea nitrogen of 29 mg/dl, creatinine of 4.7 mg/dl (unknown prior creatinine levels), lactate dehydrogenase of 900 units/l, low haptoglobin, serum potassium of 2.1mg/dl and normal coagulation profile. With control of blood pressure, the platelet counts improved. ADAMTS13 test and stool Shiga toxin were negative. Peripheral blood smear showed schistocytes. Workup for secondary hypertension were all negative. A diagnostic CT guided left kidney biopsy revealed active and chronic TMA.

Discussion: In our patient presenting with renal TMA and severe hypertension, TTP was thought to be less likely as the patient did not have the classical presentation of fever and neurological symptoms. In addition, thrombocytopenia and LDH levels normalized with aggressive control of blood pressure. Hence, plasma exchange was deferred. Since the patient presented with diarrhea, HUS was high on the differential, but a negative Shiga toxin PCR ruled out the possibility. Renal biopsy revealed acute and chronic TMA in renal blood vessels with focal severe arteriolosclerosis, fibrin, and onion skinning of arteries supporting the diagnosis of malignant nephrosclerosis as the cause of TMA.



Arteriolar narrowing with fibrin

PO0184

Drug-Induced Thrombotic Microangiopathy from Trimethoprim-Sulfamethoxazole

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Introduction: Thrombotic microangiopathy (TMA) is a common condition manifesting with microangiopathic hemolytic anemia, thrombocytopenia and end-organ damage including, acute kidney injury. TMA can be associated with many clinical syndromes and is most often due to malignant hypertension, malignancy or complement dysregulation but can also be triggered by medications. Here we describe a rare case of TMA caused by trimethoprim-sulfamethoxazole (TMP-SMX).

Case Description: A 62-year-old man with recent diagnosis of Sweet's syndrome was started on high dose prednisone and TMP-SMX for prophylaxis. He presented 4 days later with confusion, profuse diarrhea and "brown-colored" urine. He was normotensive on exam, without cardiac murmurs, clear lungs, soft non-tender abdomen and no skin rashes. Initial labs showed microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury with hyperkalemia. Blood smear showed schistocytes. He received emergent hemodialysis followed by plasma exchange for suspected TTP/HUS. Extensive workup during his hospital admission revealed a normal ADAMTS13 activity, negative blood and urine cultures, negative 0157:H7 stool antigen, negative urinary streptococcal antigen, negative autoimmune screen, negative hepatitis and HIV serologies, normal vitamin B12 level, normal bone marrow and pan-imaging without malignancy. A renal biopsy confirmed TMA. He remained anuric and dialysis dependent on discharge.

Discussion: Patients with TMA have symptoms arising from anemia, thrombocytopenia, renal failure, or from underlying diseases like systemic infections, malignancies or drug toxicities. Once TMA is confirmed, elucidating the cause of TMA is important because there are specific treatments available for primary TMA syndromes like TTP and complement-mediated TMA. High suspicion of TTP requires urgent plasma exchange until ADAMTS-13 levels return, and if complement-mediated TMA is likely, the terminal-complement inhibitor eculizumab can be used. Drug-induced TMAs require prompt discontinuation of the drug and supportive management. Trimethoprim-sulfamethoxazole is a rare cause of thrombotic microangiopathy, and the exact mechanism is not understood. Our case highlights the importance of considering TMP-SMX as a potential cause in patients presenting with TMA.

PO0185

Hemoglobin Cast Nephropathy in Rifampin-Induced Hemolytic Anemia

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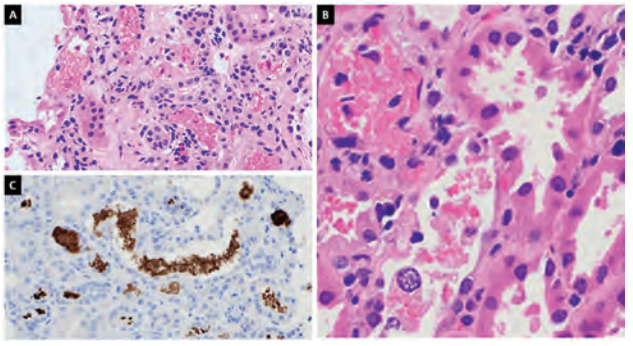
Introduction: Hemoglobin released after intravascular hemolysis causes acute kidney injury (AKI) by various mechanisms including hemoglobin cast nephropathy. This can resemble other causes of AKI such as acute tubular necrosis, acute interstitial nephritis (AIN) and thrombotic microangiopathy (TMA). Few studies have demonstrated immunohistochemically-proven hemoglobin casts on kidney biopsy associated with intravascular hemolysis. Below is a case of Rifampin-induced hemolysis associated hemoglobin cast nephropathy.

Case Description: A 64-year-old female with recurrent pulmonary Mycobacterium Avium Complex (MAC) infection treated with Rifampin, Ethambutol and Azithromycin presented with nausea and vomiting two weeks after starting therapy. Physical exam was remarkable for small purpuric lesions on the back. Labs showed a serum creatinine of 6.6 mg/dL, BUN 66 mg/dL, hemoglobin 11.1 g/dL and platelets 9,000/uL. Haptoglobin was normal. LDH was elevated at 507 units/L. A direct antibody test was negative. Urinalysis showed large blood and microscopy showed 2-5 RBCs per hpf and dark granular casts.

Renal ultrasound was unremarkable. Plasma exchange was initiated for possible TMA but discontinued when ADAMTS13 level returned normal. On day four, serum creatinine was 8.1 mg/dL. She received methylprednisolone 120 mg daily for three days due to concern for possible Rifampin induced AIN. A kidney biopsy was planned and hemodialysis was performed to optimize platelet function. Kidney biopsy demonstrated intratubular pigmented casts that were strongly positive for hemoglobin A immunohistochemical stain confirming the diagnosis of hemoglobin cast nephropathy [Figure 1]. She received supportive care with kidney function gradually improving. Creatinine was 2.87 mg/dL on discharge and 1.18 mg/dL four weeks later.

Discussion: Hemoglobin cast nephropathy is a rare diagnosis and requires high index of suspicion in patients with hemolysis and AKI. Diagnosis is multifaceted requiring a clinical history, exam, lab workup and most importantly, a kidney biopsy.



PO0186

Recurrent Stage 3 AKI Resolves with Establishing the Diagnosis of TAFRO Syndrome and Treatment with Anti-IL-6 Antibody

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Introduction: TAFRO syndrome, a unique variant of idiopathic multicentric Castleman's disease (iMCD), is a syndrome with a constellation of **T**hrombocytopenia, **A**nasarca, **F**ever, **R**eticulin myelofibrosis/renal insufficiency, and **O**rganomegaly. Its pathogenesis is driven by excessive cytokine storm, most notably from IL-6, causing multiorgan failure. 30% of patients with TAFRO-iMCD patients require dialysis. Glomerular thrombotic microangiopathy (TMA) and membranoproliferative glomerulonephritis are the most characteristic lesions. We present a challenging case of recurrent dialysis requiring AKI in whom recognition of TAFRO syndrome and glomerular TMA-like lesion led to successful treatment with anti-IL-6 therapy and subsequent definitive diagnosis of iMCD.

Case Description: A 35-year-old Hispanic female presented in May 2019 with fever, hypotension, anemia, thrombocytopenia, anasarca, hepatosplenomegaly, generalized lymphadenopathy, and anuric AKI. She was admitted to the intensive care unit, required vasopressors, mechanical ventilation, and initiation of continuous renal replacement therapy (CRRT). A comprehensive workup for infectious and autoimmune etiologies was unrevealing. This puzzling presentation was presumed to be driven by an unidentified viral illness. She received an empiric course of IVIG and steroids with mild improvement in anemia, thrombocytopenia, and complete renal recovery. A month later, she was admitted with a similar presentation and proteinuria. She once again required CRRT. Lab work revealed elevated IL-6. Lymph node and bone marrow biopsy were non-contributary. A renal biopsy revealed glomerular capillary endotheliosis. This time it became clear that she had a TAFRO phenotype and decided to treat her with tocilizumab (anti-IL-6 antibody) every two weeks. She had complete recovery of AKI, anemia, and thrombocytopenia within four weeks. She has been on anti-IL6 antibody for one year, and the disease is in remission. An excisional lymph node biopsy in May 2020 confirmed the diagnosis of Castleman's disease.

Discussion: TAFRO syndrome-iMCD related renal involvement has been reported from Japan and France. For the first time, we describe these findings from a North American center. This case highlights that knowledge of TAFRO syndrome as a cause of AKI, its diagnostic approach, and renal histology is valuable for Nephrologists.

PO0187

Apparent AKI in a Patient with Ascites Following Laparoscopic Hysterectomy

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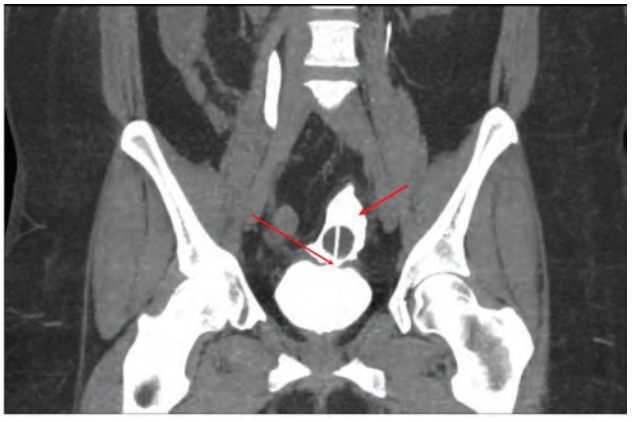
Introduction: Bladder injury occurs following blunt or penetrating trauma. Gynecological and colorectal surgeries are the most common surgeries associated with bladder injury. Bladder injury can be classified as intra versus extra-peritoneal. Clinical manifestations include gross or microscopic hematuria, ascites, and/or difficulty voiding. Peritonitis and sepsis are common complications.

Case Description: A 39-year-old woman who underwent laparoscopic hysterectomy presented to ED 4 days following surgery with abdominal pain. Her vitals revealed hypotension and tachycardia. Initial laboratory values were as follows: WBCs 18.0x 10^9/L, Na 134 mmol/L, K 4.9 mmol/L, Cl 101 mmol/L, HCO3 17 mmol/L, BUN 45 mg/dL, serum Cr 7.4 mg/dL, lactate 2.4 mmol/L. UA was remarkable for hematuria with 25 isomorphic RBCs/HPF. Abdominal US revealed moderate ascites. An indwelling bladder catheter was placed, and she underwent diagnostic paracentesis, with WBC noted at 1288/µl (35% neutrophils) and ascites-to-serum Cr ratio of 2.14. CT abdomen with IV contrast confirmed a full-thickness tear of the superior wall of the urinary bladder, with the bulb of the indwelling catheter extending beyond the bladder and an associated urinoma surrounding the catheter (Figure 1). She was diagnosed with bladder perforation and underwent open bladder repair emergently. Her serum Cr improved to 0.5 mg/dL in 24 hours.

Discussion: Uroperitoneum can result in the reabsorption of urine into the systemic circulation, while sodium and chloride ions move in the opposite direction. This results in hyponatremia, metabolic acidosis, azotemia and rise in serum Cr. Uroperitoneum should be expected when ascites to serum Cr ratio is >1.0. It is essential to recognize that the rise in serum BUN and Cr is due to pseudo-azotemia from the reabsorption of urine and not from true kidney dysfunction. Bladder injury is diagnosed by CT cystography, which was deferred in our patient giving the clear evidence of bladder injury in the CT abdomen. Complex extraperitoneal and all intraperitoneal bladder injuries require surgical repair.



PO0188

Urine Proteomics Among Children Developing AKI After Hematopoietic Stem Cell Transplant (HCT): A Pilot Study

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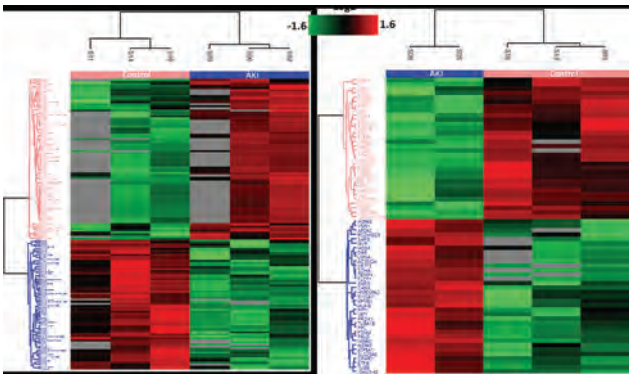
Background: AKI is common after HCT and contributes to high morbidity and mortality. Understanding the mechanisms of injury is essential to develop targeted therapies. Our objective was to examine urinary proteins among children after HCT to provide insights into the pathophysiology of AKI in a population whose immune system is newly developing.

Methods: Children (>2 years old) undergoing their first allogeneic HCT and enrolled in a prospective, observational cohort had urine collected at baseline and monthly for the 4 months post HCT. Six patients were selected for pilot proteomic analysis (age 7-19 years, median 10 years, 66% male, 3 with AKI, 3 without AKI). Stored urine samples were tested pre-HCT and at 1 and 4 months post-HCT. Samples were tested with liquid chromatography/tandem mass spectrometry with data-independent acquisition. Proteins were assigned and intensities compared between AKI and controls using t-tests at $p<0.05$. AKI was defined as a 1.5-fold increase in the monthly serum creatinine value compared to baseline.

Results: At 1 month post-HCT, 143 proteins were found distinct among the urine of children with AKI(n=3) compared to those without AKI (n=3). Pathway enrichment analysis linked these proteins to cell cycle and ubiquitous pathways. The 4 month time point resulted in identification of 67 proteins which were differentially expressed between AKI and control groups. These proteins were mostly involved in immune regulation. In both groups, unsupervised hierarchical clustering perfectly segregated the subjects based on AKI or control status (Figure).

Conclusions: The urinary proteomic fingerprint is distinct after AKI and are mostly cell cycle proteins in early AKI (first month) and immune mediated at 4 months, when most patients are fully engrafted. Additional studies are needed to define and understand the specific pathways.

Funding: Private Foundation Support



Urine proteomics comparing AKI and controls at 1 and 4 months.

PO0189

Triptan-Induced Vascular CKD, the Importance of a Differential Diagnosis

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Introduction: Triptans are selective (5-HT) receptor agonists resulting in vasoconstriction reversing the vasodilatory mechanisms of migraine headaches. Animal studies have shown 5-HT2 receptors in the renal arteries and intense vasoconstrictive effect of 5-HT on the renal arteries. We describe a case of progressive CKD with biopsy proven vascular injury due to sumatriptan use.

Case Description: A 52-year-old male with history of CKD stage 3, migraine headaches, and hyperlipidemia presented to nephrology clinic for evaluation of CKD. Review of records revealed a rise in sCr from 1.2 to 2.8 mg/dl over the preceeding 4 years. Urinalysis was negative for hematuria, proteinuria, and pyuria. CT revealed symmetric kidneys without dilation. A kidney biopsy was performed and showed patchy cortical atrophy and interstitial fibrosis with moderate vascular sclerosis and focal remodeling of the glomerular basement membranes consistent with prior vascular injury as well as acute tubular injury. A hematologic evaluation did not reveal an etiology and further history revealed use of sumatriptan 8-10 times per month. After discontinuation of sumatriptan, sCr improved from 2.8 to 2.2 mg/dl

Discussion: This case highlight the broad differential diagnosis of acute and chronic kidney injury. The biopsy findings of primarily vascular injury were initially felt to be cryptogenic, but further review revealed the etiology to most likely be triptan induced. After discontinuation of sumatriptan the creatinine improved in spite of increased NSAID use. Currently botulinum injections are being used as migraine prophylaxis. This case highlights the importance of a review of all medications and for potential nephrotoxicity.

PO0190

Roid Renal Failure

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Introduction: Athletes and bodybuilders often utilize anabolic steroids and high-protein supplements to gain muscle mass, however the use of such performance enhancers comes with a significant risk of renal failure.

Case Description: A 34-year-old male weightlifter presented with worsening exertional dyspnea, hemoptysis, and bilateral leg swelling over 2-3 months. He admitted to weekly testosterone injections, testosterone-increasing supplements, and a high-protein diet for the past 5 years. To address his lower leg swelling, the patient started Expel, an over-the-counter potassium-sparing diuretic, 2 months ago. Labs were significant for bicarb 19 mmol/L (21-30), BUN 166 mg/dL (8-25), Cr 13.4 mg/dL (.3-1.2), and CPK 2630 U/L (26-308). Chest X-ray showed right lower lobe pneumonia. Urinalysis showed proteinuria. Renal ultrasound revealed cortical echogenicity with no hydronephrosis. The patient was admitted for acute renal failure, rhabdomyolysis, and pneumonia. He was started on Ceftriaxone and Azithromycin and placed on IV fluids. During the hospitalization, the patient's renal function deteriorated. Renal biopsy showed global and segmental glomerulosclerosis, tubular atrophy, severe interstitial fibrosis, arteriosclerosis, and arteriolar hyalinosis. The patient was counseled at length about long term renal replacement therapy and the gravity of his diagnosis. He underwent placement of a tunneled dialysis catheter and was discharged with close outpatient follow up. Unfortunately despite multiple hospitalizations, the patient repeatedly missed dialysis treatments and continued to use anabolic steroids and high-protein supplements.

Discussion: The utilization of anabolic steroids and high-protein supplements is widespread among athletes and bodybuilders seeking to enhance performance and achieve greater muscle mass. However, steroids and high-protein supplements are not benign and their use comes at the risk of renal failure requiring possible long term renal replacement therapy. High-protein supplements increase glomerular filtration rates (GFR) and are associated with the development of focal segmental glomerulosclerosis (FSGS). Anabolic steroids are directly toxic to renal glomeruli. Anabolic steroids bind to podocyte androgen receptors resulting in the apoptotic destruction of podocytes. The patient's clinical course highlights the significant risk of renal failure in young athletes abusing anabolic steroids and high-protein supplements.

PO0191

Crystal Clear: A Case of Oxalate Nephropathy

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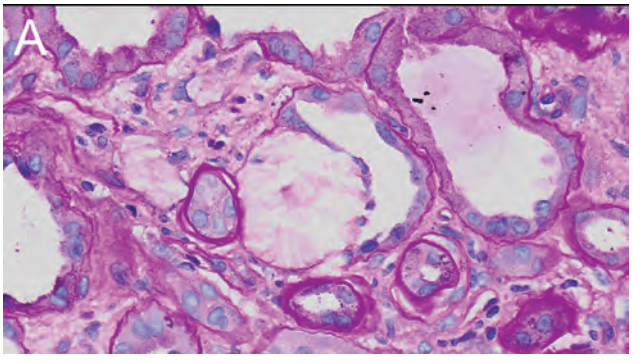
Introduction: Oxalate nephropathy is an uncommon and potentially devastating cause of acute kidney injury that can lead to end-stage kidney disease. Oxalate nephropathy can be hereditary (as in hereditary hyperoxaluria), related to toxins (such as ethylene glycol), medications, like high-dose vitamin C, or enteric malabsorption (such as gastric bypass surgery or malabsorptive disorders). Oxalate nephropathy occurs when calcium oxalate crystals form and deposit in the renal tubules and interstitium, leading to acute tubular necrosis.

Case Description: A 71 year old female with a medical history of pancreatic adenocarcinoma s/p Whipple procedure seven months earlier and chronic kidney disease stage 3 (baseline creatinine 1.0 mg/dL) presented to the hospital with elevated serum creatinine found incidentally on outpatient labs. Initial evaluation was concerning for volume depletion, as she improved with intravenous fluids. Over the next several months, she had repeated hospital admissions with worsening non-oliguric renal failure that seemed to respond to intravenous fluids in the hospital but worsened at outpatient visits. Urinalysis repeatedly showed no microscopic hematuria and low-level proteinuria, and urine microscopy showed coarse granular casts, consistent with acute tubular necrosis. Kidney biopsy was consistent with acute tubular injury and extensive tubular calcium oxalate deposition concerning for oxalate nephropathy.

Discussion: Oxalate nephropathy is a rare complication of pancreatic surgery and ascorbic acid use. Vitamin C is metabolized to oxalate and then excreted in the urine. In malabsorptive disorders, a higher concentration of fatty acids are present in the gastrointestinal tract, which bind calcium, leaving less to bind oxalate, and thus more oxalate is absorbed. High urinary oxalate can cause crystallization in tubules, leading to acute renal failure. Treatment is supportive, with removal of offending agents, oral calcium supplementation, and adequate oral hydration. Despite this, our patient progressed to end-stage renal disease requiring dialysis.



PO0192

A Novel Flow Cytometry Approach Identifies Kidney Mononuclear Phagocyte Subsets Involved in Mouse Kidney Injury Models

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Background: Mononuclear phagocytes (MNPs) are heterogenous in phenotype and function, which reflects their double-edged role as drivers of inflammation and repair after kidney injury. Dissection of this complex network of cells into functional subunits has been challenging and more granular approaches could help to identify relevant subsets in preclinical kidney injury models. Here we used a novel flow cytometric approach to phenotypically and functionally dissect renal MNPs and perform a thorough comparison of MNP dynamics between two different kidney injury models.

Methods: The dynamic regulation of MNP subsets was monitored over 10d in two frequently used murine kidney injury models: ischemia reperfusion injury (IRI) and unilateral ureter obstruction (UUO). Using flow cytometric markers F4/80, CD11b and CD11c, kidney MNPs were phenotypically divided into five distinct subsets, which were further subdivided into functional subsets of proinflammatory M1-like (CD86+MHCII+CD206-) and regulatory M2-like (CD206+) cells.

Results: Three of the five renal MNP subsets were heavily contributing to both M1- and M2-like cell pools in both IRI and UUO, highlighting their functional multimodality regarding for example *in vitro* phagocytosis. The F4/80^{high} MNP subset contributed most M2-like cells as from day 3 with a comparable MNP profile in both models. However, M1-like cells from two CD11b^{high} subsets spiked 24h after IRI, while this spike was shifted to day 3 in the UUO model, which had a temporary early influx of M1-like F4/80^{high} cells after 3h in turn. After 10d, total MNP numbers were decreasing in the UUO model, while M2-like F4/80^{high} cells persisted in IRI kidneys.

Conclusions: Our novel flow cytometric approach unravels functional multimodality among MNP subsets and identifies distinct subsets responsible for an earlier M1-response and a more persistent M2-response in IRI compared to UUO. These results might support preclinical model selection and disease understanding in kidney injury.

Funding: Commercial Support - Bayer AG

PO0193

Microparticles Containing M2 Monocyte and Other Inflammatory Markers Are Released in AKI

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Background: Renal epithelial cell injury in AKI and induces a pleiotropic inflammatory cell response. Monocyte phenotypes (M1 = $CD14^+/CD16^-$; M2 = $CD14^+/CD16^+$), and subsequently derived tissue-resident macrophages play a critical role in inflammation and repair in acute kidney injury (AKI). It is accepted that M1 phenotype serves a pro-inflammatory/phagocytic role, whereas M2 phenotype influences tissue repair and remodelling. We have previously shown that microparticles (MP) derived from renal epithelial cells are released in the setting of kidney injury and can be detected in vitro as well as in human plasma, and can carry the biological activity.

Methods: In this study, we evaluated presence of MP expressing markers of inflammation in AKI (defined by standardized criteria). Human samples were derived from a prospectively collected repository (31 cases of AKI in critically ill patients compared to 22 living kidney donor healthy controls). Samples were prepared to measure MP (standard methods), and flow cytometric analysis was evaluated using antibodies against inflammatory proteins. FlowJo software was used for analysis. Mann-Whitney test was used for comparisons.

Results: The average age was 54 years; mean admission creatinine was 1.8 mg/dl, and the time between admission and sample collection was 3-4 days. MP containing M2 Monocyte markers were significantly higher in AKI patients compared to controls (347.03 vs 271.36 /ml respectively; p=0.02). MP containing M1 markers were similar compared to control (177.85 vs 285.40 /ml, p=0.19), AKI cases also showed significantly higher levels of MP containing other inflammatory markers: Leukocytes (CD45, p=0.015), eosinophils (CD66b, p=0.0001), and also in platelets (CD42b, p=0.05).

Conclusions: MP containing monocyte/macrophage markers of M2 phenotype are released in the early phase of AKI, which can influence tissue modelling and repair. Moreover, a pattern of MP representing markers of M2 and other inflammatory cells may have prognostic significance to predict the severity of tissue injury or the prospect of recovery.

PO0194

Novel Immune Defense Cells of the Kidney Epithelia

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Background: Urinary tract infections (UTIs) are one of the most common bacterial infections worldwide, affecting infant boys, older men, and most prominently, women of all ages. It is predominately caused by uropathogenic *E. coli* and can lead to urosepsis and kidney failure if untreated. We have found a major role for kidney epithelia, specifically the intercalated cells (IC), that are activated in defense against bacteria. Given the heterogeneity of kidney cell types, we hypothesized that there could be other cells that respond to a UTI.

Methods: We performed 10x Genomics single cell RNA-seq (scRNAseq) of whole kidneys from mice with UTI at 12 hrs and from mice without infection. We also performed scRNAseq of IC from lipopolysaccharide (LPS)-induced mice at 0, 8, and 24 hrs using a novel mRNA profiling method, pooled library amplification for transcriptome expression (PLATE)-seq. We used $ROSA26^{nT\text{-}nG}$;Atp6v1b1Cre mice that activated GFP in IC and subsequently sorted GFP+ cells for PLATE-seq.

Results: scRNAseq across 16 samples from 10 mice (5 UTI-Control pairs) yielded 64,760 cells and resulted in populations of all major kidney cell types, as well as rare populations, i.e., pelvic transitional epithelial cells and double positive (DP) collecting duct cells, which have markers of both intercalated and principal cells. By gene set enrichment analysis, we found that DP cells activated gene sets involved in cell killing and innate immune responses at 12 hrs of UTI. DP cells were also found to be highly transcriptionally active in response to infection in a cross analysis with our dataset from 4-thiouracil-labeled nascent RNAs purified from Atp6v1b1+ cells. scRNAseq on Atp6v1b1+ population after LPS induction (525 cells) further revealed time-dependent activation of immune responses. We found that these IC/DP cells increased *Umod* expression in both UTI (1.6 fold change; padj=1E-2) and LPS (1.7 fold change; padj=1E-6) analyses. *Umod*, known to have immune properties, is commonly expressed in the loop of Henle and distal tubule, but may have a novel bacterial defense role in the IC/DP cells.

Conclusions: We found a novel immune defense role of the double positive collecting duct cells in response to UTI. These transcriptionally active cells induce genes involved in cytotoxic and innate immunity and can provide new insights into the epithelial defense of the kidney.

Funding: NIDDK Support

PO0195

Role of Glomerular Filtration Rate (GFR)-Modifying Drugs in Prevention of Anticoagulant-Related Nephropathy (ARN)

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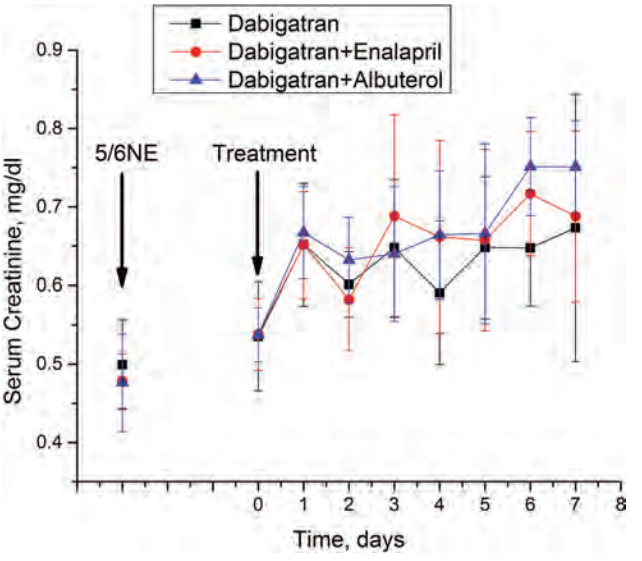
Background: Acute kidney injury (AKI) with red blood cell (RBC) tubular casts secondary to different anticoagulants has been recognized as ARN. ARN is seen in patients with underlying kidney diseases. 5/6 nephrectomy (5/6NE) animal model reproduces morphologic features of ARN. One of the possible pathogenetic mechanisms of ARN proposed to be increased GFR. Aim of the current study was to investigate the role of GFR-modifying drugs in prevention of ARN.

Methods: 5/6NE rats 3 weeks after the surgery were treated with direct thrombin inhibitor dabigatran (150mg/kg/day) and with GFR-reducing Enalapril (1.5mg/kg/dl) or GFR-increasing Albuterol (4mg/kg/day) for 7 days. Daily monitoring of serum creatinine (SCr), blood pressure and hematuria was performed. Morphology of the kidney was evaluated at day 7 after animals were euthanized.

Results: Dabigartan resulted in gradual increase in SCr (Fig 1), hematuria, acute tubular necrosis (ATN) and RBC tubular casts in all treatment groups. Neither of GFR-modifying drugs significantly changed there parameters. ATN was 0.75±0.27, 0.67±0.25 and 0.79±0.27 in Dabigatran, Dabigatran + Enalapril and Dabigartan + Albuterol treatment groups, respectively. Systolic blood pressure was reduced with Enalaprilbut did not change significanlty with Albuterol. Diastolyc blood presuure was not changed significantly with either treatment.

Conclusions: Our data indicate that GFR-modifying drugs do not prevent or aggravate ARN at least secondary to direct thrombin inhibitor.

Funding: NIDDK Support



PO0196

Tubular β-Catenin Ameliorates AKI by Regulating Apoptosis and Necroptosis

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Background: Renal tubular β-catenin signaling plays a protective role in acute kidney injury (AKI) but the underlying mechanisms remain debatable. Apoptosis and necroptosis of tubular cells are responsible for the renal dysfunction in AKI. This study aims to investigate the role of β-catenin activation in tubular cell death upon AKI and its underlying mechanism.

Methods: Transgenic 'Tubcat' mice conditionally expressing stabilized β-catenin in renal tubules following tamoxifen administration were used to establish septic (LPS-induced) and non-septic (ischemia-reperfusion injury or IRI-induced) AKI models. Tubcat mice and their littermate controls were divided into the LPS and IRI groups. LPS mice received intraperitoneal injection of LPS (20 mg/kg). IRI mice received bilateral ischemia for 28 minutes, followed by 24 hours of reperfusion. All the mice were sacrificed at 24 hours. Kidney function and renal histological changes were assessed. Renal apoptosis and necroptosis were evaluated by real-time quantitative PCR, western blot and TUNEL assay. Signaling cascade was examined by western blot.

Results: Compared to the controls, Tubcat mice under septic and non-septic AKI had significantly improved renal function (lower serum creatinine levels) and reduction of (i) tubular injury score; (ii) apoptosis (Bax/Bcl2 ratio and number of renal TUNEL-positive apoptotic cells); (iii) necroptosis (expression of RIP1, p-RIP3 and p-MLKL); and (iv) renal expression of phosphorylated p53. Renal expression of phosphorylated Akt was increased significantly.

Conclusions: Activation of β-catenin signaling in tubular cells reduces apoptosis and necroptosis in septic and non-septic AKI. Tubular β-catenin might play a protective role in AKI by regulating cell death via modulating the p53/Akt signaling pathway. **Fundings:** General Research Fund (HKU 17119818), RGC Collaborative Research Fund (Ref: C7018-16G) and Hong Kong Society of Nephrology Research Grant (2019)

Funding: Government Support - Non-U.S.

PO0197

Pulsed Ultrasound Improves Dysregulated Oxygen Metabolism and Reduces Tissue Injury in Sepsis-Associated AKI

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Background: Sepsis associated-acute kidney injury (SA-AKI) results in part from oxidative stress and cytokine-induced inflammation. We showed that pulsed US (pUS) reduces inflammatory conditions and kidney injury in sepsis (PMID: 25644106). Using multi-parametric photoacoustic microscopy (PAM) we demonstrated that the imbalance between oxygen supply and oxygen demand is one of the earliest (10 min) findings in the pathogenesis of S-AKI. We tested the hypothesis that US attenuates kidney injury and improves early tissue oxygen metabolism and cellular bioenergetics.

Methods: We used PAM imaging to assay the change of renal blood oxygen saturation (sO_2), peritubular capillary (PC) blood flow (BF) and the metabolic rate of oxygen (MRO_2) in saline- and LPS-treated mice and mice pretreated with US 24 hr before LPS (as described PMID: 25644106). Mice received a single injection of LPS (5 mg/kg, i.p.), and oxygen consumption and blood flow were measured 10-80 min later by PAM imaging with an image penetration depth of up to 200 μm, and MRO_2 was calculated. Additional animals were treated with LPS and euthanized at increasing time intervals for measurement of blood creatinine and injury and inflammatory biochemical markers.

Results: PAM imaging revealed heterogeneous cortical regions of LPS- induced markedly enhanced oxygen consumption and MRO_2. Pretreatment with US reversed the early renal sO_2 decline observed 30-80 min after LPS and reversed the cortical regions of increased MRO_2. pUS prevented the overall reduction of PCBF. LPS-induced AKI, confirmed by increased plasma creatinine, mRNA expression of kidney injury marker Kim1 and Ngal 12-24 hr after LPS, and acute tubular necrosis (by H&E staining), was attenuated by US pretreatment. pUS reduced Kim1 expression in the brush border membrane of proximal tubules in cortex and medulla. pUS attenuated the increase in *IL-6* and *IFN-γ*, but not TNF-α, mRNA expression.

Conclusions: Our results demonstrate that pUS reverses kidney MRO_2, improves oxygen metabolism and reduces proinflammatory cytokines in SA-AKI. These results provide insight into the mechanisms of kidney tissue protection by US in AKI.

Funding: NIDDK Support

PO0198

Targeting Gadd34 Upstream Open Reading Frame to Treat Sepsis-Induced Kidney Injury

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Background: Sepsis-induced acute kidney injury remains a major clinical problem with no effective therapy to date. We have previously shown that bacterial sepsis causes global translation shutdown via phosphorylation of the eukaryotic translation initiation factor 2α (eIF2α). Under physiological conditions, this eIF2α phosphorylation is counter-regulated by two eIF2α holophosphatases. Of the two holophosphatases, Growth Arrest DNA-inducible Gene 34 (Gadd34) is the only stress-inducible regulatory subunit. Using ribo-seq, we found that Gadd34 is translationally repressed during late phase sepsis even though eIF2α is heavily phosphorylated. We postulate that this blunted Gadd34 induction could explain the sustained phosphorylation of eIF2α and translation shutdown that contributes to delayed renal recovery in sepsis.

Methods: The 5'-untranslated region (UTR) of Gadd34 has an upstream open reading frame (uORF) that is conserved across mammalian species. Our ribo-seq analysis of the kidney from septic mice revealed high ribosomal occupancy of the uORF, but not the main protein coding sequence (CDS), consistent with a model in which the uORF serves as a translational inhibitor of the downstream CDS. To investigate the inhibitory role of the Gadd34 uORF, we designed plasmid constructs consisting of a full length Gadd34 5'UTR where a single nucleotide mutation was introduced to abolish the uORF start codon. We also designed antisense oligonucleotides (ASO) that are complementary to a specific portion of the uORF to modulate ribosomal scanning on the native Gadd34 mRNA.

Results: The uORF point mutation led to a two-fold increase in the readout luciferase signal compared with the wild-type control, confirming the inhibitory property of the Gadd34 uORF. We also found that masking of uORF by ASO resulted in sequence-specific increases in translation of the downstream CDS, possibly due to enhanced leaky ribosomal scanning. Finally, we tested the applicability of antisense approach in vivo using a mouse model of endotoxin-induced kidney injury. Despite late intervention (8 hrs post endotoxin challenge), the administration of uORF-targeted ASOs rescued translation and reduced kidney injury.

Conclusions: These findings indicate that translational suppression of Gadd34 in late phase sepsis is a maladaptive response that could be therapeutically modulated by targeting its uORF.

Funding: NIDDK Support

PO0199

STC1 Prevents Lipopolysaccharide-Induced AKI via TGF-β

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Background: Lipopolysaccharide (LPS)-induced Epithelial injury plays a critical role in the pathogenesis of acute kidney injury (AKI). Stanniocalcin-1 (STC1), a pleiotropic glycoprotein, has been reported to protect ischemic renal injury by reducing redox oxygen species, modulating inflammatory release, and inhibiting cell apoptosis. However, regulators of STC1 expression as well as its physiologic function in kidneys were unknown. We sought to elucidate the relationship between TGF β and STC1 in LPS-induced kidney injury in vitro and in vivo and to define the functional role of STC1 expression in renal tubular epithelium.

Methods: C57BL/6 J mice, STC1-/- (C57BL/6 J background) mice were randomly divided into blank control group, experimental control group. A mouse model of AKI was established. Primary mouse renal tubular epithelial cells isolated from wide type mice and STC 1-/- mice were cultured. We detected changes in serum creatinine (Scr) and blood urea nitrogen (BUN) before and after model establishment, observed and scored renal tubular injury, and measure the expression of signal pathway proteins and downstream inflammatory factors.

Results: LPS caused elevation of SCr, BUN level, morphological injury and tubular apoptosis, enhanced NLRP3 and Col 1 expression, and increased expression of TGF β and STC 1 ($P<0.05$).

Conclusions: Our study reveals a novel TGF β-STC1 pathway that has homeostatic as well as LPS-induced cytoprotective functions in renal tubular epithelium. STC 1 has protective effects on LPS-induced acute renal tubular injury in mice, possibly by targeting TGF β, enhencing TLR4 expression, regulating the TGF β/STC1 signaling pathway, and inhibiting the expression of downstream inflammatory factors.

Funding: Government Support - Non-U.S.

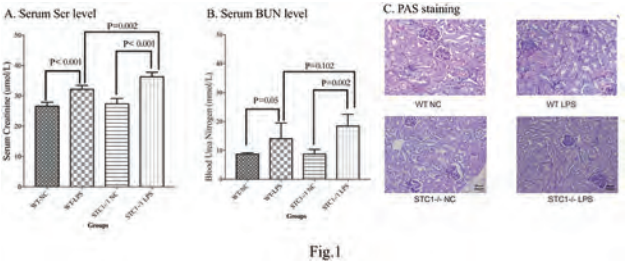
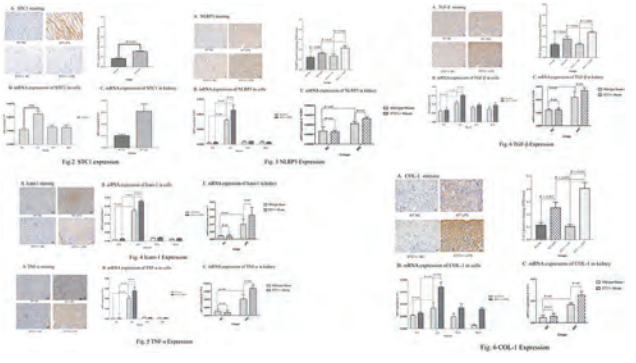


Fig.1



PO0200

Lipopolysaccharide Induces NEAT 1 Expression in AKI via TLR4/NF-κB Signaling

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Background: Toll-like receptor 4 (TLR4)/ Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) have been implicated in the pathogenesis of acute kidney injury(AKI). Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) is a long non-coding RNA that plays key roles in a variety of biological processes and is involved in many other diseases. Beyond its fundamental role of maintaining function of the nucleus, it remains unknown whether interaction between TLR4/NF-κB signaling and NEAT1 is involved in the process of the development of AKI.

Methods: Septic AKI model was established with injection of LPS into mice. Mouse tubular cells were stimulated with LPS for the study of tubular inflammation. The role and upstream regulatory mechanisms of NEAT1 in the inflammatory processes were studied by using signaling inhibitors.

Results: In LPS-induced AKI, NEAT1 expression was upregulated in tubular cells, accompanied by elevated TLR4/NF-κB signaling In vitro, mouse tubular cells treated with LPS also showed increase in NEAT1, prior to the production of proinflammatory

cytokines including IL-6 and CCL-2, whereas treatment with an inhibitor of TLR4 or NF-κB signaling suppressed LPS-induced NEAT1 expression.

Conclusions: NEAT1 expression was induced in LPS-induced AKI model via TLR4/NF-κB signaling, suggesting its potential role in the inflammatory process. Our findings open the door to exploit NEAT1 expression as a potential novel therapeutic approach for AKI and other inflammation-related renal diseases. **Funding:** Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2019.

PO0201

Effect of Renal Tubular Epithelial Cell Forkhead Box O1 on Endotoxin-Induced AKI

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Background: Mitochondrial damage in renal tubular epithelial cells (RTECs) is a hallmark of endotoxin-induced acute kidney injury (AKI). Forkhead box O1 (FOXO1) is responsible for regulating mitochondrial function and is involved in several kidney diseases. Herein, we investigated the effect of FOXO1 on endotoxin-induced AKI and related mechanism.

Methods: In vivo, the mouse model of endotoxin-induced AKI was induced by intra-abdominal injection of LPS (10 mg/kg). The expression of FOXO1 and PGC1-α in mouse kidney were determined. Then we established a mouse model of renal overexpression of FOXO1 by in situ injection of FOXO1 adeno-related virus in renal cortex before intra-abdominal injection of LPS. In vitro, Human proximal tubular epithelial (HK-2) cells were stimulated with LPS (40μg/ml), then infected with FOXO1 overexpression adenoviruses. The cell viability was measured by MTT assay. The morphological changes of mitochondria were observed using mitotracker staining. Mito-SOX was used to detect the changes of mitochondrial superoxide content and the expression of FOXO1.

Results: *In vivo*, FOXO-1 downregulation in mice RTECs and mitochondrial damage was found in endotoxin-induced AKI. Overexpression of FOXO1 could improve renal function and reduce mitochondrial damage. PGC1-α was reduced in endotoxin-induced AKI and reversed by FOXO-1 overexpression. *In vitro*, exposure to LPS led to HK-2 cell viability decline, mitochondrial fragmentation, and mitochondrial superoxide accumulation, as well as downregulation of the FOXO1, PGC1-α and mitochondrial complex I/V. Moreover, over-expression of FOXO1 in HK-2 cells could increase HK-2 cell viability and PGC1-α expression, and alleviated altered mitochondrial injury and superoxide accumulation induced by LPS. Meanwhile, inhibition of FOXO1 in HK-2 cells by siRNA decreased PGC1-α expression and HK-2 cell viability. Chromatin immunoprecipitation assays and PCR analysis confirmed FOXO1 binding to the PGC1-α promoter in HK-2 cells.

Conclusions: In conclusion, downregulation of RTECs FOXO1 mediated endotoxin-induced AKI and mitochondrial damage. Over-expression of FOXO1 could improve renal injury and mitochondria dysfunction, at least partly via PGC1-α signaling. FOXO1 might be a potential target for the prevention and treatment of endotoxin-induced AKI.

Funding: Government Support - Non-U.S.

PO0202

Humanin Improves Mitochondrial Function and Alleviates Renal Tubular Injury in Lipopolysaccharide-Induced AKI

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Background: Mitochondria dysfunction is increasingly recognized to be a key role in the pathogenesis of sepsis-induced AKI. Whether Humanin (HN), a well-known mitochondrial-encoded cytoprotective peptide, has similar effect in septic AKI remains unknown. We hypothesize that HN improves mitochondrial function in sepsis-induced AKI.

Methods: LPS (10mg/kg) was given to C57BL/6 mice intraperitoneally to induce murine septic AKI, and HNG (a potent analog of humanin, 1mg / kg) was injected 15 minutes later. Mice were euthanized at 24 h after LPS injection. Blood samples and kidney tissues were collected. Blood urea nitrogen was measured to evaluate renal function. Electron microscopy was used to observe mitochondrial morphology and structure. Renal inflammation (IL-1β, IL-6 and HMGB1) was evaluated by real-time PCR. The expression of PGC1-α and TFAM, which can promote mitochondrial biogenesis, was measured by real-time PCR, western bolt and immunohistochemistry.

Results: HNG significantly reduced blood urea nitrogen levels (62.10 ±3.554 mg/dl vs. 30.30±2.558 mg/dl, n=3, $p<0.05$). Electron microscopy showed mitochondrial damage of renal tubular epithelial cells in the LPS group, such as mitochondrial swelling and deformation and the crista disorder or disappearance. Treatment with HNG restored mitochondrial morphology and structure. Compared with LPS group, HNG reduced the renal expression of IL-1β, IL-6 and HMGB1 and significantly increased the expression of PGC1-α and TFAM in the kidney.

Conclusions: Our data showed that humanin ameliorated renal dysfunction and attenuated renal tubular injury by alleviating mitochondrial dysfunction in LPS-induced AKI, which may be associated with upregulation of PGC1-α and its downstream transcriptional factor TFAM.

Funding: Government Support - Non-U.S.

PO0203

Renal Angiotensin (Ang) Receptor Changes Following Cecal Ligation and Puncture (CLP)-Induced AKI

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Background: Angiotensin-II (Ang2) modulates renal function and thus may contribute to sepsis-induced acute kidney injury (SIAKI). We have shown that CLP reduced renal Ang2 type-1 receptors (AT1R), but effects on non-classical Ang receptors are unknown. We hypothesized that CLP altered renal abundance of Ang2 type-2 receptors (AT2R) and Ang(1-7), Mas receptors (Ang(1-7)R, MasR), initiators of signaling axes that oppose AT1R.

Methods: C57BL6 mice were randomized to euthanasia at 6, 24, or 48hrs post-CLP (n=5/group). Unoperated mice (T0) served as controls. Mice were resuscitated (50mL/kg NS SQ) immediately and 25 hrs post-operatively. Prior to sacrifice we removed the kidneys under deep isoflurane anesthesia to minimize tissue ischemia. We obtained blood by cardiac puncture. Kidney Injury Molecule-1 (KIM-1) was measured in whole tissue homogenate (ELISA). AT1R, AT2R, and MasR were measured within specific regions of the kidney using immunofluorescence, (IF). We also used IF to compare kidney sections collected from sepsis patients within an hour of death (n=7) to sections from healthy controls (n=10).

Results: KIM-1 and BUN increased 6h post-CLP. Creatinine increased 48h post-CLP. We have previously shown that CLP reduced AT1R in arterioles, macula densa, and glomeruli. However, CLP did not alter MasR abundance in any region ($p>0.05$). The ratio of total renal MasR to AT1R more than doubled by 6hrs post-CLP ($p<0.001$ vs. T0). Renal AT2R intensity was increased in renal mesangium by 24h and in glomeruli by 48h ($p<0.01$ for both). We previously showed decreased AT1R IF in human sepsis kidney sections. In contrast, human sepsis kidneys did not show any decrease in MasR ($p>0.05$), again suggesting an increase in the MasR to AT1R ratio.

Conclusions: 1. Data on CLP-induced changes in KIM-1 in tissue and BUN in blood suggest that these are earlier markers of CLP-induced renal injury than serum creatinine. 2. CLP and septic AKI may be associated with a shift from classical to non-classical angiotensin signaling in the kidney. Studies of non-classical angiotensin system modulation in septic AKI may enhance understanding of pathobiology and reveal therapeutic targets in septic AKI.

PO0204

The Fibrogenic Response to Renal Injury Is Epigenetically Regulated Through the Activation of Bivalent Genes

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Background: Bivalent genes are regions of epigenetically modified nucleosomes that carry both H3K4me3 and H3K27me3 simultaneously and exist in a poised transcriptional state, ready for activation or repression depending on stimuli. While important in directing gene expression during development, the role of bivalency has not been fully characterized in renal injury. In this work, we demonstrate that activated bivalent genes are associated with upregulation of genes that drive the response to unilateral ureteric obstruction (UUO) in the mouse.

Methods: CUT&RUN ChIP-Seq analysis using antibodies to H3K4me3 and H3K27me3 was carried out on normal kidneys and kidneys of mice 5 days after UUO. Enriched peaks were identified using SEACR, and HOMER was used to perform peak annotation. To determine fold change gene expression, RNA was collected and analyzed from samples 5 days after they were subjected to sham or UUO surgery.

Results: Through peak annotation of CUT&RUN results, 1546 bivalently marked genes were identified in the normal kidney. With the onset of UUO, 62% of these bivalent genes (951/1546, *activated bivalent genes*) are activated by the loss of the repressive H3K27me3 mark and the persistence of the activating H3K4me3 mark, indicating these genes are available for transcription. Upon correlation of *activated bivalent genes* with RNA Seq data after UUO only 13% were significantly upregulated (fold change >1.5, FDR <0.05). Functional analysis of these *activated bivalent genes* identified enriched pathways associated with kidney injury including apoptotic signaling, regulation of fibroblast proliferation and inflammation. Significantly increased expression of genes involved in these pathways were noted after UUO, including *Nfkb2* (7 fold), *Rhob* (6 fold), *Cdkn1* (5 fold) and *Tgfbr2* (2.5 fold). The activated bivalent gene with the most significant increase in gene expression (20 fold in UUO compared to sham) was *Atf3*, a transcription factor which plays a protective role in kidney injury by attenuating the inflammatory response.

Conclusions: We provide evidence to suggest that the response to renal injury via inflammatory, apoptotic and fibrogenic pathways is orchestrated through the epigenetic regulation of bivalent genes that are poised for response in the normal kidney.

Funding: NIDDK Support

PO0205

The Effect of Overexpression of Intestinal Alkaline Phosphatase (IAP) on Intestinal Permeability and Renal Failure in Lipopolysaccharide (LPS) Treated IAP Transgenic (IAPTg) Mice

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Background: LPS associated sepsis is known to cause intestinal dysfunction in septic AKI. IAP is known to dephosphorylate LPS and render it inactive. We generated IAPTg mice who overexpress human IAP. We hypothesized that if IAPTg mice were subjected to septic AKI their kidney function and intestinal barrier permeability will be better preserved than non-transgenic mice.

Methods: IAPTg mice were developed in C57Bl6 background using human chimeric IAP under the control of villin promoter making them intestine and kidney specific overexpressing IAP. LPS (10 mg/Kg) was given to IAPTg (IAPTg+LPS) and C57Bl6 (C5+LPS) to induce septic AKI. The control IAPTg (IAPTg-LPS) and C57Bl6 (C5-LPS) received saline. FITC-Dextran (FD) was gavaged 2 hours before sacrifice to measure intestinal permeability. Blood, intestine (duodenum, jejunum, ileum), and colon were harvested for biochemical and immunoblot analysis.

Results: Serum urea and creatinine of IAPTg mice were 0.6 mg/dl and 65 mg/dl respectively which were 2 and 1.5 fold lower than C5+LPS mice ($p<0.05$). Serum FD levels of IAPTg+LPS (1.2± 0.1 ng/μl) were 2.5 fold lower than C5+LPS ($p<0.05$) suggesting improved intestinal integrity. Expression of tight junction protein (ZO-1), pro-apoptotic proteins (Caspase3, Bax), antiapoptotic protein Bcl2 in the colon, and intestine was measured by immunoblot. ZO-1 expression in the intestine and colon of C5+LPS was significantly lower than IAPTg+LPS ($p<0.05$) and the controls ($p<0.01$). Expression of intestinal and colon caspase 3 in the IAPTg was 4 fold lower than C5+LPS ($p<0.01$). Intestinal and colon Bax of IAPTG+LPS were lower and Bcl2 higher than C5+LPS ($p<0.05$). Apoptotic markers of IAPTg+LPS were not significantly different from the control suggesting low apoptosis in IAPTg. Plasma TNFα and IL-6 levels of IAPTg+LPS were 70±20 and 95+26 pg/ml respectively which were about 1.5 fold lower than C5+LPS ($p<0.05$) suggesting decreased inflammation in transgenic mice.

Conclusions: Improved ZO-1 expression probably due to reduced apoptosis decreases intestinal permeability in transgenic mice subjected to endotoxemia. This can prevent leakage of bacterial contents from the gut and result in improved renal function and decreased inflammation, as evidenced by decreased plasma cytokines, in IAPTg group.

Funding: Private Foundation Support

PO0206

Changes in NAD and Lipid Metabolism Drive Acidosis-Induced AKI

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Background: The kidney has an important role in maintaining normal blood pH. Mitochondria in the proximal tubule (PT) produce ammonia and bicarbonate from glutamine, and during metabolic acidosis (MA) this pathway (ammoniagenesis) is acutely upregulated. MA is frequently associated with acute kidney injury (AKI); however, to what extent the former causes the latter was unclear.

Methods: Multiphoton imaging of mitochondrial function in mouse kidney cortical slices and *in vivo*; oxygen consumption rate (OCR) in isolated PTs; histological analysis and electron microscopy (EM) in fixed tissue. MA was induced using an established protocol (gavage with 0.8 g/kg NH_4Cl).

Results: Acutely lowering extracellular pH to 6.5 decreased mitochondrial NADH fluorescence signal specifically in PTs, without changing total NADH content, baseline OCR or mitochondrial membrane potential. However, maximal OCR was decreased and response to rotenone was exaggerated, suggesting a switch to complex I and increased oxidation of NADH to NAD^+, which is required for ammoniagenesis. PTs in acidotic animals displayed intense Oil Red O staining and large multi-lamellar bodies (MLBs), consistent with a major decrease in lipid metabolism. Supplementing or reducing NAD (with lactate) and increasing pH back to 7.4 inhibited/reversed the appearance of MLBs, implying that changes in NAD and lipid metabolism are linked. Histological analysis of acidotic animals showed thinning of PTs and shedding of debris, indicative of AKI. Intravital imaging revealed that mitochondria remained energized, but endocytosis of fluorescently labeled dextrans was markedly decreased, confirming a severe functional defect in solute transport. Partially reversing MA with intravenous injection of bicarbonate (0.42 g/kg) or supplementing NAD with nicotinamide (0.4 g/kg, prior to MA induction) both substantially improved dextran uptake.

Conclusions: MA induces major changes in PT NAD and lipid metabolism that result in a functional AKI state, which can be reversed or prevented. These findings might also help to explain why MA accelerates decline in function in chronic kidney disease.

PO0207

Loss of HDAC8 Leads to γH2AX-Induced Cellular Repair and Decreased Epithelial-Mesenchymal Transition in Renal Tubule Epithelial Cells

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Background: Acute kidney injury (AKI) remains a significant worldwide problem. Our previous work has shown that *hdac8*$^{-/-}$ larval zebrafish model of AKI improved survival and increased repair and proliferation after AKI. However, these mechanisms have not been elucidated. AKI is known to induce double stranded DNA breaks (DSB), activating factors including the phosphorylation of the histone variant H2AX producing γH2AX. Damaged cells undergo a complex multifactorial fate determination leading to either DNA repair and cell survival or apoptosis.

Methods: hdac8$^{sa14948/-}$ and hdac8 $^{sa14948/+}$ mutant zebrafish were injected with gentamicin to induce AKI. Immunofluorescent microscopy, fluorescently activated cell sorting (FACS) of renal tubule epithelial cells (RTEC) were isolated for RNA-seq.

Results: We evaluated DNA DSB in RTEC through immunohistochemistry of γH2AX in WT and *hdac8*$^{-/-}$ zebrafish with and without AKI. There were a greater number γH2AX foci in RTEC of the *hdac8*$^{-/-}$ larvae with AKI than in either the uninjured *hdac8*$^{-/-}$ or WT AKI larvae. *hdac8*$^{-/-}$ zebrafish with AKI exhibited less apoptosis compared to WT zebrafish with AKI, and as expected there were undetected levels of TUNNEL positive cells in WT and *hdac8*$^{-/-}$ uninjured tubules. We observed more Pax2a positive cells in *hdac8*$^{-/-}$ larvae with AKI than WT larvae with AKI. Immunohistochemical analysis of Na^+/K^+-ATPase, a marker for epithelial polarization, in *hdac8*$^{-/-}$ zebrafish tubules maintain partial to full polarization during AKI, whereas WT larvae with AKI had complete mis-polarization of RTEC. RNA-Seq data analysis confirmed the epithelial polarization data demonstrating increased expression of mesenchymal genes and decreased epithelial gene expression in WT tubules with AKI compared to *hdac8*$^{-/-}$ in AKI injured zebrafish.

Conclusions: This study suggests a mechanism of repair and recovery after AKI in *hdac8*$^{-/-}$ zebrafish is mediated through increased γH2AX at sites of DNA damage. *hdac8*$^{-/-}$ mutant zebrafish preferentially uses mechanism of DDR for repair and proliferation, as opposed to apoptosis. In the absence of apoptosis *hdac8*$^{-/-}$ tubules can prevent depolarization of epithelial membranes and maintain their epithelial gene signatures, whereas the WT zebrafish lose their polarization and begin EMT. These data support our hypothesis that the loss of HDAC8 allows cells to repair after injury from AKI

Funding: NIDDK Support, Other U.S. Government Support

PO0208

Protein Phosphatase 2A Cα Reprograms Cellular Energy Metabolism to Promote Tubular Cell Death and Kidney Injury

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Background: Protein phosphatase 2A (PP2A), one of the primary serine-threonine phosphatases in mammalian cells, regulates various biological processes. The role and mechanisms for PP2A in kidney injury remains to be determined.

Methods: Generating the mice with PP2Aca ablation with Cre-Loxp system. Mice were injected with cisplatin to induce AKI. UUO was performed on the mice to induce kidney fibrosis.

Results: In this study, we found that the expression of protein phosphatase 2A Cα (PP2Acα) in tubular cells was upregulated in both patients and animal models with acute and chronic kidney injury. Ablation of PP2Aca in tubular cells alleviated cisplatin-induced acute kidney injury and unilateral ureteral obstruction-induced kidney fibrosis in mice. In cultured tubular cells, ablation of PP2Acα promotes oxidative phosphorylation of fatty acids by increasing p-ACC levels and thus protects against cisplatin-induced cell death and TGFβ1-induced fibronectin production.

Conclusions: This study reveals the essential role for PP2Acα in regulating tubular cell energy metabolism and survival, which may shed light on treating patients with kidney injury.

PO0209

In Vitro Inhibition of Renal OCT2 and MATE1 Secretion by Antiemetic Drugs

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Background: The organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1) regulate the renal secretion of drugs including metformin, cisplatin, and entecavir. Studies suggest that ondansetron, an antiemetic drug and 5-HT_3 antagonist, can inhibit OCT2- and MATE1-mediated transport. The purpose of this study was to test five structurally similar 5-HT_3 antagonist drugs for their ability to inhibit the OCT2 and MATE1 transporters.

Methods: Transport of the fluorescent prototypical cation ASP^+ (25 μM) was assessed in the presence and absence of 5-HT_3 antagonists (0.5-20 μM) using two *in vitro* models: 1) HEK293 kidney cells overexpressing human OCT2 or MATE1 and 2) double-transfected hOCT2-MATE1 MDCK cells. Cimetidine (50 μM) was included as a positive control.

Results: The relative order of potency for inhibition of ASP^+ uptake by OCT2 was palonosetron > ondansetron > granisetron > tropisetron > dolasetron and by MATE1 was ondansetron > palonosetron = tropisetron > granisetron > dolasetron. In hOCT2-MATE1

MDCK cells, ondansetron (0.5-20 μM) inhibited the transcellular transport of ASP^+ up to 64%. Palonosetron, tropisetron, and dolasetron (10 and 20 μM) reduced the transcellular transport of ASP^+ up to 80-90%. Granisetron did not alter the transcellular transport of ASP^+ at concentrations up to 20 μM.

Conclusions: 5-HT_3 antagonist drugs may inhibit the renal secretion of cationic drugs resulting in potential drug-drug interactions. These data could have important implications for drug-induced kidney injury since 5-HT_3 antagonists are routinely prescribed with the highly emetogenic and nephrotoxic chemotherapeutic drug cisplatin. Funded by NIH GM123330, ES005022, ES007148, CA072720, and CA046934.

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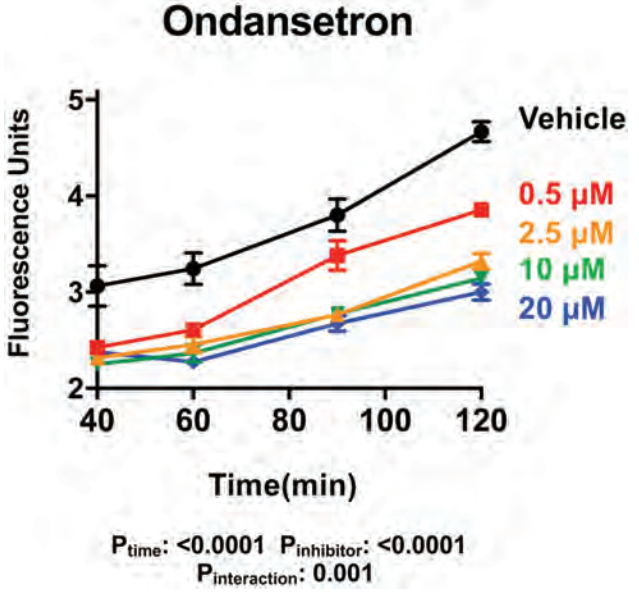

Inhibition of OCT2-MATE1 Secretion of ASP^+ by Ondansetron in MDCK Cells

PO0210

Klotho Deficiency Intensifies Hypoxia-Induced Expression of INF-α/β Through Upregulation of Rig-I

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Background: Hypoxia is a common pathway to progression of end-stage kidney disease. Although numerous studies have provided evidence that inflammation plays a major role in this process, the mechanism by which hypoxia induces inflammation remains unknown. Retinoic acid-inducible gene-I (RIG-I) encodes an RNA helicase that recognizes viruses including SARS-CoV2, which is responsible for production of interferon (IFN)-α/β to prevent the spread of a viral infection. Recently, RIG-I activation was found under hypoxic conditions, and klotho deficiency intensified the activation of RIG-I in mouse brains. However, the roles of these functions in renal inflammation remain elusive.

Methods: *In vitro*, expression of RIG-I and INF-α/β was examined in normal rat kidney (NRK)-52E cells incubated under hypoxic conditions (1% O_2) for 30, 60, 90, and 120 min. Next, siRNA targeting RIG-I or scramble siRNA was transfected into NRK52E cells to examine expression of RIG-I and INF-α/β under hypoxic conditions. *In vivo*, we induced renal hypoxia by clamping the renal artery for 10 min in wildtype mice (hypoxic WT mice) and Klotho knockout mice (hypoxic $Kl^{-/-}$ mice). Lastly, we investigated the expression levels of RIG-I and INF-α/β in 33 human kidney biopsy samples diagnosed with IgA nephropathy.

Results: *In vitro*, incubation under hypoxic conditions increased expression of Rig-I and IFN-α/β in NRK52E cells. Their upregulation was inhibited in NRK52E cells transfected with siRNA targeting Rig-I. *In vivo*, the expression levels of Rig-I and IFN-α/β were upregulated in kidneys of hypoxic WT mice and further upregulation was observed in hypoxic $Kl^{-/-}$ mice. In patients with IgA nephropathy, immunohistochemical staining of renal biopsy samples revealed that expression of Rig-I was correlated with that of IFN-α/β (r=0.57, *P*<0.001, and r=0.81, *P*<0.001, respectively).

Conclusions: These findings suggest that hypoxia induces expression of INF-α/β through upregulation of Rig-I, and that klotho deficiency intensifies this hypoxia-induced expression.

PO0211

suPAR Determines Outcomes in Septic AKI

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Background: Sepsis is the main contributor to the development of acute kidney injury (AKI) in critically ill patients. Plasma soluble urokinase plasminogen activator receptor (suPAR) is a circulating risk factor for AKI and a prognostic marker for the need of renal replacement therapy (RRT). We analyzed the pathophysiological role and kinetic properties of suPAR in septic AKI in critically ill patients and in a murine model of septic AKI.

Methods: 200 critically ill patients were enrolled prospectively after meeting Sepsis-3 criteria. Serum suPAR levels were measured at 0, 12, 24, 48, 72, 96, 120 and 168-hour after enrollment and the need for RRT within 7 days was assessed as the primary outcome measure. Polybacterial sepsis was induced by cecal slurry injection in three mouse strains, respectively wild type (WT, N=9), uPAR-knockout (KO, N=13), and suPAR transgenic overexpression (OE, N=11).

Results: No or mild AKI occurred in 62 patients (31.0%), moderate or severe AKI without the need for RRT in 102 patients (51.0%), criteria for RRT were met in 36 patients (18.0%) and 7 patients (3.5%) died within the 7-day period. Compared to all other maximum AKI stages and AKI disease courses within 7 days, patients requiring RRT showed significantly higher suPAR levels at all time-points. Patients with suPAR levels ≥ 12.7 ng/mL (highest quartile) had an adjusted odds ratio of 5.22 (95% confidence interval [CI], 2.16-12.65) for the need for RRT; and 4.44 (95% CI, 1.98-9.97) for RRT or death within 7 days compared to patients with levels < 12.7 ng/mL. Compared to KO mice, WT and OE mice showed a significantly greater impairment of renal function and structure 24 hours after induction of sepsis. Kaplan-Meier analysis revealed a survival benefit of KO mice over OE mice within 24h (84.6% vs. 45.5%, p=0.041).

Conclusions: SuPAR distinguishes between divergent AKI stages/courses and the need for RRT at any time within 7 days after sepsis diagnosis. Our experimental data suggest that suPAR is a pathophysiological driver of septic AKI and may serve as a target for future interventional strategies.

PO0212

Cardiorenal Effects of the American College of Radiology (ACR) Group II Agent Gadobutrol (Dotarem): Renal Proximal Tubular Mitochondrial Toxicity and Acute Tubular Damage

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Background: Patients are concerned about gadolinium (Gd) deposition from magnetic resonance contrast agents. Gd is the known cause of iatrogenic 'nephrogenic' systemic fibrosis and long-term gadolinium retention in every organ. Without prospective evidence, the ACR partitions brands of Gd-based contrast agents (GBCAs) into three groups: I, associated with the greatest number of systemic fibrosis cases; II, associated with few, if any, unconfounded cases of iatrogenic systemic fibrosis; and III, data are limited.

Methods: Male and female mice were randomized to GBCA treatment with an increasingly popular, ACR group II macrocyclic agent (Dotarem, 2.5 mmol/kg intraperitoneally, 20 doses over 4 weeks). Echocardiographic parameters were compared at the endpoint, tissues examined with transmission electron microscopy.

Results: Gd *reduced* cardiac systolic volume (29 ± 6 vs 34 ± 4 μL, mean ± SD, M-mode), *increased* fractional shortening (30 ± 4 vs 25 ± 2%, M-mode), and *increased* ejection fraction (57 ± 5 vs 50 ± 4%, M-mode). Renal tissue was characterized by tubular damage, pathologic lipid vacuolization, and diffuse mitochondrial toxicity (**Figure**).

Conclusions: GBCA treatment leads to diffuse and long-term intracellular retention in every vital (and non-vital) organ. These studies demonstrate that the American College of Radiology group II agents are far from clinically inert. Consistent with the first element of the Nuremberg Code, voluntary consent for GBCA administration should be obtained from every patient.

Funding: NIDDK Support, Veterans Affairs Support, Commercial Support - DCI

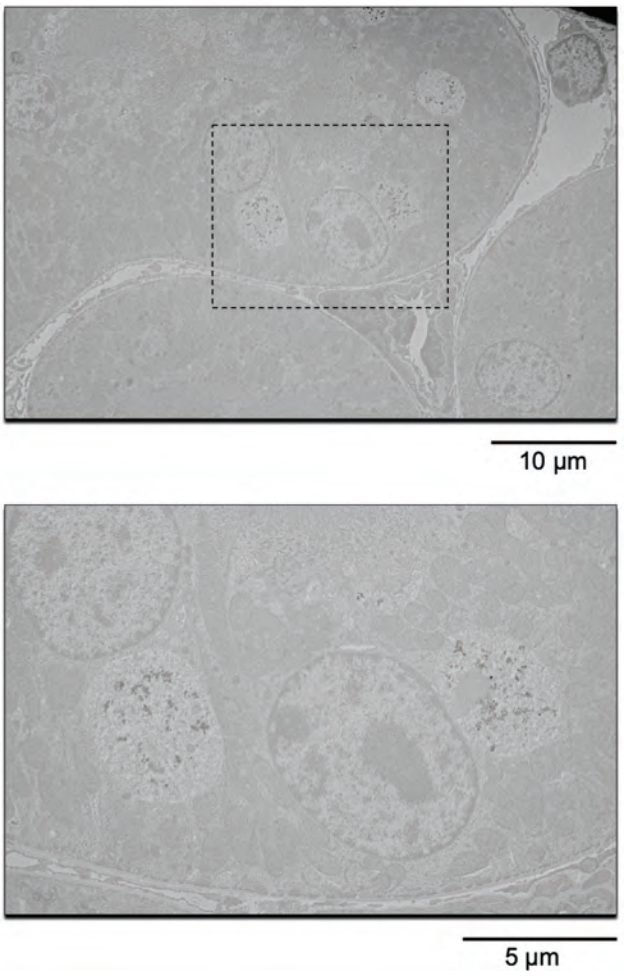

Figure. Systemic Gd treatment induced lipid-laden vacuoles with electron-dense material and pathologic mitochondrial changes. Transmission electron microscopy, renal proximal tubule.

PO0213

Identification of Predictive Biomarkers Associated with Antibiotic Associated Nephrotoxicity from Polymyxin and Tobramycin Antibiotics Using a Kidney Microphysiological Device

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Background: With the emergence of multi-drug resistant gram-negative infections, polymyxin and aminoglycoside antibiotics are ever more important for effective bacterial treatment. However, the use of these antibiotics is limited due to concerns of acute kidney injury (AKI). We have employed a kidney microphysiological device system (MPS) with cultured human primary proximal tubule epithelial cells (PTECs) to identify potential sensitive renal biomarkers arising from exposure to aminoglycosides and polymyxins.

Methods: We exposed human PTECs to various concentrations of Polymyxin B (PMB), Polymyxin E (colistin) and tobramycin for 72 hours and collected daily effluents for biomarker discovery. In addition, we evaluated PTEC mRNA transcripts (RNAseq) from control and antibiotic treated MPS devices after 72 hours of antibiotic exposure. Biomarkers associated with epithelial cell injury [kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL)], inflammation/apoptosis [soluble Fas Receptor (sFAS), Fas Ligand and tumor necrosis factor receptor 1 (TNFR-1)] were measured in the MPS effluents using ELISA.

Results: In MPS devices, we observed with PMB and colistin, elevations of KIM-1 at 24 and 48 hours, sFAS at 24 hours and NGAL at 48 hours. In contrast, tobramycin exposures up to 100 mg/mL (5 times clinical Cmax) showed no evidence of toxicity either through lack of elevation of nephrotoxicity biomarkers in effluents or by changes in differentially expressed genes compared to controls. In discovery RNAseq analyses, 7641 genes were differentially regulated between colistin and control MPS. Specific pathways included upregulation of metallothionein and cholesterol biosynthesis genes with colistin exposure. With tobramycin exposure, no genes were differentially regulated compared to controls.

Conclusions: We found that different biomarkers have variable kinetics after PTEC injury. sFas and KIM-1 concentrations rose the earliest after antibiotic exposure. In RNAseq analyses, we found that pathways of metallothionein and cholesterol biosynthesis were dysregulated after colistin exposure. Finally, we found minimal PTEC injury with tobramycin, suggesting that this antibiotic may be less toxic than previously believed. Future work seeks to test these candidate biomarkers in human urine samples.

PO0214

GTS-21 Attenuates the Inflammation of AKI Independent of α7 Nicotinic Acetylcholine Receptor

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Background: Vagus nerve stimulation protects from kidney injury by activating the cholinergic inflammatory pathway (CAP). It is considered that α7 nicotinic acetylcholine receptor (α7nAChR) in splenic macrophages are important for CAP activation. To elucidate the mechanism of receptor signaling, we promoted further experiments using macrophage-specific α7nAChR knockout mice.

Methods: We generated macrophage-specific α7nAChR-deficient mice by crossbreeding LysM-Cre and α7nAChR flox mice. *In vivo*, GTS-21 (an α7nAChR specific agonist) was intraperitoneally injected to either wild type C57BL/6J mice (WT) or macrophage-specific α7nAChR-deficient mice prior to administration of lipopolysaccaride (LPS). 4 hours after LPS administration, the mice were euthanized and, plasma TNF-α level, plasma creatinine, BUN were evaluated. *In vitro*, murine macrophage cell line RAW264.7 and primary peritoneal macrophages from either WT or α7nAChR-deficient mice were used. These cells were stimulated with LPS after nicotine (pan nicotinic acetylcholine receptor agonist) or GTS-21 was administrated, then TNF-α level was evaluated 4 hours later.

Results: GTS-21 protected the kidney and suppressed the increase of plasma TNF-α induced by LPS in WT mice. Surprisingly GTS-21 decreased plasma TNF-α level induced by LPS in not only WT mice but also macrophage-specific α7nAChR-deficient mice. In vitro experiments, GTS-21 or nicotine treatment suppressed TNF-α induction by LPS in RAW264.7 cells or peritoneal macrophages from WT mice. Furthermore, nicotine also suppressed the induction of TNF-α by LPS even in peritoneal macrophages from α7nAChR-deficient mice.

Conclusions: These results suggest that nicotine or GTS-21 might suppress the inflammation independent of α7nAChR in macrophages *in vivo* and *in vitro.*

PO0215

Platelets vs. Neutrophils as Therapeutic Targets in Cholesterol Embolism-Related Arterial Occlusion, Kidney Infarction, and AKI

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Background: Cholesterol crystal embolism (CCE), a life-threatening complication, is a consequence of the rupture of atheromatous plaques in patients with advanced atherosclerosis. CCE often missed as a cause of AKI. We hypothesized that platelet contributes to CCE-related artery occlusion leading to AKI and kidney infarction.

Methods: C57/BL6 mice were injected with various doses of cholesterol crystals (CC) to induce CCE in kidney. Primary endpoint: GFR. Secondary endpoints: infarct size, vascular occlusions. 3D MRI and µCT. In vitro studies CC with neutrophils, platelets, endothelial cells.

Results: At 24h, MRI and µCT showed perifocal edema around ischemic lesion and vascular rarefication in CCE kidney. CC-induced clots causing a dose-dependent GFR loss and infarct size. Immunostainings revealed crystal clots contained fibrin, platelets, ecDNA, neutrophils. To study the role of platelets in this process, we treated mice with platelet antagonist clopidogrel. At 24h, clopidogrel completely protected mice from intravascular obstructions, GFR loss, and kidney infarction. In contrast, neutrophil depletion significantly decreased kidney infarction but not arterial obstructions or GFR loss. Maybe because mononuclear cells had partially replaced neutrophils within clots and ecDNA was still present. DNase I treatment also significantly reduced the percentage of ecDNA positive clots, occluded arterial, GFR loss, infarct size. In vitro studies show, CC induced ATP secretion and enhanced fibrinogen release from platelet granules which promotes fibrin clot formation. DNase I can strongly inhibit ATP secretion, fibrin formation, also normalized collagen-driven platelet aggregation.

Conclusions: In summary, not CC itself but the CC-induced fibrin clots obstructed peripheral arteries causing tissue infarction and organ failure. Platelets and ecDNA are central for crystal clots formation. Hence, crystal clots represent the primary target for therapeutic interventions. Among the possible molecular targets in thrombosis, especially enhancing fibrinolysis or inhibiting platelet purinergic signaling could reduce arterial occlusions, infarction, and organ failure. DNase I could have a synergistic effect on CC induced clot formation in mice and might be a prophylactic/therapeutic approach in human patients with a risk for procedure-related CC embolism.

Funding: Government Support - Non-U.S.

PO0216

Characterizing De Novo Lymphangiogenesis During AKI Using 3D Imaging and Tissue Cytometry

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Background: The renal lymphatic system is essential for fluid and electrolyte homeostasis, lipid and cholesterol transport, and immune surveillance with lymphatic vessels (LV) primarily intertwined with the blood vasculature. LV development, or lymphangiogenesis (LA) is regulated by its master transcription factor, prospero-related homeobox-1 (Prox-1), which determines lymphatic cell fate. LA is accentuated during inflammation or injury states such as acute kidney injury (AKI), though mechanisms of LA in AKI remain unclear. Understanding the LA process is essential because it will elucidate potential therapeutic targets in AKI.

Methods: Using 10-week old male Prox1-tdTomato lymphatic reporter mice (ProxTom), we investigated the effect of AKI on the abundance and distribution of Prox-1$^+$ cells at the mesoscale level using large scale three-dimensional (3D) imaging and tissue cytometry. ProxTom mice and their controls were subjected to ischemia-reperfusion (IR) or no surgery and kidneys were fixed on day 3. Large scale 3D imaging with confocal microscopy was done on 50mm thick sections spanning the entire cross section of the kidney, followed by tissue cytometry using the volumetric tissue exploration and analysis (VTEA) software tool.

Results: The average number of cells surveyed per specimen was 347,360 ± 36,647. Using VTEA, a gating strategy was devised to account for autofluorescence in the red channel, which was increased after IR due to cell debris and injury. IR samples displayed a significant increase in Prox-1$^+$ cells compared to baseline controls: 717.2 ± 161.8 vs. 174.4 ± 62.1 Prox-1+ cells/mm^3, respectively ($p<0.05$). In baseline controls, Prox-1$^+$ cells were well-organized and predominately localized around large vessels in the hilum. However, after injury, the distribution of Prox-1$^+$ cells shifted to the hilar parenchyma and inner medulla in a consistent pattern. Few cells could also be detected in the outer medulla and cortex.

Conclusions: We demonstrate a scale of analytics that is amenable to characterizing de novo renal LA during AKI, which informs the origin and distribution of renal LVs and the dynamics of LA. Such findings will enhance our understanding of the functional role of LVs during injury and help identify novel therapeutics for intervention in AKI.

Funding: NIDDK Support, Other NIH Support - NIH-NRSA Training Grant Research Fellowship Interdisciplinary Training in Kidney Related Research, Veterans Affairs Support

PO0217

Peritubular Transcytosis Enables Mesoscale Nanoparticle Treatment of AKI

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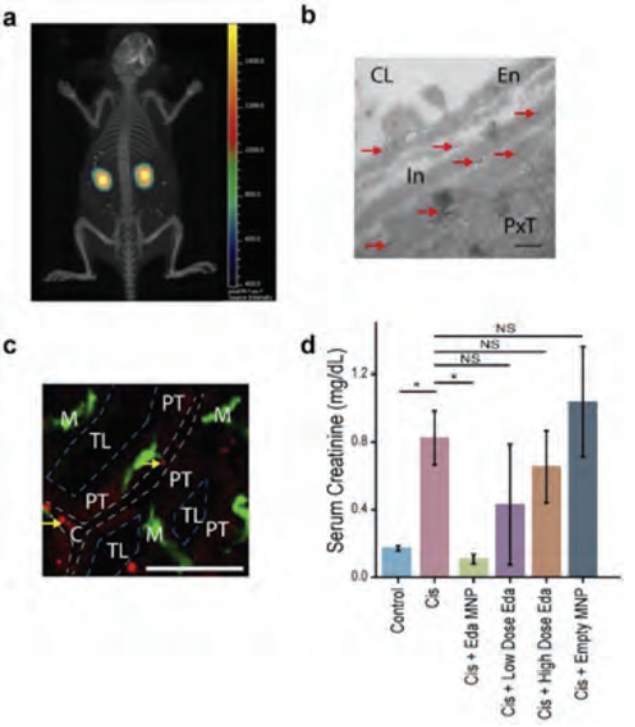
Background: In prior studies we demonstrated that mesoscale nanoparticles (MNP) localize to the kidneys up to 26-fold more than to any other organ and that they specifically target the renal tubular epithelium. In this study we investigated the mechanism of MNP localization to the renal tubules and evaluated this platform's potential for therapeutic delivery in a model of cisplatin-induced acute kidney injury (AKI).

Methods: We synthesized ~400 nm diameter MNPs from the biocompatible polymers poly(lactic-*co*-glycolic acid) and polyethylene glycol (PLGA-PEG). MNPs were encapsulated with a fluorescent far-red dye or the reactive oxygen species scavenger edaravone. Male C57BL/6 mice, were sacrificed 30 minutes after injection for immune-electron microscopy studies. We also performed intravital microscopy to visualize the transit of MNPs in *Cx3cr*$^{gfp/+}$ C57BL/6 mice with GFP-expressing renal macrophages. We also evaluated their therapeutic potential in a cisplatin-induced AKI (25 mg/kg IP) model. 24 hours following cisplatin, mice received edaravone-loaded MNPs or appropriate controls. Serum creatinine and histology were analyzed 72 hours following cisplatin.

Results: We found that MNPs localize to the proximal tubular eoithelium via transcytosis from the peritubular capillaries. We observed MNPs flowing in these capillaries and in transit across the tubular interstitium. We also found that transcytosis of MNPS was not facilitated by macrophage uptake. Finally, we found that therapeutic MNPs use this mechanism to localize to the proximal tubules of mice with cisplatin-induced AKI (Figure).

Conclusions: These studies characterized transcytosis from the peritubular capillaries as the mechanism of particle localization to the kidneys and portend the development of additional therapeutic targeting tools for renal diseases.

Funding: NIDDK Support



PO0218

Role of the Exocyst, Cilia, and Mitochondria in AKI

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Background: AKI has high morbidity and mortality. Management consists of supportive care. Among the critical pathways in AKI are alterations of tubular mitochondrial metabolism, and, as recently suggested, disruption of primary ciliary homeostasis. Mitochondria are also involved in ciliopathies. Here we tested if cilia acting via mitochondria are involved in AKI.

Methods: We previously showed that the exocyst trafficking complex is necessary for ciliogenesis. Overexpression of Exoc5, a central exocyst component, protected renal tubule cells against H_2O_2-induced injury, whereas Exoc5 knockdown worsened it. In AKI, proximal tubules are most susceptible to injury. To determine the effect of Exoc5 loss, we crossed Exoc5$^{fl/fl}$ mice with mice expressing CreERT2 driven by the proximal tubule sodium-dependent inorganic phosphate transporter (SLC34a-CreERT2). Proximal tubule-specific Exoc5 knockout (KO) mice and littermate controls were subjected to bilateral ischemia reperfusion (I/R) injury by clamping the renal arteries. In order to gain mechanistic insight, we evaluated mitochondrial function in Exoc5 overexpressing (OE), Exoc5 knockdown (KD), Exoc5 ciliary targeting sequence point mutant (cts-mut), and control Madin-Darby canine kidney tubule (MDCK) cells.

Results: Proximal tubule-specific Exoc5 KO mice had worse renal injury, and higher serum creatinine following I/R injury compared to control mice ($p=0.005$). Seahorse assays revealed diminished spare respiratory capacity in Exoc5 KD and Exoc5 cts-mut cells, which was increased in Exoc5 OE cells, compared to control MDCK cells. Tetramethylrhodamine methyl ester was employed to measure mitochondrial membrane potential and we found mitochondrial uncoupling in Exoc5 KD and Exoc5 cts-mut as compared with control cells. Transmission electron microscopic imaging revealed healthy circular-shaped mitochondria with dense matrix in control and Exoc5 OE cells. Exoc5 KD cells exhibited mitochondrial damage and swelling consistent with the observed reduced respiration. Interestingly, Exoc5 cts-mut cells demonstrated formation of elongated mitochondria with pronounced cristae and large intracristae spaces, which could indicate less intensive bioenergetics, and would explain the reduced respiration.

Conclusions: For the first time we show that the exocyst and cilia are centrally involved in AKI and the effect may be mediated through mitochondria.

Funding: Veterans Affairs Support

PO0219

Ascending Vasa Recta Responsible for Medullary Vascular Congestion

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Background: Vascular congestion of the renal medulla is common in acute kidney injury and has been shown to prolong ischemia and promote injury. We have reported that pretreatment with low dose lipopolysaccharide (LPS) attenuates ischemia reperfusion (IR) induced congestion. The temporal localization of congestion during IR and how LPS prevents congestion remains unknown. We hypothesized that 'vascular congestion

originates in the medullary vasa recta (VR) prior to the peritubular (PT) capillary plexus, and that pretreatment with low dose LPS aids in early VR reperfusion'.

Methods: To test this hypothesis, male WKY rats (10wks) were pretreated (i.p) with 1000μg/kg LPS or saline daily for 3 days and a 45-minute warm, bilateral ischemia was performed. Rats were randomized to 0, 1, 2, 6, 10, or 24 hour(s) of reperfusion (n=4-6/group). Congestion of the medullary VR and PT capillaries was assessed in histological sections (scale: 0-5, 0=0%, 5=100% congestion).

Results: At time 0 (no reperfusion), congestion of the medullary VR averaged 80% in both saline and LPS treated rats. Following reperfusion for 1, 2, 6, and 10 hours, VR congestion was >60% in saline treated rats. In contrast, VR congestion in LPS rats rapidly declined within 1 hour (<20%) and remained lower than saline scores through 24 hours ($p_{TREATMENT}$<0.0001). In both groups, PT congestion was less than 20% at time 0 (no reperfusion) but rapidly increased in saline treated rats to >60% by 6 hours of reperfusion. Conversely, in LPS treated rats, PT congestion remained low (average 13.4%, $p_{INTERACTION}$=0.0144) across the 24-hour reperfusion period. Immunofluorescent staining of neural-glial antigen 2 (NG2) and urea transporter (UTB) localized initial congestion to the ascending VR (AVR).

Conclusions: Our data provides the first evidence that congestion originates in the medullary AVR during the ischemic period and that blockage of AVR drives congestion in the PT capillary plexus during reperfusion by preventing drainage of the renal medullary circulation. Rapid reperfusion of the AVR (LPS group) prevented congestion of the PT capillaries. These data provide new insight into the pathophysiology of vascular congestion following ischemia and identify the AVR as the renal defect responsible for PT congestion. Understanding the mechanisms by which LPS aids in AVR reperfusion may be critical in order to find therapeutic targets for vascular congestion.

Funding: Other NIH Support - NHLBI

PO0220

VEGF-R2 Signaling in Renal Stroma Exacerbates Post-AKI CKD Progression

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Background: Acute Kidney Injury (AKI) is widespread, identified in 30% of post-operative and 50% of ICU patients, and associated with increased rates of chronic kidney disease (CKD) and end stage renal failure. Peritubular capillary beds are significantly damaged, and it causes vascular rarefaction during many types of AKI. Vascular rarefaction is closely associated with post-AKI CKD progression. Vascular endothelial growth factor (VEGF) is a well defined angiogenic protein via its major receptor, VEGF receptor 2 (VEGF-R2). However, prior work from others demonstrated a role of VEGF as a negative regulator of pericyte function and vessel maturation. The functional implications of the VEGF-R2 signaling in renal stroma remains poorly understood.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of VEGF-R2 with constitutively expressed Foxd1-Cre (*cVEGF-R2$^{RSC-/-}$*) and tamoxifen inducible Foxd1-Cre (*iVEGF-R2$^{RSC-/-}$*). AKI/CKD models induced either by a renal ischemia/reperfusion injury (IRI) model or by low/dose repeated treatment of cisplatin were performed. Mice are monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis.

Results: *cVEGF-R2$^{RSC-/-}$* protects against ischemic AKI in male and female mice. Specifically, *cVEGF-R2$^{RSC-/-}$* reduces renal tubular injury and microvascular rarefaction. *cVEGF-R2$^{RSC-/-}$* also mitigates CKD progression post ischemic-AKI. *cVEGF-R2$^{RSC-/-}$* reduces expression of kidney injury markers, *Havcr1* and *Lcn2*, in a cisplatin-AKI/CKD model. Interestingly, *iVEGF-R2$^{RSC-/-}$* demonstrates higher degree of protection against ischemic AKI as compared to *cVEGF-R2$^{RSC-/-}$* studies. We showed previously that *cVEGF-R2$^{RSC-/-}$* shows mild defects in kidney development. Our new data suggests that *iVEGF-R2$^{RSC-/-}$* bypasses deleterious effect by the mutation during kidney development.

Conclusions: These data suggest that VEGF-R2 signaling in renal stromal cells exacerbates ischemic AKI and its post-AKI CKD progression as well as cisplatin AKI.

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PO0221

Pericyte and Macrophage C5aR1 Mediate Renal Fibrosis

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Background: We reported that kidney complement plays an important role in the pathogenesis of renal scarring. Here we used a floxed green fluorescent protein (GFP)-C5aR1 reporter mouse and the model of Folic acid (FA)-mediated fibrosis to examine mechanisms by which C5aR1 contributes to fibrosis.

Methods: We used flow cytometry, confocal microscopy and image stream analysis of kidney tissue cell suspensions from vehicle and FA-treated GFP-*C5ar1$^{fl/fl}$* reporter mice to characterize cell types where *C5ar1* mRNA and protein levels were expressed. To address the functional role of C5aR1 during fibrosis we generated pericyte-specific and myeloid-specific C5aR1 KO mice by crossing GFP-*C5ar1$^{fl/fl}$* mice with mice expressing Cre-recombinase under the control of the *Foxd1* or *LyzM* promoter, respectively. We established primary cell cultures of PDGFRß+ kidney pericytes isolated from GFP-*C5ar1$^{fl/fl}$* mice and FoxD1-C5aR1 KO mice and performed qPCR and luminex analysis.

Results: Immunofluorescence confocal microscopy demonstrated increased GFP$^+$ (C5aR1+) cells in tubulo-interstitium of FA-treated mice, which co-stained with F4/80 antibody. ImageStream analysis confirmed surface expression of C5aR1 in GFP$^+$PDGFRB+ cells and CD45+F4/80+ cells. Flow cytometry showed increased GFP in CD45+F4/80+ cells. Mice with pericytes-specific deletion of C5aR1 had reduced fibrosis, measured by picrosirious red staining, and reduced α-SMA, fibronectin and collagen1A1, compared to wild-type mice. Pericytes isolated from Foxd1-C5aR1 KO mice treated with FA showed reduced expression and secretion of IL6, TNF, macrophage inflammatory proteins, and MMP-9, when compared to pericytes isolated from GFP-C5aR1$^{fl/fl}$ mice. Myeloid-specific deletion of C5aR1 resulted in significant reduction of C5aR1 in kidney homogenates, confirming macrophages as the major population expressing C5aR1 following FA injury. These mice also showed reduced kidney fibrosis by picrosirious red staining, and qPCR analysis of fibronectin and collagen.

Conclusions: Our findings demonstrate that pericytes and macrophages play important roles in the pathogenesis of renal scarring and implicate C5aR1 as a key mediator. Conditional deletion of C5aR1 in these two interstitial cell types reduces inflammation and extracellular matrix protein formation in pericytes as well as macrophage migration and profibrotic phenotype of kidney macrophages.

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PO0222

Selective Expansion of Kidney Double-Negative T Cells Is Driven by Renal Tubular Epithelial Cells Through Direct Cell-Contact and by Soluble Mediators

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Background: Kidney TCRα/β$^+$CD4$^-$CD8$^-$CD1d$^-$ double negative (DN) lymphocytes are a recently recognized unconventional T cell population with important roles in AKI and possibly other diseases like lupus. DN T cells expand after experimental AKI and exogenous delivery improves outcome. However, mechanisms underlying their regulation and expansion in the kidney are poorly understood. Here, we demonstrate a direct role for renal tubular epithelial cells (RTEC) in regulating homeostasis of kidney DN T cells.

Methods: Age-matched B6 WT, MHC I KO, MHC II KO and DKO (MHC I and II KO) mice were studied. T cell functional assays and an *in-vitro* co-culture system were used to investigate the functional relationship between RTEC and DN T cells. RTECs were isolated, purified and cultured in collagen-coated plates. Lymphocytes from both kidney and periphery were isolated, co-cultured with RTEC and analyzed by FACS.

Results: DN T cells were anergic when cultured alone, even after stimulation with anti-CD3/CD28, but spontaneously proliferated when co-cultured with RTEC (DN; 1.2 ± 0.6% **vs** RTEC+DN; 13.8 ± 3.5%, p≤0.0001). Expansion was due to increased proliferation and decreased apoptosis of DN T cells. RTEC mediated expansion of DN T cells occurred by multiple mechanism including direct cell-contact and secretion of IL-7. Although activation of T cells required direct TCR crosslinking, activation of DN T cells was TCR-MHC independent as indicated by the ability of RTEC from mice lacking MHC class-I, class-II or DKO mice to induce proliferation of DN T cells (DN; 2.1 ± 0.8% **vs** RTEC (WT)+DN; 17.1 ± 1.5%, **vs** RTEC (MHC I KO)+DN; 21.2 ± 0.5%, **vs** RTEC (MHC II KO)+DN; 17.9 ± 1.8%, **vs** RTEC (DKO)+DN; 32.8 ± 0.3%, p≤0.0001). Reciprocally, DN T cells increased survival of RTEC as demonstrated using *in-vitro* assays. Our ongoing experiments are focusing on identifying surface molecules involved in mediating interactions between DN T cells and RTEC.

Conclusions: These results demonstrate a previously unknown functional relationship between RTEC and DN T cells that may explain the selective accumulation of DN T cells in the kidney and roles in normal and diseased kidney. The results have important implications for developing strategies to ameliorate AKI by promoting the survival of kidney DN T cells.

Funding: NIDDK Support

PO0223

TGF-β-Induced CD8+CD103+ Regulatory T Cells but Not Nature Regulatory T Cells Alleviates Acute Renal Injury Induced by Ischemia-Reperfusion

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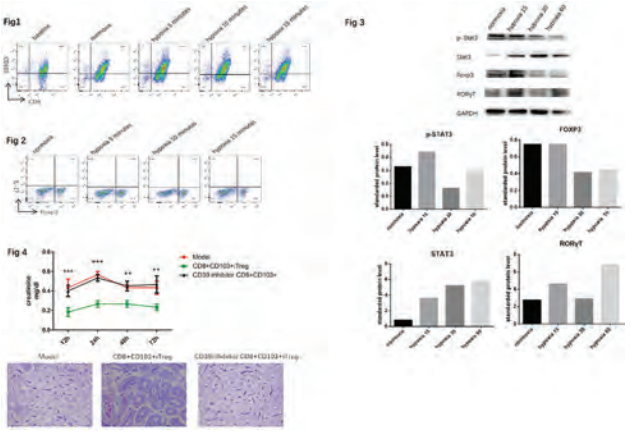
Background: Acute kidney injury (AKI) is one of the most common complications in clinical practice, inflammatory response induced by hypoxic-reoxygenation is the key mechanism of ischemia-reperfusion acute kidney injury. Regulatory T cells are crucial players in the maintenance of immune homeostasis. Our previous researches show that natural regulatory T cells (nTreg) tend to transfer into Th17 under conditions of inflammation and hypoxia. On the contrary, TGF-b induced CD8+CD103+Treg (CD8+CD103+iTreg), a new subpopulation of iTreg we have identified, maintains stable phenotype and immunomodulatory function. The instability of nTreg under conditions of inflammation and hypoxia suggesting that nTreg are not suitable for treatment of AKI. Accordingly, we studied the role of CD8+CD103+iTreg in alleviating AKI.

Methods: In vitro study, we test the phenotype and immunomodulatory function of CD8+CD103+iTreg or nTreg under 1% O2 concentration. In vivo study, CD8+CD103+iTreg(2×10^6/mouse)or nTreg(2×10^6/mouse)were injected intravenously daily to the AKI mice from the day of surgery (for 3 days).

Results: The expression of CD103 is stable in CD8+iTreg in vitro under 1% O2 concentration(Fig 1). nTreg transfer into Th17 under hypoxic condition. However, CD8+CD103+iTreg seldom transfer into Th17, remain Foxp3 under hypoxic condition (Fig 2,3). In addition, the suppressive function of CD8+CD103+iTreg over T cells proliferation under hypoxia remain steadily. In vivo study, we found that CD8+CD103+iTreg ameliorate the development of AKI by decreasing the level of serum creatine, alleviating acute tubular necrosis (ATN) and reducing the mortality of AKI mice. (Fig 4).

Conclusions: CD8+CD103+iTreg maintains stable phenotype and immunomodulatory function under condition of hypoxia, decrease the severity of AKI induced by ischemia-reperfusion. CD8+CD103+iTreg provide a promising approach for the treatment of AKI.



PO0224

A Novel Renoprotective Strategy: Upregulation of PD-L1 Expression Mitigates Cisplatin-Induced AKI

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Background: Cisplatin is an effective chemotherapeutic agent against various types of cancers; however, the use of cisplatin is associated with a major side-effect of nephrotoxicity, resulting in acute kidney injury (AKI). Growing evidence suggests that programmed death-1(PD-1)/programmed death ligand (PD-L1) immune checkpoint signaling plays a critical role in mediating inflammatory responses and immune homeostasis. While PD-L1 has emerged as a promising target for immunotherapy, little is known concerning how PD-L1 is regulated. In this study, we aimed to determine the expression and contribution of PD-L1 in cisplatin-induced AKI.

Methods: PD-L1 expression in kidney cells and tissues were determined by immunohistochemistry (IHC), real-time polymerase chain reaction and western blot assays. PD-L1-containing lentiviruses were subcapsularly injected into the kidneys of mice. 7 days after the injection, mice were intraperitoneally treated with cisplatin for 3 days and subjected to kidney function tests. High-dimensional single-cell mass spectrometry was used to reveal immune profiling and discover the underlying immunological mechanisms of PD-L1 in an AKI mouse model.

Results: IHC staining of PD-L1 shows a significantly lower intensity of staining and less stained proximal tubule epithelial cells in cisplatin-exposed mice tissues than that in the PBS controls. Next, we demonstrate that cisplatin exposure decreased mRNA expression and protein levels of PD-L1 in primary renal proximal tubular epithelial cells and this inhibition appeared to be dose-dependent. Interestingly, we also find a decrease in PD-L1 expression with a concomitant increase in pro-inflammatory cytokines in response to cisplatin. Mass spectrometry analyses reveal cisplatin-induced multiple pro-inflammatory leukocytes infiltration in kidneys. Through genetically engineered kidney tissues in mice, ectopic expression PD-L1 in kidneys was able to suppress leukocytes infiltration and pro-inflammatory cytokines. In addition, both serum creatinine and blood urea nitrogen levels were significantly reduced in cisplatin-treated mice with PD-L1 overexpression.

Conclusions: Our data suggest a renoprotective effect of PD-L1 upregulation on cisplatin-induced AKI and also provide an alternative therapeutic strategy against nephrotoxicity.

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PO0225

Regulation of Renal Calbindin Expression During Cisplatin-Induced Kidney Injury

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Background: Since the discovery of calbindin release into urine during renal injury, there has been growing interest in the utility of this calcium-binding protein as a biomarker of nephrotoxicity. However, little is known about the intrarenal regulation of calbindin during acute kidney injury. We sought to characterize the time-dependent expression and excretion of the distal tubule protein calbindin in comparison to the proximal tubule protein Kim-1 in a mouse model of cisplatin nephrotoxicity.

Methods: Male C57BL/6 mice were administered saline vehicle or 20 mg/kg of cisplatin i.p. Urine was collected in metabolic cages for 24 h periods on days 0 – 4. Blood and kidneys were collected between days 2 and 4. Kim-1 and calbindin proteins were measured in urine, kidneys, and blood. *Kim-1* and calbindin (*Calb1)* mRNAs were quantified in kidneys by qPCR.

Results: SCr and BUN levels increased in cisplatin-treated mice by day 3, confirming development of acute kidney injury. Urinary concentrations of calbindin and Kim-1 were elevated by 11.6-fold and 2.5-fold, respectively by day 2. Time-dependent decreases in intrarenal calbindin protein to levels 60% of control were observed on days 3 and 4. A 200-fold up-regulation of *Calb1* and *Kim-1* mRNAs was seen on day 3. These data suggest that early loss of calbindin protein into the urine along with declines in renal calbindin protein initiates a compensatory induction of mRNA expression at later time points (days 3 and 4).

Conclusions: Understanding the regulation of calbindin during cisplatin nephrotoxicity further enhances its utility as a urinary biomarker of kidney damage. The results of the current study support the combined use of a proximal (Kim-1) and distal tubule (calbindin) marker to phenotype acute kidney injury secondary to cisplatin administration.

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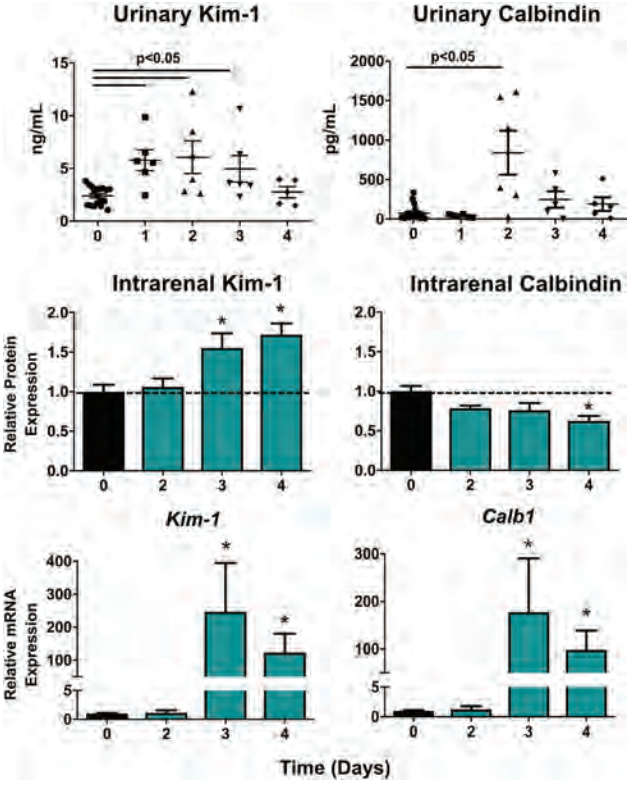

PO0226

Neutral Ceramidase and Autophagy Play Diverse Roles in Cisplatin-Induced AKI and Fibrosis

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Background: Cisplatin (CDDP) is a commonly used chemotherapeutic agent with a dose-limiting nephrotoxicity. 30% of patients given CDDP develop acute kidney injury (AKI), increasing risk of chronic kidney disease (CKD) development and mortality. Currently, there are no agents to treat or prevent CDDP-induced kidney injury. We believe this is due in part to a lack of clinically relevant animal models. In the past, only a single high-dose model has been used to study CDDP-induced AKI. Our lab and others have developed a repeated low dose model to also study CKD development following CDDP treatment. Acute and chronic injuries can both be affected by sphingolipids, a family of bioactive lipids. Metabolism of sphingolipids is carried out in part by neutral ceramidase (nCDase), which hydrolyzes ceramide into sphingosine that can then be phosphorylated to form sphingosine-1-phosphate. The regulation of these sphingolipids affects cellular processes implicated in the pathology of CDDP-induced kidney injury, including cell proliferation, autophagy, and apoptosis. Additionally, our lab has previously observed that nDCase knockout protected mouse embryonic fibroblasts from ER-stress induced apoptosis *in vitro* by upregulating autophagic flux. We hypothesized that loss of nCDase would confer protection from CDDP-induced kidney injury.

Methods: We assessed renal outcomes in nCDase knockout (KO) and wild type (WT) C57BL/6 mice in both the acute and chronic models of cisplatin treatment.

Results: We demonstrated that nCDase KO provides protection from AKI in the high-dose model of CDDP-induced kidney injury. This protection was reversed when the autophagy-inhibitor chloroquine was co-administered. In the repeated low dose CDDP model, however, we found nCDase KO does not protect against development of renal fibrosis. We also observed that nCDase KO reduces induction of ER stress in the single high-dose model but not in the repeated low dose model.

Conclusions: This study suggests that there are different underlying mechanisms that induce divergent pathologies in the two models of CDDP dosing.

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PO0227

Cisplatin-Induced MARCKS Phosphorylation Activates NF-kB Signaling and Contributes to AKI

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Background: Cisplatin is widely used for cancer treatment but is known to induce nephrotoxicity with severe damage to the proximal tubules, leading to acute kidney injury (AKI). Although a major substrate of protein kinase C, MARCKS, was shown to be induced phosphorylation at Ser 159/163 (phospho-MARCKS) in response to cisplatin, the molecular mechanism underlying increased phospho-MARCKS and its functional consequence in AKI remain to be established. Herein, we investigated how phospho-MARCKS is regulated in proximal tubular cells, and its role in the context of cisplatin exposure.

Methods: The clinical relevance of phospho-MARCKS was first confirmed using immunohistochemistry. Next, we examined the effect of cisplatin exposure on phospho-MARCKS levels in kidney tubular epithelium. The MARCKS-interactome was identified by mass spectrometry. We also used genetic and pharmacological approaches to verify the functionality and molecular mechanism of cisplatin-induced phospho-MARCKS.

Results: In a screen of 75 renal biopsies from patients, we find that strong phospho-MARCKS expression was observed in kidney specimens from patients with acute renal tubular necrosis and was positively correlated. Western blot analyses demonstrate that an elevated abundance of phospho-MARCKS in cisplatin-exposed tubular epithelial cells and this increase appeared to be concentration–dependent. Mechanistically, we show that MARCKS protein directly bound to nuclear factor-kappa-B-activating protein (NKAP). Following cisplatin-induced phosphorylation at ser159 and ser163, the interaction of MARCKS with NKAP was inhibited, contributing to p65 phosphorylation and NF-κB activation. Surprisingly, an elevation of phospho-MARCKS by cisplatin occurred in parallel with upregulation of inflammatory cytokines and markers of nephrotoxicity. Conversely, targeting of MARCKS phosphorylation with the MPS peptide, a novel MARCKS inhibitor, downregulated NF-κB signaling as well as suppressed levels of serum creatinine and blood urea nitrogen in cisplatin-treated mice.

Conclusions: Our results suggest that MARCKS phosphorylation is a novel NF-kB activator in cisplatin-induced proximal tubule damage and also present a proof of concept for the use of MPS peptide as a renal protection agent for AKI.

Funding: Other U.S. Government Support, Commercial Support - Dialysis Clinic, Inc. (C-3917)

PO0228

Mechanistic Insight for Enhanced Cisplatin (CIS) Nephrotoxicity in Na-H Exchanger Regulatory Factor 1 (NHERF1) Deficiency

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Background: Proximal tubule transport and metabolism of CIS play critical roles in the development of CIS-induced acute kidney injury (AKI). Mice lacking NHERF1 have exacerbated CIS nephrotoxicity. We hypothesize that NHERF1 loss leads to altered oxidative state and/or altered CIS metabolism resulting in increased CIS toxicity.

Methods: We treated 2-4 mo old male wild-type (WT) C57BL/6 and NHERF1 knock out (KO) mice with vehicle or CIS (20 mg/kg IP) for 4, 24, or 72h. Glutathione (GSH), glutathione disulfide (GSSG), cysteine (Cys), cystine (CySS), cysteine-glutathione disulfide (CySSG) were measured in plasma and kidney cortex by HPLC. Kidney cortex was assayed for γ-glutamyl transferase (GGT) activity, platinum (Pt) levels by ICP-MS, cysteine s-conjugate beta lyase (CCBL1) and GGT by Western blot and immunohistochemistry (IHC); and RT-qPCR for glutathione s-conjugate-translocating ATPase (ABCC1) and γ-glutamylcysteine synthetase (GCLC).

Results: KO mice showed decreased plasma CySS and increased kidney GSSG at baseline. GGT activity was similar 4h after CIS treatment, but significantly greater at 24h in CIS treated WT compared to KO. ABCC1 and GCLC mRNA levels were upregulated 72h post CIS treatment in KO compared to WT. GGT and CCBL1 protein levels were similar by Western blot regardless of genotype or treatment 24h post CIS, but IHC showed greater brush border membrane GGT loss in KO kidneys. CCBL1 localization showed a checkered staining pattern in KO proximal tubules compared to WT linear pattern at baseline. Pt levels were similar 24h post CIS treatment, but decreased significantly more 72h post treatment in KO compared to WT.

Conclusions: We conclude loss of NHERF1 results in increased levels of GSSG, upregulation of genes involved in GSH synthesis in oxidizing conditions, and lower GGT activity that sensitize the kidney to increases in oxidative stress induced by CIS nephrotoxicity. While NHERF1 loss does not affect initial Pt uptake, the aberrant CCBL1 localization in KO proximal tubules suggests a role for enhanced production of toxic CIS metabolite.

Funding: Veterans Affairs Support

PO0229

Decreased IFT88 Causes Cilia Shortening and Mitochondrial Dysfunction in Cisplatin-Induced Tubular Injury

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Background: Renal primary ciilia are associated with the pathogenesis of various diseases, including acute kidney injury (AKI). The length of the primary cilia dynamically change during the progression of diseases: tubular primary cilia shortened in cisplatin-induced AKI mouse model. However, its relevance in kidney disease and the underlying mechanism are largely unknown. Tubular damage in AKI closely links to mitochondrial dysfunction. Thus, we investigated the interaction between primary cilia and mitochondria in cisplatin-induced tubular injury.

Methods: C57BL6 mice with cisplatin-induced AKI were euthanized at 72 h after disease induction to collect blood and kidney samples. In *in vitro* experiments, we used RPTEC/TERT1 cells, which are human proximal tubular epithelial cells that maintain the cilia length at high cell densities, and knocked down Ift88 (Ift88-KD), a cilia maintenance protein, by siRNA. Cisplatin-treated or Ift88-KD cells were assessed for the cellular phenotypic changes or mitochondrial metabolic function using the Flux Analyzer.

Results: We found that the expression of protein IFT88 was decreased in damaged tubules of cisplatin-induced AKI mice. These data were consistent with that Ift88 expression decreased in the cilia of cisplatin-treated RPTEC/TERT1 at mRNA and protein levels in association with shortening of the primary cilia, suggesting the pathogenic link between tubular damage and Ift88-mediated cilia alteration. Interestingly, Ift88-KD cells significantly exhibited shorter cilia as compared to control siRNA-transfected cells and showed downregulation of mitochondrial oxidative phosphorylation capacity and decreased ATP production, indicating the contribution of Ift88 to mitochondrial homeostasis. Of note, such mitochondrial alteration linked to tubular inflammation. Our findings suggest that tubular mitochondrial dysfunction in cisplatin-induced AKI is mediated by a decreased Ift88 with shortening cilia, at least in part.

Conclusions: Tubular mitochondrial damage followed by tubular injury in AKI may occur by the alteration of Ift88 expression, and subsequent cilia shortening in the tubular epithelial cells.

PO0230

Apobec 1 Limits Cisplatin-Induced AKI by Regulating the Disposal of Pro-Ferroptotic Lipids

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Background: Cisplatin (CP) causes proximal tubules to undergo regulated necrosis. We previously reported that the RNA editing-specific cytosine deaminase Apobec1, which regulates mitochondrial metabolism, cell fate and proliferation pathways, plays a crucial role in recovery from this injury. Among the known RNA editing targets for APOBEC1 is the lipid transport protein *Apob* and as the resultant smaller APOB48 is the preferred secretory route of potentially cytotoxic triglycerides (TG), we now ask if absence of *Apobec1* during CP-induced AKI, whose toxicity is accompanied by the accumulation of TGs and oxidant stress, worsens AKI.

Methods: *Apobec1* knockout (ko) mice were given CP 15 mg/kg i.p. and renal function, histology, mRNA, protein and lipid content were analyzed and compared to wild type (WT) mice of similar genetic background. We overexpressed rat Apobec-1 in PT cells and assessed cell viability histologically and by WST-1 assay after CP exposure.

Results: *Apobec-1* deletion resulted in more severe AKI, plasma creatinine 2.07 mg/dL ± 0.59 (n=13) vs 0.23 mg/dL ± 0.09 (n=8) 3d, $p < 0.01$ in WT. Remarkably all *Apobec1* ko mice died after 6 days, while WT animals all survived. *Apobec1* KO kidneys showed greater necrosis and neutrophil counts. mRNA and protein levels of RIPK3, MLKL, TLR2, TLR4, and ASCL4 were markedly increased in *Apobec-1* ko compared to WT kidneys ($p<0.01$). Overexpression of Apobec-1 in mouse PT reduced CP-induced cell death 2.35-fold versus cells transduced with vector alone ($n = 4$, $p < 0.05$). Overexpression of Apobec-1 increased the activities of kinases associated with survival (ERK, STAT3, and AKT) and inhibited those inducing cell death (IRF4, and JNK). Plasma tTG increased 2-fold higher in CP-treated Apobec1 ko mice compared to WT animals (104.3 ± 12.6 vs. 57.4 ± 9.1, n=4, $p<0.05$), while renal TG trended upward (437.1 ± 130.0 vs. 223.8 ± 121.5, n=4, $p=0.27$).

Conclusions: We have identified Apobec1 as a crucial gene regulating the necrotic response to CP-induced nephrotoxicity. Apobec1 limits lipid accumulation in the kidney following CP-induced AKI and limiting lipotoxicity. Increasing Apobec-1 activity could be an effective strategy to reduce or prevent CP-induced AKI.

Funding: NIDDK Support

PO0231

Lipidomics Approach to Characterize Lipid Alterations in Human Kidney 2 Cells Treated with Iohexol

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Background: In our previous study, we found plasma high density lipoprotein cholesterol and apolipoprotein A-I levels were significant lower in the contrast induced nephropathy (CIN) group, compared to the non-CIN group. The aims of our study was to uncover lipid alterations that may contribute to the development of CIN.

Methods: We investigated lipids of HK-2 cells treated with iohexol (100mg I/ml, 6hrs and 12hrs), compared with HK-2 cells treated without iohexol (as control) using nontargeted lipidomics based on ultrahigh-performance liquid chromatography-Orbitrap Q-Exactive plus mass spectrometry.

Results: Based on the principles of t-test P-value < 0.05, variable importance at projection (VIP) value >1 and fold change >1.5 or <0.67, differential expression of 134 lipids were identified in both HK-2 cells treated with iohexol for 6hrs and 12hrs, compared with the control HK-2 cells. The top three class to which these lipids belonged were phosphatidylcholine (PC, 42 species), triglyceride(TG, 39 species) and phosphatidylethanolamine (PE, 18 species).

Conclusions: Our results indicate that PC, TG and PE may contribute to the development of CIN, providing the basis for further evaluation of the role of lipids in the mechanism of CIN.

PO0232

Proximal Tubular S3 Cells Expressing Angiotensinogen Localize to the Outer Stripe of the Outer Medulla

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Background: The S3 segments of proximal tubules (PT) are observed in the cortex as well as the outer stripe of the outer medulla (OS-OM). Using single cell RNA sequencing (scRNAseq), we and others have identified a unique S3 population, referred to as S3-Type 2 (S3T2, Figure a). These S3T2 cells express *Rnf24* and *Slc22a7* as defining genes, in addition to other classical S3 markers. In this work, we combined spatial transcriptomics (SpT) and scRNAseq to further localize this novel S3T2 cell population in the murine kidney.

Methods: We performed SpT on OCT frozen murine kidney sections stained with hematoxylin & eosin. Images were collected with Keyence BZ-810 microscope. RNA was isolated from tissue, sequenced, and clustering performed with Seurat R package. This yielded seven clusters that could be overlaid over the tissue section. To increase resolution, we combined scRNAseq data with SpT. Gene expression was visualized with the Loupe Browser. Expression of specific genes was also confirmed with single molecule FISH (smFISH).

Results: The combination of scRNAseq with SpT increased the spatial resolution and resulted in 15 unique cell clusters that could be easily overlaid over the tissue section. While regular S3 cells localized to the cortex, S3T2 cells localized specifically to the OS-OM (Fig. b). In addition to *Rnf24* and *Slc22a7*, S3T2 cells showed strong expression of angiotensinogen (*Agt*, Fig. c). smFISH of *Agt* and *Aqp1* confirmed these results (Fig. d).

Conclusions: The combination of scRNAseq and SpT allows for a greater resolution in the spatial layout of renal cell populations. This approach localized S3T2 cells specifically to the OS-OM. These cells also exhibited strong expression of *Agt*, possibly indicating an important role in the renin-angiotensin system. These transcriptomic differences between classical S3 and S3T2 are likely dictated by the unique microenvironments of the cortex and the OS-OM.

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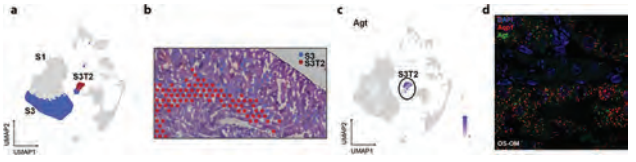

Figure a-d: **a** scRNAseq UMAP highlights S3 and S3T2 **b** SpT highlighting S3 and S3T2. **c-d** Feature plot of *Agt* and smFISH of *Agt* (green) localizes to S3T2.

PO0233

Salubrinal Attenuates Proximal Tubular Cell Injury Induced by Cisplatin

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Background: Cisplatin is a widely used chemotherapy drug, but it has notorious side effects in kidneys. Effective kidney protective agents are not available for clinical use. Salubrinal is a specific inhibitor of eIF2alpha phosphatase, it promotes eIF2alpha phosphorylation which blocks the formation of the pre-initiation complex and halts global protein translation and protein synthesis. In this study, we examined the effect of salubrinal on cisplatin-induced injury in kidney proximal tubular cells.

Methods: Rat proximal tubular cells (RPTC) were treated with cisplatin or cisplatin with salubrinal for 4, 8, and 24hrs. Cell lysates were collected for immunoblot analysis to examine phospho-eIF2alpha and its related proteins. In addition, other signaling proteins implicated in cisplatin injury were examined, including p53, JNK, p38, and pkcdelta, and ERK. Apoptosis was determined at 24hrs of treatment by phase contrast and fluorescence microscopy following nuclear staining with Hoechst. Caspase activities were measured enzymatically by using DEVD. AFC, a fluorogenic peptide substrate. To examine cell survival, the cells were changed to fresh medium for 48 hrs after 24 hrs of cisplatin treatments with or without Salubrinal.

Results: Salubrinal suppressed apoptosis and caspase activation in RPTC during cisplatin treatment. It also promoted long-term cell survival after cisplatin treatment. In immunoblot analysis, during cisplatin treatment salubrinal increased eIF2alpha phosphorylation. It also increased PERK phosphorylation and the expression of GRP78 and CHOP, indicative of ER stress or unfolded protein response. Signaling pathways including MAP kinases, PKCdelta, and p53 are involved in cisplatin-induced kidney injury. In this regard, Salubrinal decreased JNK and p38 phosphorylation, but increased ERK phosphorylation during cisplatin treatment. Salubrinal diminished phosphorylation of PKCdelta at late time point of cisplatin treatment. However, Salubrinal did not affect p53 expression or its phosphorylation.

Conclusions: Salubrinal has protective effects against cisplatin-induced kidney cell injury. Mechanistically, the protective effects are associated with the increase of UPR and suppression of MAPK signaling but not with p53 activation. The results also suggest that inhibition of global protein synthesis may be a new therapeutic strategy for the side-effects of cisplatin chemotherapy.

Funding: NIDDK Support, Veterans Affairs Support

PO0234

Quantitative Prediction of Cisplatin-Induced AKI Using RENAsym, a Mechanistic Quantitative Systems Toxicology Model, and Renal Proximal Tubule Epithelial Cell In Vitro Assays

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Background: Nephrotoxic drugs like cisplatin cause acute kidney injury (AKI) through complex cellular mechanisms that include mitochondrial dysfunction, oxidative stress, and immune mediated injury pathways. However, quantitative prediction of the underlying toxicity mechanisms remains a challenge. Quantitative system toxicology (QST) modeling offers a promise for quantitative description of toxicity mechanisms leading to drug-induced AKI. We developed a QST model of cisplatin induced AKI using *in vitro* assays to characterize key cellular injury mechanisms.

Methods: RENAsym was used to quantify cisplatin induced AKI. The model represents aspects of renal proximal tubule epithelial cells (RPTEC) including cell life cycle and death pathways, bioenergetics, immune signaling pathways and biomarker responses. *In vitro* data related to cisplatin mitochondrial toxicity and oxidative stress generation were measured using RPTEC assays incubated with cisplatin (Cyprotex Inc.). To quantify cisplatin-induced mitochondrial dysfunction, oxygen consumption rate (OCR) was measured using the Seahorse XF analyzer. Cisplatin-induced oxidative stress was measured using high content imaging (HCI).

Results: The Seahorse study shows substantial OCR decline at 24 hours, suggesting cisplatin-induced electron transport chain (ETC) inhibition. Similarly, HCI reveals significant oxidative stress elevation after 9 days. Toxicity parameters for cisplatin-induced mitochondrial dysfunction and oxidative stress mechanisms were determined using the *in vitro* data. Simulations predict dose-dependent cisplatin toxicity as quantified by elevations in αGST, a biomarker that marks RPTEC death. A simulated single high dose of 533 mg/m^2 i.v. cisplatin results in 14-fold change in αGST, while a simulated clinical dose of 100 mg/m^2 shows 7-fold increase. The 100 mg/m^2 result is in qualitative agreement with 3.4-fold change observed in a clinical study where patients administered 100 mg/m^2 i.v. cisplatin exhibited 20% incidence of AKI (Ummer. 2012, IJBBB).

Conclusions: RENAsym simulations predicted dose-dependent cisplatin-induced AKI that is in qualitative agreement with clinical data. RENAsym shows promise in providing a unique tool for drug-induced AKI prediction.

Funding: NIDDK Support

PO0235

Diuretic Resistance: When to Consider Hydralazine?

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Introduction: We present a case of acute cardiorenal syndrome complicating heart failure with preserved ejection fraction (HFpEF) leading to severe diuretic resistant fluid retention that was alleviated by coincident hydralazine therapy.

Case Description: A 52-Year-old woman with a history of obesity, hypertension, congestive heart failure with HFpEF (EF60-65%), and alcoholic liver disease presented with a 3-day history of mental status change. Her serum creatinine was 3.6mg/dL, compared to 0.8mg/dL a month prior. She was volume overloaded with distended jugular veins, pulmonary crackles, and +2 edema to her lower abdomen; she had a 30Kg weight gain over 5 months. Her urine sodium and chloride were <10mmol/L. Urine analysis had a SG of 1.017 without proteinuria. Diuretic therapy was initiated with IV furosemide 80 mg twice daily and was escalated progressively to IV furosemide 20 mg/h with IV

chlorothiazide 500 mg twice daily. However, these large doses of intravenous diuretics failed to increase daily urine output above 1000 ml. After 20 hours of stable diuretics, vasodilator therapy was initiated with low dose hydralazine 10 mg thrice daily. Within one day, her urine output more than doubled and, over the next 3 days of the stable therapy, it peaked at 4 liters. Her fraction Na excretion (FE_{Na}) was initially 0.1%; it increased to a maximum of 1.9% with the high IV continuous diuretic therapy but increased further to 3.8%-6.2% over 9 days after hydralazine was added to the diuretic regimen. After addition of hydralazine, her congestion dissipated, she lost 23 Kg and the diuretic regimen was reduced eventually to furosemide 80 mg BID and spironolactone 200 mg daily prior to her discharge with a serum creatinine of 1.3 mg/dl. At follow up after 3 months, her symptoms remained well controlled, her weight was reduced by a further 10 kg and her serum creatinine was 0.9 mg/dl.

Discussion: Hydralazine has been recommended to treat diuretic resistance in HF by increasing cardiac output, renal blood flow and renal diuretic delivery. However, our case suggests that hydralazine greatly improves renal tubular diuretic responsiveness as her FE_{Na} increased 3 fold. This is not likely due to better renal diuretic delivery since the patient received constant IV infusions of two diuretics at doses well above their ceiling. Further clinical trials and mechanistic studies of hydralazine-diuretic interaction are warranted.

PO0236

Carfilzomib-Induced Thrombotic Microangiopathy Effectively Treated with Eculizumab

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Introduction: Proteosome inhibitor (PI), Carfilzomib, have been associated with drug-induced microangiopathy (DITMA) in rare cases[1-7]. We present a patient with acute kidney injury (AKI) from Carfilzomib-induced DITMA who was successfully managed with Eculizumab, which is a monoclonal antibody that inhibits the alternate pathway of the complement cascade.

Case Description: A 56-year-old woman with refractory IgG Lambda Multiple Myeloma (MM) was admitted with fatigue and decreased oral intake one week after restarting Carfilzomib. She had been on Carfilzomib in the past and tolerated it well. On admission, she had non- oliguric AKI with a serum creatinine (sCr) of 12mg/dL (one week prior to starting Carfilzomib, her SCr = 0.8mg/dL). Peripheral smear revealed anemia with schistocytes and thrombocytopenia. Carfilzomib was immediately discontinued. Serologic work up, including ADAMTS13, was within normal limits. Her free kappa/ lamba ratio 0.41. She was dialyzed twice for clearance and underwent a renal biopsy. The renal biopsy showed diffuse thrombotic microangiopathy (TMA) with minimal tubular injury and interstitial fibrosis. Eculizumab 900mg weekly was started, and sCr declined to 1.6mg/dL over 3 weeks. She did not require further hemodialysis treatments. Currently, her sCr is 1.1mg/dL, and she is on Eculizumab 1200mg every two weeks.

Discussion: Our case is the fourth report using Eculizumab in Carfilzomib induced DITMA. The timing of our patient's Carfilzomib exposure supports that DITMA caused her AKI (as opposed to MM- induced TMA). The first line of treatment requires immediate cessation of the drug. Interestingly, Bhutani et al, demonstrated the activation of the alternate complement pathway in a patient with Carfilzomib- induced TMA, indicated by elevated levels of fragment Bb and membrane attack complex (MAC)[6]. Portuguese et al, proposed that Carfilzomib may lower the gene expression of Complement factor H resulting in decreased inhibition of the alternate complement pathway[7]. Given the effects of Carfilzomib on the alternate pathway, Eculizumab is a reasonable therapeutic option because it targets complement C5 and inhibits the assembly of the MAC.[4,5,6,7]. Since PIs are the mainstay of MM treatment, the nephrologist should be aware of the rare but serious consequences of PI- associated DITMA and should consider Eculizumab as a management strategy[1,2,3].

PO0237

Tubulointerstitial Lupus Nephritis with Coexisting Renal Limited IgG4 Disease

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Introduction: The classic pattern of Lupus Nephritis (LN) is an autoimmune complex mediated glomerulonephritis. Rare cases have been described with predominant tubuluinterstitial nephritis (TIN) with tubulointerstitial immune deposits in the absence of significant glomerular lesions. We describe a patient with such pattern of disease along with co- existing renal limited IgG4 related disease (IgG4 RD).

Case Description: 27-year- old man with no past medical history presented with fever, malaise and cough for 3 days. It was associated with occasional epistaxis and weight loss for 3 months. He denied any rash, joint pains, oral ulcers or photosensitivity. On admission he was noted to have creatinine of 7.2 mg/ dl with eGFR of 9ml/ min/1.73m2. His UA showed 3 + blood, protein to creatinine ratio of 1.61 microgram/ mg and microalbumin to creatinine ratio of 334 microgram/ mg. His pertinent positive blood work includes ANA titer of 1:1280, complements levels C3 < 26.3 and C4 < 7.9. He underwent a renal biopsy that showed immune complex mediated chronic active interstitial nephritis and increased IgG4 positive plasma cells, minimal glomerular alterations with rare mesangial deposits. Full house pattern was observed in tubules on immunoflorence. Lymph node FNA performed did not demonstrate increased IgG4 levels, however his serum IgG4 levels returned high at 205 mg/dl. He was diagnosed with Tubuluinterstitial Lupus Nephritis with renal limited IgG4 disease. He was started on high pulse dose steroid followed by taper and mycophenolate mofetil (MMF). He demonstrated good response with improvement in proteinuria, complement levels and ANA titers. His serum creatinine improved to 2.6 mg/ dl at 6 months.

Discussion: A very few cases of lupus TIN without glomerular involvement are described in the literature and management options remain unclear. The most frequent renal manifestations of IgG4-RD are TIN, membranous glomerulonephropathy and obstructive nephropathy due to retroperitoneal fibrosis. The presence of an overlap of LN with IgG4 RD has been reported in very limited number that our patient had. Our patient responded well to the treatment with MMF and Steroids. However, there is need to describe and study more such cases to delineate management protocols. We continue to follow him in clinic and monitor him for involvement of other organ system.

PO0238

Hepatorenal Syndrome Type 1 as a Consequence of Transarterial Chemoembolization

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Introduction: Hepatorenal syndrome (HRS) is characterized by marked kidney dysfunction in the setting of advanced liver disease. HRS can manifest in two different patterns, type 1, representing an acute onset of kidney injury and type 2, corresponding to the chronic manifestation of kidney injury secondary to liver dysfunction. Here we present a case of HRS type 1 following transarterial chemoembolization (TACE) in a patient with advanced cirrhosis and hepatocellular carcinoma (HCC).

Case Description: A 69-year-old male presented to the hospital with worsening weakness, lethargy and decreased urinary output. His family stated the symptoms began shortly after his last session of TACE the week prior. There were no fevers, sick contacts or recent travel. He had underlying CKD stage IIIa (baseline SCr 1.7 mg/dL) and alcoholic cirrhosis with HCC treated with partial resection and multiple sessions of TACE. On admission, the SCr was 9 mg/dL associated with symptomatic hyperkalemia, anion gap metabolic acidemia, severe hyponatremia, junctional bradycardia and hypotension. Additionally, urinary sodium was < 20 mmol/L with a bland sediment. Once admitted to the ICU, he required vasopressors and emergent hemodialysis. He was given HRS treatment with albumin 1gm/Kg/day plus vasopressin for 2 days. His urine output and kidney function improved back to baseline in the following days with no further requirement of hemodialysis.

Discussion: HRS represents an entity of kidney dysfunction secondary to severe renal vasoconstriction in response to splanchnic vasodilation. HRS occurs in states of advance liver disease. Our patient had alcoholic cirrhosis and HCC. TACE had been implemented as a palliative treatment to the unresected lesions. Iodinated contrast and chemotherapeutic agents are used in low dose with this therapeutic option, however, several cases of acute kidney injury have been reported likely due to contrast induce nephropathy. The need for renal replacement therapy has been not extensively reported but overall long-term outcomes were satisfactory. HRS as a consequence of TACE has never been described but given the laboratory findings and significant improvement following treatment we suspected this case was HRS type 1

PO0239

Thyroid-Cardiorenal Syndrome

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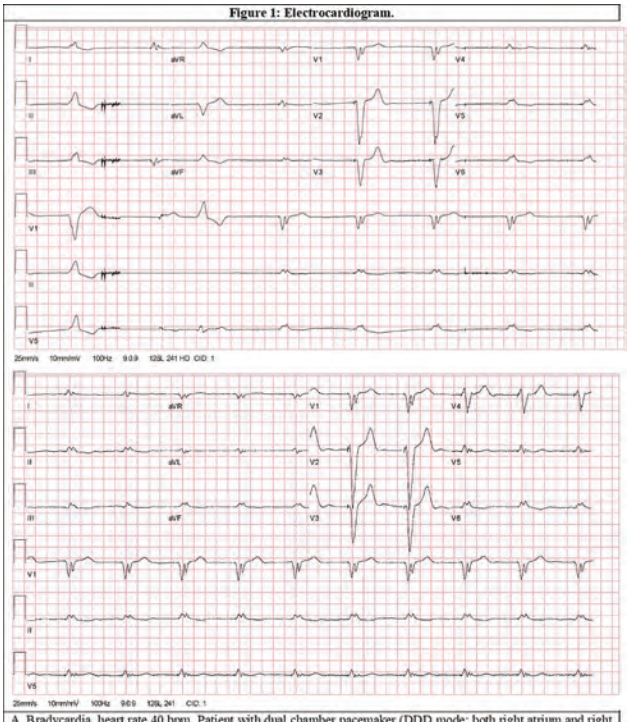
Introduction: In severe hypothyroidism, acute kidney injury (AKI) may occur from hypothyroidism-induced myopathy. We report the first case of AKI in the setting of severe bradycardia without rhabdomyolysis.

Case Description: An 85-year-old man with heart failure and a dual-chamber implantable cardio defibrillator was admitted with bilateral lower extremity edema. Vital signs included asymptomatic bradycardia 40 bpm (Figure 1), blood pressure 107/74 mmHg, without fever or respiratory distress. Laboratories showed serum creatinine (SCr) of 2.3 mg/gL (baseline 1.5 mg/dL), serum sodium 127 mg/dL, serum creatine kinase (CPK) levels of 170 U/L (38-174 U/L), thyroid secreting hormone levels (TSH) of 97.77 uIU/L (0.45 – 4.70 uIU/mL) and free thyroxine levels (Free T4) of 1.4 ng/dL (0.71 – 1.85 ng/mL). Renal ultrasound was unremarkable. The pacemaker was programmed to VVI mode 60 bpm (ventricular pacing and sensing) with prompt improvement in the heart rate and renal function. He was discharged on oral levothyroxine.

Discussion: Hypothyroidism increases systemic vascular resistance and decreases blood volume, cardiac contractility, and heart rate, with an overall decrease in cardiac output. AKI may occur from hypothyroidism-induced rhabdomyolysis; however, SCr is rarely elevated or may increase over several weeks. Our case contrasts given the acute rise in SCr and prompt recovery after the bradycardia resolved. We believe that the AKI was predominantly due to hypothyroidism-induced bradycardia, with a subsequent reduced cardiac output and effective renal flow. AKI workup should include hypothyroidism screening, particularly in the context of persistent bradycardia, even with normal blood pressure and CPK levels. We propose the term Thyroid-Cardio-Renal syndrome for this unusual association.

Figure 1: Electrocardiogram.



A. Bradycardia, heart rate 40 bpm. Patient with dual chamber pacemaker (DDD mode: both right atrium and right ventricle sensing and pacing), found to have atrial undersensing with ventricular paced rhythm.
B. After this episode of bradycardia, the pacemaker was programmed to VVI mode 60 bpm (ventricular pacing and sensing).

PO0240

Cat Scratch Kidney

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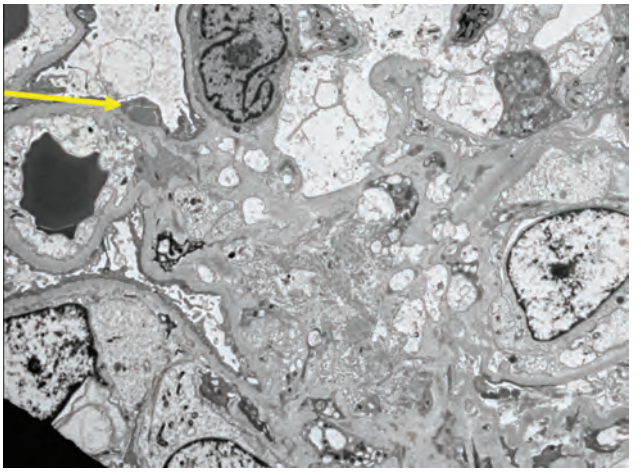
Introduction: A case of anuric RPGN secondary to post infectious glomerulonephritis in setting of bartonella infection

Case Description: An 84-year-old female presented with creatinine of 7.85mg/dl (baseline 0.81mg/dl) during a workup for painless hematuria. She developed progressive hypoxia and blood-tinged sputum concerning for pulmonary/renal syndrome and was treated with immunosuppression and plasma exchange. Serologic tests including ANA/ENA, anti-GBM, C-ANCA, P-ANCA, and MPO Ab were negative. However, PR3 Ab was elevated at 29.3 Units. Complement C3 and C4 levels were normal. Blood/urine cultures, assays for hepatitis B/C, HIV and Respiratory panel were negative. Renal biopsy showed an MPGN-pattern proliferative glomerulonephritis with necrotizing crescents. IF displayed global 3+ granular staining for both IgG and C3 as well as trace granular C1q. EM confirmed mixed mesangial (dominant), subendothelial, and a few distinct subepithelial hump-like deposits by EM, suggestive of an infection related glomerulonephritis. With a biopsy suggesting an infectious process and BAL without evidence of alveolar hemorrhage, immunosuppression and PLEX were discontinued. Broader infectious workup was negative for ASO titers, Borrelia antibody, Quantiferon/AFB cultures, and BAL for fungal organisms. However, Bartonella IgG was positive at 1:1024 (normal <1:128). Bartonella PCR was negative. Both TTE and TEE were negative for valvular lesions. Additional patient history elucidated recent acquisition of a pet cat and multiple scratches. Treatment focus shifted from immunosuppression to antibiosis.

Discussion: Our case highlights an underappreciated entity associated with GN, particularly in the absence of overt clinical endocarditis. There has been a crossover association reported with ANCAs, particularly anti-PR3, which can demonstrate either a pauci-immune or immune complex pattern as with our patient. The case demonstrates how renal biopsy and social history remain vital diagnostic tools in patients presenting with non-specific systemic illness.



PO0241

Two Cases of Oxalate Nephropathy: An Uncommon Disease, Often Missed

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Introduction: Oxalate nephropathy is a state of excess oxalate availability leading to damaging calcium oxalate crystal deposition in the renal tubules and interstitium. It is an uncommon but severe cause of renal damage and leads to dialysis dependence in the majority of patients; thus, diagnostic index of suspicion must be high.

Case Description: Patient A was a 58 year old male with 2 prior renal stones but no history of gastric bypass, IBD, or other malabsorptive state who presented with vomiting, metallic taste, and behavior changes. Serum creatinine (SCr) on admission was 10.2 mg/dL (baseline 1.1 mg/dL). Basic workup including ANCA, ANA, dsDNA, C3, C4, and Hepatitis B and C was unremarkable. A renal biopsy showed severe interstitial fibrosis and tubular atrophy with abundant calcium oxalate crystals, and dialysis was initiated. Dietary history revealed daily consumption of 1,000 mg Vitamin C, salads, and nuts. Genetic testing for primary hyperoxalosis was negative. After 1.5 months he was no longer dialysis-dependent but only attained partial renal recovery (SCr 2.67 mg/dL, eGFR 25). Patient B was a 68 year old male with no history of renal or GI disease who presented with emesis, weakness, and urinary retention. Admission SCr was 7.7 mg/dL (baseline 1.4 mg/dL). Renal function improved slightly after Foley placement for newly diagnosed BPH, but SCr remained elevated with negative initial AKI workup. Renal biopsy showed oxalate nephropathy. Further history revealed only occasional consumption of nuts with daily servings of tea and polyethylene glycol. Patient B's genetic testing was also negative. He remains on hemodialysis and has been referred for transplant.

Discussion: Oxalate nephropathy can result from primary (genetic) or secondary mechanisms. The most common secondary causes include increased intestinal oxalate availability ("enteric" hyperoxaluria) and increased dietary consumption. A basic medical history can reveal risk factors for enteric hyperoxaluria, while a thorough review of diet and supplements is often deferred, delaying the diagnosis. In some cases a single cause is not identified, and instead a combination of dietary and pharmacologic factors are to blame. We present 1 case of oxalate nephropathy most likely caused by high-dose Vitamin C, and another case with a less clear etiology aside from vague dietary and medication factors.

PO0242

AKI due to Renal Limited Thrombotic Microangiopathy (TMA) in a Patient with Metastatic Prostate Cancer

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Introduction: In this report we describe a case of AKI caused by TMA without evidence of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia as a paraneoplastic syndrome due to metastatic prostate cancer versus radiation injury.

Case Description: 65 year old man with metastatic prostate cancer treated with hormonal therapy, Cabazitaxel (last dose 5 months ago) and radiation to the prostate, T-12-L5 and pelvic region was admitted for gastrointestinal bleed and AKI. He was hypertensive to 182/82 mmHg and labs with white blood cell count 13.8 K/mcL, hemoglobin 6.7g/dl, platelets 228 K/mcl and Creatinine 2.3mg/dl (baseline 0.6 mg/dl). Urine sodium was 54 meq/L, creatinine 57 mg/dl and proteinuria of 4.9g/day. Peripheral smear had 2-3 schistocytes per high power field. Lactate dehydrogenase was 449 U/L, haptoglobin 155 mg/dL and ADAMTS13 level 47%. Renal ultrasound showed mild right hydronephrosis. He was given blood, intravenous fluids and right percutaneous nephrostomy was place but creatinine rose to 5mg/dl so renal biopsy was done. The specimen had 120 glomeruli and 12 were sclerosed There was focal organizing arterial and arteriolar thrombi. C5b-9 positive staining was seen within the affected glomeruli and

most arteriolar walls and tubular basement membranes. There was no immune complex electron dense deposits. This was indicative of severe, acute, subacute and chronic TMA involving all small arterial vessels with acute tubular necrosis. The patient required hemodialysis without renal recovery.

Discussion: TMA is reported in metastatic adenocarcinomas. Cancer treatment can also lead to TMA's. Cabazitaxel was unlikely etiology for the TMA as it had been a few months since the last dose. There are no cases reported of radiation causing renal limited TMA which we thought could also be a potential cause. Hypertension and severe anemia with schistocytes were the only clues to a TMA process. The elevated haptoglobin and normal platelet count was unusual. The TMA is thought to be likely secondary to paraneoplastic syndrome or possibly from the radiation treatments.

PO0243

Myeloid-Specific PKM2 Deletion Reduces Kidney Damage in Oxalate-Induced AKI

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Background: Reprogramming of immune cell metabolism have been associated with the development of kidney injury. The M2 isoform of pyruvate kinase (PKM2) catalyzes a critical stage of glycolysis, which was shown to be a crucial metabolic pathway for pro-inflammatory macrophages. We investigated whether deletion of PKM2 in myeloid cells exerts renoprotection in calcium oxalate (CaOx) crystal-induced acute kidney disease (AKI).

Methods: AKI was induced in myeloid-specific PKM2-knockout ($PKM2^{fl/fl}$;LysM-Cre^{+}) mice and their Cre-negative littermates ($PKM2^{fl/fl}$) by a single *i.p.* injection of sodium oxalate (NaOx, 100mg/kg) and 3% NaOx in drinking water for 24hr before sacrifice. Healthy controls received vehicle only. Serum creatinine and urea were evaluated as markers of renal function. CaOx crystal deposition (Pizzolato staining), IL-6, NGAL and KIM-1 mRNA expression (quantitative PCR), macrophage number/phenotype (FACS), and lactate levels were assessed in kidney tissue.

Results: In $PKM2^{fl/fl}$, intrarenal CaOx deposition increased the serum levels of creatinine and urea, as well as the expression of IL-6, NGAL and KIM-1 in kidney tissue compared to healthy controls ($p<0.01$). Despite a similar deposition of crystals, loss of renal function and markers of renal inflammation/injury were reduced in $PKM2^{fl/fl}$;LysM-Cre^{+} ($p<0.05$). FACS analysis indicated that the number of F4/80+CD11b+ cells in kidneys were similarly elevated by CaOx in both $PKM2^{fl/fl}$ and $PKM2^{fl/fl}$;LysM-Cre^{+}, while macrophages with the pro-inflammatory phenotype Ly6C+CD206- were significantly reduced in $PKM2^{fl/fl}$;LysM-Cre^{+} mice ($p<0.01$). In addition, PKM2 deletion also reduced renal levels of lactate ($p<0.05$).

Conclusions: The pro-inflammatory status of macrophages relays on glycolysis in CaOx nephropathy. Therefore, deletion of PKM2 in myeloid cells can reduce CaOx-induced renal inflammation and injury. FAPESP (2019/02893-9 and 2017/05264-7), CNPq and CAPES.

Funding: Government Support - Non-U.S.

PO0244

High-Content Imaging of Kidney Cell Function to Elucidate Mechanisms of Antiviral Drug Toxicity

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Background: Globally, millions of people live with HIV and hepatitis B virus (HBV). Toxicity from antiviral drugs is a major cause of kidney disease in these individuals. Tenofovir disoproxil fumarate (TDF) is a first line therapy for HIV and HBV. TDF induces functional proximal tubule (PT) defects for reasons that are unknown, partly due to a lack of appropriate experimental models. Clinically, TDF toxicity is characterized by two major phenotypes: isolated defects in PT solute transport; and severe tubular damage (Fanconi syndrome/acute kidney injury) associated with grossly enlarged mitochondria. The aim of our study was to establish realistic *in vitro* models of TDF toxicity, to investigate the underlying mechanisms.

Methods: Experiments were performed on monolayers of differentiated human-derived PT cells (RPTEC/TERT1). A high-content image analysis pipeline was established, using automated microscopy and machine learning, to quantify transport function, using dome formation as a readout. Metabolism was evaluated by antibody staining for mitochondrial morphology and autophagy.

Results: We screened numerous treatment regimens and generated phenotypes matching those observed in patients, including transport inhibition and mitochondrial hypertrophy. Further experiments using these models revealed that TDF caused a dose dependent decrease in ATP despite increased glycolysis and mtDNA content. Basal and ATP-linked respiration were decreased but maximal respiration was achieved, suggesting inhibition of complex V (ATP synthase). Metabolomic analysis confirmed that TDF was converted to the active antiviral metabolite Tenofovir diphosphate (TFVpp), a structural analogue of ATP. Using an *in vitro* assay of complex V activity, we observed a dose dependent inhibition with TFVpp. Metabolomics revealed no major defects in the TCA cycle or beta-oxidation, but clear evidence of oxidative stress.

Conclusions: In summary, we have developed a high-content image analysis pipeline of human-derived PT cells to generate realistic *in vitro* models of functional TDF toxicity. Metabolic characterization of these revealed a clear phenotype consistent with ATP synthase inhibition, which most likely explains toxicity observed in patients, since PT solute transport is heavily dependent on aerobic respiration. ATP depletion might trigger compensatory mitochondrial biogenesis, leading to hypertrophy.

Funding: Government Support - Non-U.S.

PO0245

Immunological Changes Following Cholinergic Anti-Inflammatory Pathway Stimulation

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Background: The cholinergic anti-inflammatory pathway (CAP) protect mice from ischemia reperfusion injury (IRI). The interactions and mechanisms that regulate this effect are of great interest as targets for clinical intervention. Vagus nerve stimulation (VNS) induces neurotransmitter cascades that culminate in release of norepinephrine (NE) in the spleen. NE stimulates CD4+ T cells to produce acetylcholine via the choline acetyltransferase enzyme. Acetylcholine then stimulates anti-inflammation via splenic immune cells that express the α7 nicotinic acetylcholine receptor (α7nAChR). Adoptive transfer of splenic cells from VNS-treated mice protects kidneys from IRI. However, the downstream effects on splenic structure and function that lead to protection are still not fully understood. The goal of this study is to profile immune cells following CAP stimulation and identify key downstream mechanisms.

Methods: VNS was performed on mice in vivo and nicotine stimulation on immune cells ex vivo. Vagus nerve stimulation was triggered optogenetically using blue light to target the vagus nerve of mice expressing channelrhodopsin-2 under control of the vesicular glutamate transporter 2 promoter. Cells were collected from the spleen between 24- and 48-hours post-stimulation. A concentration of 50 μM nicotine in culture media was used to stimulate α7nAChR-expressing immune cells collected from the peritoneum of mice. Analysis of immune cell populations was performed with flow cytometry and single cell RNA sequencing.

Results: Overall optogenetic VNS led to a reduced number of CD45+ cells from the spleen. Within the CD45+ population, B1 cells and macrophages exhibited increased representations of ~30% and 60%, respectively. Monocyte and neutrophil representation remained relatively stable, but eosinophils displayed a marked reduction of ~60%. Single cell RNA sequencing showed increased novel gene expression in subpopulations of macrophages, including cell-cell adhesion genes (*Spa17*) and guanine nucleotide exchange factors (*Arhgef5*) that could regulate function.

Conclusions: Cholinergic stimulation triggers reorganization of immune cell populations and alterations in gene expression that are likely important for regulating the inflammatory environment. Additional characterization and functional studies are currently underway to fully identify the importance of observed changes.

Funding: NIDDK Support

PO0246

Reduced Levels of Cyclic-GMP and Inhibition of cGMP-Dependent Protein Kinase Activate $p21^{Cip1}$/$p27^{Kip1}$ and Lead to Renal Fibrosis and Dysfunction

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Background: Targeted-deletion of *Npr1* (coding for guanylyl cyclase/natriuretic peptide receptor-A, GC-A/NPRA) exhibits hypertrophic and proliferative effects in target organs of *Npr*1 gene-knockout mice; however, the molecular mechanisms of these pathologies are poorly understood. Fibrosis and hypertrophy are regulated by $p21^{Cip1}$ and $p27^{Kip1}$, cell-cycle regulatory proteins that inhibit cyclin and cyclin-dependent kinase (cyclin-CDK) complex.

Methods: We examined the activation of CDK blocker ($p21^{Cip1}$/$p27^{Kip1}$) in *Npr1* gene-knockout (0-copy; $Npr1^{-/-}$) mice and the GC inhibitor, A71915-treated and cGMP-dependent protein kinase (cGK) inhibitor, Rp-8-Br-cGMPS (Rp)-treated wild-type 2-copy ($Npr1^{+/+}$) and gene-duplicated 4-copy ($Npr1^{++/++}$) mice using Western blot and quantitative real-time PCR. Systolic blood pressure (BP) was determined by non-invasive tail-cuff method.

Results: Renal cGMP levels and cGK activity were significantly decreased in 0-copy mice ($p<0.0001$), A71915-treated ($p<0.001$) and Rp-treated ($p<0.05$) 2-copy and 4-copy mice as compared with control animals. The results showed a high BP level in 0-copy mice (138.6 ± 3.1 mmHg; $p<0.001$) and significantly lower BP in 4-copy mice (86.0 ± 2.8 mmHg; $p<0.01$) compared to 2-copy mice (102.2 ± 1.7 mmHg). Treatment with A71915 and Rp showed significant increase in BP in 2-copy mice but only a small increase in 4-copy mice compared with untreated control animals. Increased phosphorylation of p-Erk1/2 (3-fold), p-p38MAPK (4-fold), $p21^{Cip1}$ (6-fold), and $p27^{Kip1}$ (5-fold) occurred in 0-copy, A71915-treated 2-copy, and A71915-treated 4-copy mice; however, Rp treatment caused minimal changes compared to controls. Proinflammatory and profibrotic cytokines, including TNF-α (6-fold), IL-6 (3-fold), and TGF-β1 (4-fold) were increased in plasma and kidney of 0-copy and A791915-treated 2-copy mice, but less in A71915-treated 4-copy mice. Renal pathology, including fibrosis, mesangial matrix expansion, and tubular hypertrophy were significantly higher in 0-copy and A71915-treated 2-copy mice but minimally in 4-copy mice compared with controls.

Conclusions: The present results suggest that *Npr1* has a pivotal role in inhibiting the renal fibrosis and pathology and exerts renal protective effects through the cGMP/cGK axis by repressing the CDK inhibitors, $p21^{Cip1}$ and $p27^{Kip1}$.

Funding: Other NIH Support - NHLBI

PO0247

Inhibition of Acetyl-CoA Carboxylase in Acutely Injured Tubular Cells Exacerbates DNA Damage and Mitochondria Fission in Diabetic Nephropathy

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Background: Both diabetes and acute tubular injury (ATI) alter lipid metabolism of proximal tubules. Inhibiting lipogenesis causes G2/M cell cycle arrest, which can cause maladaptive tubular repair. Acetyl-CoA carboxylase (ACC) stimulates lipogenesis and inhibits fatty acid oxidation (FAO). Phosphorylation (p-ACC) inhibits ACC, which inhibits lipogenesis and promotes FAO. We hypothesized that p-ACC exacerbates DNA damage and mitochondria dysfunction in diabetic nephropathy (DN) after ATI.

Methods: Human DN samples were co-stained for p-ACC, KIM-1, and a-SMA. ATI was introduced by a single diphtheria toxin (DT) injection in Akita mice in which the DT receptor (DTR) was introduced genetically into the kidney tubule (Akita$^{SIX2\text{-}DTR}$). Mice were fed a high-fat diet (HFD). The expression ratio of p-ACC/ACC was determined at 3 days after DT and markers for tubular injury and DNA damage (g-H2AX) were evaluated at 3 days and 4 months. Cisplatin-injured HK2 cells were treated with an ACC inhibitor, PF-05175157 (ACCi) or a carnitine palmitoyltransferase 1 inhibitor, etomoxir (CPT1i) and examined for DNA damage and mitochondria fission.

Results: P-ACC expression was increased and correlated with expression of tubular injury marker KIM-1 and myofibroblast marker a-SMA in human DN specimens. At day 3 after DT, ATI increased the p-ACC/ACC ratio in the Akita $^{SIX2\text{-}DTR}$ mice on HFD and resulted in enhanced expression of g-H2AX in KIM-1 positive tubules and kidney fibrosis at 4 months. When cisplatin-injured HK2 cells were treated with ACCi, which allowed b-oxidation of acyl-CoA, there was an increase in mitochondrial fission factor (MFF) without a further increase of g-H2AX. Etomoxir, which blocked acylcarnitine entry into mitochondria, reduced MFF and g-H2AX expression.

Conclusions: Increased levels of p-ACC were associated with increased tubular injury and fibrosis in human DN. P-ACC in injured renal epithelial cells permitted b-oxidation of acyl-CoA in damaged mitochondria and enhanced mitochondrial fission resulting in DNA damage plausibly from reactive oxygen species. Prevention of mitochondrial overload of acyl-CoA is a potential therapeutic target to mitigate mitochondria damage and DNA damage after ATI in DN.

Funding: NIDDK Support

PO0248

The Effect of ANG-3777 on In Vitro Cell Proliferation

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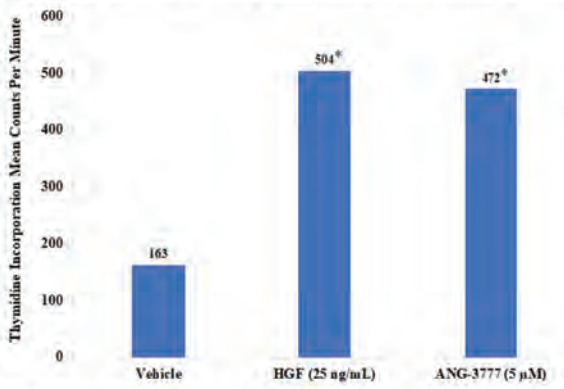
Background: Hepatocyte growth factor (HGF) regulates tissue growth and development by inducing cell motility, proliferation and morphogenesis in multiple cell types including endothelial and epithelial cells. However, it has no effect on proliferation in fibroblasts. ANG-3777 is a novel molecule that exerts similar cytoprotective and regenerative effects as HGF. This study compared the effect of ANG-3777 with that of HGF in stimulating cell proliferation.

Methods: *In vitro* cell proliferation assays were conducted in triplicate using human umbilical vein endothelial cells (HUVEC), rat neuronal Schwann cells, and mouse fibroblasts. HUVEC and fibroblasts were exposed to 5 μM ANG-3777 or 25 ng/mL HGF for up to 24 hours. Schwann cells were exposed to increasing doses of ANG-3777 (up to 10 μM) or HGF (up to 100 ng/mL) for 16 to 24 hours to evaluate the effective concentration at 50% proliferative activity (EC_{50}). Radiolabeled [3H]-thymidine incorporation was used as a measure of cell proliferation. An unpaired T-test was used to compare ANG-3777 or HGF versus vehicle (dimethyl sulfoxide) treatment.

Results: A statistically significant increase in cell proliferation (~3-fold) was observed in HUVECs exposed to ANG-3777 and HGF compared with vehicle ($p<0.01$; Figure 1). Similarly, Schwann cell proliferation increased in a concentration-dependent manner following exposure to ANG-3777 (EC_{50} 0.012 μM) and HGF (EC_{50} 6.5 ng/mL). In mouse fibroblasts (negative control), neither ANG-3777 nor HGF exposure stimulated cell proliferation compared with vehicle.

Conclusions: *In vitro* cell-based proliferation assays confirmed that the activity of ANG-3777 is comparable to that of HGF in inducing cell proliferation in HUVECs and rat Schwann cells with neither agent stimulating proliferation in mouse fibroblasts.

Figure 1. Effect of ANG-3777 vs HGF on Human Umbilical Vein Endothelial Cell Proliferation



*p<0.01 vs vehicle

PO0249

The Effect of ANG-3777 on the Growth of c-MET-Expressing Human Tumor Cells in Immunocompromised Mice

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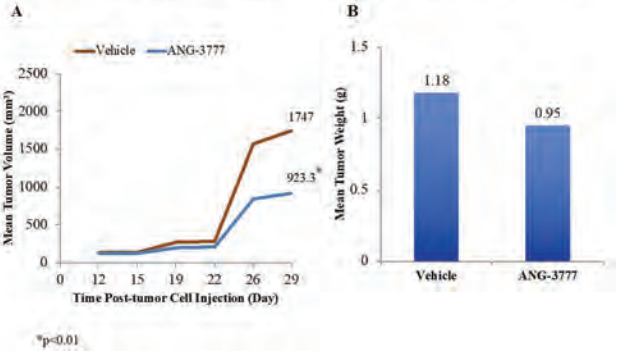
Background: In the injured organs, hepatocyte growth factor (HGF) stimulates c-MET, leading to the activation of intracellular pathways involved in tissue repair. ANG-3777 is an HGF mimetic. In a Phase 2 study, renal transplantation patients with signs of delayed graft function treated with ANG-3777 showed renal function improvement relative to placebo up to 1 year post-transplantation. However, uncontrolled activation of c-MET can stimulate tumor growth. The objective of these studies was to assess the potential of ANG-3777 to stimulate tumor growth in human cell lines.

Methods: c-MET-expressing human tumor xenografts (U87-MG glioma cells, HT29 colon cancer cells, and SUIT-2 pancreatic ductal carcinoma cells) were implanted into 20 BALB/c nude mice per xenograft model. The animals were administered an intraperitoneal injection of 2 mg/kg ANG-3777 or vehicle (dimethyl sulfoxide) daily for up to 28 days. Overall survival (glioma transplant model) and tumor growth and weight (colon and pancreatic tumor xenograft models) were assessed.

Results: Overall survival did not differ in animals treated with ANG-3777 vs vehicle. No significant increase in tumor growth or weight was observed with ANG-3777 treatment. ANG-3777 significantly reduced the mean volume of pancreatic tumors (1747 vs 923.3 mm^3, $p<0.01$;), but not the weight of the tumor (Fig. 1 A&B).

Conclusions: Administration of ANG-3777 in human tumor cells expressing c-MET was not associated with increased tumor volume or weight in pancreatic and colon tumor models and did not increase mortality in the glioma model in BALB/c nude mice.

Figure 1. Effect of ANG-3777 on SUIT-2 Pancreatic (A) Tumor Volume and (B) Weight



*p<0.01

PO0250

A Combination of Contrast Media and Radiation Increases DNA Damage and Delays DNA Damage Repair in Mouse Kidneys

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Background: Contrast-induced nephropathy (CIN), resulting from contrast media (CM) administration, is a major complication of angiographic procedures. CIN may also be induced by exposure to radiation. However, the molecular mechanism of CIN has only been investigated using a CM-injected rodent model. Here, we examined the dual effect of CM and irradiation (IR) on DNA damage and repair in *in vitro* and *in vivo*.

Methods: Human renal tubular epithelium (HK)-2 cells were stimulated by medium containing 100 mg iodine/ml of iohexol (Ihx-HK2), 1 Gy of X-ray irradiation (IR-HK2), or both (Ihx+IR-HK2). Mannitol-treated cells were used as an experimental control (Man-HK2 or Man+IR-HK2). For the *in vivo* study, ischemic reperfusion injury (IRI)

was induced in mice after right kidney removal, then IRI mice were treated with 200 μL iohexol (IRI/CIN) and/or 10 Gy X-ray irradiation (IRI+IR or IRI/CIN+IR). We performed immunohistochemistry, immunofluorescence staining, and western blotting for DNA damage markers (γH2AX, pATM, 53BP1, and RAD51), an oxidative stress marker (8-OHdG), a macrophage marker (F4/80), and klotho.

Results: Immunofluorescence staining revealed increased expression of γH2AX, 53BP1, and RAD51 in Ihx+IR-HK2 compared with Ihx- or IR-HK2. These proteins remained highly expressed at 24 h in Ihx+IR-HK2, but not in Ihx- or IR-HK2. Cells positive for γH2AX, pATM, 53BP1, and RAD51 were significantly increased in IRI/CIN+IR mice, and 8-OHdG and F4/80 expression was also remarkably increased, whereas that of klotho was decreased in IRI/CIN+IR mouse kidneys.

Conclusions: Both CM administration and exposure to radiation induce DNA damage and delay DNA damage repair, which are accompanied by increased levels of oxidative stress and inflammation and downregulation of klotho expression.

PO0251

Whole-Transcriptome Sequencing of Proximal Tubule Cells Exposed to Free Light Chains

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Background: Despite medical advancements, molecular markers for early detection of kidney injury (KI) are limited. Serum creatinine, the only functional marker for KI, has poor predictive accuracy, particularly in the early stages of acute KI due to free light chains in multiple myeloma (MM) patients. Identification of new markers would be highly useful in a select group of MM patients who do not present initially with a detectable rise in creatinine level.

Methods: Human kidney proximal tubule cells (PTCs; RPTEC cell line) were exposed to κ or λ FLCs. Control/ treated cells were harvested, and total RNA (mRNA+miRNA) was isolated following standard procedures for whole transcriptome analysis. After checking RNA quality by Bioanalyzer (Agilent Bioanalyzer 2100), RNA sequencing for whole transcriptome was performed by using Illumina NextSeq 500 to generate >60M paired-end 75bp reads per sample. After initial data quality checking by FastQC and RSeQC, bioinformatics analysis was performed using TopHat, Samtools, and Picard. Further classification, annotation, and visualization were facilitated by Partek and R statistical packages. RNA sequencing data were validated through qPCR.

Results: Whole transcriptome RNA-Seq data suggested role of several genes involved in innate immunity (VNN1, MX1, OAS2, TLRs, IFI6, IFI27, IFIT1, ISG15, BST2), ERK signaling (KCTD12, IFI6, MAP3K, ERK1/2, JNK,p38), and inflammation (CXCL6, TNFA, IL6, CXCL8, IL8, IRAK1, IRAK4, TRAF6, NFKB, IKBA, IKK) as well as miRNAs (hsa-146a-5p, hsa-miR-574-3p, hsa-miR-331-3p, hsa-miR-125a-5p) in FLC induced tubular injury in MM patients. We also found a KI mechanism involving cross-talk among innate immunity, ERK signaling, and the inflammatory pathway by different FLCs types.

Conclusions: Our results show differentially expressed genes and a mechanism of injury involving cross-talk between innate immunity and inflammatory pathways in PTCs exposed to FLCs.

Funding: Private Foundation Support

PO0252

Single-Cell Profiling of AKI in Mice Highlights Differential Immune Cellular Response Programs in Regeneration and Fibrosis

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Background: After acute injury the kidney has the ability to regenerate and repair to a certain extent. On the other hand, maladaptive injury response leads to kidney fibrosis and chronic kidney disease. We are only beginning to understand the complex interactions of epithelial, stromal and immune cells involved in these adaptive processes.

Methods: Here we profiled gene expression changes at single cell resolution over time in acutely injured kidneys of mice subjected to mild and severe bilateral ischemic reperfusion injury (IRI). Kidney function, structure, bulk and single cell gene expression analysis was performed on day 1, 3 and 14. We used gene regulatory network and trajectory analyses to define key drivers of successful and failed regeneration.

Results: Bilateral ischemia resulted in similar kidney function decline as analyzed by serum BUN, however long ischemia led to severe kidney fibrosis, while mild ischemia prompted minimal structural changes. In total, we obtained scRNAseq data for >160,000 cells. IRI lead to very significant cell proportion changes including a decrease in renal tubule cells and increase in immune cell fractions. Proximal tubules showed distinctly different differentiation signatures for successful repair vs. maladaptive response in animals subjected to moderate vs. severe IRI. We also identified several discrete immune cell clusters, such as progenitors, naïve B and T cells, T memory and Tgd cells, natural killer and dendritic cells, Ly6Chi and lo monocytes, macrophages and granulocytes and we define their differentially expressed gene network along pseudotime trajectories towards either successful or maladaptive repair.

Conclusions: Single cell RNA-seq analysis of kidney cells revealed differential gene expression changes during regenerative vs. maladaptive response after acute injury. We define patterns of maladaptive proximal tubule repair and characterize important signatures in immune cell composition and activation in regenerating vs. fibrosing kidneys.

Funding: NIDDK Support, Private Foundation Support

PO0253

Spatial Transcriptomic Signatures in Murine AKI Models

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Background: The localization of whole transcriptome differential expression in different forms of acute kidney injury (AKI) is incompletely understood. We investigated the distribution of expression across the entire kidney, mapping expression patterns to renal histology in the ischemia-reperfusion injury (IRI) and cecal ligation and puncture (CLP) murine models of AKI.

Methods: Sham, IRI, and CLP kidneys were excised and sections were affixed to Visium 10x genomics slides. Sections underwent H+E staining, followed by permeabilization, RNA isolation, and sequencing. The IRI and CLP samples were clustered using Seurat and differential expression was assessed in clusters co-defined by histology and marker gene expression in both models. We then assessed pathway enrichment of differentially expressed genes (DEGs) using ClusterProfiler and ReactomePA.

Results: We examined the distribution of total expression (sum of all gene counts) across the entire kidney between IRI and CLP. In CLP, uniform upregulation was seen in the medullary S3 cluster. In contrast, total expression differences were patchy in the IRI model with regions of increased and reduced expression seen in both the cortex and medulla. Using spatial transcriptomics clustering, we compared the affected clusters, including the cortical collecting duct, S3 outer stripe proximal tubule, and thick ascending loop of Henle. The IRI model was enriched in wound healing and apoptosis related pathways, while the CLP model was enriched in oxidative phosphorylation and energy metabolism. Strong neutrophil signatures were identified in IRI and macrophage signatures in CLP.

Conclusions: Using spatial transcriptomics, we uncovered regional differences in total RNA expression between the IRI and CLP models. The identified regions housed specific cell types with differences in enriched pathways. The enriched apoptotic pathways in IRI may be consistent with a lower relative expression compared to sepsis. The neutrophil and macrophage spatial distribution indicate how those models respond to injury. The localization of transcriptomic alterations in AKI is not uniform across both models.

Funding: NIDDK Support

PO0254

Long-Term Use of Ferric Citrate in the Treatment of Iron Deficiency Anemia in Patients with Non-Dialysis-Dependent CKD: The COMPASS Trial

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Background: Ferric citrate (FC) is an FDA-approved oral iron replacement for adults with iron deficiency anemia (IDA) and non–dialysis-dependent (NDD) CKD and as a phosphate binder in adults with dialysis-dependent CKD. For IDA, the recommended FC starting dose is 1 tablet (1 g, contains 210 mg ferric iron) 3 times daily (TID) titrated to maintain hemoglobin (Hb) goal. We studied the long-term efficacy and safety of various FC regimens for IDA treatment in adults with NDD-CKD (stages 3-5).

Methods: 48-wk, phase 4, randomized, open-label, multicenter study (NCT03236246). Patients received (1:1) FC 1 g tablet TID (3 g/day) or 2 tablets BID (4 g/day). At Wk 12, if Hb was <10 g/dL or changed <0.5 g/dL from baseline (BL), dose was increased to 2 tablets TID (from 1 TID) or 3 tablets BID (from 2 BID). Primary endpoint was change in Hb from BL to Wk 24. Secondary endpoints included change in transferrin saturation (TSAT), ferritin, and phosphate to Wk 48.

Results: This analysis included 183 of 206 randomized patients. Groups were well matched, with mean age 69.5±10.3 y and 54% with CKD due to diabetes. Mean BL eGFR was 33.6±10.9 mL/min/1.73 m^2, and Hb was 10.45±0.74 g/dL. Efficacy measures at 48 wks are presented in the Table. Adverse events (AEs) occurring in ≥5% included diarrhea (13.2%), discolored stool (12.7%), and constipation (12.2%). Incidence of serious AEs was 13.9% in BID and 17.3% in TID groups. Five deaths were reported, none deemed FC related by investigators.

Conclusions: Both FC regimens studied increased and maintained Hb through 48 wks in patients with NDD-CKD with IDA. Patients with lower baseline Hb and iron parameters had a higher increase in Hb with FC treatment. Serum phosphate remained within normal range over study duration. Mean changes in Hb, TSAT, ferritin, and phosphate were similar in the BID and TID and the 3 and 4 g/day dosing groups. These results support the potential for FC dosing flexibility in the long-term treatment of IDA.

Funding: Commercial Support - Akebia Therapeutics, Inc.

Changes from baseline in efficacy variables after 48 wks of FC dosing

PO0255

Triferic (Ferric Pyrophosphate Citrate, FPC) Maintains Hemoglobin and Reduces IV Iron: Results from a Single-Site 2-Year Observational Analysis

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Background: Triferic (ferric pyrophosphate citrate, FPC) is approved as an iron (Fe) replacement product to maintain hemoglobin (Hgb) in adult patients (pts) receiving chronic hemodialysis (HD). Trial data have demonstrated that FPC maintains Fe stores and Hgb while reducing IV Fe usage with a well-tolerated safety profile. We now report one clinic's experience using FPC for all HD patients (pts) during a 2 yr period.

Methods: FPC was added to centrally delivered liquid bicarbonate to provide 110 µg Fe/L dialysate. All patients received FPC at each HD. Anonymized retrospective data from the electronic health record were collected between Sep 2016--Dec 2018. A recommended FPC Fe protocol was provided, but the clinic was allowed to adjust anemia management at their discretion. Supplemental Fe gluconate (IV Fe) was administered according to a protocol based on serum ferritin and TSAT values. All pts receiving IV Fe received single doses of 125 mg elemental Fe up to a max of 500 mg Fe/month when criteria for supplementation was met. During the first 4 months of FPC, the center converted pts from epoetin alfa (EPO) to darbepoetin alfa (INN), therefore INN equivalents were calculated using the published conversion guide (EPO dose/300). IV iron and ESA dose were standardized and changes from pre-FPC were reported for Hgb, IV Fe and ESA usage. KDQoL data were available for the years 2016--2018.

Results: Within 3 months of initiation of FPC, Hgb increased by 0.3 g/dL and was maintained during the observation period. Total IV Fe dose was significantly reduced by 78.4%. Darbepoetin equivalent doses were reduced from pre-FPC by 31.5% by the end of the observation period. Compared to the first year of assessments (2016), post FPC assessments of QoL showed improvements in the Burden of Kidney Disease (KD), Symptoms and Problems of KD and Effects of KD on daily life scales. No adverse events related to FPC were reported.

Conclusions: This observational study demonstrates that FPC is a well tolerated replacement for IV Fe when administered to all patients in a HD unit. The findings of this real-world observational study align with those of clinical trials in terms of reduction of IV Fe use and maintenance of Hgb. ESA was gradually reduced and the KDQoL showed a trend to improvement in the burden and symptoms of kidney disease.

Funding: Commercial Support - Rockwell Medical Inc.

PO0256

Roxadustat Lowers Risk of Red Blood Cell Transfusion in Patients with Anemia of CKD

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Background: RBC transfusions may cause reactions, lead to allo-sensitization, or rarely transmit infections, so treatments reducing transfusions are desirable. This analysis assessed whether roxadustat, an oral hypoxia–inducible factor prolyl hydroxylase inhibitor, reduced the need for RBC transfusions in patients with non-dialysis-dependent (NDD) and dialysis-dependent (DD) chronic kidney disease (CKD) and anemia.

Methods: Data from six completed randomized Phase 3 studies (up to 4y duration) in patients with Stage 3–5 CKD, comparing roxadustat with placebo in NDD-CKD, and with epoetin alfa in DD-CKD were assessed. Risk of first RBC transfusion was evaluated in individual studies and within pooled NDD and DD populations.

Results: In total, 4277 patients with NDD-CKD were evaluated (2391 roxadustat; 1886 placebo). Mean ± SD baseline Hb was 9.10 ± 0.74 g/dL (roxadustat) and 9.10 ± 0.73 g/dL (placebo). The DD-CKD studies comprised 3857 patients (1929 roxadustat; 1928 epoetin alfa). Mean ± SD baseline Hb was 9.63 ± 1.30 g/dL (roxadustat) and 9.67 ± 1.30 (epoetin alfa). Roxadustat reduced the risk of RBC transfusion by 74% versus placebo in NDD patients and by 18% versus epoetin alfa in DD patients (**Table 1**).

Conclusions: Roxadustat markedly and significantly reduced the risk of RBC transfusion during anemia treatment compared with placebo in NDD CKD and, versus epoetin alfa in DD CKD in the pooled patient populations.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table 1. Risk of RBC transfusion in NDD-CKD and DD-CKD patients treated with roxadustat compared with placebo or epoetin alfa - FAS

NDD pool (N=4277)				
Study	HR (roxadustat vs placebo)	Risk reduction for roxadustat vs placebo	95% CI	p- value
001† (OLYMPUS)	0.37	−63%	0.30, 0.44	<0.001
060 (ANDES)	0.26	−74%	0.17, 0.41	<0.0001
608 (ALPS)	0.34	−66%	0.21, 0.55	<0.001
Pooled	0.26	−74%	0.21, 0.32	<0.0001
DD pool (N=3857)				
Study	HR (roxadustat vs epoetin alfa)	Risk reduction for roxadustat vs epoetin alfa	95% CI	P value
002 (ROCKIES)	0.83	−14%	(0.64, 1.07)	0.151
064 (SIERRAS)	0.67	−33%	0.47, 0.97	0.034
063 (HIMALAYAS)[b]	1.26	+26%	0.79, 2.02	0.328
Pooled	0.82	−18%	0.679, 0.997	0.046

aFull analysis set.

CI, confidence interval; CKD, chronic kidney disease; DD, dialysis-dependent; HR, hazard ratio; NDD, non-dialysis-dependent.

PO0257

Hemoglobin (Hb) Correction with Roxadustat Is Associated with Improved Iron Homeostasis in Patients with Non-Dialysis-Dependent CKD (NDD-CKD)

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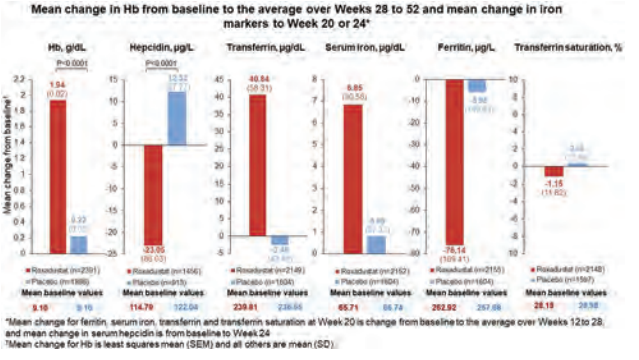
Background: Anemia in CKD is multifactorial, with contributions from reduced erythropoietin production and hepcidin-induced functional iron deficiency. Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor, treats anemia by enhancing erythropoietin synthesis and increasing iron availability via reducing hepcidin and increasing iron transport. We assessed the effect of roxadustat on iron parameters in patients with NDD-CKD.

Methods: Patients were randomized to double-blind roxadustat or placebo in 3 pivotal NDD-CKD trials. Oral iron was administered without restriction per discretion of the treating physician, and intravenous (IV) iron use was limited to rescue therapy. Mean changes from baseline (BL) in Hb, hepcidin, and iron parameters were evaluated. Pooled results are reported.

Results: Overall, 4277 patients were evaluated (roxadustat N=2391; placebo N=1886). Mean eGFR was 20 ml/min/1.73 m^2 in both groups. Roxadustat was superior to placebo in increasing mean Hb from BL (9.1 g/dL for both groups) averaged over Weeks 28–52: 1.9 vs 0.2 g/dL (P<0.0001). IV iron use was required in 2.1% of roxadustat vs 4.8% of placebo patients during the first 52 weeks after randomization. Roxadustat reduced hepcidin and increased both transferrin and serum iron (Figure). Reductions in ferritin and transferrin saturation occurred predominantly in patients with the highest BL values of these parameters when assessed by quartile (>328 µg/L and >35%, respectively).

Conclusions: Roxadustat increased both serum iron and iron-carrying capacity (transferrin) while simultaneously inducing erythropoiesis and correcting anemia in patients with NDD-CKD, without the need for regular IV iron supplementation.

Funding: Commercial Support - AstraZeneca



PO0258

Health-Related Quality of Life in Roxadustat-Treated Patients with Anemia and Non-Dialysis-Dependent CKD

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Anemia in CKD impacts health-related quality of life (HRQL) by reducing physical capacity and energy levels. Studies have demonstrated a direct relationship between HRQL scores and hemoglobin (Hb) levels in non–dialysis-dependent (NDD) and dialysis-dependent patients with CKD. We assessed the impact of roxadustat on HRQL in patients with NDD-CKD.

Methods: Pooled data from three pivotal, phase 3, randomized, double-blind, placebo-controlled studies of roxadustat for the treatment of anemia in patients with NDD-CKD were assessed. Patients with data up to the time of dialysis treatment and who had pretreatment and ≥1 post-treatment HRQL measurement were included. Mean changes from baseline to Week 12 in HRQL scores were compared between the treatment groups.

Results: Least-squares mean treatment differences favored the roxadustat group at Week 12 (all *p*-values <0.05) in the majority of measures analyzed (Table). Between-group differences were larger in subgroups with lower (ie, worse) baseline scores.

Conclusions: Roxadustat demonstrated improvement in most HRQL measures vs. placebo in patients with NDD-CKD.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: Change from Baseline in HRQL Outcomes at Week 12

Outcome	LSM (SEM) Treatment difference* (95% CI)	P-value
SF-36 Physical Functioning Subscore		
All patients	0.53 (0.25) (0.05, 1.01)	0.0311
Patients with BL score <50	0.67 (0.28) (0.13, 1.21)	0.0151
SF-36 Vitality Subscore		
All patients	0.96 (0.26) (0.44, 1.47)	0.0003
Patients with BL score <50	0.80 (0.33) (0.15, 1.45)	0.0161
FACT-An Anemia Subscale Score		
All patients	1.10 (0.33) (0.45, 1.74)	0.0008
Patients with BL score <55	1.36 (0.49) (0.41, 2.31)	0.0052
FACT-An Total Score		
All patients	1.81 (0.65) (0.54, 3.08)	0.0051
Patients with BL score <135	2.00 (0.85) (0.33, 3.67)	0.0189
EQ-5D-5L VAS Score (all patients)	1.68 (0.47) (0.76, 2.59)	0.0003
PGIC responder† rate at Week 12 (all patients)	2.03 (1.74, 2.36)‡	<0.0001

*MI ANCOVA. †Defined as a patient who selected an outcome of 'Much Improved' or 'Very Much Improved.' No multiplicity adjustments were performed. ‡Roxadustat vs. placebo OR (95% CI) from CMH method adjusting for study; region (US, Europe, Other); BL Hb (<8.0 vs. ≥8.0 g/dL); BL eGFR (<30 vs. ≥30 mL/min/1.73 m²); and history of cardiovascular, cerebrovascular, and/or thromboembolic diseases (Yes vs. No). BL, baseline; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EQ-5D-5L, EuroQol Questionnaire-5 Dimensions 5 Levels; FACT-An, Functional Assessment of Cancer Therapy-Anemia; Hb, hemoglobin; HRQL, health-related quality of life; LSM, least-squares mean; MI ANCOVA: multiple imputation analysis of covariance; OR, odds ratio; PGIC, Patient's Global Impression of Change; SF-36, Short-Form 36; US, United States; VAS, visual analogue scale.

PO0259

Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients with Incident Dialysis-Dependent CKD

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism.

Methods: Pooled data from 3 pivotal phase 3 studies of roxadustat v. epoetin alfa forincident–dialysis-dependent dialysis patients (ID-DD; on dialysis for ≤4 m)were assessed. Prespecified, subgroups were analyzed for mean change from baseline (CFB) in hemoglobin (Hb) (weeks 28–52 regardless of rescue therapy) and mean monthly IV iron use (Weeks 28–52). Death, MI, and stroke (MACE), as well as heart failure or unstable angina requiring hospitalization (MACE+) were adjudicated.

Results: Roxadustat- (n=760) v. epoetin alfa-treated patients (n=770) achieved non-inferiority (NI:lower limit of 95% CI >0), and a significantly larger mean (SD) CFB in Hb (g/dL) (2.12 [1.45] v. 1.91 [1.42]), with a least-squares mean (LSM) difference of 0.22 (95% CI: 0.05, 0.40) (*p*=0.013). All subgroupswere consistent with the overall population, achieving NI for Hb CFB (Table). Subgroup analyses of mean monthly IV iron use during Weeks 28–52 were significant in favor of roxadustat v. epoetin alfa in the overall population and by age group (18–64), gender (male), race (white), region (US, Europe), baseline iron status (ferritin ≥100 ng/mL & TSAT ≥20%), baseline Hb (<8.0 and ≥8.0 g/dL), and dialysis modality (hemodialysis). HR of MACE and MACE+ were lower in the roxadustat v. epoetin alfa group: 0.70 (95% CI: 0.51, 0.96) (*p*=0.03) and 0.66 (95% CI: 0.50, 0.89) (*p*=0.005).

Conclusions: The efficacy of roxadustat vs. epoetin alfa for improving Hb level and reducing IV iron use was consistent across prespecified subgroups in the ID-DD population. Roxadustat reduced MACE and MACE+ vs. epoetin alfa.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: Mean CFB in Hb averaged over Weeks 28-52 Regardless of Rescue Therapy (ID-DD)*

	LSM Difference (95% CI)†	*P*-value
Overall	0.22 (0.05, 0.40)	0.0130
Age group, y		
18–64	0.21 (−0.01, 0.43)	0.0659
65–74	0.42 (0.03, 0.82)	0.0349
≥75	0.05 (−0.40, 0.50)	0.8430
Sex		
Male	0.25 (0.04, 0.46)	0.0177
Female	0.16 (−0.14, 0.47)	0.2904
Race		
Asian	0.39 (0.01, 0.77)	0.0438
Black	−0.06 (−0.49, 0.38)	0.8024
White	0.27 (0.03, 0.50)	0.0248
Region		
US	0.23 (0.01, 0.45)	0.0399
Europe	0.16 (−0.02, 0.34)	0.0744
Other	0.14 (−0.05, 0.34)	0.1557
Iron status		
Ferritin <100 ng/mL and/or TSAT <20%	0.12 (−0.39, 0.63)	0.6444
Ferritin ≥100 ng/mL and TSAT ≥20%	0.24 (0.06, 0.43)	0.0110
Diabetes		
Yes	0.26 (0.03, 0.48)	0.0261
No	0.19 (−0.10, 0.48)	0.2053
CRP		
≤ULN	0.21 (−0.00, 0.43)	0.0509
>ULN	0.32 (0.02, 0.62)	0.0349
Hb, g/dL		
<8.0	0.41 (0.08, 0.74)	0.0161
≥8.0	0.20 (0.02 (0.37)	0.0259
Weight, kg		
<70	0.18 (−0.11, 0.47)	0.2140
≥70 to <100	0.27 (−0.00, 0.54)	0.0504
≥100	0.35 (−0.16, 0.85)	0.1827

*US primary efficacy endpoint. † Multiple imputation strategy combining ANCOVA results with BL Hb as covariate, and study; treatment; study-by-treatment interaction; and history of cardiovascular, cerebrovascular, or thromboembolic diseases as fixed effects. Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; LSM, least-squares mean; NA, not available; TSAT, transferrin saturation; ULN, upper limit of normal; US, United States.

PO0260

Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism.

Methods: Data from three pivotal, phase 3, randomized, double-blind, placebo-controlled studies of roxadustat for the treatment of anemia in patients with non–dialysis-dependent (NDD) CKD were assessed. Data from prespecified, clinically relevant patient subgroups were analyzed for: mean change from baseline (CFB) in hemoglobin (Hb) averaged over weeks 28–52 regardless of rescue therapy (primary US efficacy endpoint) and patients (%) that received rescue therapy in the first 52 weeks.

Results: Roxadustat- (n=2391) vs. placebo-treated patients (n=1886) achieved a significantly larger mean (SD) CFB in Hb level (1.85 [0.94] vs. 0.13 [1.01]), corresponding to a least-squares mean (LSM) difference of 1.72 (95% CI: 1.65, 1.79) (*p*<0.0001). The results of all subgroup analyses were consistent with those for both the primary US efficacy endpoint and the percentage of patients requiring rescue therapy in the overall NDD population (Table). Significantly fewer patients required rescue therapy during roxadustat treatment vs. placebo (8.9% vs. 31.1%), corresponding to a hazard ratio of 0.19 (95% CI: 0.16, 0.23) (*p*<0.0001). The effect was consistent in all subgroups and especially pronounced in patients with baseline Hb <8.0 g/dL (18.1% vs. 59.3%) and those with baseline eGFR <10.0 mL/min/1.73m² (14.8% vs. 48.3%).

Conclusions: The efficacy of roxadustat vs. placebo for a larger mean CFB in Hb and fewer patients that received rescue therapy was consistent across a wide range of prespecified subgroups in the NDD-CKD population.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: Subgroup Analyses of Primary US Efficacy Endpoint and Use of Rescue Therapy (NDD)

	Primary US Endpoint*	Use of Rescue Therapy†
	LSM Difference (95% CI)‡	Rate Difference (95% CI)
Overall	1.72 (1.65, 1.79)	−22.2 (−24.58, −19.79)
Age group, y		
18–64	1.71 (1.62, 1.81)	−22.8 (−26.13, −19.42)
65–74	1.73 (1.60, 1.87)	−18.4 (−22.98, −13.76)
≥75	1.73 (1.58, 1.88)	−25.6 (−30.62, −20.57)
Sex		
Male	1.72 (1.61, 1.84)	−23.2 (−27.00, −19.49)
Female	1.73 (1.64, 1.82)	−21.2 (−24.33, −18.12)
Race		
Asian	NA	−22.3 (−26.28, −18.26)
Black	1.35 (0.95, 1.76)	−15.9 (−24.29, −7.48)
White	1.58 (1.48, 1.68)	−22.8 (−26.27, −19.33)
Other	1.70 (1.48, 1.91)	−24.3 (−32.37, −16.24)
Region§		
US	1.61 (1.48, 1.74)	−20.2 (−25.01, −15.36)
Europe	1.65 (1.53, 1.77)	−23.8 (−28.78, −18.81)
Other	1.62 (1.48, 1.77)	−22.4 (−25.67, −19.07)
Iron status		
Ferritin <100 ng/mL and/or TSAT <20%	1.61 (1.50, 1.72)	−18.9 (−22.58, −15.29)
Ferritin ≥100 ng/mL and TSAT ≥20%	1.81 (1.71, 1.90)	−24.3 (−27.43, −21.12)
Diabetes		
Yes	1.71 (1.61, 1.81)	NA
No	1.76 (1.66, 1.87)	NA
CRP		
≤ULN	1.74 (1.65, 1.82)	NA
>ULN	1.67 (1.53, 1.82)	NA
Hb, g/dL		
<8.0	2.44 (2.17, 2.71)	−41.2 (−50.43, −31.90)
≥8.0	1.66 (1.59, 1.73)	−20.4 (−22.78, −17.92)
Weight, kg		
<70	1.76 (1.65, 1.86)	NA
≥70 to <100	1.64 (1.54, 1.75)	NA
≥100	1.83 (1.57, 2.10)	NA
eGFR, mL/min/1.73m²		
<10.0	1.99 (1.79, 2.19)	−33.5 (−39.59, −27.34)
10.0 to <15.0	1.85 (1.71, 1.98)	−24.2 (−29.40, −19.02)
15.0 to <30.0	1.65 (1.54, 1.76)	−19.9 (−23.43, −16.28)
≥30.0	1.46 (1.28, 1.65)	−13.0 (−17.50, −8.43)

*CFB in Hb averaged during Weeks 28–52 regardless of rescue therapy. †Patients (%) that received rescue therapy over 52 weeks. ‡Multiple imputation strategy combining ANCOVA results with BL Hb and eGFR as covariates, and study; treatment; study-by-treatment interaction; region; and history of cardiovascular, cerebrovascular, or thromboembolic diseases as fixed effects. §Region (US, Europe, Other) was removed from the model for this subgroup. Abbreviations: ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; EU, European Union; Hb, hemoglobin; LSM, least-squares mean; NA, not available; TSAT, transferrin saturation; ULN, upper limit of normal; US, United States.

PO0261

Risk of Transfusion in Patients with Non-Dialysis-Dependent CKD Increases with Hemoglobin Levels <10 g/dL vs. ≥10 g/dL: Pooled Results from Roxadustat Phase 3 Studies

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Background: Roxadustat is a novel, orally bioavailable, heterocyclic small molecule that reversibly inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase enzymes and activates HIF and transcription of HIF-responsive genes, including erythropoietin. In patients with ESRD, the risk for blood/RBC transfusion is higher in patients with hemoglobin (Hb) levels <10 g/dL vs. those with Hb ≥10 g/dL. We evaluated the efficacy of roxadustat vs. placebo on blood/RBC transfusion by Hb level in US-based patients with non–dialysis-dependent (NDD) CKD.

Methods: Data from three pivotal phase 3, randomized, placebo-controlled studies of roxadustat for the treatment of anemia in NDD patients were assessed. Patients were randomized to receive roxadustat or placebo with periodic dose evaluation/titration. Transfusion was allowed at any time if it was deemed a medical necessity by the Investigator. The incidence rate of transfusion was calculated based on Hb level categorized as: <8.0, 8 to <10, and ≥10 g/dL. Data were evaluated for the on-treatment period + 28 days after the last dose of study drug.

Results: In the overall pooled population of patients with NDD-CKD, roxadustat reduced the risk of transfusion by 74% (HR, 0.26 [95% CI: 0.21, 0.32]; p<0.0001) vs. placebo. When patient-exposure data were stratified by achieved Hb levels, the risk for transfusion increased as Hb levels decreased (Table). The incidence rate of transfusion increased approximately 4-fold in patients with Hb between 8.0 and <10.0 g/dL vs. those with Hb ≥10 g/dL regardless of treatment arm.

Conclusions: In US-based patients with NDD-CKD and anemia treated with roxadustat, the risk of transfusion was approximately 4 times higher in patients with Hb between 8.0 g/dL and <10 g/dL vs. those with Hb ≥10 g/dL.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: Incidence rate of transfusion (events/100 PEY) based on Hb level and treatment group

	Roxadustat (n=545)				Placebo (n=436)			
Hb (g/dL)	Events	PEY	Transfusion Rate*	% of PEY	Events	PEY	Transfusion Rate*	% of PEY
≥10.0	50	780.7	6.40	84.7	13	181.7	7.16	31.5
8.0 to 10.0	35	133.5	26.21	14.5	93	349.1	26.64	60.5
<8.0	14	8.0	175.22	0.9	81	46.4	174.42	8.0
Total	99	922.3	10.73	100.0	187	577.3	32.39	100.0

*Number of events per 100 PEY; Hb, hemoglobin; PEY, patient-exposure years

PO0262

Roxadustat Favorably Modifies Iron Indices in Patients with Non-Dialysis-Dependent CKD-Related Anemia

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis by increasing endogenous erythropoietin and improving iron metabolism.

Methods: We analyzed data from a Phase 3, randomized, double-blind study (ANDES) comparing roxadustat to placebo for the treatment of anemia in NDD-CKD patients. 922 patients were randomized (2:1) to receive roxadustat (n=616) or placebo (n=306) thrice weekly with monthly dose titrations. Patients were encouraged to receive oral iron daily unless not tolerated. Change in Hb was compared to changes in key iron and red blood cell (RBC) parameters.

Results: All baseline (BL) parameters were comparable between the study arms. Roxadustat was superior to placebo in increasing mean Hb from BL over weeks (wks) 28-52: +2.00 vs. +0.16 g/dL (p<0.0001), respectively. As expected, Hb, iron and RBC parameters were unchanged over time in the placebo arm. In the roxadustat arm, significant erythropoiesis was noted with mean Hb increases of 1.52 and 1.89 g/dL at wks 4 and 24; mean decrease in hepcidin was –54.6 µg/L at wk 4 and DTIBC was +63.1 µg/dL at wk 8. An initial decline in mean ferritin and TSAT was noted primarily in the higher BL quartiles, with little change in the 2 lower BL quartiles. Serum iron increased by 13.6 µg/dL at wk 20 from baseline. All initial changes in iron parameters plateaued by wks 16-20, and remained unchanged thereafter. Reticulocyte Hb content at wk 20 were at baseline level, and it was maintained at Weeks 28- Week 52. Mean MCV was slightly increased by 1-4 fL at wk 4 before plateauing and stabilizing, while mean MCHC was unchanged.

Conclusions: Roxadustat lowered serum hepcidin, accompanied with initial decline in ferritin and TSAT in patients with high BL levels but little change in ferritin and TSAT in patients with low-normal BL levels despite active erythropoiesis. Maintenance of reticulocyte Hb content level during treatment reassures sufficient iron availability during erythropoiesis with roxadustat. These findings in iron parameters suggest that iron is efficiently absorbed and mobilized for erythropoiesis during anemia correction and Hb maintenance with roxadustat in NDD-CKD patients.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO0263

Roxadustat Increases Hemoglobin in Anemic Non-Dialysis-Dependent (NDD) CKD Patients Independent of Inflammation

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Background: Inflammation is a common cause of decreased responsiveness to erythropoiesis-stimulating agents. Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, treats anemia by inducing endogenous erythropoietin production and increasing iron utilization via reducing hepcidin. Roxadustat efficacy has been shown in those with inflammation, as defined by baseline (BL) elevation of high sensitivity C-reactive protein (hsCRP). This pooled analysis explored the efficacy of roxadustat in correcting Hb in NDD-CKD patients across the spectrum of BL hsCRP values.

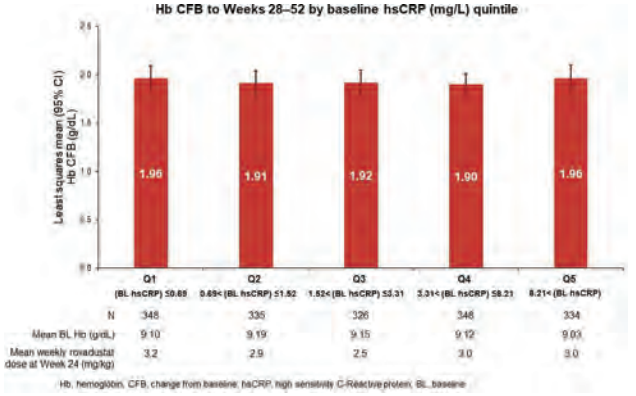
Methods: Data from three randomized Phase 3 pivotal trials in anemic patients with Stage 3–5 NDD-CKD were pooled and the efficacy of roxadustat in increasing hemoglobin (Hb) from BL was assessed. hsCRP concentration was used as a marker of inflammation; patients with hsCRP >5 mg/L were considered to have inflammation at BL. Mean Hb change from BL (CFB) to Weeks 28–52 was summarized by baseline hsCRP quintile. Roxadustat dose requirements at Week 24 were based on mean weekly dose in mg per kg of mean BL weight.

Results: Overall, 1691 roxadustat-treated NDD-CKD patients were assessed and had a mean BL hsCRP of 7.4 mg/L. Mean BL Hb measures were similar across the hsCRP quintiles (range 9.0–9.2 g/dL). In patients with BL inflammation (n=523), mean Hb CFB to Weeks 28–52 was 1.95 g/dL with roxadustat. Mean Hb CFB to Weeks 28–52 was also

similar across all hsCRP quintiles in roxadustat-treated patients (**Figure**). Mean weekly roxadustat doses at Week 24 for baseline hsCRP quintiles 1 through to 5 were comparable at 3.2, 2.9, 2.5, 3.0, and 3.0 mg/kg, respectively.

Conclusions: Roxadustat increased Hb in anemic NDD-CKD patients independent of inflammation.

Funding: Commercial Support - AstraZeneca



PO0264

Roxadustat Treatment Corrects Anemia to Hemoglobin (Hb) Values ≥10 g/dL in the Majority of Patients with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)

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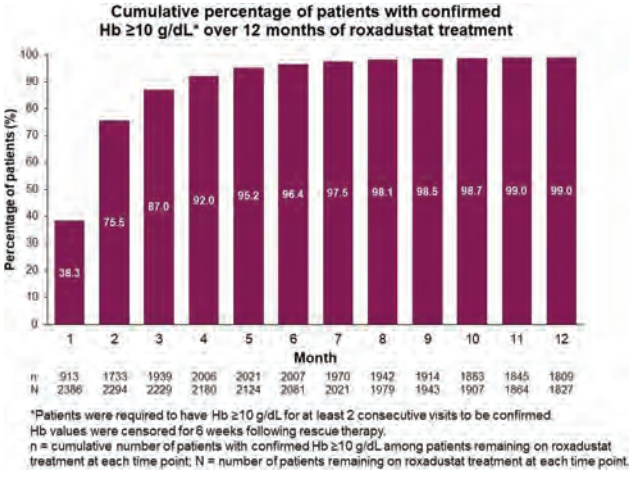
Background: The KDIGO clinical practice guidelines recommend the treatment of anemia in NDD-CKD patients with Hb <10 g/dL to reduce associated symptoms and prevent the need for red blood cell transfusions. Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor studied for the treatment of anemia in patients with CKD through increasing erythropoietin synthesis and enhancing iron utilization. We studied the percentage of patients with NDD-CKD treated with roxadustat achieving Hb ≥10 g/dL.

Methods: Patients with Hb <10 g/dL and eGFR <60 mL/min/1.73 m^2 were randomized to roxadustat or placebo in 3 pivotal double-blind NDD-CKD trials (OLYMPUS, ANDES and ALPS). The cumulative percentage of patients with Hb ≥10 g/dL for at least 2 consecutive visits was analyzed monthly over 12 months of roxadustat treatment, using the number of patients remaining on roxadustat treatment at each time point as the denominator. Hb values were censored for 6 weeks following rescue therapy.

Results: In total, 2391 patients received roxadustat. Mean Hb at baseline was 9.1 g/dL and mean eGFR was 19.7 mL/min/1.73 m^2. Among patients still on roxadustat treatment, the cumulative percentage of patients with Hb ≥10 g/dL for at least two consecutive visits was 38.3%, 75.5%, and 87.0% at months 1, 2, and 3, respectively, and 96.4% at month 6 (Figure). Among patients still receiving roxadustat treatment at 12 months, the cumulative percentage with confirmed Hb ≥10 g/dL was 99.0%.

Conclusions: Roxadustat effectively raised Hb levels in NDD-CKD patients, with over 95% of patients achieving Hb ≥10 g/dL after 5 months of treatment.

Funding: Commercial Support - AstraZeneca



Figure

PO0265

Roxadustat Increases Hemoglobin in Anemic Dialysis-Dependent (DD) CKD Patients Independent of Inflammation

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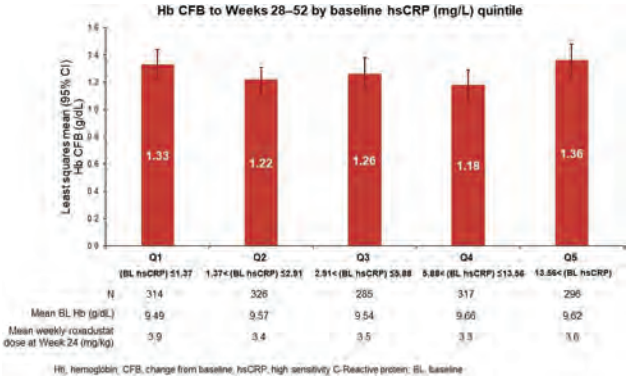
Background: Inflammation is a common cause of decreased responsiveness to erythropoiesis-stimulating agents. Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, treats anemia by inducing endogenous erythropoietin production and increasing iron utilization via reducing hepcidin. Roxadustat efficacy has been shown in those with inflammation, as defined by baseline (BL) elevation of high sensitivity C-reactive protein (hsCRP). This pooled analysis explored the efficacy of roxadustat in correcting Hb in DD-CKD patients across the spectrum of baseline hsCRP values.

Methods: Data from three randomized Phase 3 pivotal trials in anemic patients with DD-CKD were pooled and the efficacy of roxadustat in increasing hemoglobin (Hb) from BL was assessed. hsCRP concentration was used as a marker of inflammation; patients with hsCRP >5 mg/L were considered to have inflammation at BL. Mean Hb change from BL (CFB) to Weeks 28–52 was summarized by BL hsCRP quintile. Roxadustat dose requirements at Week 24 were based on mean weekly dose in mg per kg of mean BL weight.

Results: Overall, 1538 roxadustat-treated DD-CKD patients were assessed and had a mean BL hsCRP of 10.5 mg/L. Mean BL Hb measures were similar across the hsCRP quintiles (range 9.5–9.7 g/dL). In patients with BL inflammation (n=723), mean Hb CFB to Weeks 28–52 was 1.29 g/dL with roxadustat. Mean Hb CFB to Weeks 28–52 was similar across all hsCRP quintiles in roxadustat-treated patients (**Figure**). Mean weekly roxadustat doses at Week 24 for BL hsCRP quintiles 1 through to 5 were comparable at 3.9, 3.4, 3.5, 3.3, and 3.6 mg/kg, respectively.

Conclusions: Roxadustat increased Hb in anemic DD-CKD patients independent of inflammation.

Funding: Commercial Support - AstraZeneca



PO0266

Effects of Roxadustat Treatment on Serum Parathyroid Hormone (PTH) in Hemodialysis Patients with Erythropoiesis-Stimulating Agent (ESA) Resistant Anemia

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Background: Roxaduastat, an oral HIF-prolyl hydroxylase inhibitor, is shown to stimulate erythropoiesis thereby improving iron metabolism. Of note, recent research suggests that iron utilization plays a key role in bone turnover in hemodialysis patients.

Methods: A total of 64 hemodialysis patients with ESA-resistant anemia despite high-dose epoetin α (3000 units 3 times weekly) therapy participated in the study after giving informed consent. Patients were switched from intravenous epoetin α to oral roxaduastat therapy (100 mg 3 times weekly), with no dose change in any of the iron supplements, calcimimetics or vitamin D formulations being used, and were assessed after 8 weeks of roxaduastat therapy for improvements in anemia, as well as for changes in parameters related to iron metabolism and bone turnover.

Results: The study included 39 men and 25 women (age, 70.8 ± 11.8 years; Hb concentration, 10.3 ± 1.2 g/dL). After 8 weeks, the Hb concentration tended to be increased ($P = 0.06$). As shown in Table, the serum iron, ferritin concentration and TSAT significantly decreased ($p < 0.05$), suggesting increased iron utilization. Again, the serum calcium concentration was significantly decreased from 8.54 to 8.36 mg/dL, while the intact-PTH (i-PTH) concentration was significantly decreased from 98.61 to 75.80 pg/mL ($P < 0.001$).

Conclusions: Switching hemodialysis patients with ESA-resistant anemia from intravenous ESA to oral roxadustat therapy may result in a decrease in their serum PTH concentrations presumably through improved iron utilization, thus potentially improving their bone mineral metabolism.

Funding: Private Foundation Support

Effects of Roxadustat Treatment on HD Patients with ESA-resistant Anemia

	Week 0	Week 4	Week 8
Hb (g/dL)	10.36±0.85	10.62±1.28	10.52+±1.28
iron (µg/dL)	49.48±17.69	45.86±25.75**	45.61±23.15*
ferritin (g/dL)	63.87±66.72	56.08±97.60*	46.96±62.61*
TSAT	0.18±0.06	0.14±0.08*	0.14±0.10*
calcium (mg/dL)	8.54±0.65	8.43±0.72*	8.36±0.81*
i-PTH (pg/mL)	98.61±88.72	70.38±61.13**	75.80±75.86**

* p<0.05, ** p<0.01

PO0267

Ophthalmological Effects of Roxadustat in the Treatment of Anemia in Dialysis-Dependent and Non-Dialysis-Dependent CKD Patients: Findings from Two Phase 3 Studies

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Background: Roxadustat is an orally active hypoxia-inducible factor prolyl hydroxylase inhibitor in late-stage development for the treatment of chronic kidney disease (CKD) anemia. Nonclinical data had suggested that hypoxia-inducible factor stabilization may promote angiogenesis, increasing the risk of retinal pathologies. We herein report the 24-week ophthalmological findings from two phase 3 studies of roxadustat in Japan.

Methods: Dialysis-dependent (DD) and non–dialysis-dependent (NDD) CKD patients (pts) with anemia were randomized to roxadustat (three times weekly) or darbepoetin alfa (DA; once weekly [DD]; once every two weeks [NDD]). Doses were titrated to maintain target hemoglobin. Ophthalmological assessments (funduscopic photograph, optical coherence tomography) were performed by centralized grading; visual acuity was assessed locally.

Results: A total of 302 DD pts (150, roxadustat; 152, DA) and 262 NDD pts (131, roxadustat; 131, DA) were randomized and received ≥1 dose of study drug. Results from the ophthalmological funduscopic photograph assessments are reported in Table 1. No meaningful changes occurred in visual acuity or retinal thickness in the treatment groups of either study.

Conclusions: In DD and NDD CKD pts with anemia, the risk of developing ophthalmic abnormalities was comparable between roxadustat and DA.

Funding: Commercial Support - Astellas Pharma, Inc.

Ophthalmological Assessments

	Dialysis-Dependent		Non-Dialysis-Dependent	
Parameter	Roxadustat	Darbepoetin	Roxadustat	Darbepoetin
Pts with previous or concurrent retinal vascular disorders at baseline	62/150 (41.3%)	57/152 (37.5%)	64/130 (49.2%)	63/131 (48.1%)
Pts with new or worsening retinal hemorrhages[a] during 24-week treatment period	46/142 (32.4%)	53/145 (36.6%)	38/121 (31.4%)	51/128 (39.8%)
Pts with new retinal hemorrhages in pts with no retinal hemorrhage at baseline	18/94 (19.1%)	24/96 (25.0%)	8/62 (12.9%)	18/72 (25.0%)
Pts with new or worsening retinal hemorrhages[a] in pts with ≥1 retinal hemorrhage at baseline	28/48 (58.3%)	29/49 (59.2%)	30/59 (50.8%)	33/56 (58.9%)

[a] Any evidence of retinal hemorrhage, from "No" at baseline to "Yes," and/or an increase from baseline in the total number of retinal hemorrhages.

PO0268

Risk of Transfusion in Patients with Dialysis-Dependent CKD Increases with Hemoglobin Levels <10 g/dL vs. ≥10 g/dL: Pooled Results from Roxadustat Phase 3 Studies

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Background: Roxadustat is a novel, orally bioavailable, heterocyclic small molecule that reversibly inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase enzymes and activates HIF and transcription of HIF-responsive genes, including erythropoietin. In patients with ESRD, the risk for blood/RBC transfusion is higher in patients with hemoglobin (Hb) levels <10 g/dL vs. those with Hb ≥10 g/dL. We evaluated the efficacy of roxadustat vs. epoetin alfa on blood/RBC transfusion by Hb level in US-based patients with dialysis-dependent (DD) CKD.

Methods: Data from three pivotal phase 3, randomized, active-controlled studies of roxadustat for the treatment of anemia in DD patients were assessed. Patients were randomized to receive roxadustat or epoetin alfa with periodic dose evaluation/titration. Transfusion was allowed at any time if it was deemed a medical necessity by the Investigator. The incidence rate of transfusion was calculated based on Hb level categorized as: <8.0, 8 to <10, and ≥10 g/dL. Data were evaluated for the on-treatment period + 28 days after the last dose of study drug.

Results: In the overall pooled population of patients with DD-CKD, roxadustat vs. epoetin alfa reduced the risk for transfusion by 18% (HR, 0.82 [95% CI: 0.68, 1.00]; *p*=0.0461). When patient-exposure data were stratified by achieved Hb level, the risk for transfusion increased as Hb levels decreased (Table). The incidence rate of transfusion increased approximately 5-fold in patients with Hb <10 g/dL vs. those with Hb ≥10 g/dL.

Conclusions: In US-based patients with DD-CKD and anemia treated with roxadustat, the risk for transfusion was approximately 5 times higher in patients with Hb <10 g/dL vs. those with Hb ≥10 g/dL, regardless of treatment arm.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: Incidence rate of transfusion (events/100 PEY) based on Hb level and treatment group

	Roxadustat (n=874)				Epoetin alfa (n=879)			
Hb (g/dL)	Events	PEY	Transfusion Rate*	% of PEY	Events	PEY	Transfusion Rate*	% of PEY
≥10.0	72	1166.9	6.2	79.0	134	1208.8	11.1	69.3
8.0 to <10.0	93	298.1	32.3	19.5	160	507.8	31.5	29.1
<8.0	51	22.4	227.7	1.5	57	28.2	202.1	1.6
Total	216	1477.4	14.6	100.0	351	1744.9	20.1	100.0

*Number of events per 100 PEY; Hb, hemoglobin; PEY, patient-exposure years

PO0269

A Phase 3, Multicenter, Randomized, Open-Label, Active Comparator Conversion Study of Roxadustat in Non-Dialysis-Dependent (NDD) Patients with Anemia in CKD

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Background: Roxadustat is an orally active hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of anemia in CKD. Efficacy and long-term safety of roxadustat was assessed, following conversion from darbepoetin alfa (DA), recombinant human erythropoietin (rHuEPO), or epoetin beta pegol (EBP) to roxadustat, in NDD-CKD patients (pts) with anemia. Noninferiority of roxadustat efficacy against DA was evaluated.

Methods: This study enrolled adult Japanese NDD-CKD pts receiving DA, rHuEPO, or EBP for ≥8 weeks before prescreening. Patients who had used rHuEPO or DA were randomized to receive roxadustat or DA (comparative group [CG]). EBP-using pts were allocated to receive roxadustat (referential group [RG]). The primary endpoint was change in average hemoglobin (Hb) from baseline (BL) at Weeks 18-24. Roxadustat efficacy was confirmed if the 95% CI of average Hb at Weeks 18-24 was within 10-12 g/dL; noninferiority of roxadustat to DA was confirmed if the lower limit of the 95% CI of the difference between roxadustat and DA (CGs) was above -0.75 g/dL. Treatment-emergent adverse events (TEAEs) were assessed.

Results: A total of 262 pts were randomized to CGs and received ≥1 dose of roxadustat (n=131) or DA (n=131); 70 pts were allocated to RG and received ≥1 dose. The mean (95% CI) of average Hb at Weeks 18-24 in roxadustat (CG) was 11.14 (11.01, 11.27) g/dL, confirming the efficacy of roxadustat. The difference between roxadustat and DA (CGs) in the change in average Hb from BL at Weeks 18-24 was -0.07 g/dL (95% CI: -0.23, 0.10), confirming noninferiority of roxadustat to DA. The incidence of TEAEs observed during the 24-week treatment period was 78.6% in roxadustat (CG), 70.2% in DA (CG), and 77.1% in roxadustat (RG). Common TEAEs included nasopharyngitis, CKD, hyperkalemia, and hypertension; rates of these were comparable between groups.

Conclusions: This study confirmed the efficacy of roxadustat after conversion from DA, rHuEPO, or EBP, as well as its noninferiority to DA, in NDD-CKD pts with anemia. The safety profile of roxadustat was consistent with previous reports. A final analysis of this study (including 52-week data) will be presented at the congress.

Funding: Commercial Support - Astellas Pharma, Inc.

PO0270

HIF Prolyl Hydroxylase Inhibitor Improves Exercise Endurance and Hardly Affects Instantaneous Force in Mice

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Background: Erythropoietin (EPO) and hypoxia-inducible factor (HIF) stabilizers (PH inhibitors) are efficient therapeutic modalities against anemia in CKD. Compared to EPO and EPO receptor system, extra-renal action of PH inhibitors has still not been fully investigated. Previous reports caution us about the actual misuse of PH inhibitors in doped athletes, but nonhematopoietic effects of PH inhibitors on skeletal muscles remain controversial. Metabolic shift from oxidative phosphorylation toward glycolysis in myotubes *in vitro* was previously reported. Direct pharmacological effects of PH inhibitors on skeletal muscles and exercise performance were assessed *in vivo*.

Methods: Roxadustat, one of PH inhibitors, was administered via oral gavage to 8-week-old C57BL6 mice. Plasma EPO levels and HIF-targeted gene expression were

analyzed after a single administration. Exercise ability was also assessed by treadmill exhaustion test, forelimb grip test, and electric-pulse-induced isometric plantar flexion torque measurement after a single dose or chronic 5-week treatment, in addition to which muscle weight and muscle fiber-type were also measured.

Results: Even a single administration of roxadustat increased plasma EPO levels and gene expression downstream of HIF in skeletal muscles. Mice treated with the agent for 5 weeks showed higher blood hemoglobin levels and improved exercise endurance in treadmill exhaustion test, while the treatment provided comparable results in isometric plantar flexion torque measurement. Although PH inhibitor treatment induced fast-to-slow muscle fiber-type conversion which seem beneficial to exercise endurance, better running performance with increased hemoglobin level was blunted with forced hemodilution alone.

Conclusions: Treatment with a PH inhibitor, roxadustat, improves exercise endurance principally via pharmacological hematopoietic effect and hardly affects instantaneous force in mice although it also affects skeletal myocytes at molecular levels.

PO0271

Temporal Trends in Anemia Management and Major Clinical Outcomes in Incident Dialysis Patients in Canada

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Background: Several jurisdictions have adopted a more conservative approach to anemia in patients receiving dialysis amid safety concerns from target hemoglobin trials. Outside of the US, it is unknown if this has contributed to a change in outcomes. In this retrospective national cohort study, we sought to examine the association between the era of anemia management and major clinical outcomes in incident dialysis patients in Canada.

Methods: The Canadian Organ Replacement Register was used to identify 35,945 adult patients who initiated hemodialysis or peritoneal dialysis from Jan 1 2007 to Dec 31 2015. Time at risk started on day 90 of dialysis and continued for a minimum of 12 months to capture outcomes via data linkage with hospital discharge diagnoses. Patients were categorized into 3 time periods anchored to landmark target hemoglobin trials and publication of anemia guidelines: Era 1 (Jan 2007-Dec 2009); Era 2 (Jan 2010-Dec 2012); Era 3 (Jan 2013-Dec 2015). Cox proportional hazards regression models were used to investigate the association between era and the primary composite outcome (acute myocardial infarction (AMI), stroke or mortality).

Results: The mean hemoglobin at dialysis initiation decreased from 102.9g/L in 2007 to 95.5g/L in 2015, corresponding with a doubling in the prevalence of hemoglobin <80g/L (8% to 17%) and a reduction in ESA use (49% to 44%). A total of 11,810 events were observed during 66,844 person years of follow-up. After multivariable adjustment, Era 3 was associated with an 8% relative risk reduction in the primary outcome compared to Era 1 (hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.88-0.96), driven by a reduction in all-cause mortality (HR 0.90, 95% CI 0.85-0.94) without a reduction in AMI or stroke. In a model without era, neither hemoglobin nor ESA use was an independent predictor of mortality.

Conclusions: There have been modest declines in average hemoglobin values and ESA use among incident dialysis patients in Canada. Unlike the US, there has been no temporal reduction in stroke. Patient survival has improved over time, likely for reasons other than anemia management. An increasing number of patients are starting dialysis with a hemoglobin <80g/L, which represents a substantial shift in practice and merits further investigation in terms of patient-centered outcomes.

PO0272

Reported Caregiver Burden in CKD with and Without Anemia: A US-Based Survey

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Background: Chronic kidney disease (CKD) has a far-reaching impact that extends beyond the affected patients. An online survey was conducted to explore caregiver burden in providing care for an adult with CKD, with or without anemia.

Methods: The survey was administered in January-February 2020 to adult participants recruited from the American Association of Kidney Patients (AAKP) and a third-party recruiter, Dynata. Eligible participants provided care to an adult with CKD within the last 4 weeks. The 15-20 minute survey included questions related to caregiver and patient demographics, clinical characteristics, preferences on anemia treatment, caregiver quality of life (Burden Scale for Family Caregivers [BSFC-S]), and work productivity (Work Productivity Activity Impairment: Caregiver). Outcomes were summarized descriptively for caregivers of patients with anemia (A+) and without anemia (A-).

Results: Among 258 caregivers who completed the survey, 42.6% cared for a patient with anemia (A+; non-dialysis dependent [NDD], 38.2%; dialysis dependent [DD], 61.8%) and 57.4% cared for a patient without anemia (A-; NDD, 45.9%; DD, 54.1%). Nearly 90% identified themselves as the primary caregiver; ≥60% were aged 35 to 64 years and >70% were female. Comorbidities reported most frequently by caregivers included anxiety (A+, 43.6%; A-, 32.4%), depression (A+, 36.4%; A-, 30.4%), headache (A+, 35.5%; A-, 31.8%), and sleep disturbance (A+, 30.9%; A-, 31.1%). Most caregivers reported a high burden (BSFC-S≥15: A+, 69.1%; A-, 58.8%) and work impairment (absenteeism: A+, 19.0%; A-, 14.8%; presenteeism: A+, 37.9%; A-, 33.2%). In the A+ group, >75% of caregivers described anemia as being moderate or severe, and >90% of patients had received anemia treatment in the past month (oral iron, 45.5%; intravenous iron, 33.6%; erythropoiesis-stimulating agents, 22.7%; red blood cell transfusion, 20.9%). If a patient was to initiate a new anemia treatment, 46.4% of caregivers would prefer an oral agent, of which 41.2% prefer a once daily formulation.

Conclusions: There is substantial burden experienced by caregivers of patients with CKD, especially when anemia is present. Further studies are needed to better understand its full extent and explore support strategies for caregivers.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc. & Akebia Therapeutics, Inc.

PO0273

Understanding Treatment of Severe Anemia due to CKD: A Descriptive Study in Non-Dialysis Medicare Advantage Prescription Drug Plan Patients

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Background: Chronic kidney disease (CKD) is more common in people over 65 years (38%) than in people aged 45–64 (13%) or 18–44 (7%). Anemia, a common sequela in CKD patients, affects 8-53% and is more prevalent as CKD progresses. These patients are also at greater risk for hospitalizations and emergency department (ED) visits. The objective of this study was to examine patient characteristics, treatment rates, and time to treatment among Medicare Advantage Prescription Drug Plan (MAPD) patients with CKD Stage 3-5 and severe anemia (defined as lab of Hgb <10 g/dL) within a non-dialysis dependent (NDD) cohort.

Methods: This retrospective cohort study of CKD patients with anemia used Humana claims data (medical, pharmacy, lab) from 2016-2019. The index date was the first anemia diagnosis (Hgb <10 g/dL) date after CKD diagnosis. CKD stage and dialysis independent status were classified in the 12 months pre-index. Treatments [(intravenous (IV) iron, oral iron, erythropoiesis-stimulating agents (ESA), red blood cell transfusions (RBCT)] and all-cause healthcare resource use (HCRU) were examined 12 months post-index.

Results: A total of 31,026 NDD CKD patients with anemia were identified (mean age, 75 years; 60% female). Overall, 36% had an anemia treatment. As the CKD progressed, the percentages of treated patients increased (32%, 39%, and 50% in stage 3, 4, and 5, respectively), ESA use increased (7%, 17%, and 34%), as did IV iron use (11%, 15%, and 21%). RBCT rates (9%) and oral iron use (~13%) stayed consistent across all stages. The median number of days from anemia diagnosis to first anemia treatment was 48 days. As CKD advanced, HCRU increased; in NDD patients with anemia, inpatient admissions in stage 3, 4, and 5, respectively were 46%, 53%, 59% and emergency visits were 64%, 70%, 72% in the 12 months post-index period.

Conclusions: This descriptive examination of treatment by CKD stage for NDD patients with anemia found that anemia was oftentimes left untreated, especially in the stage 3-4 CKD patients. After NDD CKD patients were diagnosed with anemia, it was almost 1.5 months before treatment was initiated. In NDD CKD patients with anemia, as stage increased, HCRU increased, highlighting the importance of care coordination as CKD progresses.

Funding: Commercial Support - Astra Zeneca

PO0274

Cost and Healthcare Resource Use in Patients with Anemia in CKD Using Linked US Claims and Electronic Health Records

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Background: Anemia is a routinely occurring complication in patients with chronic kidney disease (CKD), but current data regarding its economic impact are lacking. This study described direct costs and healthcare resource utilization in non-dialysis CKD patients with and without baseline anemia in real-world practice.

Methods: This retrospective analysis of the integrated Limited Claims and Electronic Health Record (IBM Health, Armonk, NY) spanned Jan 1, 2012 to Sept 30, 2018. Patients were aged ≥18 years with ≥2 eGFR measures <60 mL/min/1.73 m^2 ≥90 days apart. Anemia was defined as any hemoglobin (Hb) value <10 g/dL observed within 6 months of confirmatory eGFR (baseline period). Total and site-specific costs and selected healthcare resource utilization were analyzed and stratified by presence of baseline anemia, Hb range, CKD stage, sex, and insurance type.

Results: Of 22,720 patients, 23% (n=5283) had baseline anemia, 77% (17,437) did not; females accounted for 60% and 56% of the patients, mean ages (± SD) were 70 (14) and 70 (12) years, and median follow-up times were 2.9 and 3.8 years, respectively. Baseline anemia prevalence by CKD stage was 18% (stage 3a), 25% (3b), 41% (4), and 73% (5). Median per patient total costs were $49012 and $31667, total hospitalization costs were $33479 and $22695, and total ER costs were $2232 and $1891, respectively. Median annual number of transfusions doubled (2 vs 1) and annual transfusion cost was 50% greater in patients with vs without baseline anemia, respectively. Slightly increased

costs were associated with male sex and were markedly increased by advancing CKD stage (>3a), baseline Hb <10, and supplemental Medicare and non-capitated insurance coverage.

Conclusions: Anemia is associated with substantially added direct cost and healthcare resource utilization experienced by patients with non-dialysis CKD, in both early and advanced stages and with lower Hb. Effective management of anemia in CKD offers an opportunity to address this ongoing burden.

Funding: Commercial Support - AstraZeneca

PO0275

Modelling the Clinical and Economic Burden of Anaemia in Patients with CKD

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Background: Chronic Kidney Disease (CKD) imposes a significant societal burden. Anemia is a common complication of CKD and is independently associated with poorer patient outcomes, including CKD progression, cardiovascular (CV) events and death. The objective of this study was to develop a natural history model to characterize the consequences of anemia in patients with CKD.

Methods: A lifetime Markov model was developed to estimate the economic impact of anemia. Two cohorts aged 58 years with CKD stage 3b were modelled with and without anemia (Hb 9-10 g/dL and Hb > 12 g/dL) to estimate differences in life expectancy (LE) and quality adjusted life years (QALYs), and event incidence. Hb level was linked to CKD progression, CV hospitalization and mortality using published data. Published direct costs and utility estimates associated with CKD and event incidence were incorporated, and costs were inflated to 2019 US dollars. Costs associated with anemia treatment such as erythropoiesis-stimulating agents or supplemental iron were not considered. Future costs and benefits were discounted at 3.0% per annum.

Results: Predicted LE was 10.21 years in patients with anemia compared to 12.36 years in patients without anemia, or a reduction of 2.15 years. Decreased patient LE and reduced quality of life with anemia resulted in 2.18 fewer QALYs. Time to end stage renal disease was 10.4 years with anemia and 12.5 years without anemia. Patients with anemia experienced 25 additional CV-related hospitalizations per 1,000 patients. Total lifetime costs were higher in the non-anemic cohort due to improved LE ($342,867 vs. $316,510), however, annual costs were lower with an undiscounted saving of $2,628 per year due to reduced CV event incidence and CKD management costs.

Conclusions: This analysis supports that those without anemia have increased LE and QALYs, and account for less costs to the healthcare system. Therefore, anemia management, aligned with clinical guidelines, has the potential for better outcomes for both the patient and the healthcare system.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc. & Akebia Therapeutics, Inc.

PO0276

Prevalence of Severe Anemia and Transfusion Risk in Medicare and Non-Medicare Populations with CKD Stages 3 and 4

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Background: While 30 million people in the United States have chronic kidney disease (CKD), the real-world clinical burden of anemia in non-dialysis dependent (NDD) CKD patients is poorly documented, which we seek to address.

Methods: A retrospective cohort analysis was conducted using the 100% sample of Medicare Fee-For-Service (FFS) beneficiaries (parts A/B/D) and a convenience sample of Commercial (Com), Medicare Advantage (MA), and Managed Medicaid (MM) lives from Inovalon's Medical Outcomes Research for Effectiveness and Economics (MORE^2) Registry® linked to eGFR and hemoglobin (Hgb) values from Prognos laboratory data. Patients with ≥2 consecutive eGFR tests with eGFR 15-59 mL/min/1.73m^2 (≥90 days apart) between 1/1/2016 to 12/31/2018 were retained for analysis; patients on maintenance dialysis were excluded. Severe anemia was defined as Hgb<10 g/dL, measured within 90 days of index eGFR. Red blood cell transfusion (RBCT) during a 12-month follow up was identified using procedure codes. A logistic regression model identified baseline factors associated with receiving RBCT.

Results: A total of 1,305,354 patients were identified from Medicare FFS and 154,163 from MORE^2. Prevalence of severe anemia in the Medicare FFS cohort was 3.1% and 3.3% in the MORE^2 cohort (Table 1). Severe anemia was highest among stage 4 CKD patients at 11.3% in the FFS cohort and 13.4% in MORE^2 cohort, with prevalence among MM patients at 17.1%. Hgb value, cancer, diabetes, liver disease, and hospitalizations were risk factors for RBCT. Within the MORE^2 cohort, the odds of receiving RBCT increased by 47% for each 1 g/dL decrease in hemoglobin.

Conclusions: The proportion of severe anemia increases with worsening CKD stage in NDD patients primarily enrolled in Medicare FFS. Many clinical factors influence the odds of severely anemic NDD CKD patients receiving RBCT.

Funding: Commercial Support - AstraZeneca

Prevalence of Severe Anemia by Payer and CKD Stage

	Medicare FFS Cohort	Total MORE2 Cohort	Commercial	Medicare Advantage	Managed Medicaid
Patients, N	1,305,354	154,163	35,697	83,707	34,759
Prevalence of Severe Anemia, N (% of total)	40,783 (3.1)	5,033 (3.3)	930 (2.6)	2,421 (2.9)	1,682 (4.8)
Severe Anemia by Stage, N (% within payer and stage)					
3a	15,830 (1.8)	2,361 (2.1)	419 (1.5)	1171 (1.9)	771 (3.1)
3b	14,069 (4.1)	1,501 (4.7)	272 (4.6)	739 (4.0)	490 (6.5)
4	10,884 (11.3)	1,171 (13.4)	239 (13.5)	511 (11.3)	421 (17.1)

PO0277

Association of Anemia with Activities of Daily Living in CKD: The National Health and Nutrition Examination Survey (NHANES), 1999-2016

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Background: Anemia is a major contributor to clinical burden and may negatively impact patient outcomes in chronic kidney disease (CKD). We assessed the impact of anemia on activities of daily living (ADLs) among participants with CKD in the US population.

Methods: A cross-sectional study (n=33,300; aged ≥20 years) using NHANES data (1999-2016) was conducted. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. Participants were classified as no CKD, CKD stage 1-2, and CKD stage 3-5 using KDIGO criteria. Anemia was defined using WHO criteria. ADL impairment was defined as "some difficulty" or worse in ≥1 activity (19 items).

Results: Mean age of participants was 46.7 years; 51.0% were female. The percentage of participants with no CKD, CKD stage 1-2, and CKD stage 3-5 was 86.4%, 7.6%, and 6.0%, respectively. Anemia prevalence in each CKD category was 4.9%, 8.7%, and 18.6%, respectively. Multivariable-adjusted prevalence of impairment in ≥1 ADL, by CKD and anemia status, is presented along with covariates in the **Table**. Compared to participants with no anemia, the adjusted prevalence ratio for impairment in ≥1 ADL was 1.06 (95%CI: 0.98-1.14; p=0.13) in no CKD, 1.14 (0.99-1.28; p=0.06) in CKD stage 1-2, and 1.20 (1.05-1.35; p=0.01) in CKD stage 3-5.

Conclusions: In a large representative sample of US adults, anemia was significantly associated with an increased prevalence of impaired ADLs in subjects who are CKD stage 3-5. The clinical implications of this association should be investigated further.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc. & Akebia Therapeutics, Inc.

Adjusted prevalence (95%CI) of impairment in ≥1 ADL, by CKD and anemia category

	No CKD	CKD stage 1-2	CKD stage 3-5
No anemia	30.9 (24.3, 37.5)	32.7 (26.4, 39.1)	33.5 (27.0, 40.0)
Anemia	32.7 (25.8, 39.6)	37.3 (29.9, 44.7)	40.2 (32.9, 47.4)
p-value	0.13	0.06	0.01

Table reports percentages.

Marginally-adjusted prevalence derived using logistic regression models (age, sex, race, education, marital status, income, health insurance, employment, smoking, alcohol use, congestive heart failure, coronary heart disease, angina pectoris, heart attack, stroke, arthritis, chronic obstructive pulmonary disease, body mass index, hypertension, diabetes, and hyperlipidemia).

P-values compare anemia vs. no anemia.

PO0278

Clinical Outcomes in Patients with Anemia in CKD Using Linked US Claims and Electronic Health Records

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Background: Anemia is common in pts with CKD, yet contemporary outcome data to understand the long-term clinical burden are scarce. This analysis describes selected cardiovascular and renal outcomes in non-dialysis CKD pts with and without anemia at baseline (BL) in US real-world practice.

Methods: This retrospective observational study evaluated the integrated Limited Claims and Electronic Health Record data (IBM Health, Armonk, NY). Pts were aged ≥18 y with ≥2 eGFR measures <60 mL/min/1.73 m^2 ≥90 days apart. Anemia was defined as the presence of any observed Hb <10 g/dL within ± 6 months of confirmatory eGFR (anemia BL period). In addition, the BL period for disease history was defined as the start of pt data + 6 months, and for lab measures and medications was defined as date of the second confirmatory eGFR + 6 months. Pts with active bleeding, chronic dialysis, and iron deficiency anemia were excluded. BL pt characteristics and clinical outcomes during follow-up were analyzed for the period from Jan 1, 2012 to Sep 30, 2017. Descriptive data were summarized; no inferential statistics were performed.

Results: Of the total study cohort (N=22,720), 23% (n=5283) had BL Hb <10 g/dL. The following results are for pts with and without anemia at BL, respectively. Females accounted for 60% and 57% and mean ages (± SD) were 70 (14) and 71 (12) y. Proportions by BL CKD stage were: 3a, 50% and 68%; 3b, 27% and 24%; 4, 15% and 7%; 5, 9% and 1%. Median follow-up times were 2.9 and 3.8 y. Acute coronary syndrome (ACS) events during follow-up occurred in 2.2% of pts with BL anemia and 2.3% of pts without BL anemia, heart failure hospitalizations (hHF) occurred in 5.9% and 3.7%, and stroke hospitalizations and emergency visits (S) occurred in 2.8% and 3.0% of pts. Incidence rates rates/100 pt-y were 0.8 and 0.7 for ACS, 1.6 and 0.8 for hHF, respectively, and 0.7 in both groups for S. ESRD occurred in 4% and 1%, 40% eGFR decrease in 44% and 25%, and CKD stage progression in 67% and 59% of pts. Median change in eGFR slope was –0.6 and –0.3 mL/min/1.73 m^2.

Conclusions: This analysis highlights worsened outcomes associated with anemia in CKD, particularly hHF and eGFR decline, in pts of a large US cohort.

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PO0279

Prevalence of Anemia and Associated Erythropoiesis-Stimulating Agent Use in 5.9 Million Non-Dialysis CKD Patients

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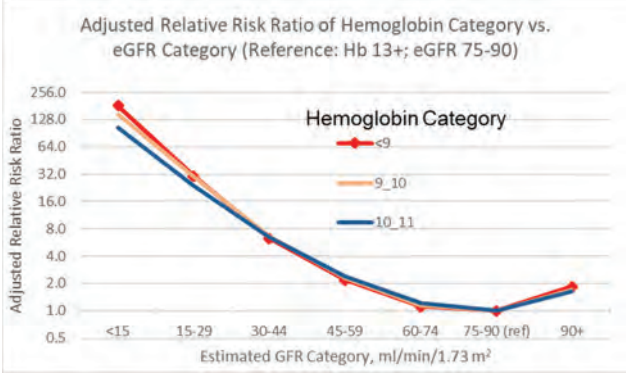
Background: Chronic kidney disease (CKD) leads to anemia through erythropoietin deficiency and resistance, and a heightened inflammatory state. Characterizing the burden and factors associated with severe anemia (hemoglobin < 10 g/dL) is of particular interest since treatment with erythropoiesis-stimulating agents (ESAs) or other therapies is often considered at this level.

Methods: We analyzed patients in the OptumLabs® Data Warehouse, which contains de-identified claims and electronic health record data, with a complete blood count and serum creatinine measured within 30 days of each other in 2016. Patients requiring dialysis were excluded. We examined the association between low hemoglobin (Hb) categories (<9 g/dL, 9-10 g/dL, 10-11 g/dL) and age, sex, diabetes, history of cardiovascular disease (CVD), and categories of eGFR using polychotomous logistic regression to estimate adjusted relative risk ratios (RRR).

Results: Among 5,875,383 patients in 52 centers, mean age was 56 years (SD 17), and 42% were male. The prevalence of Hb <10 g/dL in CKD stages G1-2, G3a, G3b, G4 and G5 was 2.0%, 4.2%, 9.2%, 20.3% and 36.1%, respectively. Lower eGFR categories were strongly associated with increased risk of anemia, even after adjustment for female sex (RRR 2.6-3.9), diabetes (RRR 1.4-1.8), history of CVD (RRR 1.7-1.9), and age (RRR 2.2-2.4 for age 75+). The frequency of ESA use in patients with hemoglobin <10 g/dL was 0.24%, 0.41%. 0.96%, and 1.0% in CKD stage G3a, 3b, 4 and 5.

Conclusions: Severe anemia was common and strongly associated with low GFR, female sex, older age, diabetes and history of CVD in a wide range of health care systems. ESA use in non-dialysis CKD patients was very uncommon.

Funding: Private Foundation Support



PO0280

Lower Transferrin Saturation (TSAT) Index Is Associated with an Anemia-Independent Risk of Increased Mortality in Non-Dialysis (ND) CKD Patients

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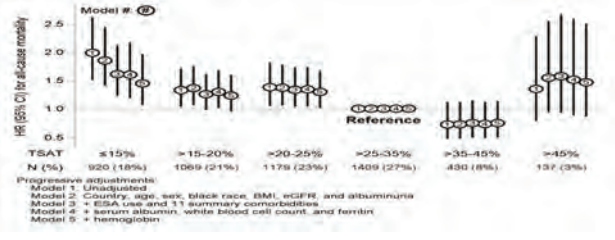
Background: Iron Deficiency (ID), defined by a TSAT index <20 %, is present in approximately half of ND-CKD patients, varying little by CKD stage. Distinct from approaches in conditions such as heart failure, the importance of iron reserves and the basis for iron therapy in CKD has focused primarily on supporting effective erythropoiesis. A comprehensive approach and design to estimate the impact of ID, independently from hemoglobin (Hb) levels, on mortality risk has not been explored in ND-CKD until the present.

Methods: 5144 patients from Brazil (N=294), France (N=2227), the US (N=494), and Germany (N=2129) enrolled in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) from 2013-2019 with available TSAT were included in the analysis. We categorized patients by first available TSAT at enrollment. Hb measurements at same time as TSAT were used. Cox models were used to estimate hazard ratios (HR) of TSAT on mortality, censored at start of dialysis or kidney transplantation. Models were progressively adjusted for confounders, including demographics, comorbidities, inflammation surrogates, treatment with erythropoietin stimulating-agents and Hb.

Results: Sample characteristics were: 59% male; 45% diabetes; and mean (SD) age 69 (13) years, eGFR 28 (11) mL/min, Hb 12 (2) g/dL, TSAT 24 (2) %, ferritin 196 (214) ng/dL. TSAT levels below 25% were progressively associated with higher mortality risk, while patients with TSAT greater than 45% tended to have higher risks for mortality (Figure).

Conclusions: ID, as measured by the TSAT index, is associated with higher risk of all-cause mortality in ND-CKD patients, even after extensive adjustments for clinical, demographic and biochemical confounders, including Hb levels. Interventional studies evaluating the impact of iron supplementation and alternative targets on clinical outcomes in ND-CKD patients are needed to better inform ID management strategies.

Funding: Commercial Support - Vifor Pharma



PO0281

Lower Transferrin Saturation (TSAT) Is Associated with Worse Health-Related Quality of Life (HRQOL) in Non-Dialysis CKD (NDD-CKD) Patients Independently from Hemoglobin (Hb) Levels

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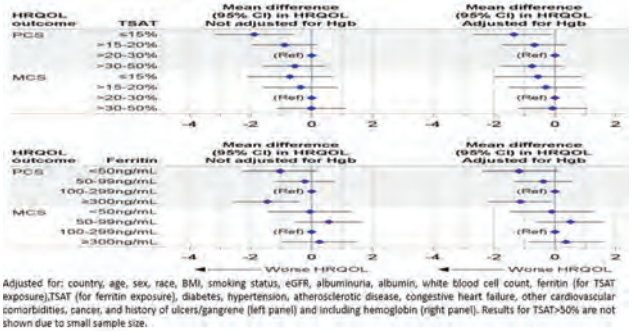
Background: Iron Deficiency (ID) is a common condition in NDD-CKD patients that is associated with poorer outcomes. However, the effect of ID on HRQOL in this population is unknown. We analyzed real world data from a multinational cohort of ND-CKD stage 3 to 5 patients to test the association between TSAT and ferritin with HRQOL.

Methods: Patients from Brazil (N=205), France (N=2015), and the US (N=293) in the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps, 2013 to 2019) with TSAT, ferritin, and HRQOL data were included. We grouped patients according to TSAT and ferritin levels closest to the HRQOL measurement. Our primary analyses evaluated the associations of TSAT and ferritin with mean differences in physical component summary (PCS) and mental component summary (MCS). Secondary analyses evaluated joint TSAT and ferritin categories, as well as additional pre-specified HRQOL measures. Linear mixed models were adjusted for potential confounders including Hb level.

Results: 2513 patients were included. In the primary analyses, TSAT ≤15% and both ferritin <50 ng/mL and ≥300 ng/mL were associated with worse PCS scores, while MCS was not directionally associated with iron parameters (Figure). Patients with the composite TSAT ≤15%/ferritin ≥300 ng/mL had lower functionality scores and worse PCS, compared to those with TSAT between 20-30% and ferritin 50-299 ng/mL. Adjustment for Hb only slightly attenuated the effects, and the results were similar for subgroups of patients with Hb <11.5 vs ≥ 11.5 g/dL.

Conclusions: Low TSAT levels, and both low and high ferritin levels, are associated with poorer physical HRQOL in ND-CKD patients, even after adjustment or stratification by Hb level. Intervention studies of iron therapy on HRQOL among ND-CKD individuals are needed to confirm these findings.

Funding: Commercial Support - Vifor Pharma



PO0282

Predicting the Optimal Approach to IV Iron: Understanding the Requirements to Attain and Maintain Target Haemoglobin in Non-Haemodialysis CKD

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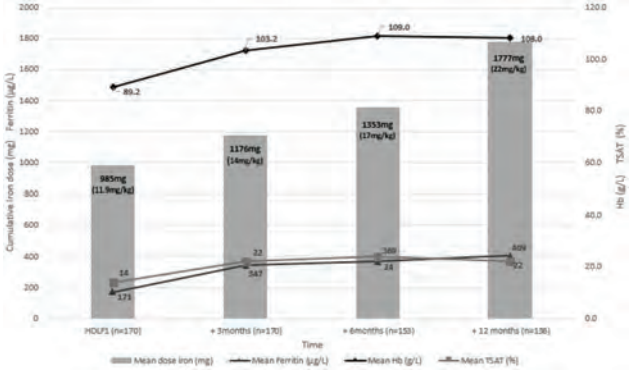
Background: The UK Renal Association recommends a High-dose Low-frequency (HDLF) approach to IV iron management for non-haemodialysis (non-HD) CKD. HDLF is defined as at least 500mg per infusion with a maximum of two infusions. Reducing the frequency of repeat infusion benefits healthcare resource & patient acceptance. This study retrospectively examined IV iron strategies used to attain & maintain effective treatment response. These data may predict a future dosing strategy that is more likely to meet iron requirements in a single, or at least a minimum number of infusions.

Methods: This retrospective analysis of 170 non-HD patients examined a 12 month Hb response to a single infusion of iron isomaltoside (HDLF1); max permissible 20mg/kg/infusion. The cumulative amount of iron to attain and maintain a target Hb >100g/L was determined.

Results: Of the 170 patients 111 (65%) attained a Hb target of 100g/L with a mean single infusion dose (HDLF1) of 985mg (equating to 11.9mg/kg); the mean time to Hb target was 91 days. Repeat doses were defined as either HDLF (>500mg) or LDHF (Low dose - High frequency). Where a 2nd dose was given the mean dose for the two approaches was 946mg for HDLF and 200mg for LDHF. The number with at least 1 additional infusion given by 3, 6 & 12 months were: for HDLF n=26, 56, & 113, & for LDHF n=24, 43 & 70.

Conclusions: These data suggest that the majority of patients with a Hb <100g/L who are treated with a 12mg/kg HDLF approach to IV iron will require repeated infusions within 12 months. The maximum permissible dose in a single infusion varies by product label. In this UK study the maximum single infusion dose of 20mg/kg meant that the mean cumulative iron requirements at 3 & 6 months could have been achieved in one infusion. At 12 months this threshold was exceeded. This gives an insight into how future approaches to iron dosing could be considered.

Funding: Commercial Support - Pharmacosmos



PO0283

A Novel, Fast-Acting Iron Sucrose Formulation for CKD Patients with Iron Deficiency Anemia

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Background: Intravenous (IV) iron is commonly used to treat iron deficiency anemia in patients with chronic kidney disease (CKD). We report the results of the physicochemical and safety profile of RBT-3, a novel iron sucrose formulation, which was assessed in a Phase 1b study conducted in healthy volunteers and subjects with chronic kidney disease (CKD) Stage 3 or 4.

Methods: Analytical testing was conducted to examine the physicochemical profile of RBT-3. Safety of RBT-3 was assessed in a Phase 1b study in healthy volunteers and subjects with CKD. RBT-3 was administered IV as a single dose of 120, 240, or 360 mg. Plasma and urine ferritin were measured at baseline, then 2 h (plasma) or 24 h (urine) through 168 h post-treatment to assess clinical response.

Results: RBT-3 particle size is similar to commercially available iron sucrose. However, RBT-3 has a lower molecular weight and higher water content than similar IV iron formulations, suggesting faster uptake and greater solubility, respectively. RBT-3 also has a negative Zeta potential, demonstrating low cytotoxic potential. The quantity of labile iron in RBT-3 is 1.48%, suggesting very low availability of free inorganic iron hydroxide, with a low cytotoxic potential. Furthermore, Fe2+, which is associated with oxidative stress, is present in much lower quantities in RBT-3 (3.4%) compared to commercially available iron sucrose (15.8%). In this Phase 1b study of RBT-3, 18 subjects were enrolled; 6 subjects (3 healthy volunteers and 3 subjects with CKD) randomized to 3 cohorts received a single dose of RBT-3 at 120, 240, or 360 mg. Mean age was 60.3 years; 66.7% of the subjects were female. Dose-dependent increases in plasma ferritin were observed in all subjects within 2 h of treatment and reached statistical significance by 8-12 h. Urine levels were increased at 24 h. Both plasma and urine ferritin levels remained elevated through 168 h (7 days). No treatment-related adverse events (AEs) were observed, and no serious AEs (SAEs) were reported.

Conclusions: RBT-3 represents a novel iron sucrose formulation with desirable physicochemical characteristics that makes it a fast-acting mediator of iron hemodynamics. This is the first report of ferritin level increases within only 2 h by an iron formulation. RBT-3 is safe and well tolerated in healthy volunteers and subjects with CKD at a single dose up to 360 mg.

Funding: Commercial Support - Renibus Therapeutics

PO0284

Response to Oral Iron Therapy in Children with Anemia of CKD

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Background: Anemia is a common complication of chronic kidney disease (CKD). Current guidelines recommend oral iron therapy as the initial treatment of anemia in CKD. However, the efficacy of iron therapy in children with pre-dialysis CKD has not been evaluated. Factors determining the response to oral iron in pediatric CKD remain poorly understood.

Methods: An ongoing retrospective observational study. Data were abstracted from health records of children with pre-dialysis CKD at the time of iron therapy initiation and at the next clinic visit and compared using paired T-test. Children receiving erythropoiesis-stimulating agents were excluded. Response to iron therapy was defined as improvement in both hemoglobin and hematocrit after iron therapy. Changes of serum iron were used as a surrogate measure of adherence to iron therapy. Data are presented as median (interquartile range).

Results: We identified 44 children (48% boys) who met the inclusion criteria. Median age was 11 (5-15) years, glomerular filtration rate (GFR) 46 (31-60) mL/min/1.73m^2. Ferrous sulfate was used in 86.4% of children. The interval between visits was 61 (31-120) days. Iron therapy resulted in a significant increase in transferrin saturation (14 to 21%, p<0.001) and serum iron (45 to 65 µg/dL, p<0.001). While there was an overall improvement of hemoglobin (from 10.6 to 11.2 g/dL, p=0.02), 45% of children did not respond to iron therapy. Non-responders had a significantly smaller change in serum iron after iron therapy compared to responders (3 vs. 35 µg/dL, p=0.03), likely indicating low adherence to iron therapy by non-responders. Baseline age, GFR, hemoglobin, transferrin saturation, serum iron, and serum ferritin were not different between responders and nonresponders. Baseline body weight and height Z scores were significantly lower in non-responders than in responders (-0.67 vs. 0.12, p=0.04 and -1.66 vs. -0.25, p=0.02, respectively), possibly representing differences in nutritional status.

Conclusions: This is the first study that systematically assesses response to oral iron therapy in children with pre-dialysis CKD after 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Response to iron therapy may be related to medication adherence and baseline nutritional characteristics of study participants.

PO0285

Improving Knowledge of Nephrologists Regarding an Emerging Class to Treat Anemia Associated with CKD

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Background: As emerging therapies hold promise to improve treatment of anemia in patients with CKD, clinicians need to understand mechanisms of action in order to understand the potential place in therapy when available. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologist related to emerging Hypoxia-Inducible Factor Prolyl Hyproxylase Inhibitors (HIF-PHIs).

Methods: The effect of 2 online, 30-minute, CME-certified activities were analyzed. Multiple-choice knowledge and self-efficacy confidence questions were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and chi-square test (5% significance level, P <.05) assessed educational effect. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activity launched June 20, 2019 and data were collected through July 11, 2019.

Results: In total, 167 nephrologists were included in the study. Overall improvements were seen for both activities after participation: Activity 1: N=75, P<.001, V=.156; Activity 2: N=93, P<.001, V=.162 Individual question-level improvement was also demonstrated: 21% of nephrologists (N=75, *P*<.05; V=.169) improved at correctly identifying the mechanism of action of HIF-PHIs 20% of nephrologists (N=75, *P*<.05; V=.197) improved at recognizing clinical trial data for HIF-PHIs 33% of nephrologists (N=92, *P*<.05; V=.315) improved at recognizing clinical trial data for HIF-PHIs 21% of nephrologists (N=93, *P*<.05; V=.103) improved at recognizing CVOTs for HIF-PHIs 45% (N=75) and 47% (N=92) reported increased confidence in understanding HIF PHI clinical trial data Continued educational gaps: 55% (activity 2) and 59% (activity 1) of nephrologists did not recognize the mechanism of action of emerging HIF-PHIs 46% of nephrologists did not recognize clinical trial data for emerging HIF-PHIs 62% of nephrologists did not recognize CVOT data for emerging HIF-PHIs

Conclusions: This study demonstrates the success of online, video-based CME on improving knowledge of nephrologists related to emerging treatments for anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca ad Fibrogen

PO0286

Online CME Successful at Improving Nephrologist Understanding of Emerging Class to Treat Anemia Associated with CKD

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Background: As emerging therapies hold promise to improve treatment of anemia in patients with CKD, clinicians need to understand mechanisms of action in order to understand the potential place in therapy when available. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologist related to emerging Hypoxia-Inducible Factor Prolyl Hyproxylase Inhibitors (HIF-PHIs).

Methods: The effect of an online, CME-certified, roundtable video discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and McNemar's chi-squared test (5% significance level, P <.05) assessed educational effect. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activity launched June 27, 2019 and data were collected through August 27, 2019.

Results: In total, 62 nephrologists answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation in both CME activities: 24% of nephrologists (*P*<.05; V=.216) improved at correctly identifying the mechanism of action of HIF-PHIs 11% of nephrologists (*P*=.72; V=.032) demonstrated improvement at selecting the recommended use of erythropoiesis stimulating agents (ESAs) in the treatment of anemia 21% of nephrologists (*P*<.05; V=.181) improved at recognizing clinical trial data of HIF-PHIs 47% reported increased confidence in understanding of HIF stabilizers in the treatment of anemia in patients with CKD Continued educational gaps: 52% of nephrologists did not recognize the mechanism of action of emerging HIF-PHIs 47% of nephrologists did not recognize the role of ESAs in the treatment of anemia 31% of nephrologists did not recognize clinical trial data for emerging HIF-PHIs

Conclusions: This study demonstrates the success of online, video-based roundtable discussion on improving knowledge of nephrologists related to emerging treatments for anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - independent educational grant from AstraZeneca and Fibrogen

PO0287

Treatment Pathways of Non-Dialysis-Dependent CKD Patients with Anemia: A Report from the DISCOVER CKD Retrospective Cohort

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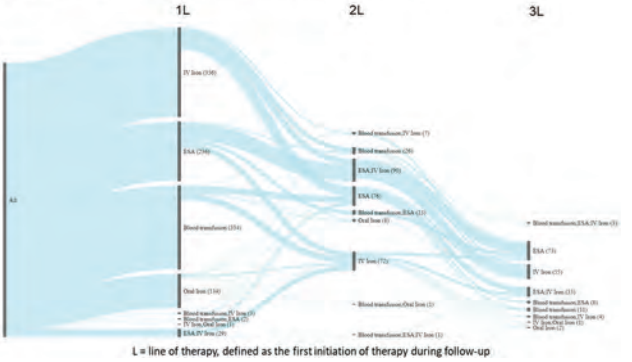
Background: Anemia is a frequent complication of chronic kidney disease (CKD), yet most patients experiencing this problem remain untreated until the initiation of renal replacement therapy. We describe treatment pathways of key medications prescribed to non-dialysis dependent (NDD) CKD patients with anemia in DISCOVER CKD.

Methods: Patients included in this analysis were extracted from the Limited Claims and EHR (LCED) data. The study cohort included patients aged >18 years with 2 estimate glomerular filtration rate (eGFR) measures <60 mL/min/1.73m2 >90 days apart between January 2008 and September 2018. The index date was the first Hb measure (<12 g/dL [females], <13 g/dL [males] per WHO criteria), or an anemia therapy (iron, ESA or blood transfusion) prescription after the 2nd eGFR measure. Exclusion criteria were: <1-year registration/medical history prior to index, active bleeding in the 30 days preceding and inclusive of index, an Hb value (only) within 30 days from transfusion or bleeding and no Hb measure within a year after CKD diagnosis. Oral iron was incompletely captured in LCED. Sankey Plots were used to visualize chronological treatment pathways (1st to 3rd line) post-index of key treatments commonly prescribed to CKD patients with anemia including: oral iron, IV Iron, ESA and blood transfusion.

Results: Preliminarily, 1446 (2.6% of anemia base cohort) patients were prescribed anemia therapies during follow-up, with IV iron (32.5%), transfusions (30.5%), ESA (21.6%), oral iron (12.2%) and ESA+IV Iron (2.7%) used as 1st-line therapies, Figure 1. Median times to 1st-line therapy initiation after index were: 108 days for oral iron, 194 days for ESA, 197 days for IV iron, and 244 days for blood transfusion.

Conclusions: In routine clinical care, anemia in NDD CKD is under treated and rescue therapies are used for anemia more often than preventive therapies.

Figure 1 – treatment pathways of key treatment in patients with NDD CKD anemia.



L = line of therapy, defined as the first initiation of therapy during follow-up

PO0288

Physician Attitudes Toward Diagnosis, Treatment Initiation, and Unmet Needs in the Management of Anemia due to CKD: Results from a Real-World Survey in Germany, Italy, and the United Kingdom

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Background: Anemia, a complication of chronic kidney disease (CKD), is often defined as serum hemoglobin (Hb) levels of <12 g/dL in women and <13 g/dL in men. Traditionally, primary care physicians (PCPs) have less involvement managing and treating patients with anemia due to CKD while nephrologists play a greater role in treatment decisions. We describe current physician perceptions towards the diagnosis and treatment of anemia due to CKD and unmet needs in anemia management, in a real-world setting.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme, a point-in-time study conducted between November 2019 and April 2020 with nephrologists and PCPs from Germany, Italy and the United Kingdom. Physicians completed an online survey providing information on their demographics, opinions on the diagnosis and treatment of anemia, and the current unmet needs they believe exist in the management and treatment of anemia. Results were descriptively analyzed.

Results: A total of 200 physicians (n=140 nephrologists; n=60 PCPs) were included in the analysis. Among those who responded, the majority (98% nephrologists; 80% PCPs) used Hb levels to diagnose anemia in CKD patients. Over two thirds of physicians mentioned using ferritin to diagnose anemia and over half reported using transferrin saturation (TSAT) levels. Approximately 4 in 5 nephrologists and PCPs (78%

nephrologists; 81% PCPs) reported Hb levels to be the most important factor that triggers initiation of anemia treatment in CKD patients. The top unmet needs in the management and treatment of CKD anemia reported by both nephrologists and PCPs were treatment for refractory/resistant patients (37% nephrologists; 40% PCPs) and the need for more oral treatments (31% nephrologists; 37% PCPs).

Conclusions: These data reinforce that Hb levels, ahead of ferritin and TSAT levels, have an important role in the diagnosis and initial prescription of therapy for anemia in CKD patients. It also highlights an unmet need for treatment of refractory/resistant patients and the desire among nephrologists and PCPs for more alternative modes of administration to treat anemia due to CKD.

Funding: Commercial Support - Otsuka

PO0289

Patient Preferences Study for Treatments of Anemia in CKD Patients Not on Dialysis (NDD)

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Background: Erythropoietin analogues (EAs) are a mainstay of treatment of anemia in adult patients with CKD but they are associated with increased risk of cardiovascular (CV) events. Furthermore, their mode of administration (intravenous or subcutaneous [SC]) may represent a barrier to some patients. As such, the aim of this study was to understand patients' valuation of attributes associated with CKD anemia treatments.

Methods: Adult (≥18 years) patients from UK, Spain, Germany, and France, who had self-reported NDD CKD anemia and were being treated with EAs, participated in this online discrete choice experiment (DCE). Patients were presented with choice tasks, each with two anemia treatment options described in terms of five attributes (mode of administration, need for iron supplementation, risk of gastrointestinal [GI] side effects, risk of major CV events, and impact on energy levels). A multinomial logit model with an error component was used to analyze participants' choices and estimate their treatment preferences. Estimated preferences were used to determine maximum level of CV and GI risk that patients were willing to tolerate to improve other treatment features.

Results: Between November 2019 and March 2020, 200 eligible patients (53% male) completed the DCE survey. The mean (SD) age was 53.78 (12.73) years; patients had been diagnosed with CKD 6.02 (7.49) years prior, and with CKD anemia 3.45 (3.44) years prior. Patients were found, on average, to value each of the five attributes associated with the treatments of CKD anemia. Patients were willing to tolerate a 5.12% (95% CI: 1.99; 8.25) increase in the risk of a major CV event and an 11.73% (95% CI: 4.96; 18.50) increase in the risk of GI side effects to switch from an at-home SC injection administered once every 2 weeks to an at-home oral pill administered three times a week. Patients would be willing to tolerate a 20.31% increase in the risk of GI side effects and an 8.86% increase in the risk of a major CV event to move from sometimes having a lot of energy to always having a lot of energy.

Conclusions: Patients would be willing to tolerate increased risks of CV and GI events to obtain an oral treatment for NDD CKD anemia and to always have a lot of energy.

Funding: Commercial Support - Astellas Pharma, Inc.

PO0290

Success of CME/CE in Promoting Performance Improvements Related to Iron Deficiency Anemia Management in Women

Amy Larkin, Kelly L. Hanley. *Medscape LLC, New York, NY.*

Background: We studied the effect of online education designed to improve the clinical performance of clinicians in the OB/Gyn and primary care setting related to iron deficiency anemia (IDA) management in women.

Methods: The continuing medical education (CME) activity was a 45-minute online text- and video-based activity focusing of different aspects of anemia management in the women's health setting. The impact of the education on performance outcomes was measured with a follow-up Planned Change Assessment® (PCA) survey immediately post-education to assess planned changes in clinician practice. Survey participants were contacted 8 weeks later to assess self-reported actual changes in practice.

Results: In total, 1,239 clinicians completed the initial PCA questionnaire 275 OB/Gyn physicians, 142 OB/Gyn NPs and PAs, 446 PCPs, and 376 NP/PA in the primary care setting Of those, 1,171 (95%) indicated they planned to make changes 3,610 changes were planned, an average of 3.1 per completer Of immediate PCA completers, 92 completed the follow-up PCA 89 completers (97%) made 331 changes in practice, an average of 3.7 changes per completer Most common changes in practice: better screening for new mothers and those with abnormal uterine bleeding for anemia, consideration of IV iron in various cases, and improved counseling of patients related to causes and symptoms of IDA.

Conclusions: The outcomes gathered in this assessment provide compelling evidence that participation in an online CME activity can be successful at prompting changes in practice, and in this case prompted clinicians in the OB/Gyn and primary care setting to provide better care for women with or at risk for IDA.

Funding: Commercial Support - American Regent

PO0291

Amelioration of CKD-Associated Anemia by Vadadustat in Mice Is Not Dependent on Erythroferrone

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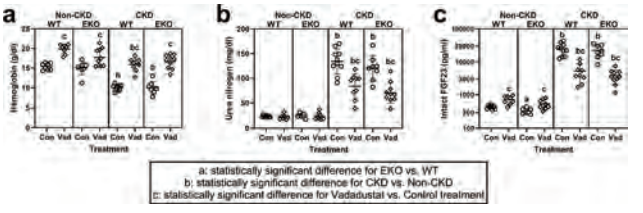
Background: Vadadustat is an investigational hypoxia inducible factor prolyl hydroxylase inhibitor that increases endogenous erythropoietin (EPO) production, and has been shown to decrease hepcidin levels, improve iron status, and increase hemoglobin concentrations in anemic chronic kidney disease (CKD) patients. Increased EPO induces erythroblast secretion of erythroferrone (ERFE), which acts on the liver to suppress serum hepcidin production. To determine whether vadadustat mechanisms of action are dependent on ERFE, we treated wild type (WT) and ERFE knockout (EKO) mice, with and without adenine diet-induced CKD, with vadadustat.

Methods: 6-week-old male C57BL/6 WT and EKO mice were placed on 8-week diets that did or did not contain 0.2% adenine. For the last 3 weeks of the diets, the mice were treated with vadadustat (75 mg/kg/day via oral gavage) or vehicle solution. Mice were euthanized at 14 weeks of age (n=8 mice per group).

Results: Unlike the WT mice, EKO mice had undetectable spleen *Erfe* mRNA, minimal marrow *Erfe* mRNA, and no increase in ERFE mRNA or protein in response to vadadustat. However, in both WT and EKO CKD models, vadadustat normalized hemoglobin concentrations (**Fig 1a**), increased expression of duodenal iron transporters, tended to lower serum hepcidin, and decreased tissue iron concentrations (consistent with increased iron mobilization), suggesting ERFE-independent pro-erythropoietic effects. Vadadustat treatment was also associated with improved kidney function (**Fig 1b**) and decreased expression of renal fibrosis markers. Lastly, vadadustat affected FGF23 profiles: In non-CKD mice, vadadustat increased plasma total FGF23 out of proportion to intact FGF23, consistent with the known effects of HIF1α and EPO on FGF23 production and metabolism. However, in the CKD mice, vadadustat markedly decreased both total and intact FGF23 (**Fig 1c**), effects likely contributed to by improved kidney function.

Conclusions: Vadadustat ameliorates CKD-associated anemia independently of ERFE, and also improves kidney function and lowers FGF23 in this CKD model. How vadadustat affects CKD progression in humans may warrant future studies.

Funding: Commercial Support - Akebia Therapeutics, Inc.



PO0292

Oxidative Stress and Heme Metabolism in Red Blood Cells of Hemodialysis Patients

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Background: We have previously described that indoxyl sulfate promotes red blood cells (RBC) ROS generation through organic anion transporter 2 as well as NADPH oxidase activity-dependent and GSH-independent mechanisms (Dias et al., 2018). However, there is little information regarding pathways of antioxidant balance to protect RBC from extensive oxidative stress that occurs during hemodialysis (HD). Intracellular free heme is degraded by Heme Oxygenase 1 (HO-1), which is regarded as the major cytoprotective enzyme (Maines, 1988; Gozzelino et al., 2010). In the current study, we assessed HO-1 activity and ROS production in RBC from healthy subjects and hemodialysis (HD) patients before and after HD.

Methods: Blood was drawn from 6 healthy individuals (CON-RBC) and 6 HD patients (HD-RBC) before (pre/HD-RBC) and after high flux HD (post/HD-RBC). Isolated RBC were stained with DCFH-DA (Abcam) for ROS measurements. To quantify HO-1, RBC were incubated with anti-HO-1 antibody (Abcam) and m-IgGκ BP-CFL 488 (Santa Cruz Biotechnology) as a secondary antibody. Samples were analyzed by flow cytometry.

Results: Our results show a 4-fold increase in ROS levels in pre/HD-RBC compared to CON-RBC. ROS levels were even further increased by 1.65-fold after HD treatment in post/HD-RBC (Figure 1). Both pre/HD-RBC and post/HD-RBC showed a similarly significant increase of 3.3-fold in HO-1 compared to CON-RBC. (Figure 1).

Conclusions: High levels of HO-1 may represent a defense against oxidative stress that occurs in ESKD and particularly during the HD session. Further research is needed to evaluate whether HO-1 overexpression could accelerate heme degradation and contribute to renal anemia.

Funding: Private Foundation Support, Government Support - Non-U.S.

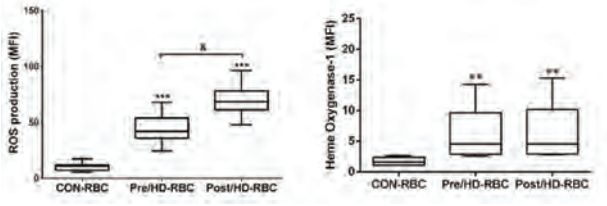

Figure 1. Reactive oxygen species (ROS) and Heme Oxygenase-1 levels in red blood cells (RBC) from healthy individuals (CON-RBC) and patients pre (Pre/HD-RBC) and post (Post/HD-RBC) hemodialysis. Data are shown as median and interquartile range of the Mean Fluorescence Intensity (MFI). ***p<0.001 and **p<0.01 represent the difference compared to CON-RBC. &p<0.001 represents the difference between pre- and post/HD-RBC.

PO0293

Daprodustat Interaction with Phosphate Binders Has Minimal Impact on Hemoglobin Values in Hemodialysis Population

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Background: Daprodustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (PHI) in phase 3 development for the treatment of anemia of chronic kidney disease. Phosphate binders (PB) are widely prescribed for patients on hemodialysis (HD) to control hyperphosphatemia. PB may interfere with medication absorption; thus, coadministration with a PHI may potentially impact the latter's efficacy on hemoglobin (Hgb). The purpose of this analysis was to determine whether administration of daprodustat in subjects receiving PB has an impact on Hgb values in the HD population.

Methods: The 24-week GSK PHI113633 study (NCT01977482) included 216 subjects on maintenance HD previously treated with recombinant human erythropoietin (*Clin Kidney J 2019;12:139–148*). Target Hgb range was 10.0 g/dL to 11.5 g/dL. Baseline PB users were defined as a prespecified study subgroup. The difference in mean Hgb values at Week 24 between treatment groups was summarized overall and by subgroup. Comparisons were performed for the Week 24 Hgb (post hoc), as well as the final dose of daprodustat, for those receiving/not receiving PB.

Results: The majority of HD subjects received PB at baseline; 136/177 (77%) of daprodustat and 33/39 (85%) of control subjects were taking PB, with comparable phosphate control at baseline (mean [±SD] phosphate: daprodustat 1.76 mmol/L [0.56]; control 1.67 mmol/L [0.44]]). All subjects receiving PB at baseline, except two, continued them throughout the study. No meaningful difference in Hgb change from baseline (CFB) at Week 24 was noted between treatment groups. The final median dose for subjects on daprodustat was the same for those receiving and those not receiving PB (6 mg), with no meaningful difference in the Hgb at Week 24 (mean [±SD]: PB use=Yes 10.40 g/dL [0.95]; PB use=No 10.79 g/dL [0.95]).

Conclusions: These results suggest that PB use does not have a major impact on Hgb values during the 24-week study. Results of an ongoing, phase 3 dialysis study of daprodustat compared with conventional treatment are awaited to confirm these initial observations.

Funding: Commercial Support - GlaxoSmithKline

Group	Mean (±SD) baseline Hgb (g/dL) for daprodustat vs control	Mean (95% CI) difference in CFB Hgb (g/dL) at Week 24
Overall population	10.39 (0.66) vs. 10.55 (0.94)	-0.12 (-0.51, 0.27)
Baseline PB use = Yes	10.38 (0.62) vs. 10.48 (0.73)	-0.21 (-0.63, 0.21)
Baseline PB use = No	10.43 (0.77) vs. 10.94 (1.76)	0.25 (-0.72, 1.23)

PO0294

Prevalence and Severity of Anemia Between Non-Dialysis and Dialysis Outpatients Referred to Nephrology Consultation: Epidemiologic Data from 1568 Mexican Patients at a National Reference Hospital

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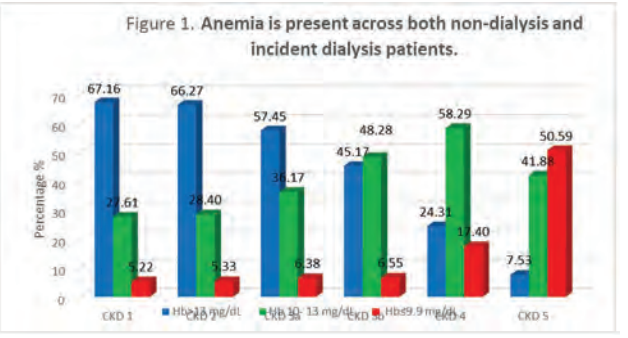
Background: Anemia is a frequent complication in chronic kidney disease (CKD), and is frequently associated with symptoms such as physical disability, decreased neurocognitive function, and poor quality of life. Our objective is to know the prevalence and severity of anemia between stages of CKD in patients who attended a nephrology clinic for the first time.

Methods: Transversal, descriptive, observational study. Records of adult patients who attended an outpatient nephrology clinic in the period from February 2019 to February 2020 were included. Anemia staging was performed according to the world health organization. Descriptive statistics were performed, with a 95% CI and a p-value ≤0.05.

Results: 1568 patient records were included. Mean age was 56.01 ± 16 years and 51% (804) were women. Distribution of patients by CKD stage: 9% stage 1, 11% stage 2, 12% stage 3a, 18% stage 3b, 23% stage 4, and 27% stage 5. 12% were undergoing renal replacement therapy. 53% of the population had anemia at the cut-off point of Hb<13 for men and <12 for women; stratification of anemia severity between stages of CKD is presented in figure 1. The main comorbidities and risk factors in the subjects with anemia were type 2 diabetes mellitus and hypertension (55%), proteinuria (38%), hypoalbuminemia (34%), hyperkalemia (37%) overweight or obesity (58%), hyperglycemia (45%) hypertriglyceridemia (35%) and hypercholesterolemia (31%).

Conclusions: In patients who attended for the first time an outpatient nephrology clinic, a high prevalence of anemia was found in CKD patients, being more frequent and more severe from stage 3b to stage 5. Identifying these findings will allow establishing public health policies and models of care for patients with CKD.

Funding: Commercial Support - AstraZeneca



PO0295

Hemoglobin Requirements of Clinical Trials Involving Anemia in CKD and Implications on Future Work: A Systematic Literature Review

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Background: Anemia is a common complication in patients with chronic kidney disease (CKD), contributing to reduced quality of life and increased risk of morbidity and mortality. Erythropoiesis-stimulating agents (ESAs) are the established standard of care for anemia management in CKD patients. This review examines hemoglobin (Hb) requirements in randomized controlled trials (RCTs) of ESAs as treatment of anemia in CKD.

Methods: Embase, Medline, and Cochrane Library were searched from 1946 to November 2019 for RCTs evaluating the safety and efficacy of ESAs as treatment for adults with anemia and CKD. Descriptive analyses were performed to assess between-trial differences with respect to baseline Hb and Hb target ranges. Studies were classified by dialysis status (non-dialysis-dependent [NDD] vs dialysis-dependent [DD] vs renal transplant recipient [RTR]), and by treatment goal (correction vs conversion).

Results: Searches retrieved 3,482 records, from which 57 trials met the inclusion criteria. Thirty-seven studies reported a Hb target, including 15 correction studies (NDD, 11; DD, 3; RTR, 1), 19 conversion studies (NDD, 2; DD, 16; RTR, 1) and 3 that were mixed/unclear (DD, 2; NDD/DD, 1). The unweighted medians (range) of the mean baseline Hb in correction and conversion studies were 10.1 g/dL (7.0-11.7) and 11.2 g/dL (9.8-12.1), respectively. There were 20 different Hb target ranges used to assess efficacy; 10-12 g/dL was utilized most often (n=8). Three of 37 RCTs used a singular Hb target threshold, whilst the remaining studies used a Hb target range, which varied from narrow (0.5 g/dL) to wide (5.0 g/dL) between the lower and upper limits. Target Hb ranges used an upper limit of >12 g/dL in 21/37 RCTs (correction, 11/15; conversion, 10/19); however, only 3/21 RCTs were published after 2012 (the last update of KDIGO Clinical Practice Guideline).

Conclusions: This systematic review shows that changing Hb requirements over time are a source of difference in RCTs of ESAs for treatment of anemia in CKD. Such differences may introduce bias when using quantitative synthesis methods (e.g. network meta-analysis) to assess the comparative efficacy and safety of ESAs relative to new treatment options.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc. & Akebia Therapeutics, Inc.

PO0296

Excessive Decrease of Hematocrit After Discontinuation of Dapagliflozin

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Background: Recently, sodium-glucose cotransporter 2 (SGLT-2) inhibitors were indicated to have hematopoietic effect, but it is still unclear how long the effect continues after discontinuation. In this study, we investigated changes in hematocrit, urinary gravity and HbA1c after discontinuation of SGLT-2 inhibitor in patients with type 2 diabetes.

Methods: A total of 8 patients (male: n=4, age: 54.4±11.9 [mean±SD] years, BMI: 27.1±3.4 kg/m², HbA1c: 9.2±1.2 %) with type 2 diabetes who were newly administered 5mg per day of dapagliflozin from March 2015 to September 2019 and discontinued the drug due to adverse events or side effects which did not require admission were retrospectively identified. Changes in HbA1c, hematocrit and urine specific gravity levels between before the administration and after the discontinuation of the drugs were evaluated.

Results: The drug was discontinued 8.4±6.6 months after administration due to non-benefit on glycemic control (n=4), polyuria (n=2), weight loss (n=1) and genital infection (n=1). HbA1c was not changed (-0.3±1.1 %; p=0.45) whereas urine specific gravity (0.014±0.009 g/mL; p<0.001) and hematocrit (1.63±1.99 %; p=0.04) were significantly increased at the time of discontinuation. Urine specific gravity (0.005±0.009 g/mL; p=0.12) and hematocrit (0.15±2.14 %; p=0.84) levels were returned to the levels of before drug administration 60 days after the discontinuation. After the 120 days of discontinuation, hematocrit was still continued to decrease below the level of baseline (-1.29±1.70 %; p=0.05) whereas urine specific gravity was not.

Conclusions: Our data demonstrate that the increased urine specific gravity and hematocrit return to original levels within 60 days after the discontinuation of dapagliflozin, and that hematocrit may continue to decrease below the original level even after.

PO0297

Human Mesenchymal Stem Cells Cultured in a Hollow Fiber Bioreactor Maintain Constant Levels of Exosomes in the Perfusion Medium: Relevance to the Simultaneous Production of Two Biotherapeutic Agents

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Background: We have shown that the administration of allogeneic Mesenchymal Stem Cells (MSC) to patients at high risk for Acute Kidney Injury (AKI) following on-pump cardiac surgery prevents AKI and progression to Chronic Kidney Disease (CKD). Treatment of rats with severe, progressive IRI AKI with MSC-derived exosomes affords significant survival benefits and rescues their renal function (see abstract this meeting). The current study examined the possibility to simultaneously collect MSC-derived exosomes while culturing human MSCs, both used for various therapies in renal and other diseases. This approach, if successful, would be cost saving, efficient and facilitate up-scaling of the production of both MSCs and their exosomes.

Methods: Human MSCs (20x10e6) were loaded into a hollow fiber Cell Expansion System (Quantum®, TERUMOBct; pre-conditioned for cell adhesion with Fibronectin) and expanded using αMEM with 5% human Platelet Lysate (hPL). The number of exosomes in aliquots of the perfusion medium were monitored (NanoSight instrument) throughout the course of cell expansion.

Results: MSCs reached ~ 90% confluence within 12 days, yielding 500x10e6 MSCs. The number of exosomes/nanoparticles derived from the 5% hPL per se was 4±1x10e11/mL. Post seeding of MSCs in the bioreactor, exosome numbers in the perfusate decreased and stabilized at 1-1.5x10e11/mL. The size of collected exosomes was between 60 and 100 nm.

Conclusions: The data from this pilot study demonstrate that hPL-derived exosomes or nanoparticles are taken up by the expanding MSCs, which lowers their total number in the perfusion medium. However, exsome numbers stabilized during the subsequent cell expansion, indicating that growing MSCs release high numbers of exosomes. This conclusion will be confirmed by speciating hPL- and MSC-derived exosomes, using specific markers for each type of nanoparticle. Together, these observations show promise for the efficient generation of MSCs and their exosomes to be used for various clinical applications.

Funding: Commercial Support - SymbioCellTech, LLC

PO0298

Clinical Study Results Confirming a Novel Fluorescent Compound Is a Glomerular Filtration Rate (GFR) Tracer Agent in Humans

Richard B. Dorshow, Jeng-Jong Shieh, Ivan R. Riley, Thomas E. Rogers. *MediBeacon Inc., Saint Louis, MO.*

Background: A fluorescent GFR tracer agent for use in the clinic would enable a noninvasive transdermal continuous GFR detection method. This would make possible a point-of-care true GFR measurement for an individual, and possibly obviate the use of estimated GFR from ensemble equations. The plasma pharmacokinetics of the novel fluorescent compound MB-102, constructed to have the properties of a GFR tracer agent, is compared to that of iohexol, an established GFR tracer agent.

Methods: Intravenous administration of MB-102 followed immediately by iohexol (Omnipague 300) was given to 120 subjects enrolled with estimated GFR in the range from normal to stage 4 CKD. Fifteen blood draws post-administration over 12 hours were obtained. Plasma was analyzed for both agent concentrations at each time point. Analysis of MB-102 in plasma used methodology developed internally, and analysis of iohexol used the standard multi-step method employing an internal standard, drying, and reconstitution.

Results: Plasma pharmacokinetic parameters, which includes GFR, were determined from the concentration vs. time data for each agent separately using standard pharmacokinetic software. For every subject, each agent exhibited a two-compartment model, the initial compartment being the vascular to tissue equilibrium, and the terminal compartment being the renal excretion only. The terminal compartment yielded a single GFR value and was unperturbed over the approximate 10 hour time span for which the subjects were eating and taking their usual medications. The comparison of GFR from the MB-102 data to that of GFR from the iohexol data is shown in Figure 1.

Conclusions: The correlation of GFR from plasma MB-102 to that of plasma iohexol is excellent (r-squared = 0.99). Thus MB-102 is a fluorescent GFR tracer agent in humans. This result is the first step in the development of a noninvasive transdermal GFR measurement at the point-of-care.

Funding: Commercial Support - MediBeacon Inc.

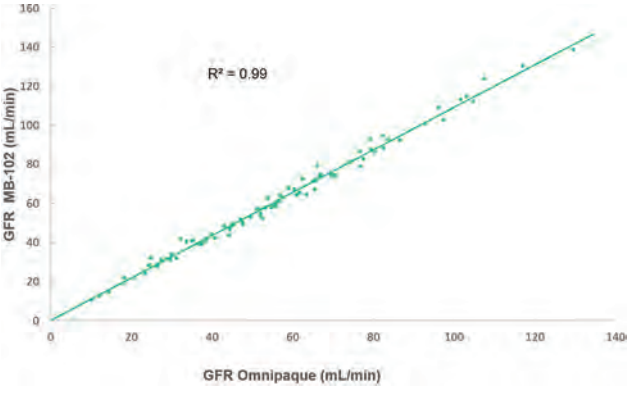

Figure 1: Circles are data, line is a linear regression.

PO0299

Dialysate Exposure Does Not Compromise the Function of Bioengineered Proximal Tubules for Bioartificial Kidney

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Background: Protein-bound uremic toxins (PBUTs) accumulate in plasma of end-stage kidney disease patients and are associated with a wide range of comorbidities. Their removal by conventional hemodialysis is severely limited, warranting the development of novel renal replacement therapies such as the bioartificial kidney (BAK). Recently, we developed bioengineered kidney tubules as functional BAK units capable of active PBUTs secretion via organic anion transporter-1 (OAT1). To accelerate their application, a comprehensive assessment under clinical-like conditions is essential. Here, we assessed the extent to which exposure to dialysate and uremic plasma would affect the viability and function of the kidney tubules.

Methods: Human conditionally immortalized proximal tubule epithelial cells equipped with OAT1 (ciPTEC-OAT1) exposed to medical-grade dialysate (10-240min) were evaluated for metabolic activity, membrane integrity (LDH release), inflammatory response (IL-6 and IL-8), oxidative stress (ROS) and OAT1 function (fluorescein uptake). Further, ciPTECs grown on biofunctionalized hollow fiber membranes were extraluminally exposed to dialysate fluid, intraluminally perfused with human uremic plasma (30min) and assessed for PBUTs clearance (indoxyl sulfate (IS), kynurenic acid (KA), L-kynurenine (L-Kyn), hippuric acid (HA) and indole-3-acetic acid (I3-AA)), determined by LC-MS/MS (n=7). Membrane integrity was evaluated by paracellular FITC-inulin leakage.

Results: Prolonged exposure (240min) of flat monolayers of ciPTEC-OAT1 to dialysate slightly reduced the metabolic activity to 80±4% (p<0.001) and OAT1 function to 81±5% (p<0.001) and an increased LDH release (from 10±2% in controls to 15±3%, p<0.05), without inducing the release of IL-6 or IL-8. After 30min, a 3.4±0.9 fold increase in ROS production was noticed. Still, exposure of ciPTEC-OAT1-containing hollow fiber membranes to dialysate enabled the concomitant clearance of five PBUTs (IS = 2980±1438; KA = 223±120; L-Kyn = 324±100; HA = 6547±1278 and I3-AA = 884±130 nmol/cm², n=6-7), without compromising the membrane integrity as observed by FITC-inulin leakage (20±4 % vs 25±5%).

Conclusions: The demonstrated functionality of bioengineered kidney tubules in PBUT clearance under clinical-like conditions advances the development of a BAK.

Funding: Government Support - Non-U.S.

PO0300

May the (Mechanical) Force Be with You: Modeling Shear Stress on the Glomerulus-On-a-Chip

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Background: In the glomerulus, mechanical forces generated on glomerular endothelial cells (GEC) by the passage of blood in capillaries and by the flow of ultrafiltrate between adjacent podocytes play a critical role in regulating glomerular filtration. In vivo modeling of shear stress is difficult and traditional in vitro 2D systems are unable to faithfully replicate shear and tensile stress. We have recently developed a barrier-free glomerulus-on-a-chip (GOAC) system that closely mimics architecture, physiology and function of the GFB. In this work we have further modeled shear stress on the chip and assessed how changes in mechanical forces affect the barrier formation and function.

Methods: Mathematical modeling of the shear stress on the GOAC was performed and shear stress was calculated for standard GOAC culture conditions. Using model simulations, angle of inclination and rocking frequency of the GOAC were changed to modify shear stress, and results were assessed after 5 days. Phenotypical analysis by IF were performed and function was measured by albumin-leakage assay. Podocytes and GEC were separated by FACS and transcriptomics and proteomics analysis performed.

Results: Under standard culture conditions, time-averaged shear stress generated by rocking the GOAC is equal to 0.1Pa. By changing angle of the rocking platform, shear stress could be modulated from 0 to ~4Pa exerted on the GEC with each rocking motion. Permselectivity was not significantly affected by different rocking angles (but was impaired under static conditions) after 5 days. Importantly, Gene and protein expression analysis on podocytes and GEC have identified important changes in cytoskeleton regulation, ECM-cell interaction, proliferation and transcription factors, suggesting that longer-term modification of the shear stress might significantly impact phenotypical and functional cell activity.

Conclusions: The glomerulus-on-a-chip is an ideal system to model architecture and function of the glomerular filtration barrier, including mechanical forces. Changes in shear stress affect cellular gene and protein expression in the GFB and can have long-term effects on phenotype and function. The glomerulus-on-a-chip system can provide an important in vitro tool to study the role of shear stress in physiological and pathological conditions.

Funding: NIDDK Support, Private Foundation Support

PO0301

Chronic AMPK Activation Reprograms Glucose Metabolism and Oxygen Respiration in Renal Tubule Epithelial Cells

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Background: *In vitro* human renal tubule epithelial cells (HREC) exhibit a glycolytic, dedifferentiated phenotype that limits their use in bioartificial kidney development. We have identified AMP-activated protein kinase (AMPK) and Transforming Growth Factor-β (TGFβ) as critical modulators of HREC differentiation. Here we show that inhibition of TGFβ signaling enhances increased respiration induced by activation of AMPK.

Methods: Primary HREC were seeded on polystyrene tissue culture plates (100,000 cells cm^{-2}). After one week, cells were supplemented with AMPK activator Metformin (200μM), TGFβ receptor I inhibitor SB431542 (10μM), or both. After five weeks, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFe96 Analyzer and respiratory inhibitors oligomycin (2μM), CCCP (2μM), Rotenone (0.5μM), Antimycin A (0.5μM) and 2-deoxyglucose (50mM). Statistical differences were estimated by paired, two-tailed Student's t-test in MatLab.

Results: Metformin and Combination treatments increased cell glycolytic capacity as shown in **Fig 1A**. Metformin and Combination treatments significantly decreased ATP-coupled respiration, while increasing maximal oxidative phosphorylation capacity and non-mitochondrial respiration capacity as shown by elevated OCR following injections of Oligomycin, CCCP, and Rotenone/Antimycin A, respectively, as shown in **Fig 1B**.

Conclusions: Concomitant increases in both glycolytic and oxidative phosphorylation capacity suggest AMPK activation and TGFβ inhibition modulate cell mitochondrial and non-mitochondrial metabolic activity.

Funding: Private Foundation Support

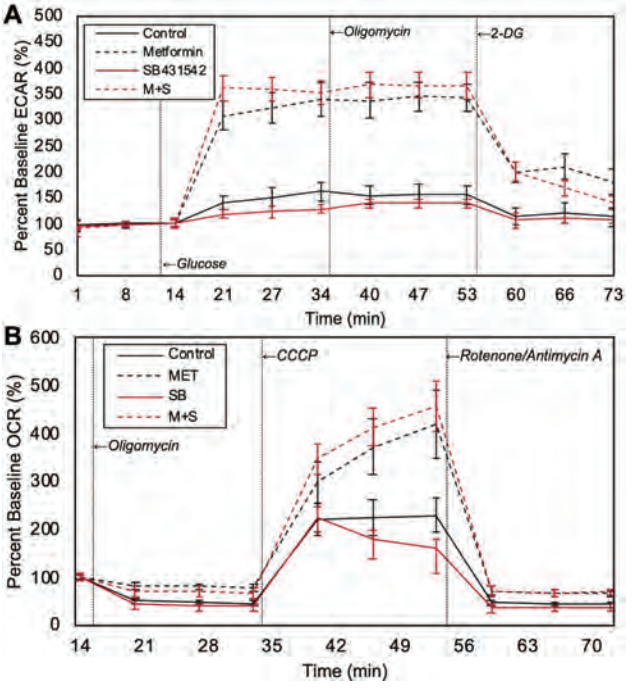

Fig 1 Metformin and SB431542 modulate mitochondrial and non-mitochondrial respiration capacity A. Glycolytic stress test (n=7); **B.** Mitochondrial stress test (n=4). All data are mean ± SD.

PO0302

An In Vitro Model of the Glomerular Filtration Barrier Using Tissue-Derived Glomerular Basement Membrane

Dan Wang, Snehal Sant, Nicholas J. Ferrell. *Vanderbilt University Medical Center, Nashville, TN.*

Background: The glomerular filtration barrier consists of the glomerular basement membrane (GBM), podocytes and endothelial cells that regulate kidney permeability to macromolecules. Damage to podocytes increases albumin permeability, resulting in proteinuria. Interactions between podocytes and the GBM are important for regulating glomerular permeability and are not captured in standard in vitro cell culture systems. This work aims to investigate molecular permeability of the GBM and podocytes using a novel in vitro model that incorporates decellularized GBM.

Methods: GBM substrates were made by pressure compacting decellularized glomeruli from porcine kidneys against a Transwell membrane in a stirred cell. GBM was evaluated by immunofluorescence staining of decellularized glomeruli. Mouse podocytes were plated on the GBM at low and high concentrations. Transepithelial electrical resistance (TEER) was measured before molecular permeability measurements. Podocytes on GBM were imaged by staining with phalloidin and DAPI. Permeability of the GBM with and without podocytes were analyzed by measuring FITC-BSA and FITC-Ficoll diffusion through the filtration barrier.

Results: GBM characterization showed that cells are efficiently removed from the glomeruli, and the GBM retains laminin and collagen IV after decellularization. GBM alone provided a stringent barrier to diffusion of both albumin and Ficoll. Podocytes attached and spread on the GBM to further restricted albumin diffusion. TEER showed an increased resistance of GBM with podocyte compared to GBM alone. Podocytes resulted in slightly lower permeability at high seeding concentration than low concentration.

Conclusions: Interactions between the GBM and podocytes are important for regulating the permeability of the glomerulus. We developed a new in vitro model of the glomerular filtration barrier that incorporates tissue derived GBM to support podocyte culture. GBM alone restricted albumin and Ficoll diffusion and incorporation of podocytes further restricted albumin diffusion. Future work will focus on the co-culture of podocytes and endothelial cells on both sides of the GBM for evaluating the permeability of the filtration barrier and evaluate how podocyte and endothelial injury regulate permeability.

Funding: NIDDK Support, Private Foundation Support

PO0303

Extraction of *Escherichia coli* in Urine by New Static Electricity Technique In Vitro

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Background: The treatment results for sepsis are poor due to infectious diseases, and the mortality rate is over 25%. It is clinically significant that the detection identifies patient specimen primary causative organisms as promptly as possible to give appropriate antimicrobial treatment, and to save patients with serious infectious disease. However, it usually takes 2-3 days from the submission of the sample to the identification of the primary causative organism. We newly developed the device (PixeeMo™ approved by **AOAC® *Performance Tested*℠** Certificate No. **012002** in January 14, 2020.) with quick extraction of bacteria in drinking water by static electricity technique. In this report, we evaluated the ability of PixeeMo™ to extract *E. coli* from urine.

Methods: Samples were prepared by adding Ecoli to artificial urine. 27 mL of a dedicated buffer was added to 3 mL of the sample, and after centrifugation (8000 xg, 20 min), 27 mL of the supernatant was removed. This operation was performed 3 times. After the preparation, E. coli was extracted from each sample using PixeeMo™ less than 0.5 hour. The number of bacteria in the sample prepared on the standard agar medium was measured by colony count.

Results: The table shows results of the experiments. The components of artificial urine and E. coli were separable and the extraction results by PixeeMo were consistent with the culture method. It was also suggested that the detection limit concentration is 10cells / mL.(Table)

Conclusions: The new technique could detect clinical pathological conc. of *E. coli* in short time less than 2.0 hour. Extremely useful possibility is suggested as the new measurement technology of sepsis to reflect a diagnosis and evaluation of treatment, curative effect, very quickly.

Conc. of E.coli in urine	10^3 cells/mL		10^2 cells/mL		10^1 cells/mL	
Measurement item	CNRV [cells/mL]	RC [CFU/mL]	CNRV [cells/mL]	RC [CFU/mL]	CNRV [cells/mL]	RC [CFU/mL]
N=1	1190	1000	110	130	10	10
N=2	1270	1000	160	130	12	11
N=3	1260	1500	140	130	10	11
N=4	1325	1500	230	260	15	11
N=5	1390	1200	270	260	18	11

CNRV:The capture number reduced value = capture number/efficiency ,
RC:Result of culture

PO0304

Kidney Segmentation with Deep Learning in MRI of 40,000 UK Biobank Subjects

Taro Langner,[1] Andreas Östling,[1] Lukas Maldonis,[2] Albin K. Karlsson,[1] Daniel Olmo,[1] Dag Lindgren,[2] Andreas H. Wallin,[2] Lowe Lundin,[2] Robin Strand,[1] Håkan Ahlström,[1,2] Joel Kullberg.[1,2] *[1]Uppsala Universitet, Uppsala, Sweden; [2]Antaros Medical AB, Mölndal, Sweden.*

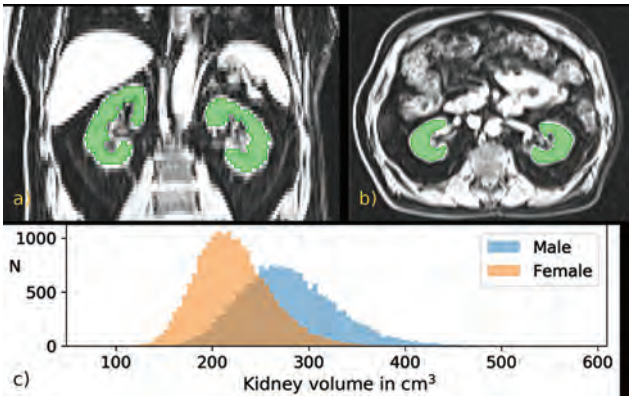
Background: Kidney volume and its association to several demographic and physiological parameters are subject of ongoing research. The UK Biobank (UKB) studies over half a million volunteers, examining blood samples, lifestyle, genetics, and body composition, including medical imaging for 100,000 participants, and 10,000 repeat scans. We have developed a system for automated kidney segmentation in 40,000 currently available MRI scans for image-based measurements of parenchymal kidney volume.

Methods: UKB neck-to-knee body MRI has been released for 40,264 participants (52% women), aged 44-82 (mean 64) years, with BMI 14-62 (mean 27). The kidneys are imaged in two 17s breath-hold stations with a Siemens 1.5T Aera device at (224 x 174 x 44) voxels of (2.23 x 2.23 x 4.5) mm. In this work, three operators marked cortex and medulla, excluding cysts, in 122 subjects (Fig a, b) for training and validation of a 2.5D U-Net with short skip connections. This neural network learned to segment axial slices.

Results: The network predictions matched the references in total kidney volume for a mean error below 4% (or 10 cm^3, Dice score 0.956), whereas human repeat segmentation yielded 3% (or 6 cm^3, Dice score 0.962). While imaging limitations such as motion may compound this error, similar performance is expected for future UKB releases. After 30 minutes of training, the network can process all scans within two days. Exclusion of anomalies, such as 40 cases of renal fusion, left 37,468 subjects with median voxel count volumes of 277 cm^3 for men and 220 cm^3 for women (Fig c).

Conclusions: The proposed system may ultimately provide measurements of left and right kidney volume for all imaged UKB subjects which can be analyzed and shared for further large-scale investigation of associations and longitudinal changes in kidney volume.

Funding: Other NIH Support - The Swedish Heart-Lung Foundation and Swedish Research Council (2016-01040, 2019-04756) supported this work, which used the UKB, application no. 14237., Government Support - Non-U.S.



Segmented kidneys in MRI (a, b) and measured volumes in the entire cohort (c).

PO0305

A Simplified Fluid Dynamics Model of Ultrafiltration

Christopher R. Cardimino,[1] Michael J. Germain,[2] Yossi Chait.[1] *[1]University of Massachusetts Amherst, Amherst, MA; [2]Renal and Transplant Associates of New England, Springfield, MA.*

Background: We recently presented a novel approach for the design of personalized ultrafiltration rate (UFR) profiles during hemodialysis (HD) treatments. The success of this approach depends on an accurate parameter estimation of a simplified fluid volume dynamics during ultrafiltration.

Methods: We used a simplified model derived from a validated fluid volume model during HD comprising intravascular and interstitial pools, microvascular refilling/ filtration, and lymphatic flow. Input data used for parameter estimation are UFR profile and hematocrit (HCT) from CLIC obtained during actual HD treatments. Estimation was based on initial 30-min segment of the data and the model was validated based on the subsequent 30-min response. Model time constant and steady-state gain were obtained for a single patient at 5 treatments over a 3-week period.

Results: Estimation/validation results (Figure 1) demonstrate reasonable accuracy of the simplified fluid dynamics model. Underlying model parameters of a single patient exhibit significant variability between similar days of treatment and between treatment days (Figure 2). Both HCT response to same UFR profile (steady-state gain) and response time (time constant) vary by as much as 100%.

Conclusions: Successful estimation of fluid volume model parameters during HD is feasible which supports the concept of online design of personalized UFR profiles, A non-negligible variability of a patient's model parameters may complicate the design of personalized UFR profiles.

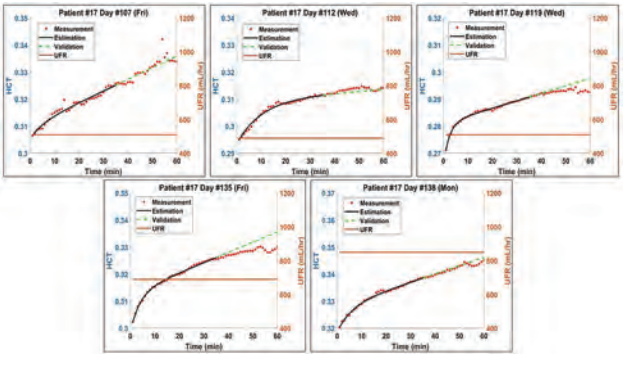


Figure 1

Treatment Day	Time Constant (min)	Steady-State Gain (HCT/(L/min))
107	5.20	0.0563
112	9.97	0.0225
119	2.40	0.0325
135	3.88	0.0329
138	5.78	0.0216

Figure 2

PO0306

Human Amniotic Membrane as a Novel Scaffold for Induced Pluripotent Stem Cell-Derived Kidney Organoids

Maria Figetakis, Kevin J. James, Richard Torres, William G. Chang. *Yale University, New Haven, CT.*

Background: Human inducible pluripotent stem cells (hiPSCs) can be differentiated into kidney organoids that could be used to tissue-engineer functional renal tissue. However, there are several challenges to therapeutic implementation. Among these is how to deliver organoids in a manner that would allow for both vascularization and filtrate outflow. Previous research has demonstrated in animal models, that kidney organoids can be perfused when implanted in the kidney subcapsular space. One limitation though is that there is no obvious filtrate outflow tract. Furthermore, in ESRD patients there would likely be significant fibrosis or even cystic disease that would prevent successful perfusion and filtrate outflow of kidney organoids implanted in a similar manner. Alternative heterotopic organoid implantation strategies should be considered. Examples include, but are not limited to, peritoneal implantation (with peritoneal dialysis catheter drainage) or tissue engineered tubular constructs for ureteral anastomoses. Here we describe a biomaterial, decellularized human amniotic membrane (dhAM), that could be used for differentiation of iPSC derived kidney organoids. Because kidney organoids will be exposed to mechanical forces in heterotopic implant locations, we examine the effects of uniaxial stretch on the structure of kidney organoid tubules.

Methods: We decellularized hAM with mild detergents, and differentiated kidney organoids in a manner previously described by the Little research group. We constructed a titanium stretch device that allowed for kidney organoid differentiation and uniaxial stretch of the dhAM acutely or over 10 days. We performed multiphoton microscopy to image the kidney organoids and then used 3D reconstructions to measure tubular volumes.

Results: We have observed that iPSC-derived kidney organoids can be differentiated on dhAM, and that uniaxial stretch of the dhAM elongates and increases tubular volumes within the kidney organoids, without tubular disruption or increased cell death.

Conclusions: dhAM is a promising scaffold for studying effects of mechanical forces on human kidney organoids *in vitro*. dhAMs could be used to facilitate the implantation of kidney organoids into the peritoneum or other heterotopic locations. The constructs have the flexibility to be used as a patch, modified into tubes after rolling, or form saclike structures.

Funding: Other NIH Support - NIH NIBIB

PO0307

Renal Cell-Derived Extracellular Vesicles Improve Functional Phenotype of Kidney Tubuloids

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Background: Kidney tubuloids (KT) are adult stem cell-derived organoid that hold great potential in therapeutic applications as cell source for bioartificial kidney (BAK). However, reproducing complete cell maturation and function remains a challenge. Extracellular vesicles (EVs) are cell-derived structures that regulate several cellular processes. In the kidney, EVs mediate intranephron communication through the transfer of bioactive molecules. This study aimed to investigate the use of renal EVs as modulator of KT phenotype by increasing the levels of organic anion transport 1 (OAT1), involved in renal waste handling, and explore their use for BAK engineering.

Methods: EVs from conditionally immortalized proximal tubule epithelial cells overexpressing OAT1 (ciPTEC-OAT1) were isolated with 100 K filters, quantified via nanoparticle tracking analysis and incubated with KT. The 24 h conditioned media (CM) of ciPTEC-OAT1, depleted or not of EVs, were used as controls. Gene expression was determined by QPCR and Western blotting. For renal tubule engineering, KT were seeded on hollow fibers and were exposed to EVs or CM. Monolayer integrity and cell polarity were analyzed by immunofluorescence and confocal microscopy.

Results: KT exposed to CM showed increased OAT1 levels (protein: 2.0±0.3-fold and mRNA: 2.8±0.5-fold). Moreover, EVs mimicked CM effects (2.6±0.4-fold), while CM EV depleted didn't induce OAT1. EVs were shown to contain OAT1 protein and mRNA as cargo. Visual observations of KT seeded on hollow fibers with CM containing EVs, presented slightly improvement in 3D tubular structure organization with the expression of tight junction protein (ZO-1) and cell polarity (apical cilia formation and Na^+/K^+-ATPase presence at the basolateral side) when compared with the control condition.

Conclusions: KT phenotype can be directed by renal EVs obtained from ciPTEC-OAT1. In addition, renal EVs can support KT to form tight monolayers on hollow fiber membranes. Further research is aimed at a full functional characterization of these bioengineered proximal tubules for application in BAK. ACKNOWLEDGEMENTS Work supported by Regenerative Medicine Crossing Borders (www.regmedxb.com). Powered by Health~Holland, Top Sector Life Sciences & Health. We acknowledge Prof. Hans Clevers for providing the kidney tubuloids.

Funding: Government Support - Non-U.S.

PO0308

Nitric Oxide (NO) Based Urinary Catheter Balloon Inflation Solution to Prevent Urinary Tract Infection

Alexander S. Yevzlin, Karthik Ramani, Faroug Suliman. *University of Michigan, Ann Arbor, MI.*

Background: UTI is the most common hospital acquired infection with indwelling catheters being a major risk factor and are difficult to treat due to the formation of bacterial biofilms which are resistant to systemic antibiotics. NO is an endogenously formed gas molecule known to play a key role in preventing infection by dispersing biofilm formed by a variety of bacterial strains. In this abstract, we describe the effectiveness of a novel urinary catheter balloon inflation fluid to effectively reduce catheter associated urinary tract infections (CAUTI) by providing up to 7 days of bactericidal effect via NO release.

Methods: Our innovative approach to prevent CAUTI involves employing a balloon inflation fluid using novel NO secreting materials based on using S-nitrosothiol type NO donors like S-nitrosoglutathione (GSNO) within the balloon of urinary catheters that slowly releases NO over a period of up to one week. The advantages of the use of NO in CAUTI prevention is its short half-life with a very low steady-state level immediately adjacent to the surface of the device required to achieve the desired anti-microbial effect with no risk of systemic effects when using NO secreting materials with fluxes that are near physiological levels.

Results: We performed in vitro studies using a Foley catheter placed in a long-necked flask with a shape resembling the urinary bladder and the urethra. (Fig 1) The Foley catheter retention balloon was filled with GSNO solution and the balloon was used to seal the neck of the flask. Then the flask was filled with synthetic urine inoculated with E. coli and incubated for seven days at 37 ^{0}C with horizontal shaking at 80 rpm. The results showed a 7-log reduction in planktonic bacterial growth (Fig 2) and a 3-log reduction in biofilm (Fig 3) of the GSNO Foley balloon solution compared to the control.

Conclusions: These data suggest that NO-based urinary catheter balloon fluid results in significant anti-microbial effects in our in vitro model of CAUTI.

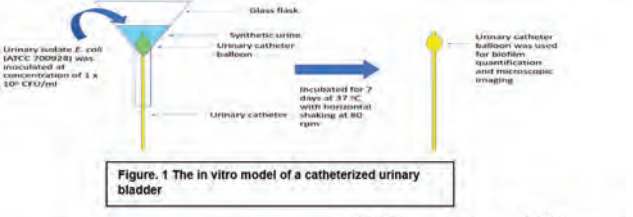

Figure. 1 The in vitro model of a catheterized urinary bladder

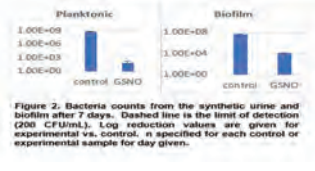

Figure 2. Bacteria counts from the synthetic urine and biofilm after 7 days. Dashed line is the limit of detection (200 CFU/mL). Log reduction values are given for experimental vs. control. n specified for each control or experimental sample for day given.

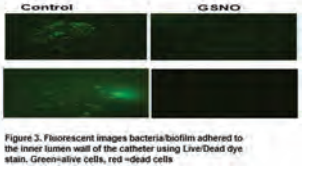

Figure 3. Fluorescent images bacteria/biofilm adhered to the inner lumen wall of the catheter using Live/Dead dye stain. Green=alive cells, red =dead cells

PO0309

Feature-Rich Covalent Stains for Interrogation of Kidney Tissue

Chenyi Mao, Min Yen Lee, Joshua C. Vaughan. *University of Washington, Seattle, WA.*

Background: Fluorescence microscopy is a workhorse tool in biomedical imaging but often poses significant challenge to practitioners in achieving bright or uniform labeling. In addition, while antibodies are effective specific labels, they often suffer poor penetration in thick tissues, loose binding in heavily fixed or processed specimens (e.g., FFPE tissue), high cost, and inconsistent reproducibility or commercial availability. Thus, it would be highly useful to develop a simple yet robust labeling alternative that could rapidly produce even staining for thick tissues and be compatible with a wide range of sample processing or clearing methods.

Methods: We use conventional fluorescent dyes to covalently label abundant chemical functional groups on kidney tissues. These include the use of amine-reactive

dyes for proteins and aldehyde-reactive dyes for carbohydrates. We term this approach Fluorescent Labeling of Abundant Reactive Entities (FLARE).

Results: We first showed FLARE's utilities in freshly fixed mouse kidney tissues (~100 μm) using super-resolution fluorescent microscopy. Within glomeruli, the carbohydrate stain specifically labeled the basement membranes of the capillary loops and the mesangial matrix, while the amine stain outlined cell boundaries and the intricate details of interdigitated podocyte epithelial cells that are a major component of the glomerular filtration barrier (**Fig. A**). In proximal convoluted tubule, the basement membrane was also labeled by the carbohydrate stain, and the amine stain revealed mitochondria and brush border microvilli (**Fig. B**). Then we stained optically cleared FFPE human kidney tissues (~50 μm) without performing antigen retrieval (**Fig C**), revealing more general features. Furthermore, FLARE does not perturb antigenicity, where immunolabeling of proteins can be easily integrated afterwards (data not shown).

Conclusions: We have shown that FLARE reveals abundant details in a wide range of kidney tissue processing methods using super-resolution and cleared-tissue microscopy, and is compatible with other staining modalities.

Funding: NIDDK Support, Other NIH Support - R01

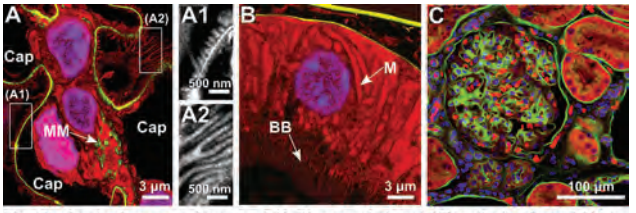

Fig. Confocal microscopy images of (**A-B**) expanded and (**C**) optically cleared kidney tissues that have been covalently stained for amines (red) and carbohydrates (green) along with conventional DNA stain (blue). Cap: capillary loop, MM: mesangial matrix, M: mitochondrial, BB: brush border.

PO0310

Ex Vivo Perfusion and Initial Function of a Recellularized Human-Scale Bioengineered Kidney

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Background: The need for more transplantable kidneys is greater than ever, with nearly 100,000 patients actively waiting for a kidney. To meet this growing demand, our team is developing a fully transplantable bioengineered kidney (BEK) by seeding cells into perfusion-decellularized porcine kidney scaffolds. Previously, orthotopic transplantation of HUVEC-only BEKs in pigs resulted in 83.3% (n=5/6 pigs) renal perfusion at 7 days post in vivo implantation. Building on these results, the focus of the current study was to recellularize the glomerulus of a clinically relevant whole kidney matrix and then assess the preliminary filtration function.

Methods: Adult porcine kidneys were decellularized via detergent perfusion through the vasculature. Primary glomerular cells were isolated from fresh porcine kidneys or rejected human kidneys. The porcine matrix was then seeded with either human umbilical vein endothelial cells (HUVECs), HUVECs and porcine glomerular cells as a model system, or HUVECS and human glomerular cells. The recellularized grafts were then cultured using a custom perfusion recellularization bioreactor until sufficient cellular coverage of the vasculature was obtained through nondestructive metabolic markers. Both HUVEC-only and co-culture BEKs were then implanted in an *ex vivo* blood loop for 30 minutes, where ureter effluent was collected and analyzed for filtration function.

Results: Sufficient histological vascular coverage with endothelial cells and thromboresistance with vascular patency was found for grafts with a minimum glucose consumption rate of 20 mg/hr. From the *ex vivo* blood loop test, the ureter effluent hematocrit concentration in the co-culture BEK was found to be undetectable. In comparison, the endothelial-only BEK and the pig's blood hematocrit levels were both 22%. Finally, the addition of glomerular cells in the BEK restored physiological flow rates of ureter effluent.

Conclusions: These results demonstrated human cellular engraftment and growth, long-term vascular patency, sustained hemoperfusion, removal of processed filtrate, and early signs of filtration and waste clearance in BEKs, which moves the field closer to an alternative for kidney transplantation.

Funding: Commercial Support - Miromatrix Medical

PO0311

Stiffening of Decellularized Tubular Basement Membrane Regulates Renal Tubular Epithelial Cell Function

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Background: Damage to renal proximal tubular epithelial cells (RPTEC) plays an important role in chronic kidney disease. Epithelial cells are supported by a specialized extracellular matrix called the basement membrane (BM). The structure of the BM is altered in various kidney diseases such as diabetic nephropathy and may result in increased BM stiffness. We have developed a novel cell culture model that utilizes tissue derived tubular basement membrane (TBM) with tunable stiffness as a culture substrate for RPTEC. The aim of this study was to determine if TBM stiffening promotes activation of pro-fibrotic signaling pathways and/or regulates RPTEC differentiation.

Methods: TBM was isolated from decellularized porcine kidneys. TBM cell culture substrates were made by pressure compacting the TBM on Tranwell inserts. Conditionally immortalized mouse RPTEC were grown TBM substrates. To induce stiffening, TBM was treated with the chemical crosslinker genipin. Decellularized TBM was characterized by western blot and immunofluorescence staining. Viability and morphology of RPTEC were performed on TBM of varying stiffnesses. Real-time PCR was performed on RPTEC to evaluate the effect of stiffness on multiple genes related to kidney fibrosis and RPTEC differentiation.

Results: Western blot analysis of decellularized TBM showed the presence of laminin and collagen IV and absence of lamin B1 showing proper decellularization of TBM. Genipin treatments (0.05% and 0.5%) resulted in average stiffness of 2 kPa and 3.2 kPa respectively, compared to 0.5 kPa for untreated TBM. Neither decellularization nor genipin modification had a significant effect on cell viability. Pro-fibrotic downstream targets of YAP activation (CTGF, AREG, and ANKRD1) were upregulated on stiff TBM substrates. Additionally, stiffness regulated expression of cell-cell junction markers E-cadherin and N-cadherin.

Conclusions: A new cell culture model was developed using tissue derived TBM as a culture substrate for tubular epithelial cells. Stiffness of the TBM was tuned using genipin. Increased TBM stiffness upregulated pro-fibrotic targets of YAP activation and altered RTPEC cell differentiation. These data show that stiffness significantly affects renal tubular cell function and suggest that TBM stiffening in chronic kidney disease may play a role in disease progression.

Funding: NIDDK Support, Private Foundation Support

PO0312

HIF-PHI Improves Anemia and Controls Circulating FGF-23 in a CKD Model

Megan L. Noonan, Pu Ni, Rafiou Agoro, Elizabeth A. Swallow, Matthew R. Allen, Kenneth E. White. *Indiana University School of Medicine, Indianapolis, IN.*

Background: The phosphaturic hormone FGF23 is a critical factor in chronic kidney disease-mineral and bone disorder (CKD-MBD), with elevated levels in blood associated with increased odds for patient mortality (>6-fold). Anemia is a potent driver of FGF23 expression, and patients with CKD ultimately develop anemia as the kidneys lose the ability to produce erythropoietin (EPO), in concert with FGF23-mediated alterations in mineral metabolism. Our goal was to investigate a HIF-PHI (hypoxia-inducible factor prolyl hydroxylase inhibitor) for effects on anemia-dependent FGF23 levels and key outcomes in a mouse model of CKD.

Methods: Female C57BL6 mice were fed a casein control or adenine-containing diet to induce CKD, which resulted in markedly elevated iFGF23 and BUN, hyperphosphatemia, and anemia. After 12 weeks of CKD induction, mice were treated with the HIF-PHI BAY 85-3934 ('BAY'; Molidustat) at a human equivalent dose every other day for 3 weeks.

Results: Compared to saline controls, BAY elevated serum EPO and restored CBCs to normal levels in CKD mice. iFGF23 was significantly elevated in saline-treated CKD mice (120-fold, $p<0.01$). Importantly, circulating iFGF23 was significantly attenuated (>60%; $p<0.05$) in BAY-treated mice with CKD, coinciding with downregulated renal Egr-1 expression ($p<0.01$). Renal 1,25D anabolic Cyp27b1 and catabolic Cyp24a1 mRNAs were up and downregulated, respectively, in BAY-treated CKD mice. This extended treatment resulted in decreased BUN ($p<0.01$) and reduced expression of renal fibrosis markers ($p<0.01$). The bone marrow Erfe, Transferrin receptor, and EpoR mRNAs were all upregulated ($p<0.05$-$p<0.01$), and liver hepcidin expression was downregulated in both control and CKD groups treated with BAY ($p<0.05$-$p<0.01$). HIF activation in osteoblasts/osteocytes is associated with increased bone mass, therefore we investigated femur trabecular parameters and cortical porosity, however saw no effect with BAY over this time course. Serum alkaline phosphatase was significantly elevated in CKD-BAY mice compared to CKD controls ($p<0.01$), suggesting increased osteoblast activity.

Conclusions: Collectively, these results support that resolving anemia using a HIF-PHI may improve kidney function and lower FGF23 during CKD, potentially providing modifiable outcomes beyond improving iron utilization for this patient population.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIAMS

PO0313

Second Harmonic Generation and Fluorescence Imaging Reveal Collagen Fibrils and Cell Nuclei in Mature Randall Plaque

Victor Hugo Canela,[1] Sharon B. Bledsoe,[1] Seth Winfree,[1] Angela R. Sabo,[1] Elaine M. Worcester,[2] Tarek M. El-Achkar,[1] James C. Williams.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]University of Chicago, Chicago, IL.*

Background: The formation of calcium oxalate (CaOx) stones on Randall's plaque (RP) is a common phenomenon (perhaps 25% of CaOx stones), yet this mechanism of stone formation is still poorly understood. The objective of the study was to devise novel techniques to study RP structure.

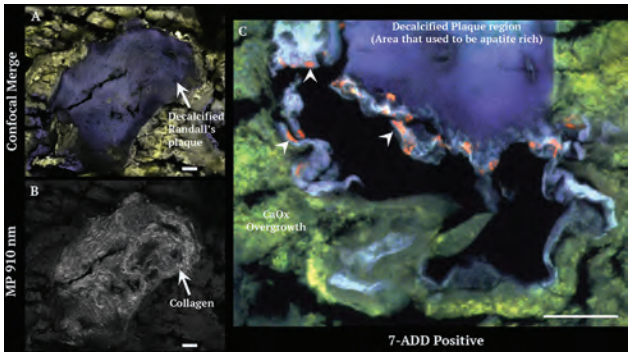
Methods: Micro CT was used to orient RP stones for decalcification and sectioning. Sections were examined for collagen using Second Harmonic Generation (SHG)

signals with multiphoton excitation. Other sections were stained with the DNA marker 7-aminoactinomycin D (7-AAD).

Results: SHG showed collagen fibrils in the plaque but not in the CaOx overgrowth region. Demineralized RP displayed autofluorescence in the far-blue region, as we have previously described in mineralized RP. Staining of plaque sections with the DNA marker, 7-AAD, confirmed the presence of cell nuclei within mature RP.

Conclusions: Our results show that collagen fibrils and cell nuclei are present in RP. The nature of cells and their role in plaque formation are yet to be determined. Our data suggest that these cells contain ordinary nuclear morphology and were well-preserved within the mature plaque. The presence of cell nuclei in the plaque raises critical questions about the role of apoptosis/necrosis and survival in this mineralized environment. Future studies exploring organization of collagen and the nature of cells in plaque will be invaluable in understanding plaque and stone pathogenesis.

Funding: NIDDK Support



Mature Randall's plaque (RP) contains collagen and cell nuclei. **A.** Representative image of a decalcified RP stone. The white arrow is pointing to the decalcified plaque area in the far-blue range spectrum. Its second harmonic generation counterpart image (**B**) shows collagen within the plaque area (white arrow). **C.** Fluorescent staining with the DNA marker 7-AAD clearly depicts cell nuclei in regions of RP (arrowheads).

PO0314

Cell Cycle Acceleration in Parathyroid Glands Is Caused by the Suppression of LncRNA Gas5 Expression in the Presence of a High-Phosphorus Diet in an Adenine-Induced CKD Rat Model

Taketo Uchiyama, Ichiro Ohkido, Yatsumu Saito, Akio Nakashima, Takashi Yokoo. *Jikei University School of Medicine, Minato-ku, Japan.*

Background: Chronic kidney disease (CKD), especially secondary hyperparathyroidisim (SHPT), is strongly associated with systemic calcification, including that in blood vessels. Therefore, it is important to elucidate its underlying pathological mechanism. SHPT is characterized by an unusually increased proliferation of parathyroid cells. We analyzed the expression of multiple cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors and demonstrated that the accelerated cell cycle in SHPT is caused by a reduction in *CDKN1B* expression (ASN 2019). To investigate the mechanism underlying SHPT development, we analyzed factors regulating *CDKN1B* expression in the parathyroid gland using two phosphorus-containing diets in a rat model of adenine-induced CKD.

Methods: CKD was induced by a diet containing 0.75% adenine. For 5 days, few rats in the CKD and control groups were fed a diet containing 0.9% phosphorus, and the remaining were fed a diet containing 1.3% phosphorus. We investigated the expression levels of approximately 20 miRNAs, such as miR-221, known to regulate *CDKN1B* expression, as well as the long noncoding RNA Gas5, using TaqMan probes for quantitative polymerase chain reactions.

Results: There were no significant differences in miRNA expression levels among the four groups (Figure 1). Gas5, known to be downregulated in prostate cancer cell, directly upregulates *CDKN1B* expression and further interacts with E2F1, which binds and activates CDKN1B. This strengthens the binding between E2F1 and CDKN1B stronger. It was observed that the expression of Gas5 was significantly decreased when the high-phosphorus diet was added to the CKD environment, and *E2F1* expression did not change significantly (Figure 2).

Conclusions: These results suggest that parathyroid cell proliferation might be due to the suppression of Gas5 expression in response to the addition of the high-phosphorus diet to the CKD environment, with a subsequent reduction in *CDKN1B* expression.

Figure 1

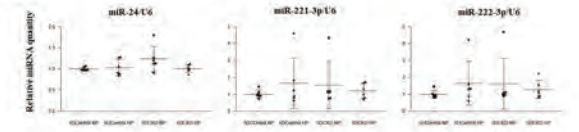
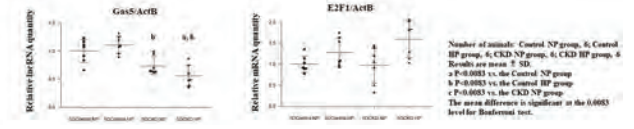


Figure 2



PO0315

Treatment with β,γ-Methyleneadenosine 5′-Triphosphate Prevents Arterial Media Calcification in a Warfarin Rat Model

Britt Opdebeeck,[1] Isabel Orriss,[2] Jessal J. Patel,[2] Geoffrey Van den bergh,[1] Patrick D'Haese,[1] Anja Verhulst.[1] *[1]Universiteit Antwerpen Laboratorium voor Pathofysiologie, Wilrijk, Belgium; [2]The Royal Veterinary College Department of Comparative Biomedical Sciences, London, United Kingdom.*

Background: Arterial media calcification (AMC) is a severe complication in patients with chronic kidney disease, diabetes and osteoporosis. *In vitro* studies showed that the synthetic P2X receptor agonist β,γ-meATP is a potent inhibitor of vascular smooth muscle cell (VSMC) calcification. Here, we aimed to evaluate whether β,γ-meATP prevents the development of AMC in a rat model of warfarin-induced AMC.

Methods: To induce AMC, rats received a diet containing 0.30% warfarin + 0.15% vitK1 throughout the entire study and were subjected to daily i.p. treatments with vehicle (n=10) or 2 mg/kg/day β,γ-meATP (n=10) from start of the study until sacrifice at wk7. Four rats on a standard chow diet were included as a control group. Serum calcium (Ca) and phosphorus (P) levels were analyzed at sacrifice. To evaluate the bone-like switch of VSMCs, aortic mRNA expression of TNAP and SOX9 were analyzed by qPCR. AMC was evaluated by analysis of total Ca content in the arteries and quantification of the area % calcification on Von Kossa stained aortic sections. To determine arterial stiffness, ultrasound-based pulse wave velocity (PWV) was evaluated in the abdominal aorta.

Results: Serum P levels were unchanged in all groups while serum Ca was significantly lower in rats treated with β,γ-meATP vs vehicle group. Exposure to warfarin induced distinct calcification in the aorta and peripheral arteries in vehicle treated rats which led to an increase in PWV score. Interestingly, daily treatment with β,γ-meATP significantly reduced the Ca content in the aorta (mean ± SEM; vehicle 1.49 ± 1.51 mg Ca/g wet tissue vs β,γ-meATP 0.38 ± 0.20 mg Ca/g wet tissue; $p<0.05$) and peripheral vessels which was further reinforced by a significant ($p<0.01$) reduction in aortic Von Kossa positive area % vs vehicle group. However, β,γ-meATP did not significantly affect PWV scores. Treatment with β,γ-meATP also did not alter the mRNA expression of bone-like marker genes.

Conclusions: β,γ-meATP significantly decreased AMC in the aorta and peripheral vessels of warfarin exposed rats, however, without affecting the bone-like switch of VSMCs suggesting that β,γ-meATP mediates its inhibitory effects on AMC probably by interfering with the formation of Ca-P crystals via its breakdown product methylene bisphosphonate. Further research will be conducted to evidence this hypothesis.

Funding: Government Support - Non-U.S.

PO0316

Efficacy of Oxidative Stress Inhibitor Alone or Combined Therapy with a Calcimimetic in a Rat Model of CKD-MBD

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Background: We previously demonstrated the role of NADPH oxidase (NOX 1 & 4) and hyperparathyroidism in the pathogenesis of arterial calcification, a component of CKD-MBD. We hypothesized that the combination of reduced NOX activity and lower PTH would have additive benefit on CKD-MBD. To test this hypothesis, we evaluated the efficacy of the NOX 1/4 inhibitor GKT137831(GKT) alone or combination with the PTH-lowering calcimimetic KP-2326 (KP) on CKD-MBD in a slowly progressive rat model of CKD, the Cy/+ rat.

Methods: We compared five groups of animals: 1: Normal (NL); 2: CKD; 3:CKD+GKT (60mg/kg s.q. daily); 4: CKD+ KP (0.6mg/kg i.p., 3x/wk) and 5: CKD+GKT+KP. Treatment began at 18 weeks of age (~60% NL kidney function) and ended at 28 weeks (~25% NL function). Serum biochemistries, aorta and heart calcification and bone architecture were assessed. One Way ANOVA was used for statistical analysis.

Results: As expected, there was a decline in kidney function in all CKD groups compared to NL. There was no difference in serum phosphorus or calcium levels between NL and any of the CKD groups. PTH and FGF23 serum levels were elevated by 5 and 2.3 fold, respectively, in CKD rats; only KP treatment reduced PTH levels ($p<0.003$). Interestingly, GKT alone or combined with KP increased FGF23 levels by 2-fold in

CKD rats (p<0.002). Serum 8-OHdG (marker of DNA oxidation) was higher in all CKD animals (p<0.01) and unaffected by treatment. There was increased aorta calcification (by 45%) and heart calcification (by 32%) in all of the CKD animal groups (p<0.01) and only GKT treatment reduced aorta calcification (p<0.03). Compared to NL, trabecular bone volume (BV/TV%) and trabecular number were lower and trabecular separation was higher in all CKD rats (p<0.001). GKT also increased trabecular separation in CKD rats (p<0.04).

Conclusions: In a progressive rat model of CKD-MBD, treatment with a NOX1/4 inhibitor (GKT) early in the course of CKD reduced aorta calcification but did not decrease oxidative stress and also increased FGF23 levels in CKD rats. KP treatment decreased serum PTH levels in CKD, but had no effect on aorta calcification or bone architecture. There were no additive beneficial or adverse effects with the combination of KP and GKT.

Funding: Veterans Affairs Support

PO0317

Comparison of the Effects of Ferric Citrate and Intravenous Iron on Markers of Mineral and Bone Disorder and Oxidative Stress in a Rat Model of CKD-MBD

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Background: Anemia and chronic kidney disease-mineral and bone disorder (CKD-MBD) are common in CKD. Ferric citrate is an oral therapy approved as an oral iron replacement product in non-dialysis dependent CKD and as a phosphate binder for dialysis-dependent CKD patients. However, studies comparing the effects of ferric citrate vs. IV iron on markers of CKD-MBD and oxidative stress in moderate CKD are limited.

Methods: We compared four groups of male rats (n=11-14 rats/group): 1) Rats with normal kidney function (NL), 2) CKD rats without iron treatment (CKD), 3) CKD rats treated with 2% ferric citrate in food (CKD + FC), and 4) CKD rats treated with 1mg/kg/every other week of iron sucrose (CKD + IV iron). Treatments started at 18 weeks of age (mild CKD) until euthanized at 28 weeks of age (moderate-to-advanced CKD). We determined biochemical markers of CKD-MBD, oxidative stress, bone morphology (by CT), and bone formation rate at 28 weeks. One-way ANOVA was performed with Tukey's post hoc comparisons.

Results: Untreated and iron-treated CKD rats had higher concentrations of BUN and creatinine than NL rats. Untreated CKD rats had elevated plasma phosphorus and intact FGF23 compared to NL. CKD+FC rats had lower plasma phosphorus and intact FGF23, while CKD+IV iron rats had lower intact FGF23 compared to CKD rats. However, the C-terminal FGF23 remained high in the untreated CKD and the CKD+IV iron rats compared to NL, but CKD+FC rats tended to be lower than the untreated CKD rats (p=0.07). PTH was elevated in the untreated and iron-treated CKD rats compared to NL. A marker of oxidative stress, 8OHdG, was increased in the untreated and iron-treated CKD rats compared to NL rats and was not different between iron treatments. At this stage of CKD, there was no cortical porosity in all the CKD rats compared to NL. CKD-induced alterations in trabecular and cortical bone properties and bone formation rate were not changed compared to untreated CKD rats in the iron-treated rats.

Conclusions: Ferric citrate led to more robust reductions in plasma phosphorus and FGF23 than IV iron, while neither source of iron had adverse effects on oxidative stress or bone parameters in a rat model with moderate CKD-MBD.

Funding: Other NIH Support - T32 AR065971-04, Commercial Support - Keryx Pharmaceuticals

PO0318

Upacicalcet, a Novel Non-Peptide Calcimimetic for the Treatment of Secondary Hyperparathyroidism, Has a Low Risk of Hypocalcemia

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Background: Calcimimetics are widely used for the treatment of secondary hyperparathyroidism (SHPT) in chronic renal failure patients. However, there are some problems with calcimimetics treatment. One of the biggest problems is hypocalcemia that leads to treatment interruption. Upacicalcet is expected to be a novel non-peptide calcimimetic that does not cause excessive hypocalcemia from the results of clinical studies. In the present study, we investigated the pharmacological characteristics of upacicalcet and effect on hypocalcemia in preclinical studies.

Methods: *In vitro* study was conducted using human CaSR-expressing (hCaSR$^+$) HEK-293T cells. In *in vivo* study, upacicalcet was intravenously administered in a single dose to Double-Nephrectomized (Double-Nx) rats, an animal model of SHPT, and serum intact parathyroid hormone (iPTH) and Ca concentrations were measured.

Results: Upacicalcet increased the intracellular Ca^{2+} concentration in hCaSR$^+$ HEK-293T cells dose-dependently. Additionally, upacicalcet shifted the EC_{50} value for extracellular Ca^{2+} to lower concentrations in a dose dependent manner. In Double-Nx rats, 0.3, 3, and 30 mg/kg of upacicalcet dose-dependently reduced the serum iPTH level at 24h and 48h after administration, and the reductions were significantly greater than that in Control (Pre; upacicalcet 0.3 mg/kg: 483±70 pg/mL vs. Control: 460±39 pg/mL, 24h; upacicalcet 0.3 mg/kg: 397±40 pg/mL vs. Control: 1306±86 pg/mL; *P<0.001*, 48h; upacicalcet 0.3 mg/kg: 795±91 pg/mL vs. Control: 1889±77 pg/mL; *P<0.001*). Upacicalcet also significantly decreased the serum Ca level dose-dependently at 24h and 48h after administration. However, interestingly, it bottomed out without getting too low even with 30 mg/kg of upacicalcet, 100-fold higher than the efficacious dose (0.3 mg/kg) (Table 1).

Conclusions: These findings suggest upacicalcet is a novel non-peptide positive allosteric modulator on human CaSR with a low risk of hypocalcemia for the patients with SHPT.

Table 1. The effect of upacicalcet on serum Ca level in Double-Nx rats

Treatment	Dose (mg/kg)	Pre	24h	48h
Sham	-	9.5 ± 0.1	9.1 ± 0.1	9.1 ± 0.2
Control	-	10.7 ± 1.1	11.2 ± 0.6	14.4 ± 0.9
Upacicalcet	0.3	11.1 ± 0.6	9.0 ± 0.5	12.2 ± 0.7
	3	10.8 ± 0.7	8.2 ± 0.4**	10.1 ± 0.6**
	30	11.2 ± 0.6	8.2 ± 0.4**	10.0 ± 0.7**

Each data (mg/dL) represents the mean ± S.E. of 6 individuals
**: *P<0.01* ; compared with Control (Tukey's test)

PO0319

Influence of Vitamin D and Uremia on Functional Expression of Drug Transporters in Human Proximal Tubule Cells

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Background: Vitamin D (VitD) deficiency is common in patients with chronic kidney disease (CKD), with prevalence rates as high as 90%. CKD and VitD have independently been shown to modulate the function and expression of various drug transporters, potentiating drug-drug interactions and pharmacokinetic alterations. However, it remains unclear how the combination of CKD and VitD alters drug transporters. The purpose of this study was to evaluate the function and expression of drug transporters in human proximal tubule cells (hPTCs) following treatment with VitD analogues under *in vitro* conditions employing human healthy serum (HS) and uremic serum (US) to mimic the CKD environment.

Methods: hPTCs were exposed to 10% HS or 10% US for 24 h, followed by treatment with cholecalciferol (D_3) or the active form, calcitriol ($1,25D_3$) at 100 or 240 nM concentrations or 2% ethanol vehicle control (VEH) for 6 days. RT-qPCR and immunoblotting were used to assess effects on gene and protein expression, respectively of P-gp (efflux) and OATP4C1 (uptake) transporters. Apical to basolateral (A->B) and basolateral to apical (B->A) transport was assessed in hPTCs using transwell inserts and the transporter probe [^{3}H]Digoxin (DIG).

Results: Data are shown in the Table. Compared to VEH, $1,25D_3$ increased P-gp gene expression under HS and US (with exception of the 240 nM concentration). $1,25D_3$ also increased SLCO4C1 protein in HS, but no increase was demonstrated in US. B->A transport was enhanced in HS under treatment with $1,25D_3$.

Conclusions: These data suggest that uremia decreases OATP4C1 expression and prevents an induction of OATP4C1 expression and function by $1,25D_3$. Enhanced B->A transport in HS under treatment with $1,25D_3$ was consistent with the up-regulation of P-gp and SLCO4C1. These alterations may help to inform disposition of transporter substrates under VitD treatments.

Funding: Other NIH Support - NIGMS

Table: Results

		Healthy Serum				Uremic Serum				Overall P-value
		VEH	100 nM D_3	240 nM D_3	100 nM $1,25D_3$	240nM $1,25D_3$	VEH	100 nM D_3	240 nM D_3	100 nM $1,25D_3$	240 nM $1,25D_3$	
ABCB1/ P-GP	Gene Expression (fold)	1.0	4.8 ± 2.5[#]	3.7 ± 1.3	6.6 ± 0.92[#]	7.5 ± 1.1[#]	4.5 ± 0.23	1.9 ± 0.51[#]	2.4 ± 1.1[#]	10 ± 0.52[#]	4.3 ± 2.3	0.0016
	Protein Expression (fold)	1.0	N/A	0.63 ± 0.05	0.77 ± 0.10	0.61 ± 0.17	0.73 ± 0.05	N/A	0.56 ± 0.04	1.02 ± 0.21	1.49 ± 0.23[#]	0.0339
SLCO4C1/ OATP4C1	Gene Expression (fold)	1.0	9.1 ± 0.67	21 ± 0.27	2.9 ± 0.22	3.0 ± 0.52	2.3 ± 0.14	2.1 ± 0.36	2.5 ± 0.62	3.0 ± 0.06	3.3 ± 1.4[#]	0.0013
	Protein Expression (fold)	1.0	N/A	2.54 ± 0.14[#]	2.43 ± 0.17[#]	2.06 ± 0.67	0.22 ± 0.02[#]	N/A	0.40 ± 0.06[#]	0.60 ± 0.02[#]	0.40 ± 0.12[#]	0.0006
Digoxin Transport	A→B (% transcellular)	21.1 ± 1.31	N/A	N/A	N/A	21.4 ± 1.01	23.5 ± 1.23[#]	N/A	N/A	N/A	21.6 ± 1.75	0.0193
	B→A (% transcellular)	29.9 ± 2.35	N/A	N/A	N/A	33.2 ± 2.02[#]	31.2 ± 1.70	N/A	N/A	N/A	32.0 ± 1.01	0.0370

Data reported as Mean ± SEM; p-values calculated using two-way ANOVA
[#]p < 0.01 vs. VEH + HS; [*]p < 0.05 vs. VEH + HS; [$]p < 0.05 vs. 240 nM $1,25D_3$ + HS

PO0320

SNF472 Inhibits Heart Valve Calcification in a Novel In Vitro Method Using Porcine Whole Leaflets

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Background: Chronic kidney disease and end-stage kidney disease (ESKD) patients are prone to develop calcific aortic or mitral valve disease. Currently, there exists no pharmacological treatment to prevent or stop the calcification process of aortic valves that causes aortic stenosis, and the models to study this process in vitro and in vivo are scarce. SNF472 is an inhibitor of calcium phosphate crystallization in development for the treatment of calciphylaxis and cardiovascular calcification in ESKD patients. The aims of this study were to develop a robust *in vitro* model of induced calcification in whole aortic valve leaflets suitable for testing potentially inhibitory drugs, and to test the effects of SNF472 in this model.

Methods: Aortic valve leaflets from commercial pig hearts were dissected free and randomized between experimental groups. Whole leaflets were cultured in individual wells. Two growth media were used for cultivation: standard growth medium and an antimyofibroblastic growth medium. The latter was employed to inhibit contraction of the leaflet into a ball-like structure. Calcification was induced in the growth media by supplementation with an osteogenic medium. Leaflets were cultivated for four weeks and medium was changed every third day. To block calcification, SNF472 was used at concentrations between 1 and 100 μM. Calcium amount in leaflets after four weeks was measured by inductively coupled plasma optical emission spectroscopy.

Results: Osteodifferentiation with calcium accumulation was in principle absent when standard medium was used. However, when the antimyofibroblastic medium was used, a strong calcium accumulation was induced (p=0.006 compared to controls), and this was blocked in a dose-dependent manner by the calcification inhibitor SNF472 (p=0.008), with an EC_{50} of 3.3 μM.

Conclusions: Cultured whole leaflets of porcine aortic valves are a new *in vitro* model to study calcification of heart valves. This model will be useful for studying the basic mechanisms of valve calcification and to test pharmacological approaches to inhibit calcification. The latter was shown by SNF472, which strongly inhibited calcification in this model of aortic valve disease.

Funding: Commercial Support - Sanifit Therapeutics, Government Support - Non-U.S.

PO0321

Amelioration of Uremic Vascular Calcification After Experimental Aorta Transplantation

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Background: CKD causes a shift in phenotype of the vascular smooth muscle cell (VSMC) to a bone-like secretory cell and promotes vascular calcification (VC). Our aim was to study whether VC is reversed by transplantation of a uremic calcified aorta into a healthy recipient.

Methods: A novel model of isogenic aorta transplantation in the rat was used (ATx). VC was induced in inbred Dark Aguti rats by 5/6 nephrectomy, high phosphate diet and alfacalcidol treatment. The abdominal aorta of the uremic rat was transplanted into a normal rat (uremic ATx, n=16). Control groups were: ATx between normal rats (normal ATx, n=9) and age-matched rats (control, n=6). Four weeks after ATx, the aorta was analyzed for genes related to the osteochondrogenic transition by RT-qPCR. Data are presented as mean±SD. mRNA levels are normalized to stabile housekeeping genes and expressed as the ratio to control.

Results: The uremic donor rat had severe CKD with disturbed mineral and bone metabolism as well as severe aorta calcification with altered expression of genes related to the osteochondrogenic phenotype. ATx mitigated some of these genetic changes as indicated by a significant downregulation of the expression levels of mineralization inhibitors and fibrosis matrix proteins. More specifically, mRNA levels of *MGP* (control 1±0.18 vs. uremic 3.74±0.18 vs. uremic ATx 1.67±0.61), *Spp1* (control 1±0.20 vs. uremic 13.69±4.47 vs. uremic ATx 2.62±0.84), *ANKH* (control 1±0.15 vs. uremic 10.43±6.90 vs. uremic ATx 4.49±1.72), *Postn* (control 1±0.34 vs. uremic 3.19±0.77 vs. uremic ATx 1.74±0.85), *Fn1* (control 1±0.25 vs. uremic 7.26±2.49 vs. 3.02±1.45), all p<0.01. No difference in expression of these genes between control and normal ATx was noticed. The VSMC markers *ACTA2 & Eln* were downregulated in uremic VC with no recovery through ATx. The upregulated Wnt inhibitor sclerostin showed a trend towards downregulation by ATx. Activin A & TGF-beta were highly upregulated in uremic VC with no reversibility. Plasma biochemistry did not differ between control, normal ATx and uremic ATx.

Conclusions: Our results for the first time show downregulation of genes related to mineralization and fibrosis, indicating amelioration of uremic vasculopathy after experimental aorta transplanation.

Funding: Government Support - Non-U.S.

PO0322

Impaired Arterial Vitamin D Signaling Is Pathogenic in Vascular Calcification

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Background: Conflicting data exists as to whether vitamin D receptor agonists (VDRa) are protective of arterial calcification. This is confounded by inherent physiological differences between human and animal experimental models and conflicting published data. Herein, the study aims to address these problems by leveraging frontiers in human arterial organ culture models.

Methods: Human arteries were collected from 24 patients (healthy controls, n=12; end-stage CKD, n=12). Cross-sectional and interventional studies were performed using arterial organ cultures treated with normal and calcifying (containing 5mmol/L $CaCl_2$ and 5mmol/L b-glycerophosphate) medium, *ex vivo*. To assess the role of VDRa therapy, arteries were treated with either calcitriol or paricalcitol.

Results: Human arteries express a functionally active vitamin D system, including VDR, 1α-hydroxylase and 24-hydroxylase (24-OHase) components and these were dysregulated in CKD arteries. Arteries from CKD patients exhibited reduced capacity to synthesize $1,25(OH)_2D$, increased basal expression and excessive induction of the vitamin D catabolic pathway in response to VDRa. VDRa therapy increased VDR expression in healthy (p<0.01) but not CKD arteries. VDRa treatment suppressed Runx2 and MMP-9 expression in CKD arteries, however only paricalcitol suppressed MMP-2. VDRa exposure did not modulate arterial calcification in all organ culture models. However, VDRa reduced senescence associated β-galactosidase (SAβG) staining in human aortic-smooth muscle cells under calcifying conditions, *in vitro.*

Conclusions: Maladaptation of arterial vitamin D signaling components occurs in CKD. VDRa exposure can exert vasculo-protective effects and seems critical for the regulation of arterial health in CKD.

Funding: NIDDK Support

PO0323

Analysis of Human Jackstone Protrusions Show a Protein-Rich Core, Suggesting That Proteins Drive Their Rapid and Linear Growth

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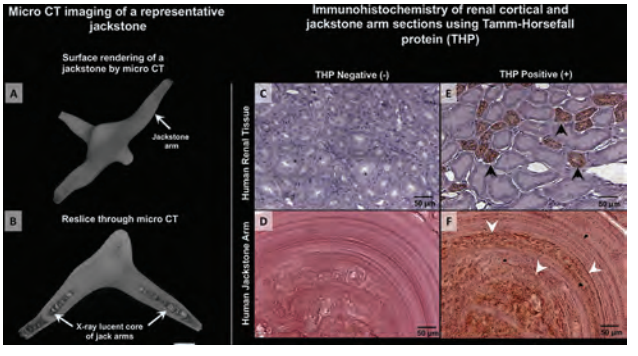
Background: Jackstones are urinary stones that have arm-like extensions from the body of the stone. This morphology of stone has been long recognized but poorly studied.

Methods: Micro CT was used to analyze 96 jackstones from 47 different patient specimens. Additional analyses included infrared spectroscopy (IR), fluorescence microscopy, and immunohistochemistry for Tamm-Horsfall protein (THP).

Results: Jackstone arms consisted of an X-ray lucent core (high in protein by IR) and a tightly layered calcium oxalate monohydrate (COM) shell that matched the COM on the stone body. The layering in the shell regions showed that the arms had grown at a faster rate away from the center of the stone than had the stone body. Microscopy studies showed brilliant autofluorescence in the core region but less in the COM shell. Immuno-staining showed that THP content was richer in the core region than in the COM shell. **Figure 1A** shows surface rendering of jackstone by micro CT. **B:** Slice through micro-CT image stack to show the x-ray lucent cores of two jack arms from **A**. **C & D** show negative controls (no primary antibody) for human cortical tissue and demineralized jackstone arm cross-section. **Panel E** shows a positive control for THP in human renal tissue (black arrowheads). **Panel F** shows THP aggregation in the core of the jackstone arm (white arrowheads).

Conclusions: We hypothesize that the protein-rich core of a jackstone arm preferentially binds more protein from the urine and resists deposition of COM, such that the arm tip grows rapidly, with the sides (shell) of the arm being covered with COM layers just like the body of the stone. This hypothesis points to enrichment of growth-accelerating proteins in the core of the jack arm, which bind preferentially to the protein-rich tip but which bind less avidly to the COM surface of the stone. Identificaiton of such proteins could provide clues as to how proteins modulate the deposition of mineral layers in kidney stone growth.

Funding: NIDDK Support



PO0324

Hyperphosphatemia Contributes to Inflammation, Iron Dysregulation, and Skeletal Muscle Wasting

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Background: Fibroblast growth factor (FGF) 23 is a phosphaturic hormone that promotes phosphate (Pi) excretion. In patients with chronic kidney disease (CKD), serum levels of Pi & FGF23 gradually rise as renal function declines & associates with various pathologies such as systemic inflammation, anemia, vascular calcification & muscle wasting. Our previous studies have showed FGF23 induces inflammatory cytokine expression by targeting hepatocytes via FGF receptor 4 (FGFR4). Other studies have shown Pi accelerates vascular calcification. However, whether Pi contributes to inflammation, anemia or skeletal muscle wasting remains unclear. Here we compare the

effects of Pi versus FGF23 to determine their contributions towards these CKD-associated pathologies, utilizing in vivo & in vitro models.

Methods: We subject mice with global FGFR4 deletion & wild-type littermates to an increasing dietary Pi load (0.7%, 2.0%, or 3.0%) or an adenine-rich diet (CKD model) to examine systemic inflammation, iron metabolism and skeletal muscle function. Furthermore, we study primary hepatocytes treated with FGF23 or Pi to examine activation of downstream signaling events & expression levels of specific target genes. We determine if co-treatment with inhibitors of Pi uptake & of downstream mediators block these observed effects.

Results: A 3% Pi diet as well as an adenine-rich diet promote inflammation, iron dysregulation & skeletal muscle wasting in mice. Outcomes are not alleviated in FGFR4 knockout mice. Furthermore, liver Pi accumulation occurs before hyperphosphatemia, as shown by 2% Pi diet. In cultured hepatocytes, inflammatory cytokine and hepcidin expression are induced by Pi in a dose-dependent manner. Moreover, Pi activates NFkB signaling. Blocking Pi uptake & NFkB attenuates the observed Pi-induced effects.

Conclusions: We postulate in CKD, gradual elevations in serum Pi as well as tissue Pi accumulation, which may occur before detectable changes in systemic Pi, promotes inflammation & anemia by targeting the liver to induce gene programs that regulate inflammatory responses & iron metabolism. In turn, these events promote muscle wasting. Our study indicates these Pi effects may be FGF23-independent. Pharmacological approaches targeting Pi uptake and excretion or Pi's direct hepatic actions may alleviate various CKD-associated pathologies.

Funding: NIDDK Support

PO0325

Extrarenal Expression of the Kidney-Related Longevity Gene, α-Klotho, in the Long-Living Naked Mole Rat (Heterocephalus glaber): A Comparative Biology Study

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Background: The naked mole-rat (NMR) is expanding in popularity as a model for studying biomarkers of aging and mineral metabolism. NMR has a lifespan of 30 years, almost ten times longer than the mouse and rat (app. 3-4 years). α-*klotho* (*Kl*) is an aging-suppressor gene. Knockout of *Kl* is associated with decreased lifespan, and overexpression of this gene is linked to extended lifespan in mice. *Kl* is predominantly expressed in the kidney. We speculated that the expression level of this gene might play a role in the longevity of NMR. The present comparative study aimed to establish the expression level of *Kl* in long-living NMR vs. normal rats, *Rattus norvegicus* (RN).

Methods: Ten NMR, kindly provided by Randers Regnskov (Danish Zoo) (N=5) and Gorbunova and Seluanov laboratory (Aging Research Center, University of Rochester, USA) (N=5) were used and compared to corresponding tissues from RN (N=9). Methods used were: QPCR, standard PCR, and Sanger sequencing.

Results: In the kidney, similar levels of *Kl* mRNA were observed between those two species by qPCR (RN: 0.9± 0.1 vs. NMR: 1.2± 0.2; n.s.). The expression of *Kl* was further examined in the lung, skin, and liver of NMR, compared to RN. There was no expression of *Kl* in the lung and skin of NMR. In the liver of NMR, a high expression of *Kl* mRNA was observed (Cp: 25) by qPCR in contrast to RN, where no expression was detected. Sanger sequencing was performed to confirm that the gene expressed in the liver was *Kl*. In order to ensure that this was not a truncated form of *Kl*, which could be a target for mRNA decay, the predicted region for alternative splicing sites for *Kl* was sequenced in NMR. These results indicated that this was not the case, neither in the kidney nor in the liver.

Conclusions: This comparative study showed for the first time that α-klotho is significantly expressed in the liver of NMR, while the gene is absent in the liver of RN. The expression levels of α-klotho were similar in kidneys of NMR and RN. Further experimental work is required to clarify whether the hepatic expression of α-klotho might contribute to the longevity of the NMR.

Funding: Government Support - Non-U.S.

PO0326

Increased Urinary Leukocyte Esterase Distinguishes Brushite Stone Formers from Patients with Other Stone Types

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Background: Compared with calcium oxalate (CaOx) stone formers (SF), patients with brushite (Br) stones have elevated neutrophil infiltration in their renal papillae which may be associated with the observed marked increase in papillary scarring and inflammation. We investigated whether a signal of neutrophil elevation in the kidney could be detected in the urine when not associated with infection.

Methods: We performed urine dipstick analyses for leukocyte esterase (LEU), an enzyme produced by neutrophils, and various markers of infection including nitrite (NIT), blood (BLO) and protein (PRO). 24-hr urine specimens were tested using the Siemens Multistix 10SG dipstick read on a Clinitek Status analyzer. We measured urine ammonia on a Beckman DxC600. We retrospectively analyzed 812 urines from 215 patients; stone type of patients was determined by stone analysis containing >50% apatite (Ap), Br, CaOx or uric acid (UA), respectively. BLO, PRO and LEU measurements were on a 5 point scale (negative=0, trace=0.5, small=1, moderate=2, large=3); NIT was yes or no.

Results: In a fully adjusted ANOVA model by stone type and sex with LEU as the dependent variable and BLO, PRO, NIT, ammonia excretion and patient age as covariates, brushite SF had significantly higher LEU than CaOx or UA (Table). By Chi-square, NIT was not different between the stone types (p = 0.25). Ammonia excretion was not different between stone types. In an ANOVA of the mean LEU by patient adjusted for the number of stone removal procedures, LEU in Br SF was higher than in CaOx SF (p<0.01).

Conclusions: Dipstick LEU is informative in SF aside from predicting infection. Dipstick LEU was significantly higher in Br SF than in CaOx SF but NIT, indicating infection, was not different between stone types. Adjusting for other indicators of infection, such as ammonia, BLO, and PRO as well as the number of stone removal procedures did not abolish this difference. Dipstick LEU may serve as a urine biomarker of the inflammatory activity and neutrophil infiltration that we have observed in the kidneys of Br SF and may reflect the papillary histopathology.

Funding: NIDDK Support

Table. Dipstick LEU by Sex and Stone Type

	Women				Men			
	Ap	Br	CaOx	UA	Ap	Br	CaOx	UA
LEU	0.59±0.07	0.95±0.06*$	0.40±0.06	0.23±0.10	0.35±0.06	0.57±0.06#+	0.17±0.07	0.12±0.05

Mean±SE. *p<0.0001 vs CaOx or UA; $p<0.001 vs Ap; #p<0.0001 vs UA; +p<0.001 vs CaOx

PO0327

Heterogeneity of Mechanisms for Idiopathic Hypercalciuria in Calcium Stone Formers

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Background: In past research, we have found evidence that patterns of segmental nephron tubule calcium reabsorption differ between the sexes in calcium (Ca) stone formers (SF) demonstrating a different underlying mechanism of their hypercalciuria. Whether or not these mechanisms differ between calcium oxalate (CaOx) and calcium phosphate (CaP) SF is not known.

Methods: We studied 18 CaOx subjects (12 male), 17 CaP subjects (9 male), and 25 normal (N) subjects (13 male) in both the fasted and fed state. Subjects ate a diet consisting of three isocaloric meals with hourly blood and urine samples for 14 hours. We measured endogenous lithium clearance to assess proximal tubule (PT) sodium reabsorption. To account for within-subject correlation due to repeated measures, generalized estimating equations (GEE) were used to estimate and test mean laboratory values between groups. Linear mixed effects models were used to model urine Ca, distally delivered Ca, absolute reabsorption of distally delivered Ca, and the urine-plasma lithium ratio.

Results: In SF women, distal Ca reabsorption is decreased compared to N women, while in SF men, PT Ca reabsorption is significantly decreased with a more modest reduction in distal Ca reabsorption compared to normal men. Among female CaP SF we found an abnormally high response of urine Ca to PTH that appears to affect post PT Ca reabsorption. Among female CaP and CaOx SF and male CaOx SF we found a clear difference of urine Ca response to ultrafiltrate Ca concentration. This difference was absent in male CaP SF who had a unique increase in the dependence of distal Ca delivery on lithium reabsorption in the PT. CaOx male SF also had other PT abnormalities such as modeled urine Ca that was abnormally dependent on the urine-plasma lithium ratio. In addition, CaOx male SF had modeled lithium reabsorption that was abnormally responsive to both urine sodium, an ECF volume marker, and UF Ca concentration, presumably mediated through the cell surface Ca receptor (CaSR).

Conclusions: CaP and CaOx SF have differing abnormalities of Ca handling as compared to their same sex normals. In particular, phenotype specific abnormalities related to the CaSR exist in CaOx men and abnormalities related to the PTH receptor exist in CaP women.

Funding: NIDDK Support

PO0328

Magnesium's Roles in the Treatment of Hyperphosphatemia of CKD

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Background: Hyperphosphatemia is causally related to atherosclerotic cardiovascular disease, the most important cause of death in all stages of renal failure and the single greatest threat to survival among ESRD patients undergoing dialysis. To meet the current K/DOQI guideline, patients use cationic binders to bind phosphate (Pi) in the gastrointestinal tract and prevent its uptake. FDA-approved phosphate binders include calcium salts, lanthanum salts, sevelamer, and ferric citrate. Combinations of calcium and magnesium salts have the potential both for phosphate binding with reduced calcium load and for reduction in oxidative stress, vascular calcification, and bone dysfunction.

Methods: Recent literature describing treatment of hyperphosphatemia with phosphate binders composed of calcium acetate/magnesium carbonate and calcium citrate/magnesium carbonate was analyzed. The results highlight aspects of magnesium's roles in the treatment of hyperphosphatemia of Stage 4-5 CKD and illustrate the potential benefits of these combination therapies in treatment of hyperphosphatemia.

Results: Recent clinical data strongly suggest that combinations of calcium and magnesium salts exhibit pleiotropic benefits for hyperphosphatemic Stage 4-5 CKD patients. In addition to reducing the calcium load, magnesium appears to act in the following ways. (1) Treatment lowered serum phosphorus into the K/DOQI target range in about 24 weeks. (2) Although treatment increased serum magnesium concentrations, [Mg^{2+}] was in the high normal range and comparable to the intracellular magnesium concentration. (3) Short-term treatment raised the T_{50} value. Since lower values are associated with accelerated conversion of soluble calciprotein particles composed of

amorphous calcium phosphate to secondary (insoluble) calciprotein particles containing needle-like calcium phosphate particles, higher magnesium appeared to beneficially slow the rate of conversion. (4) Analyses of bone turnover parameters suggested that higher magnesium may have supported more normal bone remodeling.

Conclusions: Clinical data from several sources suggest that combinations of calcium and magnesium have unique potential for providing pleiotropic benefits to Stage 4-5 CKD patients of all ages. Additional preclinical studies are underway to confirm that calcium magnesium citrates and propionates can be effectively and safely administered to hyperphosphatemic ESRD patients.

Funding: Commercial Support - BioLink Life Sciences, Inc.

PO0329

Vitamin D Deficiency, Investigating the Connection Between Osteoporosis and CKD

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Background: Chronic kidney disease (CKD) is estimated to afflict thirty-seven million people in the United States and leads to drastic alteration in bone and calcium metabolism. Metabolic bone disease is a common complication, resulting in skeletal consequences and CKD-associated osteoporosis. This occurs due to a combination of abnormalities in calcium, phosphorus, parathyroid hormone, vitamin D metabolism, and dysregulation in both bone formation, and bone resorption. One mechanism of the pathophysiology of age-associated osteoporosis is the shift in lineage commitment of mesenchymal stem cells (MSCs) towards adipogenesis at the expense of osteogenesis. Recent studies have implicated MSCs as mediators of osteoporosis due to the disrupted endocrine signaling pathways in aging individuals, similar to individuals with CKD.

Methods: We performed a re-analysis of a published single cell transcriptomics dataset investigating differentiation of MSCs to osteoblasts and adipocytes. We employed a standard pipeline from the R package "Seurat" to examine transcriptional heterogeneity of undifferentiated mesenchymal stem cells. Additionally, we tested the effects of 1,25D on MSC differentiation towards the osteogenic lineage.

Results: Here, we demonstrate heterogeneity of bone-marrow derived MSCs at the transcriptional level, implying potential underlying functional heterogeneity. Using single cell transcriptomics, we characterize the subpopulations of MSCs, multipotent stem cells and cells poised for differentiation. Once we confirmed this heterogeneity, we investigated stem cell priming with the vitamin D metabolite 1α,25-dihydroxyvitamin D3 (1,25D), testing the memory of a prior exposure to stem cells influences later lineage commitment choices. Vitamin D supplementation is a common therapeutic intervention for osteoporosis and is especially key for patients with CKD-associated osteoporosis as Vitamin D deficiency is prevalent in populations at-risk for developing osteoporosis and patients already diagnosed with CKD.

Conclusions: This project supports the commonly used treatment for development and prevention of osteoporosis and demonstrates functional heterogeneity of MSCs. Further steps in this project will explore the response to vitamin D priming at a higher resolution by employing single cell RNA-sequencing.

Funding: Other NIH Support - National Institue of Aging

PO0330

Dissecting Ferric Citrate- and FGF-23-Associated Mineral Metabolism During the Anemia of CKD

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Background: Ferric citrate (FC) is a dual therapy used in patients with chronic kidney disease (CKD). This drug is given as a phosphate (Pi) binder for dialysis-dependent CKD, and for iron deficiency anemia in non-dialysis CKD due to delivery of elemental iron. Elevated Pi and anemia both lead to increased FGF23 during CKD, however, the roles of iron and FGF23 on CKD pathologies are unclear.

Methods: Iron and Pi utilization was tested in a mouse model of CKD receiving FC, with and without osteocyte deletion of FGF23 (flox-Fgf23/Dmp1-Cre). Male mice (n=4-7) with the genotype flox-Fgf23/Dmp1-Cre+ and -Cre- were placed on a customized 0.2% adenine (AD)-containing diet for 6 weeks to induce CKD in the presence or absence of 0.5% FC.

Results: After the diet regimen, iFGF23 increased significantly in all CKD mice ($p<0.05$-0.01). iFGF23 was lower in Cre+ mice fed FC ($p<0.01$), with Cre+ AD-only mice following a similar trend, demonstrating that the Dmp1-Cre was effective in reducing circulating FGF23. Cre+ mice fed AD-only had higher serum Pi than Cre- controls ($p<0.05$), and regardless of treatment, the Cre+ mice had higher BUN ($P<0.01$), showing that FGF23 was required to maintain serum Pi and lessen renal disease. Total serum iron was higher in all mice receiving FC, demonstrating effectiveness of the drug. Consistent with increased serum iron in the FC fed mice, liver Tfrc, BMP6, and hepcidin mRNAs were increased regardless of genotype ($p<0.05$-0.01); liver IL6 showed decreased mRNA expression in FC fed mice ($p<0.01$). Key enzymes that control 1,25D production in kidney were also examined. In Cre+/- mice fed FC the 1,25D anabolic enzyme Cyp27b1 was higher ($p<0.05$-0.01), and catabolic Cyp24a1 was lower ($p<0.01$), suggesting that FC may aid in restoring vitamin D metabolism in CKD.

Conclusions: In sum, delivery of FC during genetic reductions in FGF23 allowed the identification of FGF23-dependent and -independent actions in CKD. Loss of FGF23 was associated with higher serum Pi and worse renal function, demonstrating that FGF23 was protective of mineral metabolism, an effect independent of FC. In contrast, FC had FGF23-independent actions during CKD of increasing serum iron, correcting inflammation markers, and restoring the balance of Cyp24a1 and Cyp27b1 mRNAs, potentially providing beneficial effects on renal 1,25D metabolism.

Funding: Commercial Support - Keryx Biopharmaceuticals, Inc., a wholly-owned subsidiary of Akebia Therapeutics, Inc.

PO0331

Reduced DMP1 Expression Precedes Bone Loss and FGF-23 Elevation in CKD

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Background: Chronic kidney disease (CKD) is associated with major disorders of bone and mineral metabolism, including renal osteodystrophy and increased secretion of the phosphaturic hormone FGF23 by bone, which is independently associated with cardiovascular mortality. Dentin matrix protein 1 (DMP1) is an extracellular matrix protein produced by osteocytes that stimulates osteoblast differentiation and inhibits FGF23 production. We previously showed that DMP1 supplementation prevents bone loss, FGF23 elevation and cardiovascular outcomes in mice with advanced CKD.

Methods: To determine if altered DMP1 expression contributes to the pathogenesis of renal osteodystrophy and FGF23 elevations during CKD progression, we measured bone DMP1 mRNA in wild-type (WT) and Col4a3^{KO} mice with progressive CKD every 4 weeks from 4 weeks of age until their death (24 weeks). In parallel, we assessed kidney function, serum FGF23 levels and bone microarchitecture. We also assessed osteocyte morphology in mice and in patients with early CKD.

Results: Col4a3^{KO} mice showed increased albumin to creatinine ratio (ACR) and blood urea nitrogen (BUN) levels starting respectively at 8 and 16 weeks, indicating onset of proteinuria and impaired kidney function. Consistent with BUN, FGF23 levels showed sustained increases starting at 16 weeks. This coincided with alterations in trabecular bone measured by 3D-microtomography of femurs from 16 to 24 week-old Col4a3^{KO} mice. However, analysis of cortical (Ct) bone showed reductions in bone mineral density, Ct thickness and Ct area as early as 12 weeks of age, and alterations in osteocyte morphology as early as 10 weeks in Col4a3^{KO} mice with early CKD and in patient with CKD stage 1-2. Bone DMP1 mRNA was reduced by 50% prior to the onset of proteinuria at 4 weeks of age and remained low at all time points throughout CKD progression; each $p<0.05$ vs. age-matched WT.

Conclusions: These data show that reduction in DMP1 expression occurs prior to major changes in kidney function and precedes altered osteocyte morphology, cortical bone loss, and FGF23 elevation in CKD. Although further studies are needed to identify the factors that suppress DMP1 expression in CKD, DMP1 administration might represent an effective therapeutic strategy to prevent alterations in bone and mineral metabolism in early CKD.

Funding: NIDDK Support

PO0332

A Role of FHL2 in the Pathogenesis of VOT and Calcification Induced by High Phosphate

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Background: Hyperphosphatemia is germane to the development and progression of arterial medial calcification (AMC) in patients with chronic kidney disease. Vascular smooth muscle cells (VSMCs) to osteoblast-like cells transdifferentiation (VOT) induced by high phosphate is a crucial step in AMC. Either β-catenin or HIF-1α signal activated by high phosphate promotes VOT and calcification in VSMCs. As an adaptor protein, four-and-a-half LIM domains protein 2 (FHL2) has been demonstrated involving in β-catenin and HIF-1α signaling, respectively. However, the potential role and mechanism for FHL2 in high-phosphate-induced VOT and AMC remains to be clarified.

Methods: The regulation and function of FHL2 in high-phosphate-induced VOT and calcification were examined in cultured VSMCs. The expression of FHL2 in AMC induced by high phosphate was examined in cultured arterial rings. The regulation of FHL2 on β-catenin and HIF-1α signaling during VOT was also examined in VSMCs, respectively.

Results: The expression of FHL2 was induced in VSMCs and arterial rings cultured in a high phosphate environment. Knockdown of FHL2 suppressed high-phosphate-induced Runx2 and osteocalcin expression and calcium deposition, whereas overexpression of FHL2 was sufficient to induce the expression of Runx2 and osteocalcin in VSMCs. Downregulation of FHL2 partially inhibited the high-phosphate-induced upregulation of active β-catenin and β-catenin-mediated gene transcription, whereas ectopic expression of FHL2 was able to induce active β-catenin and β-catenin-mediated gene transcription. Similarly, downregulation of FHL2 partially inhibited the expression of HIF-1α induced by high phosphate, while ectopic expression of FHL2 enhanced HIF-1α-mediated gene transcription, although it didn't significantly increase the expression of HIF-1α. Moreover, high phosphate induced physical interactions between FHL2 and β-catenin, FHL2 and HIF-1α, respectively, especially in the nucleus. Meanwhile, high phosphate also induced a combination of β-catenin and HIF-1α, suggesting that the high-phosphate-induced upregulation of FHL2 facilitates the formation of a FHL2/β-catenin/HIF-1α ternary complex.

Conclusions: Our results suggest that FHL2, through activating β-catenin and HIF-1α signaling, plays a notable role in regulating high-phosphate-induced VOT and could be a potential therapeutic target for AMC in patients with chronic kidney disease.

Funding: Government Support - Non-U.S.

PO0333

CKD Decreases Cardiac PGC-1α Through Activin A Disrupting Mitochondrial Function

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Background: The CKD-MBD syndrome is a cause of cardiac risk. Our hypothesis was that a new component of the syndrome, activin A, is responsible for systemic activation of activin receptor (ActRII) signaling in kidney disease, and is a mechanism of cardiac disease.

Methods: Two models of CKD were employed, Col4A5 Alport Syndrome mice and ablative CKD in Rosa26 cre ERT+/inhbafl/fl mice. Inhibition of Activin A in CKD was accomplished by either knockdown in Rosa26 cre ERT+/inhbafl/fl CKD mice or by monoclonal antibody in Alport mice. PGC-1α, mitochondrial gene expression and oxidative phosphorylation were measured by PCR and western analysis Cardiac mitochondrial respiration was measured by respirometry.

Results: In two kidney disease models, we show that activin A is the responsible ligand for cardiac and aortic ActRIIA activation in CKD. In untreated CKD mice, cardiac levels of pSmad2 and inhibin βa mRNA and preprotein (activin A monomer) were increased. Activin A inhibition, accomplished by either knockdown in Rosa26 cre ERT+/inhbafl/fl CKD mice or by monoclonal antibody in Alport mice, prevents CKD-induced cardiac ActRIIA activation and loss of PGC-1α, the master regulator of mitochondrial biogenesis and fatty acid oxidative phosphorylation. Mitochondrial gene expression and oxidative phosphorylation were decreased by CKD but prevented by activin A inhibition in CKD. Cardiac hypertrophy by echocardiography and heart weight was increased by CKD and prevented by activin A inhibition in the absence of vascular stiffness and without change in FGF23 levels.

Conclusions: We conclude that activation of cardiac activin/ActRIIA signaling by CKD induces mitochondrial dysfunction through decreased PGC-1α which contributes to compensated cardiac hypertrophy in the early stages of CKD associated cardiac disease.

Funding: NIDDK Support, Commercial Support - Regeneron

PO0334

Response of Bone to Acid: Effect of Deletion of the Proton Receptor OGR1 in the Osteoblast

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Background: Metabolic acidosis induces bone resorption by inhibiting osteoblast (OB) bone formation and stimulating osteoclast (OC) bone resorption. Mice generate large amounts of endogenous acid and we have shown that OGR1 is the proton (H^+) receptor in bone and is stimulated by this endogenous acid. Mice with a global deletion of OGR1 have increased bone density which appears due to increased bone formation. There is communication between OB and OC and OGR1 is present in both. To determine if the response of OGR1 in the OB is independent of a response in OC, we generated a conditional knockout with an osteoblast-specific deletion of OGR1 (OB-cKO).

Methods: OB-cKO mice were generated from a col1a-cre mouse and an OGR1flox/flox mouse. We examined bones from 3 month old female mice using micro-computed tomography (μCT) and immunohistochemistry. Bone marrow mesenchymal stem cells (BMSC) from femurs of OB-cKO and wild type (WT) mice were differentiated to OB. Mineralization was detected with alizarin red and gene expression was analyzed by QPCR. All indicated changes are significant ($p<0.05$).

Results: Immunofluorescent staining of OGR1 in differentiated OB from BMSC confirmed the absence of OGR1 in OB-cKO cells compared to WT. μCT demonstrated an increase in tibia cortical bone area (0.76±0.01 vs 0.71±0.01 mm^2), but no change in femoral cortical bone in OB-cKO compared to WT. Femoral trabecular bone was decreased (8.64±1.03 vs 11.81±0.70 %BV/TV), but there was no change in tibia trabecular bone. Alizarin red staining of differentiated BMSC showed greater mineralization of OB from OB-cKO mice compared to WT (5.14±0.02 vs 4.39±0.03 relative intensity). Relative gene expression of *col1a* (1.53±0.15 vs 0.88±0.10), *osteocalcin* (1.79±0.05 vs 1.13±0.18) and *RANKL* (2.89±0.48 vs 1.11±0.21) was higher in differentiated BMSC from OB-cKO mice compared to WT cells.

Conclusions: Our results demonstrate that specific loss of OB OGR1 alters the response of bone to endogenous acid on bone content, in vitro mineralization and gene expression compared to WT, indicating that the response of OGR1 in the OB is independent of the response in OC. Characterization of the direct role of OGR1 in acid-induced bone resorption may assist in understanding bone loss associated with the metabolic acidosis in patients with chronic kidney disease.

Funding: NIDDK Support, Private Foundation Support

PO0335

Testing Patterns for CKD-MBD Abnormalities Before and After Treatment

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Background: We examined patterns of testing, treatment, and retesting after treatment initiation in CKD-MBD to determine if they were concordant with KDIGO guidelines.

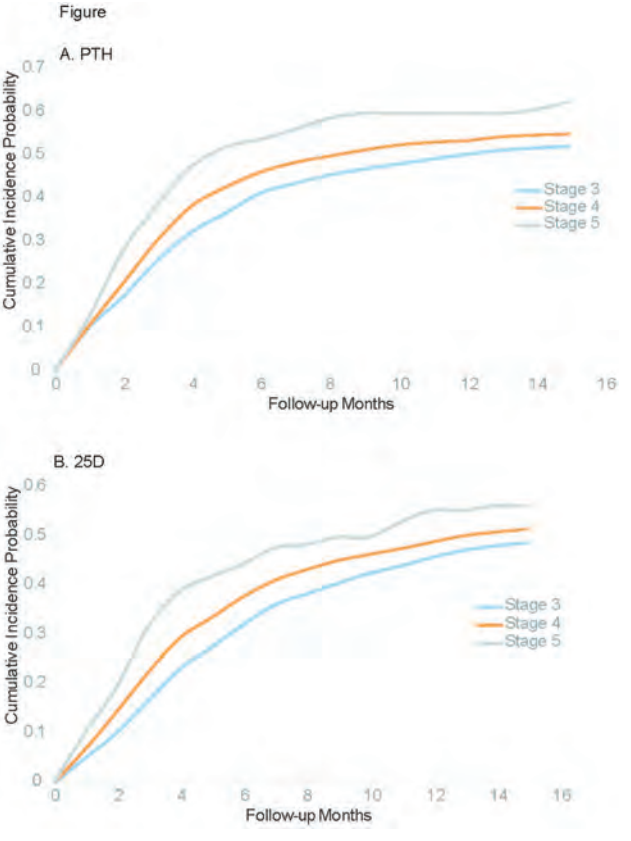
Methods: We utilized 2010-19 data from IBM Explorys, an electronic health database. We created cohorts of incident CKD stage 3, 4, and 5 patients using a diagnosis code for CKD stage and a confirmatory eGFR lab value. Patterns of lab test ordering for PTH, phosphorus, 25D, calcium, and ALP and drug prescribing for activated vitamin D compounds, nutritional vitamin D, and phosphate binders were assessed during follow-up. We estimated the cumulative incidence of lab retesting following treatment (with death as a competing risk). We used multivariable Cox regression to examine whether pre-treatment test result values predicted retesting.

Results: We identified 215,553 stage 3, 43,576 stage 4, and 11,407 stage 5 CKD patients; mean follow-up was 2.3, 1.7, and 0.6 years, respectively. Only 46% of stage 4 and 41% of stage 5 patients underwent a PTH test; only 74% and 73%, respectively, a test for phosphorus; and only 38% and 25%, respectively, a test for 25D. By one year after treatment with activated vitamin D compounds, only 50% (stage 3), 53% (stage 4), and 60% (stage 5) of patients had received retesting for PTH [Figure]. By one year after treatment with 25D, retesting of 25D occurred in 46% (stage 3), 49% (stage 4), and 55% (stage 5) of patients by one year. Pretreatment levels of PTH and 25D were not associated in a graded fashion with retesting after treatment commenced.

Conclusions: Frequency of initial testing and retesting following treatment initiation are suboptimal. Unexpectedly, patients with the highest and lowest pre-treatment levels of PTH and 25D, respectively, did not have the highest rate of retesting, suggesting room for improvement.

Funding: Commercial Support - OPKO

Figure



PO0336

Using a Quantitative Systems Pharmacology Model of CKD-MBD to Guide Therapy Minimizing Calcium Flux from Bone and into Vasculature

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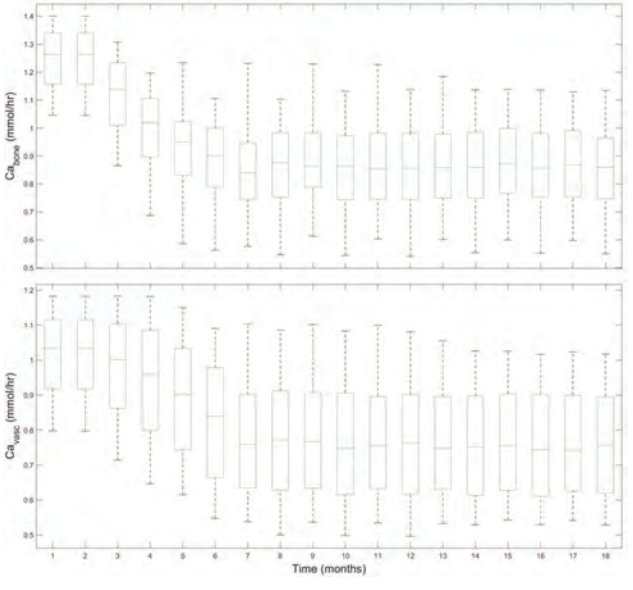
Background: CKD-MBD is characterized by bone loss and vascular calcification. Pharmacologic treatment of CKD-MBD involves dosing of three agents to minimize these complications through optimal balance of Calcium (Ca), Phosphorus (P), and PTH. Having developed a Quantitative Systems Pharmacology (QSP) model of CKD-MBD, we test the hypothesis that an AI method called Deep QLearning (DQL) in conjunction with our model can be used to determine the impact of precision therapy on the mineralization defect in patients with End Stage Renal Disease (ESRD).

Methods: Applying a quantitative systems pharmacology (QSP) model of CKD-MBD to mimic disease progression, we trained a Deep Neural Network (virtual physician) to minimize the Ca bone efflux and the Ca vascular tissue influx regardless of achieved serum Ca, P, and PTH predicted by the model. The virtual physician observed Ca, P, PTH and adjusted the doses of P binder, vitamin D, and a calcimimetic. We evaluated a trained virtual physician through simulation of CKD-MBD treatment over 18 months on a population of 100 virtual ESRD patients with varying baseline Ca, P, PTH levels, P intake, and Ca sensing receptor sensitivity.

Results: Simulations produced an average 30% decrease in bone Ca efflux and a 20% decrease in Ca influx to vascular tissue over baseline values. Average P decreased from 7.4 to 5.1 mg/dL, average Ca increased from 8.5 to 9.2 mg/dL, median PTH decreased from 1650 to 315 pg/mL.

Conclusions: Using a QSP model of CKD-MBD, we trained an AI agent to minimize the Ca fluxes from the bone and into the vascular tissue by prioritizing optimization of Ca fluxes over the achievement of specific Ca, P, and PTH levels. Our approach demonstrates beneficial synergy of Systems Biology and AI in modeling complex biologic processes.

Funding: Veterans Affairs Support



Change in Ca flux distributions over time in the simulated patient cohort.

PO0337

Mineral Metabolism Changes in Renal Transplantation

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Background: Successful renal transplant restores many physiologic abnormalities. The aim of this study was to analyse the evolution of CKD-MBD players [alpha-klotho, fibroblast grow factor (FGF) 23, sclerostin, parathyroid hormone (PTH), bone alkaline phosphatase (bAP), calcitonin, vitamin D (vitD), phosphorus (Pi), Calcium (Ca) and Magnesium (Mg)] pre and post transplantation.

Methods: Prospective cohort study of *de novo* renal transplanted patients (pts). A inclusion and after 12 months (time 0 and 1) pts performed laboratory evaluation. The difference between values (time1 - time 0) is the delta value. Associations between variables were performed using Wilcoxon matched-pairs test and Spearman correlation test. STATA software was used and $p < 0.05$ was considered statistically significant.

Results: We recruited 85 pts in 29 months and included 69 pts in the study. Mean age 50.2±12.4 years, 48 men, 53 caucasian (78.8%), median BMI 24.5 (22.7 – 27.8), median dialysis vintage 55 (42 – 84). We observe a significant reduction on Pi, Mg, PTH, calcitonin, sclerostin, bAP and FGF23. Both Ca and alpha-klotho levels increased, with no significant changes in vitD levels. With restoring renal health (time 1) and comparing with time 0, PTH maintain the negative correlation with sclerostin ($p=0.02$) and the positive correlation with FGF23 ($p=0.0002$); modify the correlation with Pi, becoming a negative correlation instead of positive ($p=0.001$) and gain new correlations with Ca ($p=0.001$) and vitD levels ($p=0.03$). Also, PTH correlated with the delta FGF23 (rho=-0.4, $p=0.003$) and sclerostin correlated with delta PTH ($p=0.01$). FGF23 didn't reveal statistical association with Pi or Ca levels after transplant, contrasting with positive associations in pre transplant ($p=0.002$, $p<0.0001$). On the contrary, sclerostin developed a new correlation with Pi ($p=0.0004$) and a negative correlation with Ca ($p=0.01$). We didn't find correlations between these molecules and alpha-klotho.

Conclusions: It seems that sclerostin influences PTH levels and that PTH is the stimulus for the increase or decrease of FGF23 serum levels. Levels of Ca and Pi seemed to be directly influenced by the level of PTH in post transplant, and those minerals seemed to be key factors for sclerostin secretion.

PO0338

Quantitative Systems Pharmacology Approach to the Treatment of CKD Metabolic Bone Disorder (CKD-MBD) Using Deep Learning

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Background: CKD-MBD is a common comorbidity that leads to serious skeletal and cardiovascular complications. Using a Systems Biology model of CKD-MBD and Artificial Intelligence (AI) -guided precision dosing approach, we tested the hypothesis that this approach can effectively achieve recommendations for Ca, P, and PTH by balancing the administration of vitamin D and a calcimimetic when faced with varying adherance to phosphate binder dosing.

Methods: Using a Quantitative Systems Pharmacology (QSP) approach to model the disease trajectory, we trained a Deep Neural Network AI-agent to adjust doses of a P binder, vitamin D, and a calcimimetic to drive P, Ca, and PTH to recommended targets. We evaluated the agent through treatment simulation in a cohort of 100 virtual patients (defined by dietary P and sensitivity of the Ca receptor) under 3 experimental conditions: 100%, 50%, and 0% adherence to P binder prescription. Using model derived doses of vitamin D and calcimimetic, we analyzed the effect of P binder adherence on achieving the recommended Ca, P, and PTH target ranges. Drug doses were determined by simultaneously maximizing the percent in range of Ca, P, and PTH while minimizing the changes in bone Ca efflux and vascular Ca influx. Simulations were performed over 18 months.

Results: Results are shown in Table 1.

Conclusions: Using a QSP model of CKD-MBD, we trained an AI agent to guide precision dosing of P binder, vitamin D, and calcimimetic. We validated the agent under three simulated scenarios of P binder adherence. Simulation results show that control of intestinal P absorption is paramount in treatment of CKD-MBD. Failure to control P level severely limits ability to control vascular tissue calcification even when Ca and PTH are controlled pharmacologically.

Funding: Veterans Affairs Support

P binder adherence (%)	100	50	0
P 3-5 mg/dL (%)	55	25	3.5
P mean±std (mg/dL)	5.1±0.9	6.1±1.2	7.3±1.3
Ca 8.5-9.5 mg/dL (%)	80	90	95
Ca mean±std (mg/dL)	9.2±0.3	9.0±0.3	8.9±0.2
PTH 200-600 pg/mL (%)	85	88	90
PTH median±iqr (pg/mL)	315±138	332±150	288±75
Δ bone Ca Efflux (%)	-30	-30	-23
Δ vascular Ca influx (%)	-20	-10	+10

PO0339

Differences in 25-Hydroxyvitamin D Clearance by eGFR and Race: A Pharmacokinetic Study

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Background: 25-hydroxyvitamin D (25(OH)D) clearance is an essential yet often overlooked determinant of circulating 25(OH)D concentration, the prevailing marker of vitamin D status. Observational studies associate markers of low 25(OH)D clearance with poor clinical outcomes and suggest differences in 25(OH)D clearance by kidney function and race, but these potential variations have not been tested using gold-standard methods.

Methods: We administered intravenous deuterated 25(OH)D_3 (d-25(OH)D_3) in a pharmacokinetic study of 87 adults with a wide range of kidney function, including normal estimated glomerular filtration rate (eGFR ≥ 60 ml/min/1.73m^2, n=43), non-dialysis chronic kidney disease (CKD; eGFR < 60 ml/min/1.73m^2, n=24), and kidney failure treated with hemodialysis (n=20). We measured d-25(OH)D_3 and deuterated 24,25-dihydroxyvitamin D_3 concentrations 5 minutes, 4 hours, and 1, 4, 7, 14, 21, 28, 42 and 56 days post-administration. We calculated 25(OH)D clearance using non-compartmental analysis of d-25(OH)D_3 concentrations over time. We re-measured 25(OH)D clearance in a subset of participants after 12-16 weeks of 2000 IU/day of oral vitamin D_3 (n=18).

Results: The mean age of the study cohort was 64 ± 11 years; 41% were female and 30% were black. Mean 25(OH)D clearances were 360 ± 108, 313 ± 86 and 263 ± 163 mL/day in participants with normal eGFR, CKD and kidney failure respectively (p = 0.02). After adjustment, lower eGFR was associated with reduced 25(OH)D clearance (-17 mL/day per 10 ml/min/1.73m^2 decrement, 95% CI: -21, -12). Black race was associated with higher 25(OH)D clearance in participants with normal eGFR (71 mL/day, 95% CI: 16, 125), but not in those with CKD or kidney failure (p-for-interaction = 0.052). 25(OH)D clearance did not differ after compared with before vitamin D_3 supplementation, although lower 25(OH)D clearance was correlated with a larger increase in serum total 25(OH)D concentration following supplementation (r = -0.41).

Conclusions: Through direct pharmacokinetic measurements, these findings confirm impaired 25(OH)D clearance as a feature of disordered mineral metabolism in CKD, and may help understand racial differences in vitamin D metabolism. Surrogate measures of 25(OH)D clearance may allow clinicians to more accurately anticipate individual response to vitamin D supplementation.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health

PO0340

The Vitamin D Metabolite Ratio and Change in Bone Density and Fracture Risk in Older Adults

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Background: Recent studies have suggested that 25-hydroxyvitamin D [25(OH)D] may be a poor biomarker of bone health. Higher concentrations of its catabolic product 24,25-dihydroxyvitmin D [24,25$(OH)_2D_3$] and a higher ratio of 24,25$(OH)_2D_3$ to 25(OH)D_3 (the vitamin D metabolite ratio [VMR]) may provide additional information on vitamin D receptor activity and bone health.

Methods: We measured 24,25$(OH)_2D_3$, 25(OH)D_3, 25$(OH)_2D_3$ and serial bone densitometry scans over a 9-year period, in 761 community dwelling older adults, that participated in the Health Aging and Body Composition Study. Participants were followed for a median time of 11 years for any fractures. 24,25$(OH)_2D_3$ and 25(OH)D_3 were used to calculate the VMR. We used linear mixed models to assess the relationship between 24,25$(OH)_2D_3$, 25(OH)D_3,1,25$(OH)_2D_3$ and the VMR with annual change in hip, lumbar and thoracic spine bone mineral density (BMD). We used Cox models to assess the relationships between these parameters and fracture risk.

Results: Study participants had mean age 75+/- 3 years, 49% were female, 42% were black, and 23% had CKD. In fully adjusted models, a doubling of VMR and 24,25$(OH)_2D_3$ were associated with an 0.6% (95% CI 0.3, 0.9%) and an 0.3% (95% CI 0.1, 0.3%) increase in annual change in hip BMD, respectively (**Table 1**). We found similar relationships with thoracic and lumbar spine BMD. 25(OH)D_3 and 1,25$(OH)_2D_3$ concentrations were not associated with any of the BMD measurements. There were 194 fractures in follow-up. A higher VMR was associated with a lower risk of fracture [HR 0.71 (95% CI 0.51, 0.97) per doubling of VMR, **Table 1**]. Associations of 24,25$(OH)_2D_3$, 25(OH)D_3,1,25$(OH)_2D_3$ with fracture risk did not reach statistical significance.

Conclusions: In diverse cohort of community dwelling older adults, a higher VMR was associated with improvement in BMD and a lower risk of fracture. Trials are needed to evaluate the VMR as a therapeutic target in persons at risk for worsening BMD and fracture.

Funding: NIDDK Support, Private Foundation Support

Table 1: Adjusted Association of Vitamin D Metabolites and the VMR with Change in Hip BMD and Risk of Fracture*

	Annual Change in Hip BMD Per Doubling of Metabolite (95% CI)	P	HR of Fracture Per Doubling of Metabolite (95% CI)	P
24,25$(OH)_2D_3$	0.3% (0.1%, 0.4%)	0.003	0.84 (0.71, 1.00)	0.051
25(OH)D_3	0.2% (-0.1%, 0.5%)	0.190	0.85 (0.65, 1.11)	0.223
1,25$(OH)_2D_3$	0.1% (-0.2%, 0.4%)	0.598	0.77 (0.56, 1.05)	0.102
VMR	0.6% (0.3%, 0.9%)	<0.001	0.71 (0.52, 0.97)	0.031

*Model adjusted for age, sex, race, season, site, BMI, eGFR, Ca, Phos, PTH and FGF23

PO0341

The Vitamin D Metabolite Ratio Is Independent of Vitamin D Binding Protein Concentration

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Background: 25-hydroxyvitamin D [25(OH)D] may be a poor marker of vitamin D status due to variability in vitamin D binding protein (VDBP) between individuals and groups. The vitamin D metabolite ratio [VMR, the ratio of 24,25(OH)2D3 to 25(OH)D3] is a marker of vitamin D status that has been hypothesized to be independent of variability in VDBP. This hypothesis has not been directly evaluated.

Methods: We measured 25(OH)D3, 24,25(OH)2D3, 1,25(OH)2D3, and VDBP in 377 community dwelling older adults that participated in the Health Aging and Body Composition Study. 24,25(OH)2D3 and 25(OH)D3 were used to calculate the VMR. We used linear regression to assess the relationship between VDBP with the VMR, 24,25(OH)2D3, 25(OH)D3, and 1,25(OH)2D3.

Results: Study participants had mean age 75+/- 3 years, 52% were female, 40% were black, and 24% had CKD. Lower VDBP concentrations were associated with male sex, lower serum albumin and Gc2/Gc2 VDBP phenotype in multivariable models. In fully adjusted models, each 1% higher VDBP was associated with a 0.92%, 0.76% and 0.57% higher 24,25(OH)2D3, 25(OH)D3, and the 1,25(OH)2D3 (**Table 1**). The VMR was independent of VDBP concentration, [0.16% (95% CI(-0.11, 0.44)) higher VMR per 1% higher VDBP, p=0.247].

Conclusions: In diverse cohort of community dwelling older adults, the VMR was independent of VDBP concentration whereas VDBP was strongly directly associated with the individual vitamin D metabolite concentrations. The VMR may serve as an important biomarker of vitamin D status and clinical outcomes that can be utilized in populations with a large spectrum of VDBP concentrations

Funding: NIDDK Support, Private Foundation Support

Table 1. Association of VDBP with Vitamin D Metabolites and the Vitamin D Metabolite Ratio

	24,25 D		25D		1,25D		VMR	
	β coef (95% CI)	P Value	β coef (95% CI)	P Value	β coef (95% CI)	P Value	β coef (95% CI)	P Value
Adjusted Model *	0.92 (0.37, 1.49)	0.001	0.76 (0.39, 1.13)	<0.001	0.57 (0.29, 0.85)	<0.001	0.16 (-0.11, 0.44)	0.247

* Data reported is for natural logarithm of the VMR, vitamin D metabolites and natural logarithm of DBP
Model adjusted for age, sex, race, season, site, BMI, eGFR, phosphate, calcium, PTH, FGF23, VDBP phenotype, and albumin.

PO0342

Meta-Analysis of the Impacts of Supplementation with Nutritional Vitamin D on Mineral and Bone Markers in Non-Dialysis CKD

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Background: Secondary hyperparathyroidism (SHPT) is a critical component of mineral and bone disorder in chronic kidney disease (CKD-MBD), characterized by excessive parathyroid hormone (PTH) secretion and low levels of vitamin D. Nutritional vitamin D (NVD) supplements are frequently used to treat SHPT, especially in early CKD. The objective of this meta-analysis (MA) was to evaluate the impact of NVD supplements on PTH, vitamin D (25D), calcium (Ca), phosphate (P) and fibroblast growth factor 23 (FGF23).

Methods: Study level results were pooled using a fixed effect model with inverted-variance weighting. The impact of the NVDs was measured in two ways: as change versus placebo or 'no treatment' and as change within the NVD study arm (before versus after NVD supplementation).

Results: Overall changes in PTH from NVD supplementation were small when measured within the NVD study arms (pooled reduction of 10.53 pg/ml, 95 % confidence interval (CI): -16.33 to -4.73) but larger when compared to placebo/no treatment (reduction of 49.74 pg/ml, 95 % CI: -70.17 to -29.3). NVDs tended to increase levels of 25D both within the NVD study arms (increase of 20.62 ng/ml, 95 % CI: 19.58 to 21.65) and when compared to placebo/no treatment (increase of 26.87 ng/ml, 95 % CI: 24.44 to 29.30). At the end of the study periods, average levels of 25D in the NVD study arms were >30 ng/ml in all but two RCTs and >50 ng/ml in only five of the included RCTs. Ca levels increased statistically significant from supplementation with NVDs versus placebo/no treatment (increase of 0.23 mg/dl, 95 % CI: 0.12 to 0.34 mg/dl). Only small and statistically non-significant impacts were observed on levels of P and FGF23.

Conclusions: Our results suggest that the magnitude of 25D increase caused by NVD may be insufficient to effectively and consistently lower PTH. While supplementation with NVDs can be used to correct vitamin D insufficiency, the potential of NVDs to actively reduce PTH in ND-CKD patients with SHPT is limited.

Funding: Commercial Support - Vifor Pharma

PO0343

Fibroblast Growth Factor 23 (FGF-23), Calcification Propensity, and Heart Failure with Preserved Ejection Fraction (HFpEF) in Patients with CKD: The CRIC (Chronic Renal Insufficiency Cohort) Study

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Background: HFpEF represents half of all HF events and is common in patients with CKD. Given lack of treatments, identifying factors that impact HFpEF development is critical. FGF23 is an osteocyte-derived hormone involved in phosphorous homeostasis and is implicated in HF development. Calcification propensity (T50) is an in vitro assessment of the time for secondary calciprotein particle formation.

Methods: Using multivariable adjusted Cox proportional hazards models, we investigated the associations of FGF23 and T50 with incident HFpEF. FGF23 and T50 were measured at the baseline and Year 1 visits, respectively. Incident HFpEF was

defined as ejection fraction > 50% on echocardiogram at the time of event or by a CRIC Study echocardiogram within 1 year. After excluding individuals with baseline HF and individuals with HF events prior to analyte measurement, we included 3502 and 3029 individuals for our FGF23 and T50 analyses, respectively.

Results: In the FGF23 cohort, 333 incident HFpEF events occurred over a median follow-up of 10.8 years. In the T50 cohort, 259 incident HFpEF events occurred over a median follow-up of 10.2 years. Individuals in the highest FGF23 and lowest T50 quartiles had the highest rates of incident HFpEF (Figure). When adjusted for demographics, cardiovascular risk factors and kidney function, elevated FGF23, but not T50, was independently associated with incident HFpEF (Table).

Conclusions: FGF23, but not T50, was associated with incident HFpEF in patients with CKD. These data are consistent with studies demonstrating cardiac toxicity of FGF23 and may inform future trials of HFpEF development in CKD.

Funding: NIDDK Support, Other NIH Support - R01s and K awards

Figure 1. Rates of Incident HFpEF Events by FGF23 and T50 Quartiles

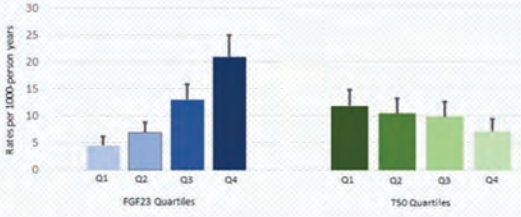

Table 1. FGF23 and T50 and HFpEF events

FGF23 and incident HFpEF events – 333 HFpEF events over 10.8 years follow-up				
Unadjusted	Model 1	Model 2	Model 3	Model 4
1.71 (1.56, 1.87)	1.73 (1.57, 1.91)	1.53 (1.36, 1.72)	1.43 (1.25, 1.62)	1.38 (1.21, 1.58)
T50 and incident HFpEF events – 259 events over 10.2 years follow-up				
Unadjusted	Model 1	Model 2	Model 3	Model 4
1.15 (1.02, 1.30)	1.04 (0.92, 1.19)	0.96 (0.84, 1.09)	0.90 (0.79, 1.02)	0.88 (0.77, 1.00)

Results are reported as hazard ratios per 1 SD increase in natural log FGF23 and per 1 SD decrease in natural log T50. Covariates for the FGF23 analyses are from Visit 3 and for T50 analyses are from Visit 5.

Model 1: adjusted for age, sex, race, and ethnicity

Model 2: Model 2 plus eGFR and UPCR

Model 3: Model 2 plus diabetes, smoking, systolic blood pressure, any cardiovascular disease, total cholesterol, statins, anti-hypertensive medications, phosphate, ln_PTH

Model 4: time-varying eGFR

Abbreviations: FGF23, fibroblast growth factor 23; HFpEF, heart failure preserved ejection fraction; SD, standard deviation; eGFR, estimated glomerular filtration rate; UPCR, urine protein-creatinine ratio; ln_PTH, natural log parathyroid hormone

PO0344

Genetic Determinants of Circulating Fibroblast Growth Factor 23 and Risk of Coronary Artery Disease

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Background: Observational studies suggest that elevated levels of circulating fibroblast growth factor-23 (FGF-23) contribute to the burden of cardiovascular disease, in the setting of chronic kidney disease and in the general population. These studies can suffer from confounding and reverse causation, limiting their ability to identify causal associations. Mendelian randomization (MR) has emerged as a powerful study design to provide evidence supporting or refuting causality by utilizing the genetic determinants of a risk factor. We used MR to evaluate whether genetically predicted higher FGF-23 levels are associated with the risk of coronary artery disease (CAD).

Methods: We performed two-sample MR of the relationship between FGF-23 and CAD with the use of summary statistics from the CARDIoGRAMplusC4D consortium's genome-wide association meta-analysis of 48 studies with a total of 60,801 CAD cases and 123,504 non-cases. We selected 5 single nucleotide polymorphisms (SNPs) robustly associated with FGF-23 at genome-wide significance among 16,624 individuals as instrumental variables.

Results: A genetic predisposition to higher FGF-23 levels was associated with CAD. In conventional MR analysis, the odds ratio of CAD was 1.44 (95% confidence interval 1.14 to 1.7, p=0.03) per 10-fold increase in genetically predicted FGF-23 levels. Results were consistent in sensitivity analyses using the weighted median and heterogeneity-penalized model averaging methods.

Conclusions: This study provides evidence that FGF-23 levels are causally associated with risk of CAD. Whether interventions to lower FGF-23 result in decreased risk of CAD remains to be determined but warrants investigation.

Funding: NIDDK Support

PO0345

Renal Clearance of Intact and C-Terminal FGF-23 in Man

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Background: The ratio of C-terminal (cFGF23) to Intact FGF23 (iFGF23) is higher in persons with higher eGFR. Mechanisms are unclear. Differential renal clearance is one possibility.

Methods: Patients were referred for clinically suspected renal artery stenosis (RAS), and maintained off BP meds for 21 days before angiography. This study includes those found without RAS (N=93). Blood was obtained from the aorta (Ao) and bilat. renal veins (RV), and renal blood flow (RBF) was measured using ^{131}Xenon washout. Single pass % reductions of each measure ([Ao – RV/Ao]*100) was calculated, left and right was averaged, and multiplied by RBF to provide renal clearance in ml/min/100g kidney tissue. To determine the relative renal clearance, we calculated the cFGF23/iFGF23 clearance ratio (C/I ratio) and evaluated its relationship with eGFR.

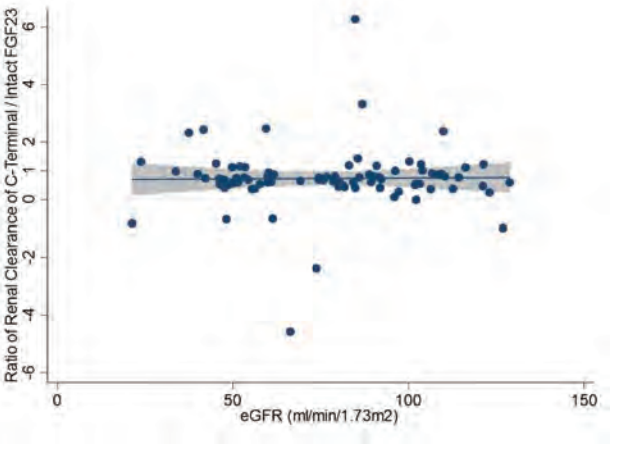
Results: Mean age was 52±11 years, 22% were women, all were white, eGFR was 77±26 ml/min/1.73m^2 and directly measured Cr clearance was 72 ± 42 ml/min/100g. Renal clearance of cFGF23 was similar to Cr, while iFGF23 was 37% higher (C/I ratio 0.73 ± 1.10). The clearance of cFGF23 and iFGF23 were directly correlated to eGFR (r=0.31 and 0.35). However, their relative clearance was similar across the range of eGFR (r=0.01). Results were similar in models adjusted for age, sex, and BMI

Conclusions: Renal cFGF23 clearances (which measures both iFGF23 and c-terminal fragments) is similar to Cr, whereas iFGF23 clearance is higher, suggesting that renal clearance of c-terminal fragment clearance is low. While renal cFGF and iFGF23 clearance were both reduced in persons with lower eGFR, the relative efficiency of clearance of cFGF23 vs. iFGF23 appeared similar across the range of eGFR.

Funding: NIDDK Support

Single Pass Percent Reduction and Renal Clearance of C-terminal and Intact FGF23 in Man (N=93)

	Single Pass % Reduction	Renal Clearance (ml/min/100g)
Creatinine	15.7 ± 8.3	71.8 ± 41.4
C-terminal FGF23	15.5 ± 11.9	69.7 ± 57.8
Intact FGF23	21.6 ± 15.4	96.9 ± 75.2



PO0346

Association of Changes in Levels of eGFR and Fibroblast Growth Factor 23 from Midlife to Late Life with Risk of Mortality: The ARIC Study

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Background: Aging from midlife to late-life involves the dynamics of levels of eGFR and fibroblast growth factor 23 (FGF23). Whether changes in levels of eGFR and FGF23 from midlife to late-life are independently and jointly associated with subsequent risk of mortality is unknown.

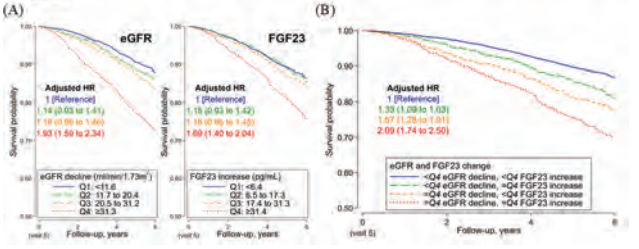
Methods: We included 5639 participants of the Atherosclerosis Risk in Communities Study who had eGFR and serum level of FGF23 measured during midlife (visit 3, 1993-1995, mean age 58 [SD, 5] years, 58% women, 23% black race) and late-life (visit 5, 2011-2013, mean age 76 years). We used Cox regression to examine the associations of past changes in levels of eGFR and FGF23 levels (in quartiles)-- separately and jointly-- with mortality from visit 5 (2011-2013) through December 31, 2017.

Results: The median eGFR 15-year decline (from visit 3 to 5) was 20.5 ml/min/1.73m^2 (from median eGFRs 87.8 to 65.7 ml/min/1.73m^2). The median FGF23 increase was 17.4 pg/mL (median FGF23s 37.5 to 54.8 pg/mL). During a median follow-up of 5.5 years after visit 5, 868 participants died. Adjusted HRs of mortality were 1.93

(95%CI, 1.59-2.34) for the highest quartile for eGFR decline, and 1.69 (1.40-2.04) for the highest quartile for FGF23 increase compared the lowest quartile (**Figure A**). When assessing in the cross-category of eGFR and FGF23 changes, the risk was highest for the highest quartiles of eGFR decline and FGF23 increase (HR, 2.09 [1.74-2.50]; **Figure B**).

Conclusions: In this community-based cohort, greater eGFR decline and FGF23 increase from midlife to late-life were independently associated with a higher risk of mortality, with the risk highest when eGFR decline was accompanied by FGF23 increase.

Figure: Changes in eGFR and FGF23 levels and subsequent risk of mortality. The HRs were adjusted for age, sex, race, Medicare Advantage enrollment status, diabetes, ever smoke, systolic blood pressure, hypertension medication, total cholesterol, high-density lipoprotein cholesterol, and history of heart failure, coronary heart disease, and stroke. Interaction between eGFR and FGF23 changes was not significant.



PO0347

Intact and C-Terminal Fibroblast Growth Factor 23 Assays: Do Kidney Function, Inflammation, and Iron Deficiency Influence Relationships with Clinical Outcomes?

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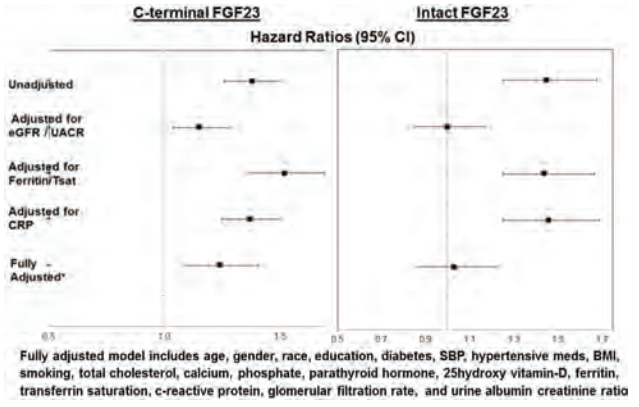
Background: Higher fibroblast growth factor-23 (FGF23) concentrations are associated with heart failure (HF) and mortality, but strengths of associations differ depending upon FGF23 assay type. We investigated whether iron deficiency, inflammation, and kidney function account for these differences.

Methods: In 844 Cardiovascular Health Study participants, using a case-cohort design, we examined associations of intact and C-terminal FGF23 with risk of mortality and HF, using modified Cox models to account for case-cohort design, adjusting sequentially by iron status, inflammation, kidney function or their combinations.

Results: C-terminal FGF23 more strongly correlated with ferritin (r= -0.26) and CRP (r= 0.21) than intact FGF23 (r=0.04 & r=0.07, respectively). The two FGF23 assays moderately correlated with one another (r=0.47). During follow up, there were 658 deaths, and 220 incident HF events. FGF23 measured by either assay was associated with mortality in unadjusted analysis (intact FGF23 HR per two-fold higher 1.45; 1.25-1.68; C-terminal FGF23 1.38; 1.26-1.50). Adjustment for kidney function completely attenuated associations of intact FGF23 with mortality (HR 1.00; 0.85, 1.17; **Figure 1**), but had less influence on the C-terminal FGF23-mortality association (HR 1.15; 1.04, 1.28). Results were similar for HF where the HR for intact FGF23 went from 1.57 (1.25, 1.97) to 0.99 (0.76, 1.28) with eGFR and albuminuria adjustment, whereas C-FGF23 went from 1.45 (1.25, 1.68) to 1.16 (0.97, 1.38). Adjustment for iron deficiency and inflammation did not meaningfully influence the differential associations of the two assays with either endpoint.

Conclusions: The associations of biologically active FGF23 with clinical endpoints may be weaker than previously thought.

Funding: NIDDK Support



Effects of Adjustment for Iron Parameters, Inflammation, and Kidney Function on the Associations of C-terminal and intact FGF23 with Mortality

PO0348

Factors Associated with Change in Fibroblast Growth Factor 23 Levels from Midlife to Late-Life: The ARIC Study

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Background: Factors associated with change in fibroblast growth factor 23 (FGF23) levels from midlife to late-life are not well-characterized in the general population.

Methods: Among 5,881 participants of the Atherosclerosis Risk in Communities Study who had serum level of FGF23 measured during midlife (visit 3, 1993-1995, mean age 58 years, 58% women, 23% black race) and late-life (visit 5, 2011-2013, mean age 76 years), we explored demographic and clinical factors associated with change in FGF23 levels. Change in FGF23 levels was regressed on pre-specified factors assessed at visit 3 of age (above vs. below median), sex, race, ever smoke, high BMI (≥ vs. <30 kg/m^2), hypertension, diabetes, history of CVD, and reduced eGFR (≥ vs. <60 ml/min/1.73m^2) using multivariable linear regression models.

Results: The mean FGF23 level increased by 21.0 (95%CI, 20.3-21.6) pg/mL from 39.7 at visit 3 to 60.6 pg/mL at visit 5. Reduced eGFR, diabetes, hypertension, female, older age, and white race were significantly associated with a greater increase in FGF23 levels (**Table**). Although history of CVD demonstrated a similar magnitude as race, the β coefficient was not significant. We also did not observe significant associations for BMI or smoking. The associations were strongest for reduced eGFR and diabetes with similar degrees of associations (ΔFGF23, 6.7 [95%CI, 2.7 to 10.6] pg/mL for reduced eGFR and 6.7 [4.4 to 9.0] pg/mL for diabetes) independent of each other.

Conclusions: In addition to reduced eGFR, we identified diabetes, hypertension, female, older age, and white race as predictors of an increase in FGF23 levels from midlife to late-life. Among these, the strong association of diabetes independent of kidney function deserves future investigations.

Table: Factors associated with changes in FGF23 levels from midlife to late-life. Multivariable linear regression simultaneously included all factors listed here.

Characteristics at visit 3 (1993-1995)		No.	Mean increase in FGF23 (pg/mL) from visit 3 to 5	Adjusted difference in FGF23 change (pg/mL)
eGFR, ml/min/1.73m^2	≥60	5714	20.7 (20.1 to 21.4)	Reference (0)
	<60	167	29.2 (22.3 to 36.2)	+6.7 (2.7 to 10.6)
Diabetes	No	5332	20.3 (19.7 to 21.0)	Reference(0)
	Yes	549	27.3 (24.7 to 29.9)	+6.7 (4.4 to 9.0)
Hypertension	No	3942	19.3 (18.5 to 20.0)	Reference(0)
	Yes	1939	24.4 (23.1 to 25.7)	+4.7 (3.3 to 6.2)
Female	Male	2457	19.2 (18.2 to 20.2)	Reference (0)
	Female	3424	22.2 (21.4 to 23.1)	+3.7 (2.4 to 5.1)
Age, years	<57	2616	18.8 (17.9 to 19.8)	Reference (0)
	≥57	3265	22.7 (21.8 to 23.6)	+3.2 (1.9 to 4.5)
Race	Black	1256	20.2 (18.6 to 21.7)	Reference (0)
	White	4625	21.2 (20.5 to 21.9)	+2.7 (1.0 to 4.3)
Prevalent CVD	No	5634	20.8 (20.1 to 21.5)	Reference (0)
	Yes	247	24.7 (20.8 to 28.6)	+2.9 (-0.3 to 6.2)
Ever smoker	No	2692	20.9 (19.9 to 21.8)	Reference (0)
	Yes	3189	21.0 (20.1 to 21.9)	+1.1 (-0.2 to 2.4)
BMI kg/m^2	<30	4099	20.8 (20.0 to 21.5)	Reference (0)
	≥30	1782	21.4 (20.2 to 22.7)	-0.8 (-2.3 to 0.6)

PO0349

FGF-23 Is Induced by Glucocorticoid Stimulation In Vivo and In Vitro: Translational Approach

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Background: Previous data have suggested that glucocorticoid (GC) treatment may induce plasma fibroblast growth factor 23 (FGF23). Recently, we have reported that in prepubertal renal trasplantion children, chronic GC treatment was associated with increased plasma FGF23 levels, that was related to decreased bone growth in vivo and in vitro. Our objective was to evaluate whether GC treatment modulate FGF23 in adult patients.

Methods: Translational approach. This included an observational clinical study of patients who began GC treatment (prednisone 1 mg/kg/day), estimated glomerular filtration rate (eGFR) over 60 mL/min/1.7m2. Measurements of intact FGF23 were performed before initiation and 2 months later. Also we performed in vitro and in vivo analysis with cell cultures and experimental rat models which were treated with GC, measurements of plasma and bone FGF23 expression were performed.

Results: We recruited 10 patients who began GC treatment. We observed a significant increase in plasma intact FGF23 levels at 2 months (57% increase as compared to baseline values): baseline values: 18.9 +/- 4.2 pg/mL; 2 months: 29.7 +/- 5.2 pg/mL; p<0.001. No significant changes in renal function were detected. Also, rats treated with prednisone had a significant increase in plasma FGF23 and bone FGF23 expression after GC treatment. Finally, pharmacological blockage of glucocorticoid receptor alpha in vitro prevented the increase of FGF23 expression in bone tissue.

Conclusions: Sustained glucocorticoid treatment is associated to increased FGF23 expression and plasma levels. This effect should be evaluated in larger groups of patients to evaluate its potential relevance.

Funding: Government Support - Non-U.S.

PO0350

PTH 1-84 and Bone Alkaline Phosphatase Are Independently Associated with Mortality, Whereas FGF-23 Predicts Dialysis Initiation in CKD Patients

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Background: Despite the fact that CKD-MBD is a risk factor for CKD morbidity and mortality, the results of studies regarding the role of individual biomarkers are variable. In addition, dimensionality reduction techniques have not been applied in CKD-MBD. The aim of our study was to evaluate a panel of CKD-MBD biomarkers, namely Ca, P, PTH 1-84, FGF-23, 25-vitamin D, 1.25-vitamin D, bone alkaline phosphatase (BAP) and sclerostin, individually and collectively in relation to death and KRT.

Methods: Events of death and KRT in 454 participants of the Progredir Cohort (Sao Paulo, Brazil) with predominantly CKD G3 and G4 were ascertained after a median follow-up of 6 years. Those with missing values were excluded (n=25) and 4 were lost to follow-up. The association of individual CKD-MBD parameters (DiaSorin® assays) and factors derived from factorial analysis was evaluated through Cox and Competitive Risk models (R package "cmprsk").

Results: Mean age was 68(12)y, mean eGFR was 38(15) mL/min/1.73m^2, 63% were male and 56% diabetic. In univariable analysis, sclerostin, BAP, PTH, and factor 1 were associated with death and 1.25vitD, sclerostin, BAP, FGF-23, PTH, Ca, P, and factor 1 were associated with KRT. After adjustments, BAP, PTH, and factor 1 remained associated with death, and FGF-23 remained associated with KRT (Table). The addition of BAP and PTH (with interaction) to a reference model significantly improved the model fit for death (p=0.01). The addition of FGF-23 with interaction with P significantly improved the model fit for KRT (p=0.0046).

Conclusions: PTH and BAP are positively associated with death and improved its prediction model. This finding suggests that BAP could be reflecting not only bone turnover but also vascular calcification. FGF-23 is associated with the risk of KRT, showing interaction with P. Factorial analysis was helpful in identifying factors significantly associated with events but did not improve prediction.

Funding: Government Support - Non-U.S.

	Unadjusted		Model 1		Model 2	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Death (n=184)						
BAP (microg/L)	1.01 (1.00 to 1.02)	0.01	1.01 (1.00 to 1.02)	0.004	1.01 (1.00 to 1.02)	0.01
whole PTH (per 10, pg/mL)	1.04 (1.01 to 1.07)	0.01	1.05 (1.01 to 1.08)	0.01	1.05 (1.01 to 1.09)	0.01
Factor 1	1.20 (1.08 to 1.33)	0.0004	1.33 (1.15 to 1.52)	<0.0001	1.25 (1.07 to 1.46)	0.004
KRT (n=61)						
FGF-23 (per 10, pg/mL)	1.02 (1.01 to 1.02)	<0.0001	1.01 (1.001 to 1.01)	0.02	1.005 (1.001 to 1.01)	0.05
Serum phosphorus (mg/dL)	3.53 (2.53 to 4.90)	<0.0001	1.63 (1.06 to 2.51)	0.03	1.40 (0.91 to 2.17)	0.13

Model 1: adj. age, sex, eGFR; model 2: same as 1 + SBP, DM, MI, AUC, smoking.

PO0351

Parathyroid Hormone Serum Levels and Mortality Among Hemodialysis Patients in the Gulf Cooperation Council Countries: Results from the DOPPS (2012-2018)

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Background: The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) has collected data since 2012 in all six Gulf cooperation council (GCC) countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates). Here, we report the relationship of PTH with mortality in the largest GCC hemodialysis (HD) patient cohort studied to date.

Methods: Data were from randomly-selected national samples of HD facilities in GCC DOPPS phases 5 and 6 (2012-2018). PTH descriptive findings and case-mix adjusted PTH/mortality Cox regression analyses were based on 1825 and 1422 randomly-selected HD patients, respectively.

Results: Mean patient age was 55 years (median dialysis vintage = 2.1 years). Median PTH ranged from 259 pg/mL (UAE) to 437 pg/mL (Kuwait), with 22% having PTH <150 pg/mL, 24% (PTH 150-300), 34% (PTH 301-700), and 20% (PTH >700) pg/mL. Patients with PTH >700 pg/mL were younger, on dialysis longer, less likely to be diabetic, have urine>200 mL/day, prescribed 3.5 mEq/L dialysate calcium, had higher mean serum creatinine and phosphorus levels, lower white blood cell counts, and more likely to be prescribed cinacalcet, phosphate binders, or IV vitamin D. A "U-shaped" PTH/mortality relationship was observed with >2-fold and 1.5 fold higher adjusted HR of death at PTH>700 pg/mL and <300 pg/mL, respectively, compared to PTH 301-450 pg/mL.

Conclusions: Secondary hyperparathyroidism is highly prevalent among GCC HD patients, with a strong U-shaped PTH/mortality relationship seen at PTH <300 and >450 pg/mL. Future studies are encouraged for further understanding this PTH/mortality pattern in relationship to unique aspects of the GCC HD population.

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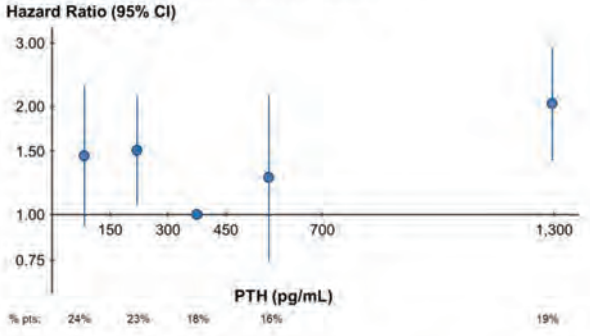
Figure: PTH categories and mortality, GCC DOPPS (2012-2018)



Footnote: N=1,422 patients and n=222 deaths; adjusted for age, sex, vintage, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease), serum creatinine, and single pool Kt/V; stratified by GCC region; placement of estimates along the x-axis determined by mean PTH in each group (< 150, 150-300, 301-450, 451-700, > 700). Categories chosen to yield approximate similar sample sizes across categories. The PTH of 301-450 pg/mL category served as the reference group.

PO0352

Effect of PTH Dosing Frequency and Amplitude on Bone Health: From Anabolism to Catabolism

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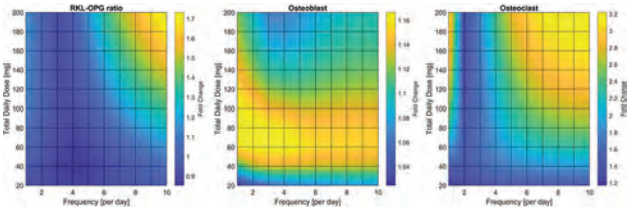
Background: In patients with chronic kidney disease or primary hyperparathyroidism, chronically elevated parathyroid hormones (PTH) levels exert catabolic effects on the bone. In contrast, PTH cycling or daily application of teriparatide (TP) promotes bone formation. These responses have important clinical and therapeutic implications. Although the anabolic effects of PTH cycling are widely accepted, the underlying dynamics are not well understood.

Methods: We developed a physiology-based model quantitating the interrelations of osteoclasts, osteoblasts and osteocytes on bone remodeling (Cherif et. al., NDT 33(1), 2018, i165-6). Using the validated model, we explore the effect of altered PTH (TP) dosing (e.g., dosing frequency and amplitude) on bone catabolism and anabolism, respectively.

Results: The model accurately predicts differential responses of anabolic and catabolic effects of continuously and intermittently elevated PTH (TP) levels, respectively. We observe that intermittent dosing of PTH with a high frequency and amplitude induces bone catabolism similar to that seen with chronically elevated PTH. We see a more than 3-fold change from baseline in osteoclastic over osteoblastic activities, resulting in catabolism. Low PTH frequency with high dosing amplitude induces both osteoclastic and osteoblastic activities, but the net result is bone anabolism. Figure 1 shows a region where high osteoblastic activities exceed osteoclastic resorption. These findings suggest the existence of optimal PTH (TP) frequency-amplitude values that enhance anabolic gains, beyond which there can be a detrimental effect on bone.

Conclusions: Our results suggest that both frequency and amplitude of PTH (TP) cycling affect the balance of catabolic and anabolic effects. Understanding the underlying mechanism of differential responses induced by intermittent and continuous levels of PTH, respectively, may provide new therapeutic options for patients and minimize unintended consequences of intervention.



Illustrates regions with high osteoblastic and osteoclastic activities corresponding to anabolic gains and/or catabolic loss in bone health as a function of dosing frequency and amplitude.

PO0353

Chemical Characterization and Quantitation of Circulating Intact Parathyroid Hormone and Parathyroid Hormone Fragments by High-Resolution Mass Spectrometry in Chronic Renal Failure

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Background: The precise concentrations of full-length parathyroid hormone (PTH 1-84) and the identity and concentrations of PTH fragments in patients with various stages of chronic renal failure (CRF) are unknown.

Methods: We developed a liquid chromatography-high resolution mass spectrometry (LC-HRMS) method to characterize and quantitate PTH 1-84 and PTH fragments in the serum of 221 patients with progressive renal dysfunction. Following capture by matrix-bound amino-terminal or carboxyl-terminal region-specific antibodies and elution from matrix, full-length PTH and PTH fragments were identified and quantitated using LC-HRMS. PTH was simultaneously measured using an intact PTH (iPTH) immunoassay.

Results: Full-length PTH 1-84 and eight PTH fragments (PTH 28-84, 34-77, 34-84, 37-77, 37-84, 38-77, 38-84, and 45-84) were unequivocally identified and were shown to increase significantly when the eGFR declined to less than 17-23 mL/min/1.73 m^2. Serum concentrations of PTH 1-84 were similar when measured by LC-HRMS following capture by amino-terminal or carboxyl-terminal immunocapture methods. Serum PTH 1-84 concentrations measured by LC-HRMS were significantly lower compared with PTH measured by an iPTH immunoassay in patients with eGFRs of less than 30 mL/min/1.73 m^2. PTH 7-84 was below the lower limit of quantitation of the method (<50 pg/mL).

Conclusions: LC-HRMS accurately quantitates full-length PTH, carboxyl-terminal PTH fragments, and mid-region PTH fragments, in the serum of patients with progressive renal failure. Serum concentrations of PTH 1-84 and PTH fragments increase when eGFR decreases to less than 17-23 mL/min/1.73 m^2. PTH values measured by LC-HRMS are lower than those obtained from an iPTH immunoassay in severe CRF

Funding: Other NIH Support - 1R01DK107870

PO0354

Management of Secondary Hyperparathyroidism Among Patients Who Transition from Daily At-Home to Three-Times-Weekly Oral Cinacalcet Given In-Center

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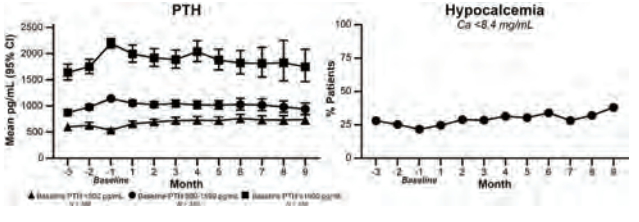
Background: Results of a small phase 1 clinical trial demonstrated the safety and potential utility of 3X weekly in-center administration of cinacalcet to control secondary hyperparathyroidism (SHPT) in hemodialysis (HD) patients. Moreover, a larger observational study demonstrated comparable control of SHPT among HD patients who initiated 3X weekly cinacalcet in-center to those who initiated cinacalcet at home. The present study assessed the effectiveness of 3X weekly in-center cinacalcet among HD patients who transitioned from cinacalcet administered daily at home in the management of SHPT.

Methods: Patients included in this analysis were ≥18 years of age, receiving standard in-center HD, Medicare beneficiaries, and had a physician order to transition from daily at-home cinacalcet to cinacalcet given 3X weekly in-center (July 2018 to December 2019). Patients were followed forward in time for up to 9 months after transition to in-center cinacalcet or until loss to follow-up or end of study. Generalized linear modeled means and 95% confidence intervals (CIs) were calculated for parathyroid hormone (PTH), calcium (Ca), and phosphorus (Phos). Hypocalcemia events were defined as Ca <8.4 mg/dL.

Results: We identified 874 qualifying HD patients who transitioned from at-home to in-center cinacalcet administration during the study period. Among patients with baseline PTH <800 pg/mL, PTH levels initially increased but stabilized after transition. Among patients with baseline PTH 800 to 1599 pg/mL and PTH >1600 pg/mL, PTH levels initially decreased but then stabilized following transition. Ca and Phos levels were generally stable for all patients following transition. Hypocalcemia was observed in approximately 25% to 38% of patients during follow-up. up.

Conclusions: These results suggest that SHPT can be stably maintained by transitioning patients from daily at-home cinacalcet to cinacalcet given in-center 3X per week. We postulate that increased prescription adherence is the likely factor mediating this effect.



PO0355

Real-World Experience with Etelcalcetide in an Academic Dialysis Program

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Background: High parathyroid hormone (PTH) levels may increase fracture risk, vascular calcification, and cardiovascular disease in end-stage kidney disease (ESKD) patients. Treatments include phosphorus binders, Vitamin D analogues, and cinacalcet. However, many ESKD patients persist with high PTH levels. Etelcalcetide (ETC) is an injectable calcimimetic recently approved to treat hyperparathyroidism in ESKD. To date, few studies have described the safety and efficacy of ETC on calcium (Ca) and PTH levels in real world usage.

Methods: This retrospective chart review of 195 in-center HD patients describes those who received a stable dose of ETC for at least 12 consecutive weeks. ETC dose, Ca, albumin, and PTH levels were obtained monthly x 3 months prior to ETC start and up to 9 months post. 23 patients were included for 2 or more doses of ETC. Overall and severe hypocalcemia were defined as corrected Ca <8.3 and <7.5 mg/dL, respectively.

Results: See Table 1. PTH changed from +3.37% (2.5mg) to -32.57% (10mg) to -3.19% (15mg). As expected, ETC use yielded a statistically significant lower PTH when compared to pre-treatment average of 1 and 2 months pre-drug PTH values versus 3 months post drug average (p=0.0034 via t-test for related samples). Corrected Ca decreased in a dose dependent fashion from 0.22% (2.5mg) to 11.89% (15mg). Overall, hypocalcemia occurred in 36.6% of patients. Severe hypocalcemia ranged between 0% (2.5, 5, 12.5, 15mg) and ~ 1% (7.5, 10mg).

Conclusions: Prior studies have used aggressive PTH lowering targets (<300pg/mL or >30% reduction from baseline) yielding high rates of hypocalcemia (61-68%). Our study is the first to describe results of a typical real world dosing strategy. Our results suggest that PTH levels decrease in a dose dependent fashion and severe hypocalcemia is rare. At doses > 10mg diminishing PTH reductions occur which could be due to a preponderance of patients with refractory / tertiary hyperparathyroidism. Rates of overall and severe hypocalcemia were lower here. Limitations of this study include limited adjustment for confounding variables, retrospective nature and small population at higher doses.

ETC dose	2.5mg	5mg	7.5mg	10mg	12.5mg	15mg
Number of patients	45	106	40	17	6	4
Percent change in corrected Ca at 3 months	-0.22%	-5.5%	-9.47%	-7.37%	-8.21%	-11.89%
Rate of severe hypocalcemia (%)	0	0	0.9	0.9	0.45	0
Percent change in PTH at 3 months	+3.37%	-16.21%	-7.32%	-32.5%	-24.18%	-3.19%

PO0356

The Cost Effectiveness of Alternate-Day Cinacalcet Therapy for Secondary Hyperparathyroidism (SHPT) in Hemodialysis Patients

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Background: CKD defines as abnormalities of kidney structure or function, present for more than 3 months with implication for health. Secondary hyperparathyroidism (SHPT) is one of implication of CKD, which eventuate with decrease in GFR. The Initial treatment starts with incremental approach, constrain of Dietary Phosphorus, use of calcium and non-calcium phosphorus binders and additional Vit D Analogues. Next approach to Secondary hyperparathyroidism (SHPT) after poor response to initial therapy is to use Cinacalcet. Cinalcalcet act by activating calcium sensing receptor of parathyroid hormone gland directly and it bypass normal physiological process. It has half-life of 30-40 hours. Cinacalcet is excreted 80 % through kidney and 20 % through liver.

Methods: We did prospective control study by following Dialysis patients (N=88) who were receiving alternate day Cinacalcet either by physician's choice or due to noncompliance to home medications. We followed Intact PTH every 3 months, Serum Calcium and serum phosphorus every month after start of alternate day therapy until six months and compared it with 6 months data before start of alternate day Cinacalcet. Data was analyzed by using paired T-Test.

Results: A total of 88 patients were enrolled in the study, who were on hemodialysis for at least one year. The mean age of patients was 49.17± 15.89, and 56.8 percent of them were males. The mean duration of dialysis was 6.68 ± 5.27 years and 40.9 percent of patients had diabetic nephropathy as a cause of End stage renal disease. The patients were transferred from once daily dosing to 3 times post hemodialysis dose. The mean post hemodialysis dose of cinacalcet was 62.73 ± 27.71 mg. The baseline mean PTH value before shifting to alternate dose was 986.69 ± 503.370 and after was 798.24 ± 526.92 and the P value was 0.001. The mean serum calcium before was 8.28 ± 2.30 and after it was 8.72 ± 1.42 with a p value of 0.03. Serum phosphorous before and after was, 4.66 ± 1.53, 4.86 ± 1.19 with a P – value of 0.147.

Conclusions: Cinacalcet effectively controls secondary hyperparathyroidism even with modified regimen as used in our study. Cinacalcet showed significant reductions of PTH with intermittent (3/week) dosing and thus is more cost effective and has better directly observed compliance.

PO0357

A Real-World Observational Study of Calcimimetic Use in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT) in Europe

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Background: Calcimimetics, oral cinacalcet (CIN) and intravenous etelcalcetide (ETEL), are approved for treating SHPT in adult patients on maintenance HD. Data on real-world use of calcimimetics are needed to provide guidance in clinical practice.

Methods: In this observational study, Chronic HD patients treated with calcimimetics for SHPT, with ≥1 parathyroid hormone value (PTH) recorded within ≤90 days before calcimimetic initiation, were included. Data on demographics, clinical history, laboratory values and calcimimetic use were abstracted from medical charts.

Results: Interim data for 503 HD (96 CIN and 407 ETEL) patients from 57 sites across 12 countries are reported. At baseline, CIN patients had been calcimimetic naive while 45% (183/407) of ETEL patients had switched from CIN to ETEL (≤90 days from last CIN prescription). ETEL patients were younger than CIN (median: 63 vs. 69 yrs). Dialysis vintage was longer for ETEL patients (median: 5 vs. 2 yrs). Starting dose was 30 mg/day for 98% of CIN, and 5 mg and 2.5 mg thrice weekly for 58% and 41% of ETEL patients respectively. **Table 1** summarizes median PTH and mean total calcium (Ca) and phosphate (P) levels. Among 341 ETEL and 79 CIN patients who had normal Ca at baseline, the cumulative incidence of hypocalcemia (<2.1 mmol/L) at 3 and 6 months was greater for CIN (47% and 58%) than ETEL (35% and 52%). As recorded in medical charts, nausea and vomiting rates at 12 months were similar for CIN (3.7% and 1.8%) and ETEL (3.6% and 1.9%). ETEL persistence (89.6%) was greater than CIN (71.8%) at 12 months. During follow-up, 13.5% switched from CIN to ETEL and 2.5% from ETEL to CIN. The proportion of patients achieving >30% reduction in PTH from baseline was greater for CIN than ETEL at 6 months (64% vs. 54%) but similar at 12 months (73% vs. 74%).

Conclusions: This is the largest real-world study on calcimimetics following 2016 approval of ETEL in Europe. There were marked reductions in PTH, Ca, and P levels. Gastrointestinal events did not differ between ETEL and CIN groups.

Funding: Commercial Support - AMGEN

Table 1. PTH, Ca, and P laboratory values at time of calcimimetic initiation (baseline) and up to 12 months

	Etelcalcetide N=407					Cinacalcet N=96				
	Baseline	*3 mos*	*6 mos*	*9 mos*	*12 mos*	*Baseline*	*3 mos*	*6 mos*	*9 mos*	*12 mos*
PTH (pg/mL) Median (IQR)	655 (450, 1016)	527 (371, 852)	442 (265, 762)	446 (262, 704)	362 (243, 671)	645 (476, 868)	405 (241, 668)	389 (263, 727)	476 (286, 708)	420 (209, 792)
Ca (mmol/L) Mean (SD)	2.27 (0.26)	2.15 (0.29)	2.15 (0.33)	2.16 (0.27)	2.18 (0.26)	2.25 (0.17)	2.20 (0.23)	2.49 (2.39)	2.21 (0.21)	2.23 (0.23)
P (mmol/L) Mean (SD)	1.84 (0.50)	1.67 (0.51)	1.63 (0.54)	1.64 (0.55)	1.75 (1.43)	1.86 (0.55)	1.78 (0.91)	1.75 (0.68)	1.71 (0.60)	1.67 (0.63)

PO0358

Indirect Comparison of Treatments for Secondary Hyperparathyroidism Through a Network Meta-Analysis

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Background: Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease (CKD) affecting mineral and bone metabolism and characterized by excessive parathyroid hormone (PTH) production and parathyroid hyperplasia. Currently the only 2 treatments indicated for the treatment of SHPT in non-dialysis CKD (ND CKD) are paricalcitol (PCT) and more recently extended release calcifediol (ERC). The objective of this analysis was to compare the efficacy and safety of ERC and PCT by assessing their effect on biomarkers PTH, calcium and phosphate.

Methods: A systematic literature research (SLR) was performed in PubMed to identify randomized control trials (RCTs) to be included in a Network Meta-Analysis (NMA). In all articles, the comparator groups were consisting of placebo. A quality assessment was done with the GRADE method. The treatment effects of ERC and PCT were compared using random effects in a frequentist setting, and a sensitivity analysis with Bayesian approach was performed using random effects model. Comparisons were made between the overall treatment effects of the drugs.

Results: Nine RCTs comprising a total of 1426 patients were included in the analyses. Compared to placebo, treatment with both PCT and ERC lowered levels of PTH in a statistically significant manner. No statistically significant differences in PTH reduction were found between PCT and ERC. Treatment with PCT significantly increased calcium levels compared to placebo (effect size: 0.30 mg/dl, 95 % CI: 0.21 to 0.40 mg/dl), while the estimated effect of ERC on calcium (effect size: 0.10 mg/dl) was not significant (95 % CI: -0.03 to 0.23 mg/dl). The calculated difference of effects between treatment with PCT and ERC shows that PCT significantly raises levels of calcium by 0.2 mg/dl (95 % CI: -0.37 to -0.04 mg/dl). No differences in effects on phosphate were observed. Sensitivity analyses using a Bayesian approach confirmed the general pattern of similar PTH reductions and larger increases in calcium from PCT observed in the analyses.

Conclusions: This NMA showed that ERC is non inferior in lowering PTH levels vs PCT. ERC displayed avoidance of clinically relevant increases in serum phosphorus and calcium, offering a new, effective and well tolerated treatment option for the early management of SHPT in patients with ND CKD.

Funding: Commercial Support - Vifor Pharma

PO0359

Parathyroidectomy Improves Muscular Function but Not Muscle Mass in Hemodialysis Patients with Severe Hyperparathyroidism

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Background: Increased levels of parathyroid hormone (PTH) are associated with a negative impact on the bone-muscle axis including sarcopenia and osteoporosis, and it is possible that treating hyperparathyroidism (HPT) can ameliorate these disturbances. However, the effects of parathyroidectomy (PTX) on muscle mass, strength and performance have not been thoroughly investigated. This study aims to evaluate the impact of PTX on muscle (mass, strength, and performance), body fat and resting energy expenditure (REE) in patients on hemodialysis with severe HPT

Methods: We are prospectively evaluating muscle mass, strength and performance of 30 patients before and after 6 months of PTX by using Actigraph GT3X accelerometer, timed-up-and-Go(TuG), Sit-to-Stand-to-Sit(STS) and muscle strength tests [handgrip(HGS), supine(SP), leg press(LP)]. Body composition was assessed by dual-energy x-ray absorptiometry, and REE was examined by indirect calorimetry. Participants completed the SARC-F questionnaire.

Results: At 6 months after PTX, 20 patients who already completed the protocol, showed a significant drop in PTH [1510(1368-1885) vs. 91(38-260) pg/mL; p<0.01], a significant increase of number of steps/day [4759(3572–6185) vs. 6343(4123–8540) p 0.01] and improvements of strength tests: HGS(27±14 vs 31±14 kg p 0.01); SP(26±15 vs 31±16 kg p 0.01] and LP[24±23 vs.50±43 kg p 0.01]. In addition, there was an improvement of SARC-F scores [6(2-8)vs 3(1-7) p<0.01] and STS [8±4 vs.10±2 p=0.02] and a reduction of TuG [10 vs. 8 s p<0.01]. A significant increase in bone mineral content [1.8(1.6-2.2) vs 2.2(2-2.6) kg p=0.001], fat mass [21±8 vs 24.5±9kg p<0.01] and visceral adipose tissue [530(287-871) vs 975(383-1476)g p<0.01] was seen. No change was noted in skeletal muscle index and in REE [1643 vs.1573 kcal/d p=0.7). We noticed an increase in IGF-1 [199 vs 201 μg/L p=0.04] and HOMA index [1.6 vs 1.72 p=0.02], but no variation was found in serum albumin.

Conclusions: In hemodialysis patients with sHPT undergoing PTX, there were improvements of muscular function and bone mass, but not of muscle mass, at 6 months after PTX. Our findings suggest that PTH-associated sarcopenia is mediated not only by a decrease in muscle mass but also by muscle dysfunction.

PO0360

Indications and Justification for Parathyroidectomy in Secondary Hyperparathyroidism

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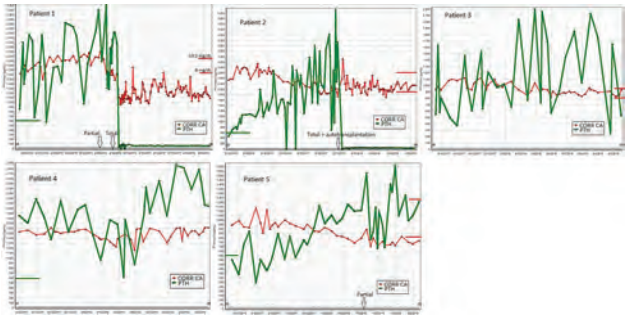
Introduction: Hyperparathyroidism (HPT) is a common complication of CKD, which is treated by diet, medications and surgery. Parathyroidectomy (PTectomy) is reserved for patients with refractory HPT. There are no guidelines for the timing or type of surgery. We describe five patients with HPT, who were treated with different modalities with unsatisfactory outcomes.

Case Description: We present 5 patients in a table format. Patient 1 had total PTectomy that resulted in serious hypocalcemia needing hospitalizations. After 3 years, she remains hypocalcemic requiring high doses of Vit D and calcium. Selecting a suitable phosphate binder in this patient was difficult due to hypocalcemia. Patient 2 underwent total PTectomy with autotransplantation which resulted in low calcium levels that resolved over time, but PTH levels remained very low. Patients 3 and 4 refused surgery and their PTH levels fluctuated significantly, falling to levels much below the acceptable level of 600 pg/ml. Patient 5 underwent partial PTectomy and 2 enlarged PT glands were removed. This resulted in lower calcium and higher PTH levels than prior to surgery.

Discussion: The medical management for HPT in all five patients failed. We opted for surgery when the PTH levels were in a range of 1300 to 4000 pg/ml. The surgeon decided the type of surgery. In patient 1, intraoperative PTH was measured that resulted in removal of only three glands. But within a very short time, the PTH bounced back to 2500 pg/ml which was much higher than presurgery level, and total parathyroidectomy was performed. We cannnot recommend specific surgical modality based on this experience. Therefore, we strongly feel that there is a need for larger controlled studies to elucidate specific guidelines for treating refractory HPT.

Patient Demographics

Patients	Age/Sex	PTectomy: P=Partial, T=Total, T+A=Total + Autotransplantation	Ca, PO4 and PTH
1	49-yr male	P then T	↓Ca, ↑PO4, ↓PTH
2	49-yr female	T+A	N Ca, N PO4, ↓PTH
3	59-yr male	No	Fluctuating
4	59-yr male	No	Fluctuating
5	56-yr male	P	↓Ca, ↑PTH, ↑PO4,



PO0361

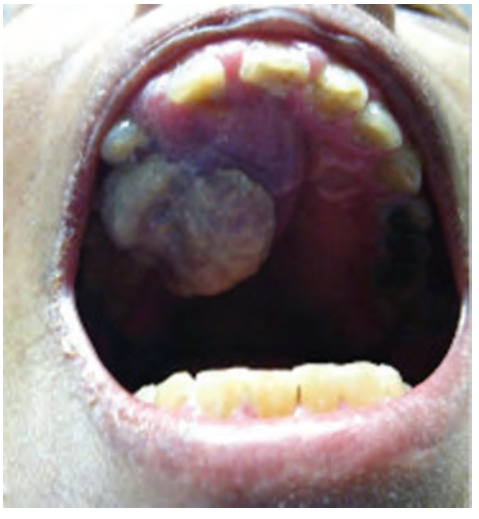
Palatal Brown Tumor in a Dialysis Patient

Nawal Habib, Scott Mullaney, Alexander Bullen, Danuta Trzebinska, Tamara T. Rubenzik. *University of California San Diego, La Jolla, CA.*

Introduction: Secondary hyperparathyroidism (SHPT) is a common complication of end stage kidney disease (ESKD) causing loss of bone density through increased osteoclastic activity. Imbalanced bone resorption and peri-trabecular fibrosis causes formation of hemosiderin-laden giant cell granulomas – brown tumors. Here is a case of palatal brown tumor in an ESKD patient which led to complications of hungry bone syndrome after parathyroidectomy.

Case Description: A 57 yo F with ESKD on HD and SHPT presented with a growing palatal mass. She reported difficulty chewing and shortness of breath. A friable mass was located over the hard palate. Labs showed serum calcium (Ca) 9.5 mg/dL, PTH 4477 pg/mL, phosphate 5.1 mg/dL, and alkaline phosphatase (ALP) 1124 U/L. Parathyroid scan showed a focus of activity in the left thyroid bed. She underwent a mass resection and parathyroidectomy. Pathology revealed an atypical parathyroid adenoma without features of carcinoma. Her postoperative course was complicated by hungry bone syndrome with prolonged hypocalcemia, hypomagnesemia and hypophosphatemia which persisted despite aggressive Ca supplementation and high Ca dialysate. She was also started on teriparatide to stimulate osteoblast activity and bone formation. After a long hospital course, she was discharged on oral supplemental Ca and calcitriol with close follow-up.

Discussion: Despite the advent of effective management strategies for renal osteodystrophy, we must be mindful of brown tumors. Surgical excision with parathyroidectomy is the preferred treatment. Post-operatively, patients must be monitored for hungry bone syndrome. As bone formation increases, rising ALP levels can serve as a biomarker for increasing Ca requirements requiring escalating dosage of supplements. Teriparatide is a recombinant human PTH which can be used to augment bone density.



PO0362

A Case of a Hemodialysis Patient with Secondary Hyperparathyroidism, Effectively Treated with Cinacalcet Hydrochloride but Not with Etelcalcetide

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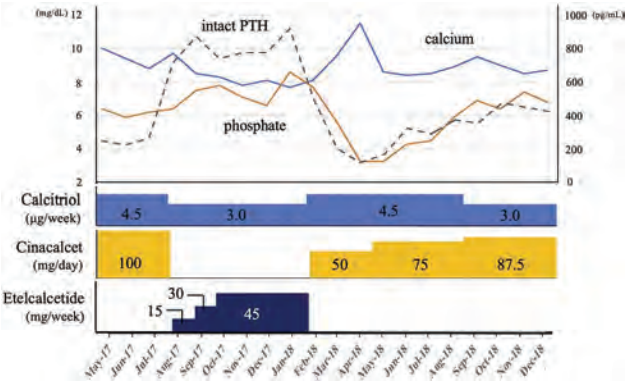
Introduction: Although both cinacalcet hydrochloride and etelcalcetide are calcimimetics that directly inhibit the parathyroid hormone (PTH) secretion by activating the calcium (Ca)-sensing receptor, their binding sites are different.

Case Description: We report a rare case of a hemodialysis (HD) patient with secondary hyperparathyroidism, in whom cinacalcet was effective to reduce serum intact PTH (i-PTH) level but not etelcalcetide. A HD patient underwent total parathyroidectomywith autotransplantation to his right forearm 19 years ago. His i-PTH level had been almost controlled with 100 mg of cinacalcet. At a month after switching to etelcalcetide, serum i-PTH level increased from 269 pg/mL to 716 pg/mL. Although the dose of etelcalcetide was gradually increased to 45 mg/week, the maximal dose of etelcalcetide, serum i-PTH level increased to 919 pg/mL. Therefore, etelcalcetide was switched to 50 mg/day of cinacalcet, and his i-PTH level decreased to 208 pg/mL.

Discussion: Thus, the present case has resistance to etelcalcetide treatment but not cinacalcet, suggesting that his parathyroid gland might have partial deletion or mutation in the extracellular domain of the Ca-sensing receptor. Therefore, we should consider the possibility of resistance to etelcalcetide treatment while treating secondary



PO0363

Hypercalcemia Resulting from Spindle Cell Tumor-Induced Calcitriol Production

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Introduction: Less than 1% of cases of hypercalcemia of malignancy are caused by overproduction and release of 1,25-dihydroxy vitamin D (calcitriol) by tumor cells.[1] Calcitriol excess has been identified most often in sarcoidosis, hematologic malignancy, and infection.[2] We present a patient who developed severe hypercalcemia and acute kidney injury as a result of spindle cell neoplasm-mediated calcitriol excess, with normalization of serum calcium and creatinine in response to treatment with prednisone.

Case Description: A 65yo man with a history of a large retroperitoneal mass presented with malaise. He was not taking calcium or vitamin D supplements. Initial lab showed serum calcium 15.7 mg/dL, 1,25-dihydroxy Vit. D 126 pg/mL (elevated), and creatinine 4.5 mg/dL. His PTH 8 pg/mL, PTHrP 0.8 pmol/L, and 25-hydroxy Vit. D 26 ng/mL were suppressed or normal. SPEP, UPEP, serum immunofixation, and serum free light chains were unremarkable. Pathology of the mass revealed a spindle cell neoplasm embedded within fibrous stroma. Prednisone was prescribed to suppress tumor-associated calcitriol production. His serum calcitriol level fell to 33.2 pg/mL, with a serum calcium of 10.9 mg/dL, after taking prednisone 40 mg/day for 2 weeks. His calcitriol 39.2 pg/mL, calcium 8.7 mg/dL, and creatinine 0.81 mg/dL levels were normal while on prednisone 20 mg/day at 76 days after starting corticosteroids and before any anti-tumor therapy or surgical debulking.

Discussion: The conversion of 25-hydroxy Vit. D to calcitriol is catalyzed by 1-alpha hydroxylase, a phenomenon that can occur in extra-renal tissues, such as within macrophages in sarcoid tissue.[3-6] We hypothesize that elevated 1-alpha hydroxylase activity in spindle tumor cells or in activated macrophages within tumor stroma was responsible for excess calcitriol production and the resultant hypercalcemia. Corticosteroids inhibit the 1-alpha hydroxylase conversion of 25-hydroxy Vit. D to calcitriol and have been used successfully to reduce malignancy-induced calcitriol production.[6,7] This case provides evidence of severe hypercalcemia due to endogenous production of calcitriol associated with a large spindle cell neoplasm, with rapid normalization of both serum calcium and calcitriol levels in response to treatment with prednisone, without anti-tumor therapy or surgical debulking.

PO0364

Unexplained Persistent Hypercalcemia After Liver Transplantation

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Introduction: Hypercalcemia has been reported as a sequela of chronic liver disease in association with hyperbilirubinemia. Previous reports of hypercalcemia post liver transplant were thought to be potential rare complication of altered bone metabolism under intense immunosuppression and from prolonged immobilization. However the pathogenesis of this rare phenomenon has not been clarified to this date. We present cases of unexplained severe persistent hypercalcemia in three liver transplant recipients.

Case Description: Hypercalcemia post liver transplant in 3 recipients described in Table 1 and calcium trends shown in Figure 1.

Discussion: Extensive work up for hypercalcemia was negative in our patients. Although immobilization could be contributory, other unrecognized possibilities are plausible. Immunosuppression with steroids and other agents, especially cyclosporine, has been hypothesized to cause calcium imbalance by inhibiting T cell activation and transcription of interleukin-2 which are involved in bone turnover. Depletion of T cells upregulates osteoclastogenesis through prostaglandin production; by interfering with receptor activator of nuclear factor kappa ligand (RANK-L) and osteoprotegerin on osteoblasts. However, only one patient was on cyclosporine. Other, yet unidentified, factors modifying calcium metabolism could be involved. We would like to draw attention to this fascinating phenomenon in order to gain more insight. Low dialysate calcium, pharmacotherapy (Calcitonin, Pamidronate and Denusomab) along with improved mobility had successfully lowered serum calcium in these patients. One patient had hypocalcemia after Denusomab administration, hence needed careful monitoring.

Descriptions of hypercalcemia cases post liver transplant.

Patient	Age / Gender	Medical History	Cause of liver failure	Associated AKI	Immunosuppression	Calcium levels (mg/dL)	Treatment of hypercalcemia	Hypercalcemia work up	Other Complications
A	54 F	-HTN -DM -CVA -Vitamin D deficiency (no supplementation)	NASH Cirrhosis	Hepatorenal Dialysis dependent prior to transplant	Cellcept Cyclosporin	Preop = 9.2 Peak =20.2 on week 8 post transplant Last follow ups 12.9	Calcitonin Pamidronate Denosumab Frequent HD low calcium bath	-SPEP neg -PTH = 8 -PTHrP <2 -25 hydroxy-D = 38 -1,25 hydroxy-D = 9 -Phos wnl -Malignancy screening neg -T bili wnl -TSH wnl	-Neutropenia -Failure to thrive - Prolonged Immobilization
B	27 M	-Alcohol abuse -Alpha 1 antitrypsin deficiency -Vitamin d deficiency (50,000 units weekly)	Alcoholic hepatitis	ATN + Bile cast nephropathy Dialysis dependent prior to transplant	Tacrolimus	Preop = 8.7 Peak = 14 on week 10 post transplant Last follow ups 9.9	Discontinued Vitamin D supplementation Calcitonin Frequent HD low calcium bath	-SPEP neg -PTH = 7 -PTHrP <2 -25 hydroxy-D <5 -1,25 hydroxy-D < 5 -Phos wnl - T bili wnl - TSH wnl	-Pericardial effusion with tamponade -Shock -Critical care myopathy -Muscle spasms -Dermal fungal infection
C	36 M	-Alcohol abuse -Vitamin D deficiency (50,000 units weekly)	Alcoholic hepatitis	ATN Dialysis dependent prior to transplant	Prograf Cellcept Prednisone	Preop = 8.3 Peak = 14.5 on week 18 post transplant Last follow ups 9.4	Discontinued Vitamin D supplementation Calcitonin Denosumab Frequent HD low calcium bath	-SPEP neg -PTH = 18 -PTHrP <2 -25 hydroxy-D =7 -1,25 hydroxy-D =12 -Phos wnl -T bili wnl - TSH wnl	-T-cell mediated rejection -CMV viremia -Pericardial effusion -Critical care myopathy

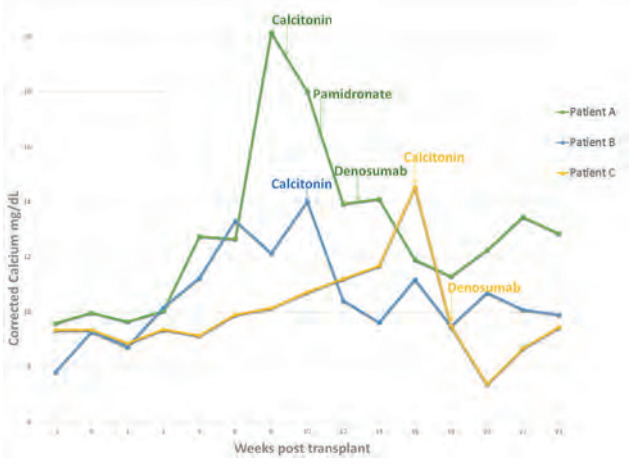

Figure 1: Calcium trends and treatments.

PO0365

A Rare Case of Hyperthyroidism Presenting with Symptomatic Hypercalcemia

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Introduction: Primary hyperparathyroidism and hypercalcemia are by far the most common causes of hypercalcemia in clinical practice. Asymptomatic hypercalcemia with minimally raise calcium levels have been documented in 20% of cases of hyperthyroidism as well and is related to increased bone resorption by osteoclasts and subsequent release of calcium into circulation. We describe a rare case of hyperthyroidism with symptomatic hypercalcemia as the first clinical manifestation.

Case Description: A 60 year old male with a history significant for chronic kidney disease, stroke and hypertension was admitted to the hospital following a syncopal event. Physical examination and baseline investigations were normal other than elevated calcium levels of 12.1 mg/dl. PTH levels and PTHrP levels were normal ruling out hyperparathyroidism and paraneoplastic related hypercalcemia. Vitamin D levels were also found to be normal. Workup for multiple myeloma was negative. Thyroid panel was done which showed extremely low levels of TSH (<0.005 mIU/L) with elevated T3 and T4 levels (12.9 ng/dL and 5.52 ng/dL respectively). Thyroid scan was performed which showed significant thyroiditis. Thyrotropin receptor antibody test also came positive. The patient was diagnosed with Graves' disease based on the laboratory investigations and subsequently started on 5 mg methimazole TID. He also received one dose of zolendronic acid in the hospital. His calcium levels stabilized, falling from 12.4 to 9-10 mg/dL within 1 month. Patient received methimazole for a total of 7 months after which it was discontinued as his TSH levels (1.38 mIU/mL), T3 levels (2.19 ng/dL) and T4 (0.78ng/dL) normalized. Patient further underwent radioiodine ablation for the treatment of Graves' disease.

Discussion: In past, multiple cases have been reported of concurrent hyperparathyroidism or vitamin D deficiency in hyperthyroid patients. This case is unique as the patient presented with symptomatic hypercalcemia in the absence of other causes and in the absence of other more common symptoms of hyperthyroidism. To our knowledge, only 2 cases of hyperthyroidism have been reported previously with hypercalcemia as the first clinical manifestation. Clinicians should be aware of association of hypercalcemia with hyperthyroidism as it will facilitate early diagnosis and appropriate intervention.

PO0366

Low Phosphate and Low Calcium Levels Predict Higher Risk for Adverse Events of Maintenance Hemodialysis

Takahiro Kuragano, Takeshi Nakanishi. *Hyogo College of Medicine Kidney and dialysis, Nisinomiya, Japan.*

Background: It is well known higher serum levels of phosphate (P) and calcium (Ca) associated with higher risk of cardiovascular disease (CVD) and premature death of hemodialysis (HD) patients. However, in the current situation that guidelines penetrated widely, there are few reports which investigated the association CKD-MBD related factors and adverse events of HD patients.

Methods: The study design was the multiple centers, observational study for 3yeras. 989 HD patients were enrolled in this study. Hb, ferritin, creatinine, total protein, albumin, total cholesterol, Ca and P levels were measured every 3 months. Hhigh-sensitivity C-reactive protein (hCRP) and intact-parathyroid hormone (int-PTH) were also measured every six months. The correlation between CKD-MBD factors and adverse events were evaluated by the time depended cox hazard model.

Results: 82% (P), 83% (Ca), and 78% (int-PTH) of patients were maintained in a target range. After correlated with age, sex, past history of CVD, Hb, albumin, and hCRP, compared with the patients with target levels of P, patients with low P levels were significantly higher risk for CVD (P=0.042, HR:2.27), hospitalization (P=0.034, HR:2.44), and all caused mortality (P=0.03, HR:2.29). Compared with the patients who maintain target int-PTH levels, patients with lower (P=0.025, HR:1.46) and higher (P=0.04, HR:1.44) int-PTH were significantly higher risk for hospitalization. Furthermore, compared with the patients who maintain the target levels both of Ca and P, the patients with target Ca and low P levels (P=0.042, HR: 2.75) were significantly higher risk for CVD. And compared with the patients who maintain the target levels both of Ca and P, the patients with low Ca and low P levels (P<0.001, HR: 4.4) and target Ca and low P levels (P=0.22, HR: 2.0) were significantly higher risk for hospitalization.

Conclusions: Although after corelated by several clinical factors, we found that patients who maintain the low serum P levels beard significantly higher risk for CVD and all caused mortality than patients who maintained higher Ca and P levels. Without doubt, extremely higher serum P, Ca, and int-PTH levels should be treated according to guidelines. However, in the current situation that guidelines penetrated widely, CKD-MBD managements which considered the clinical conditions of low P, Ca, and int-PTH are needed.

PO0367

The True State of Hyperphosphatemia Management in Dialysis

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Background: Hyperphosphatemia affects more than 80% of US dialysis patients and has been shown to have a direct link to increased morbidity and mortality. The objective of this study was to assess the current management of hyperphosphatemia in US dialysis patients and the ability to consistently control serum phosphorus over a six-month period.

Methods: Patient level data was collected via an online, HIPAA-compliant form in June 2019 as part of an independent chart audit. A total of 1,015 patient records (789 in-center HD, 200 PD, and 26 home HD) were submitted by 159 nephrologists. Patients had been on dialysis for at least six months (Mean: 26, Median: 15) and most were in LDO-affiliated units.

Results: Patients in the consistently high group had been on dialysis longer than those consistently in target or in the target-high variability group (36 months vs. 23 months) and were also younger on average (53 years vs. 61 years). Those in the consistently high and high-target group (CH/HT) had a 37% higher daily pill burden (from binders) than those consistently in target. Patients dialyzing in Fresenius units were the most likely to be consistently in target (27%). Compared to those consistently in target, those in the CH/HT group were significantly more likely to have diabetes, obesity, heart failure and coronary artery disease. They were also six times as likely to have poorly controlled hypertension. Ethnicity also was correlated with phosphate control with a disproportionate percent of non-white patients in the consistently high and high-target variability groups.

Conclusions: Not only is hyperphosphatemia rampant at any given time, but only a small minority of patients on phosphate binders (19%) are able to achieve consistent control; most patients fluctuate in and out of target. Increased phosphate binder dosing was not associated with better control and suggests that a new approach to the management of hyperphosphatemia is warranted.

PO0368

Hyperphosphatemia with Elevated Serum FGF-23 and PTH, Reduced Calcitriol, and Normal FGF7 Concentrations Characterizes Chronic Renal Failure in Humans

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Background: Fibroblast growth factor 23 (FGF23), a phosphatonin produced by osteocytes, regulates phosphate (Pi) homeostasis and is increased in CKD. A recent study showed that low serum (s) concentrations of FGF7 may contribute to hyperphosphatemia in patients with hypophosphatasia, and are elevated in some patients with tumor-induced osteomalacia and hypophosphatemia. We hypothesized that FGF7 might play a role in compensating for elevated Pi concentrations in CKD.

Methods: We measured serum concentrations of intact FGF7 (iFGF7, R&D Systems), iFGF23 (Eagle Biosciences), intact parathyroid hormone (iPTH) by enzyme-linked immunosorbent assays and determined s Pi, and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, by mass spectrometry) among 75 non-kidney transplant patients with varying estimated glomerular filtration rate (eGFR). Relationships between these parameters and eGFR were explored.

Results: For eGFR of 60 or more (n=29), 45-59 (n=14), 30-44 (n=9), 15-29 (n=13), and under 15 mL/min/1.73 m^2 (n=10), the median (IQ25-75) iFGF23 concentrations were 41.9 (33.1-47.4), 56.4 (47.4-58.6), 62.9 (53.2-75.6), 117.5 (87.6-137.2), and 327.5 (195.1-456.3) pg/mL, respectively (P <0.01). At comparable eGFRs, median (IQ25-75) iFGF7 concentrations were 46.1 (40.8-56.1), 43.1 (39.2-49.2), 45.4 (38.5-53.8), 47.7 (38.5-54.6), and 46.1 (40.8-54.6) pg/mL, respectively (P = 0.81). Negative correlations between Pi (r = –0.46; P <0.01), iPTH and eGFR (r = –0.33; P <0.05), and a positive correlation between $1,25(OH)_2D$ and eGFR (r = 0.51; P <0.01) were demonstrated. Significant increases in iFGF23, iPTH, and Pi were observed at eGFRs of less than 33 (95% CI, 26.40-40.05), 29 (95% CI, 22.51-35.36) and 22 mL/min/1.73m^2 (95% CI, 19.25-25.51), respectively. Moreover, significant decreases in $1,25(OH)_2D$ were observed at eGFRs of less than 59 mL/min/1.73m^2 (95% CI, 36.57-81.43). iFGF7 concentrations did not significantly correlate with eGFR, Pi, iFGF23, iPTH, and $1,25(OH)_2D$.

Conclusions: Increases in serum concentrations of Pi, iFGF23, iPTH, but not iFGF7, and decreases in $1,25(OH)_2D$ are observed as renal function declines in CKD.

Funding: Other NIH Support - 1R01DK107870

PO0369

Effects of a Reduced Phosphorous Diet on the Circulating Metabolome in Healthy Adults

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Background: Excess phosphorus intake is linked to hypertension, heart failure, and disorders of bone and mineral metabolism. The reasons for these associations are unclear. Most prior work on the effects of diet phospohrus have focused on changes in specific endocrine factors in the blood. Less is known about the effects of nutritional phosphorus intake on the human metabolome, which represents the integrated biologic response to changes in diet.

Methods: In 37 healthy adults, we performed a global metabolomic analysis using untargeted mass spectrometry in plasma samples obtained after consuming a high phosphorus diet (1900/day) for 2 weeks (considered baseline for this study) and after consuming a reduced phosphorus diet (1200 mg/day) fo 6 weeks. Metabolomic profiling was conducted by Metabolon, Inc. using standard protocols. Matched pairs t-tests were used to identify analytes that significantly changed from baseline to six weeks, with each individual serving as his or her own control.

Results: The mean age of study participants was 34±12 years, 36% were black and 49% were men. A total of 222 metabolites significantly changed from baseline to six weeks on a reduced phosphorus diet using a false discovery rate < 0.05 to take into account multiple comparisons. Major analytes which differed in six-week vs. baseline samples included metabolites related to tryptophan metabolism, microbiome related biochemicals, urea cycle, bile acids, corticosteroids and androgenic steroids, and acyl carnitines. Changes in specific analytes of note within each of these pathways are depicted in the Figure.

Conclusions: In healthy adults, a reduced phosphorus diet altered metabolites related to the microbiome, urea cycle, steroid hormones, energy and lipid metabolism.

Funding: Private Foundation Support

Pathway	Analyte	Fold change
Tryptophan	kynurenate	1.13
	N-acetylkynurenine	1.22
	xanthurenate	1.26
	serotonin	1.23
Microbiome	indolelactate	1.10
	indoleacetate	1.19
	indolepropionate	1.30
	Indoleacetylglutamine	1.70
Urea cycle	N-methylproline	2.49
	Trans-4-hydroxyproline	1.51
Bile Acids	glycocholate	1.69
	taurocholate	1.85
	taurodeoxycholate	1.71
	taurochenodeoxycholic acid 3-sulfate	2.07
Corticosteroids	cortisone	1.12
Androgenic steroids	epiandrosterone sulfate	1.15
	androsterone sulfate	1.13
	3b,17b-androstanediol	1.23
Acylcarnitines	nonanoylcarnitine	1.27
	margaroylcarnitine	1.48
	stearoylcarnitine	1.11
	undecenoylcarnitine	1.28
	deoxycarnitine	1.12

Change in select metabolites in response to phosphorus-reduced diet

PO0370

Hospital Admission Rates Among Hemodialysis Patients with Persistent Hyperphosphatemia Who Were Prescribed Changes in Phosphate Binder Treatment: A Retrospective Analysis of Real-World Data

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Background: Phosphate binders (PB) may have different formulations, potency, and pill burden, however, there is limited data on hard outcomes to support decisions in PB therapy. The goal of this retrospective analysis is to determine the rate of all-cause hospital admissions of patients who, at baseline, remained hyperphosphatemic despite treatment with sevelamer carbonate (SC) and had prescriptions to either (1) switch to monotherapy sucroferric oxyhydroxide (SO) or (2) switched to Non-SO binders [Calcium Acetate, Lanthanum Carbonate, or Ferric Citrate] or added one of these PBs to SC therapy.

Methods: Deidentified clinical and prescription data were retrospectively extracted from the Fresenius Kidney Care data warehouse and pharmacy records. All prescription changes were the result of routine clinical care. We aimed to control for selection bias by using Inverse Probability of Treatment Weighting (IPTW). This method was chosen due to its ability to balance baseline characteristics between the two groups and maintain adequate sample size.

Results: We identified 1,076 patients with baseline hyperphosphatemia despite SC prescription who switched PB therapy, including 319 patients with SO therapy and 757 patients with Non-SO therapy. Patients switched to SO had 27 fewer hospital admissions per 100 patient-years compared to patients with Non-SO therapy (Table 1)

Conclusions: In a retrospective database analysis of hemodialysis patients previously treated with sevelamer carbonate and switched to SO or Non-SO phosphate binder therapy, patients switched to SO monotherapy had a lower rate of hospital admissions than patients switched to other, non-SO phosphate binders

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	Incidence Rate per 100-PY [95% CI]	Incidence Rate Ratio [95% CI]	Incidence Rate Difference per 100-PY [95% CI]	p
SO (319 pts)	152.7 [147.0, 168.0]	0.849 [0.792, 0.904]	-27.1 [-41.3, -13.4]	0.002
Non-SO (757 pts)	179.8 [170.2, 189.4]			

Variables included in the Poisson regression model: HD vintage, congestive heart failure status, serum phosphorus and categories, iPTH and categories, $(iPTH)^2$

PO0371

An Observational Analysis of Hospital Admissions and Total Member Costs Associated with the Use of Various Phosphate Binders Used in Dialysis Patients Included in ESRD Seamless Care Organizations

Kristain C. Lindemann,[1] Christiana Ajala,[1] Melissa M. Rosen,[2] Claudy Mullon,[2] Robert J. Kossmann,[3] Terry L. Ketchersid,[3] Linda Ficociello.[2] *[1]Fresenius Health Partners, Waltham, MA; [2]Fresenius Medical Care Renal Therapies Group, Waltham, MA; [3]Fresenius Medical Care North America, Waltham, MA.*

Background: A prior observational study using real world data and estimates of hospitalization costs based on national data, found patients continuing sucroferric oxyhydroxide (SO) therapy had fewer hospital admissions and expected lower healthcare costs when compared to patients switching to another phosphate binder (PB). End Stage Renal Disease (ESRD) Seamless Care Organizations (ESCOs) coordinate treatment for 10% of Medicare dialysis patients in the U.S. By providing quality care, ESCOs may control costs by avoiding unnecessary hospitalizations. The aim of this analysis was to assess hospitalizations and costs associated with various PBs prescribed to dialysis patients in ESCOs.

Methods: Patients included in the analysis had PBs prescribed during 2016-2018 in ESCOs along with parathyroid (PTH) levels <600 pg/ml. Aggregated utilization and cost data from 24 ESCOs were used over 3 years. Total hospital admissions and member months (MM) were used to calculate hospital admission rates and rate ratios. *The statements contained in this document are solely those of the authors and do not necessarily reflect the view or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.*

Results: Hospital admission rates were found to be lower for SO (Table). Compared to MM treated with SO, an increased hospital admission rate of 11%, 20%, 32%, and 42% was observed for MM treated with SEV, CaAC, FC, and LC, respectively. In addition, the total per member per month (PMPM) healthcare costs were lower for SO ($5670) compared to FC ($5908), LAN ($6104), CaAC ($6303), and SEV ($6354), respectively.

Conclusions: Data from 24 ESCOs showed differences in hospital admission rates with the lowest rate in SO (7.97 per 100-member month (MM)) and the highest in CaAc (11.28 per 100- MM). In addition, total costs of care per MM where SO was prescribed were lower when compared to other PBs.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Phosphate Binder	# hospital admissions	Member Months (MM)	Hospital Admission Rate per 100 MM	Hospital Admission Rate ratio	Rate Ratio 95% CI
sucroferric oxyhydroxide (SO)	896	11239	7.97	1	–
Sevelamer (SEV)	14109	134125	10.52	1.32	1.23, 1.41
Calcium Acetate (CaAC)	11429	101302	11.28	1.42	1.32, 1.52
Ferric Citrate (FC)	869	9111	9.54	1.20	1.09, 1.31
Lanthanum carbonate (LC)	402	4538	8.86	1.11	0.99, 1.25

PO0372

Determining the Value of Pharmaceutical Treatment of Hyperp hosphatemia with Phosphate Binders: A Systematic Review

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Background: Phosphate binders (PBs) are the primary therapeutic treatment for hyperphosphatemia in ESRD patients receiving dialysis. Medicare spending on PBs has been estimated to be over $1.5 billion. There is increased focus on value-based prescribing as a method to control rising healthcare spending in the U.S. However, guidance to support such decisions is limited. The purpose of this study was to review economic evaluations of PBs to understand if specific binders are associated with greater value to patients and payers.

Methods: We conducted a systematic literature review with results restricted to economic evaluations published in English in peer reviewed journals between January 2015 and May 2020. Studies included in the review reported cost-effectiveness outcomes.

Results: After removing irrelevant articles and duplicates, 8 publications were found that met our inclusion criteria. Four (50%) studies compared either sevelamer carbonate (SEV) or lanthanum carbonate (LC) to calcium-based binders. SEV or LC was cost-effective compared to calcium-based binders. Two studies focused on ferric citrate (FC) with one comparing FC to the standard of care (either calcium acetate, SEV, or LC), and the other to SEV or calcium acetate. The results favored FC based on differences in the use of erythropoiesis-stimulating agents and hospitalization risk. However, these studies did not examine the potential for unsafe levels of iron absorption associated with FC use. The remaining two studies evaluated sucroferric oxyhydroxide (SO). One study found SO to be cost-effective relative to SEV based on clinical trial data. The other analysis looked at patients prescribed SO for two years compared to those who discontinued use after 90 days and switched to another binder. This model estimated that SO use had the potential to be cost-saving based on reduced risk of hospitalization. We were unable to find an economic evaluation that compared the two iron-based binders, SO to FC.

Conclusions: This review demonstrates the need for more economic evaluations of phosphate binders. Only one cost-effectiveness analysis was found that compared two non-calcium binders (SO vs SEV) head-to-head. In addition to cost analyses, payers may benefit from reviewing real-world data to examine the clinical benefits of specific phosphate binders.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO0373

Effect of Lanthanum Carbonate on Blood Pressure in CKD: The COMBINE TRIAL

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Background: Higher serum phosphate concentrations are associated with vascular calcification, cardiovascular events, and all-cause mortality. Emerging data suggests that higher serum phosphate may also be associated with increased blood pressure (BP). The effect of phosphate-lowering medication on BP has not been studied in a chronic kidney disease (CKD) cohort.

Methods: We evaluated patients from the CKD Optimal Management with Binders and Nicotinamide (COMBINE) Trial, a randomized, double-blind, placebo-controlled trial of phosphate binders and/or nicotinamide in patients with eGFR 20-45 ml/min/1.73m2. Our primary end point for this analysis was 12-month change in systolic BP (SBP). Randomization to lanthanum vs non-lanthanum treatment arms was our primary predictor variable. The secondary predictor variable was 24-hour urine phosphate excretion (a marker of dietary phosphate intake).

Results: 205 participants underwent randomization. The mean (± SD) baseline age was 69±12 years, eGFR was 32±7 ml/min per 1.73 m2, and SBP was 129±17 mmHg. Over the 12-month trial, compared to the non-lanthanum arms (N=102), SBP in the lanthanum arms (N=103) rose by 5 mm Hg (P value 0.0497) after adjusting for baseline BP, age, sex, baseline eGFR, clinical center and number of antihypertensives over time. Within the lanthanum arms SBP rose by 5 mm Hg (95% CI 1, 9 mm Hg) and diastolic BP rose by 2 mm Hg (95% CI 0.4, 4mm Hg). BP did not change in the non-lanthanum carbonate arms. There was no association between 24-hour urine phosphate excretion and change in BP.

Conclusions: Among trial participants with moderate to severe CKD, randomization to lanthanum carbonate was associated with increased BP. Future studies should determine whether lanthanum carbonate influences absorption of anti-hypertensive medications.

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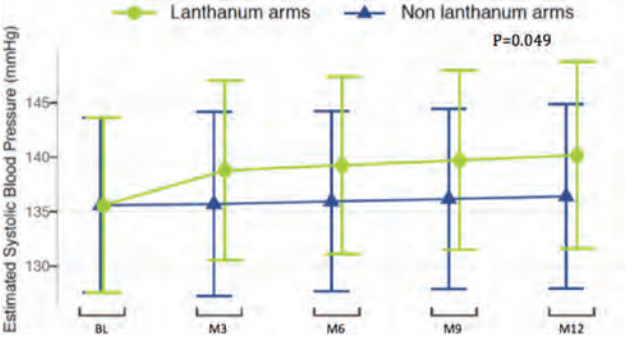

Change in Systolic Blood Pressure in Lanthanum vs Non-Lanthanum Arms

PO0374

Efficacy of Tenapanor for the Control of Serum Phosphorus in Patients with CKD on Dialysis: Novel Mechanism of Action Allows for Both Monotherapy and Dual-Mechanism Approach

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Background: Tenapanor (TEN) is an investigational, first-in-class, non-binder, phosphate absorption inhibitor being developed to control serum phosphorus (sP) in patients with chronic kidney disease (CKD) on dialysis. It has a unique mechanism of action and acts locally in the gut to inhibit the sodium-hydrogen exchanger 3 (NHE3). This results in the tightening of epithelial cell junctions, reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption, thereby reducing serum phosphorus concentrations.

Methods: Two Phase 3 studies were completed. An 8-week, double-blind (DB), randomized treatment period (RT) with a 4-week placebo (PBO)-controlled randomized withdrawal period (RW) examining the efficacy of TEN as monotherapy to treat hyperphosphatemia (HP) in patients with CKD on dialysis (NCT03427125) and a 4-week, randomized, DB, PBO-controlled study examining the efficacy of TEN administered with phosphate binders (BIND) using a dual mechanism approach to treat patients with uncontrolled HP (≥5.5. mg/dL) in patients with CKD on dialysis (NCT 03824587).

Results: In the monotherapy study, 219 patients were randomized to the RT, 164 patients (75%) completed the RT, and of these, 152 (93%) completed the RW. TEN achieved the primary endpoint with a LS mean difference of -0.8 (95% CI: -1.4, -0.2, p=0.01) in sP between TEN and PBO during the RW period. Approximately 50% of the patients treated with TEN achieved a mean sP reduction of 2.56 mg/dL from baseline to the end of the RT period. In the dual mechanism study, 236 patients were randomized to treatment. At week 4, the mean change in sP was significantly greater in the TEN+BIND arm (-0.84 mg/dL v. -0.19 mg/dL in the PBO+BIND arm, p=0.0004). Twice as many patients achieved sP<5.5 mg/dL with TEN+BIND than with PBO+BIND (up to 49.1% v. up to 23.5%, p<0.01). In both studies, the most common adverse event for patients treated with TEN was loose stools/diarrhea, leading to discontinuation in 7.8% and 3.4% of patients respectively.

Conclusions: Results from two DB PBO-controlled clinical trials have demonstrated the potential utility of tenapanor: 1. as effective monotherapy to treat HP in patients with CKD on dialysis, and 2. with phosphate binders for a dual mechanism approach in patients with CKD on dialysis who have difficult to treat HP.

Funding: Commercial Support - Ardelyx, Inc.

PO0375

Efficacy and Safety of Add-on Tenapanor to Phosphate Binders for Refractory Hyperphosphatemia in Japanese Patients on Hemodialysis: A Phase 2, Double-Blind Study

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Background: Among hemodialysis (HD) patients, some patients have poorly controlled serum phosphorus levels, even while using phosphate binders (PB). Tenapanor is a novel agent, which reduces phosphate uptake by selectively inhibiting sodium/hydrogen exchanger isoform NHE3 on the apical surface of the enterocytes and then decreasing paracellular phosphate permeability. The mechanism of action is different from conventional PB used to treat hyperphosphatemia. The additional treatment of tenapanor is expected to reduce serum phosphorus levels in HD patients with poorly managed serum phosphorus levels by PB. Here, we evaluated the efficacy and safety of add-on tenapanor to PB for refractory hyperphosphatemia in patients on HD.

Methods: This was a multicenter, randomized, double-blind, placebo (PLA)-controlled, Ph2 study. The study consisted of a screening period, a 2 or 3-week observation period, and a 6-week treatment period. Patients whose serum phosphorus level was ≥6.1 and <10.0 mg/dL with PB were randomized to either tenapanor+PB or PLA+PB group in 1:1 ratio. Starting dose of tenapanor was 30 mg BID, which could be reduced in a step-wise manner (30, 20, 10 and 5 mg BID) at the investigator's discretion, based on GI tolerability. The primary endpoint was the change in serum phosphorus level from baseline value at the end of treatment.

Results: 47 subjects were randomized. Mean change in serum phosphorus level from baseline was −1.99 mg/dL in the tenapanor group and 0.08 mg/dL in the PLA group (95%CI −2.89, −1.26 mg/dL, p<0.001). The achievement ratio of target serum phosphorus level (≥3.5, ≤6.0 mg/dL) at the end of treatment was 87.0% in the tenapanor group and 37.5% in the PLA group. Diarrhea was the most frequent adverse event (tenapanor=65.2%; PLA=16.7%), all were of mild to moderate severity.

Conclusions: Tenapanor showed a significant decrease in serum phosphorus levels compared with PLA (p<0.001) under PB combination. This result suggests that coadministration of tenapanor with PB could satisfy the unmet needs to better control serum phosphorus in HD patients with refractory hyperphosphatemia.

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

PO0376

Tolerability of Tenapanor, an Investigational, First-in-Class, Non-Binder Therapy for the Control of Serum Phosphorus in Patients with CKD on Dialysis

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Background: Phosphate binders are associated with gastrointestinal (GI) tolerability issues including constipation, diarrhea, nausea, and vomiting. Tenapanor (TEN), a first in class, targeted therapy that blocks the paracellular absorption of phosphate in the GI tract by local inhibition of the sodium-hydrogen exchanger (NHE3), and may have a different GI profile because of its unique mechanism which also reduces dietary sodium absorption, increasing the sodium and water content of stool.

Methods: Data from a 12-week monotherapy study (TEN201), a 52-week monotherapy study (PHREEDOM), and a 4-week combination study (AMPLIFY) were analyzed to evaluate the GI tolerability of TEN. Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (v 18, 20, 21). MedDRA classifies loose stool(s), loose bowel(s), and mushy stool(s) as diarrhea even without a reported increased frequency. Additionally, daily stool frequency and stool consistency using the Bristol Stool Form Scale (BSFS) were measured in TEN201.

Results: In each of the studies, the only adverse event that occurred in > 5% of TEN-treated patients was diarrhea as classified by MedDRA. Incidence of diarrhea during the treatment periods among patients on TEN 30 mg BID was 47.9%, 53.0%, and 42.7% for TEN201, PHREEDOM, and AMPLIFY, respectively, vs the placebo (PBO)-controlled randomized withdrawal period which was 2.9% vs. 2.4% in TEN201 and 4.0% vs. 1.6% in PHREEDOM, TEN vs. PBO, respectively. Across all studies, the diarrhea associated with TEN was most often mild-to-moderate and transient (with a median resolution within approximately 2 weeks); ~ 5% of patients experienced severe diarrhea. In TEN201, mean stool frequency increased by 2.8 bowel movements per week over baseline, and stool consistency increased by 0.8 points using the 7-point BSFS score, both remaining within the normal range.

Conclusions: These results demonstrate that TEN is associated with few GI side effects. Diarrhea, based on the MedDRA classification, occurred in approximately one-half of TEN-treated patients, most often reported as a modest and transient increase in stool frequency or loosening of stool.

Funding: Commercial Support - Ardelyx, Inc.

PO0377

Changes in Serum Phosphorus Among Patients Who Switch from Sevelamer Carbonate to Sucroferric Oxyhydroxide or Other Phosphate Binders After Persistent Hyperphosphatemia

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Background: Despite being prescribed phosphate binders (PB), many HD patients have persistent hyperphosphatemia. The current analysis examines serum phosphorus (sP) and pill burden changes among patients who have 3 months of sP > 5.5 mg/dl despite prescription of sevelamer carbonate (SC) and switched to (1) sucroferric oxyhydroxide (SO) monotherapy, or (2) Non-SO binders [Calcium Acetate, Lanthanum Carbonate, or Ferric Citrate] monotherapy or added one of these PBs to SC therapy.

Methods: All deidentified clinical and prescription data were extracted retrospectively from the Fresenius Kidney Care database. Follow-up was divided into quarters (Q1-Q4) to determine mean sP and PB pills/day. We applied Propensity Score Matching (PSM), Coarsened Exact Matching (CEM), and Inverse Probability of Treatment Weighting (IPTW) to address potential confounding/selection bias. PSM and CEM were used to match patients using overall PSM or agreement with each variable (CEM), and IPTW used weights on all patients.

Results: We identified 1,076 SC patients with baseline hyperphosphatemia who switched to SO (319 patients) and Non-SO (757 patients) PB therapy. Results from IPTW method that allowed retention of the entire sample size (n=1,076) are presented in Table 1. Application of CEM and PSM methods identified 197 and 257 matches for SO patients, respectively and noted results comparable to IPTW.

Conclusions: In a retrospective database analysis of HD patients with persistent hyperphosphatemia despite being prescribed SC, patients switched to SO had a mean sP decrease of 1.1 mg/dL compared to 0.79 mg/dL decrease among patients prescribed non-SO PBs. The PB pills/day decreased by 6.3 for SO-treated and 2.2 for Non-SO-treated patients.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Table 1

	Group	-Q1	Q1	Q2	Q3	Q4	P
Serum phosphorus, mg/dL	SO	7.05	6.48	6.24	6.1	5.95	<0.001
	Non-SO	7.04	6.59	6.33	6.38	6.25	
Phosphate binder pills/day	SO	10.9	4.2	4.3	4.4	4.6	<0.001
	Non-SO	10.8	8.7	8.6	8.6	8.6	
Serum calcium, mg/dL	SO	9.2	9.1	9	9	9.1	0.6
	Non-SO	9.2	9.2	9.1	9.1	9.1	
iPTH, pg/mL	SO	501	508	534	531	535	0.5
	Non-SO	489	520	532	546	505	

SO - 319 patients, Non-SO - 757 patients

PO0378

The Effect of Phosphate Lowering Using Sucroferric Oxyhydroxide on Endogenous Calciprotein Particle Formation in Dialysis Patients: Post Hoc Analysis of a Randomized Controlled Trial

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Background: We have recently demonstrated in a randomized, controlled, cross-over study in 39 chronic hemodialysis patients with hyperphosphatemia that high-dose phosphate binder therapy with 2000 mg/d of sucroferric oxyhydroxide (SO) over two weeks significantly reduces calcification propensity as determined by the T_{50}-test compared with a two-week wash-out phase (Cejka, Kidney Week 2019, FR-PO149). Based on these results, we hypothesized that SO would influence endogenous calciprotein particle (CPP) formation and crystallization, i.e. conversion from primary to secondary CPP.

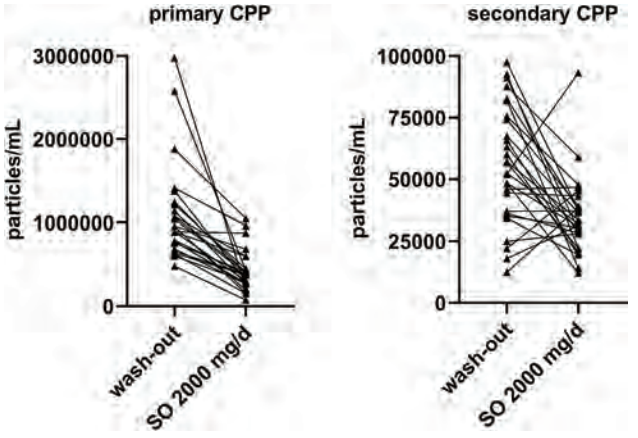
Methods: To test this hypothesis, we conducted post-hoc analyses of our RCT (74% men, mean age 63±27 years, median dialysis vintage 24, IQR 16-36 months). We compared native serum CPP levels (measured by a fluorescent probe-based flow cytometric assay) by Wilcoxson matched-pairs test and hydrodynamic radii (R_h) of secondary CPP formed after enrichment with exogenous calcium and phosphate (measured by three-dimensional cross-correlation dynamic light scattering) by paired t-test between the phosphate binder wash-out and high-dose treatment phase.

Results: Upon SO therapy serum phosphate levels decreased from 2.28±0.5 mmol/l to 1.63±0.43 mmol/l (p<0.0001), coincident with a reduction (median, IQR) in primary

(-62%, 44-78%, p<0.0001) and secondary CPP (-40%, 0.5-62%, p<0.0006, figure). Mean R_h of secondary CPP was significantly lower during SO therapy compared to wash-out (214±55 nm vs. 231±52 nm, p<0.01).

Conclusions: In dialysis patients, lowering serum phosphate with SO is associated with a reduction in the load of primary and secondary CPP and a smaller size of secondary CPP.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma AG, St. Gallen, Switzerland



PO0379

Changes in Serum Phosphorus and Pill Burden in Peritoneal Dialysis (PD) Patients Treated with Sucroferric Oxyhydroxide (SO) as Part of Routine Clinical Care: A Contemporary Cohort

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Background: Previous real-world analyses of SO in PD patients (pts) included pts first prescribed SO within the first 2 years of SO availability in the US (2014 Cohort: Kalantar 2018). A more contemporary cohort of pts prescribed SO may have different patient characteristics or treatment patterns than earlier SO pts. The current retrospective study assessed changes in serum phosphorus (sP) and phosphate binder (PB) pill burden in PD pts recently and previously prescribed SO.

Methods: Included were adult Fresenius Kidney Care PD pts first prescribed SO monotherapy during 5/2018- 5/2019 with PB monotherapy during a 3-month baseline (BL), and sP measured the month before SO initiation (-M1) and ≥4 months of the 6-month follow-up (2108 Cohort). Means were calculated monthly (-M1, M1-M6) for PB pills/day and monthly labs and quarterly for iPTH using mixed-effects linear regression.

Results: At BL, the 2018 Cohort (n=201) included slightly older pts (52.3 vs 50.6 yrs) with shorter dialysis vintage (22 vs 29 months) and different BL PB: sevelamer (42 vs 63%), calcium acetate (35 vs 21%), lanthanum (3 vs 5%), ferric citrate (12 vs 0%), or switched PB (8 vs 11%) compared to 2014 cohort. Lower pill burden (7 vs 10) and sP (6.52 vs 6.59) at BL were observed in 2018 cohort. In the 2018 cohort, pts achieving sP≤5.5 mg/dL increased from 21.9% at -1M to 40.5-47.3% during follow-up and the pattern was similar in 2014 cohort (25.8% at -1 M to 35.3-44.4% at follow-up). Mean SO pills/day was higher (4.7) in 2018-2019 cohort than the 2014 cohort (4.3).

Conclusions: PD pts prescribed SO as part of routine care in 2018 and 2014 experienced significant reductions in sP, and PB pill burden, and an increase in pts with sP≤5.5mg/dL.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	-1M (*ref*)	M1	M2	M3	M4	M5	M6	*P*-Value[a]
Phosphate binder pills/day	7.1	4.4**	4.4**	4.6**	4.8**	4.9**	4.9**	<0.001
Serum phosphorus (sP), mg/dL	6.80	6.26**	6.21**	6.23**	6.09**	6.06**	6.27**	<0.001
Patients with sP ≤ 5.5 mg/dL, %	21.9	41.4**	41.7**	40.5**	47.3**	42.3**	41.1**	<0.001
Serum calcium, mg/dL	9.05	8.89*	8.96	8.96	8.91*	8.89*	8.87**	0.005
Intact PTH, pg/mL	483		518			517		0.08
Serum albumin, g/dL	3.63	3.59*	3.60	3.59*	3.57*	3.57*	3.59*	0.03
sP-attuned albumin, $\times 10^3$	0.57	0.63**	0.63**	0.62**	0.64**	0.64**	0.61**	<0.001

*P<0.05; **P<.001 (vs. *ref*); [a]

P-Values from mixed-effects linear regression or Cochran's Q

PO0380

Assessment of Serum Phosphorus Levels in Patients Following Administration of Ferric Pyrophosphate Citrate: A Retrospective Study

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Background: Iron deficiency is common among hemodialysis patients contributing to chronic anemia. Ferric pyrophosphate citrate (FPC) is FDA-approved to replace iron and maintain hemoglobin in adult hemodialysis patients by delivering iron directly and rapidly to transferrin. FPC is a mixed-ligand iron complex in which iron is bound to pyrophosphate and citrate, along with containing phosphate, sodium, and sulfate. Phosphorus regulation in ESRD patients can be challenging thus administering products containing phosphates risks increasing serum phosphorus in addition to exacerbating underlying endocrine abnormalities. The objective of this study is to assess any changes in phosphorus levels in hemodialysis patients receiving FPC.

Methods: Retrospective data from patients at a single center hemodialysis clinic was reanalyzed looking at serum phosphorus level of hemodialysis patients receiving FPC over a one-year span of time. The data analyzed included serum phosphorus levels prior to initiating therapy compared to serum phosphorus levels after being administered FPC 1-month, 6-months, and 12-months on therapy.

Results: Forty-nine patients were included in the study. Median serum phosphorous values were at pre-therapy (median 4.8), 1-month of FPC (median 4.7, p=0.56), 6-months of FPC (median 4.8, p=0.49), and 12-months of FPC (median 5.1, p=0.36) as represented in Figure 1.

Conclusions: After analysis of serum phosphorus levels in hemodialysis patients receiving ferric pyrophosphate citrate, the findings show that there was no difference in average serum phosphorus levels before and after therapy. Clinicians who are prescribing this medication should be aware that there is no increase in serum phosphorus in patients while receiving this therapy considering how difficult it can be to regulate phosphorus along with managing the potential consequences of phosphorus abnormalities.

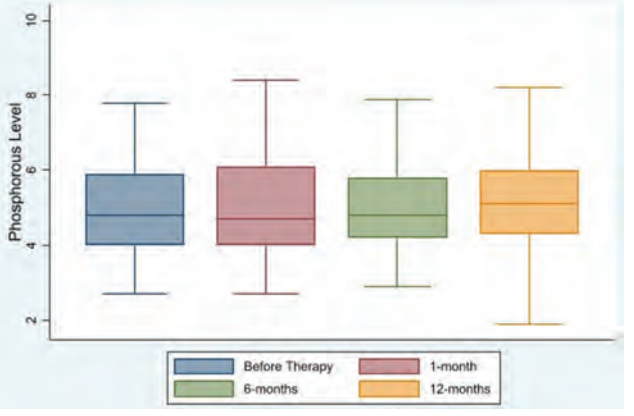

Figure 1

PO0381

Real-World Effectiveness of Sucroferric Oxyhydroxide (SO) in Lowering Serum Phosphorus (sP) Among a Contemporary Hemodialysis (HD) Cohort: A 6-Month Follow-Up

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Background: Clinical trial and real-world data demonstrated the effectiveness of SO in managing sP among dialysis pts. Previous real-world analyses included HD pts prescribed SO within the first 2 years following SO availability in the US (2014 Cohort, Coyne 2017). With greater physician experience with SO and increased availability, prescription patterns may have changed over time. The current retrospective study assessed changes in sP and phosphate binder (PB) pill burden in pts prescribed SO in 2018-2019 (2018 Cohort) and compare these results to the 2014 Cohort findings.

Methods: We included adult Fresenius Kidney Care HD pts first prescribed SO monotherapy between 5/2018- 5/2019, on other PB monotherapy during a 3-month baseline (BL), and had sP measured the month before SO start and in ≥5 months during SO. We compared BL to quarterly (Q1, Q2) means, calculated using mixed-effects linear regression, for PB pill burden and lab measurements.

Results: Compared to the 2014 Cohort, the 2018 cohort (n=2018) was larger (vs 424), older (56 vs 51 years) with shorter dialysis vintage (47 vs 56 months), more likely prescribed calcium acetate (42 vs 22%) and less likely prescribed sevelamer (41 vs 63%). The 2018 Cohort had better BL sP control (25.7 vs 15.6% pts with sP≤ 5.5 mg/dL), yet in both cohorts SO conversion was associated with significant reductions in sP (6.39 to 6.00 vs. 6.86 to 6.41) and PB pills/day (7.6 to 4.4 vs. 9.7 to 4.0). % pts with sP ≤ 5.5 mg/dL increased from 15.6 to 30.4% in 2014 Cohort and 25.7 to 41.3% in Cohort 2018.

Conclusions: Similar to the 2014 Cohort, a contemporary cohort of HD pts converted to SO experienced improvements in sP and achieving sP ≤ 5.5 mg/dL with fewer PB pills/day. Physicians are prescribing SO to a broader patient population with different distributions of baseline PB therapy.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	BL; -Q1 (ref)	SO Q1	SO Q2	P-Value†
Phosphate binder pills/day	7.6	4.3**	4.4**	<0.001
Serum phosphorus (sP), mg/dL	6.39	6.13**,b	6.0**,b	<0.001
Patients with sP ≤ 5.5 mg/dL, %	25.7	36.9**,b	41.3**,b	<0.001
Serum calcium, mg/dL	9.10	9.07**	9.0**	<0.001
Intact PTH, pg/mL	582	575	586	0.17

**P<0.001 (vs. BL)

† Mixed effects linear regression and Cochran's Q test were used to test for statistical significance

PO0382

Dose-Response Efficacy and Tolerability of Tenapanor on Hyperphosphatemia in Japanese Hemodialysis Patients: Results of a Randomized Phase 2 Study

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Background: Tenapanor is a novel, non-binder, targeted therapy that reduces paracellular phosphate absorption in the gut by selectively inhibiting the intestinal sodium/hydrogen exchanger isoform NHE3. In a US clinical trial by Ardelyx, Inc. tenapanor significantly reduced serum phosphorus level in hemodialysis (HD) patients with hyperphosphatemia as compared to the placebo (PLA). The purpose of this study was to confirm the efficacy, dose-response and tolerability of tenapanor on hyperphosphatemia in Japanese HD patients.

Methods: This was a multicenter, randomized, double-blind, PLA-controlled, parallel-group and dose-finding Ph2 study. The study consisted of a screening, a 2 or 3-week 1st washout (WO) period, a 6-week treatment period, and a 3-week 2nd WO period. Patients were enrolled when screening serum phosphorus level was 3.5–6.0 mg/dL and increased by ≥1.0 mg/dL to 6.1–9.9 mg/dL after 1st WO. Thereafter patients were randomized to one of 5 groups (PLA, tenapanor 5 mg, 10 mg, 30 mg or 30 mg down titration (DT) twice/day). 30 mg DT group could be down-titrated in a step-wise manner to 20, 10 and 5 mg on the basis of GI tolerability. The primary endpoint was the mean change in serum phosphorus level from baseline to end of treatment in each group.

Results: 207 subjects were enrolled (41 or 42 subjects were randomized to each group). The mean change in serum phosphorus at the end of treatment from baseline was 0.64 mg/dL in the PLA group, –0.93 mg/dL in the 5 mg group, –1.36 mg/dL in the 10 mg group, –1.92 mg/dL in the 30 mg group and –1.99 mg/dL in the 30 mg DT group (p<0.001 in all tenapanor groups vs PLA). The major adverse event was diarrhea, which occurred in a dose-dependent manner (PLA: 22.0%, tenapanor 5 mg: 57.1%, 10 mg: 65.9%, 30 mg: 76.2%, 30 mg DT: 70.7%). Most of the events were mild in severity, and, in each tenapanor group, only 1 to 3 subjects were discontinued from the study due to diarrhea.

Conclusions: Tenapanor was well tolerated in Japanese HD patients and significantly decreased serum phosphorus level in a dose-dependent manner compared with PLA (p<0.001).

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

PO0383

CKD and Vitamin D Status Alter Vitamin D Metabolism

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Background: Up to 90% of people with chronic kidney disease (CKD) are vitamin D (VitD) deficient. VitD is subsequently prescribed and has documented health benefits, including nephro-, cardio-, and immune- protection. This paired study sought to evaluate and compare VitD metabolism in CKD patients and healthy controls (HC) under both VitD deficiency and repletion.

Methods: VitD deficient (25[OH]D_3 <30 ng/mL) CKD patients (n=30) and HC (n=11) were recruited (Phase 1). Participants were administered 5,000 I.U. oral D_3 daily for 12 weeks. At week 12 (Phase 2), participants received their final dose of D_3 after 25[OH]D_3 was confirmed to be replete (≥30 ng/mL). Blood was collected at serial time points for up to 336 h at each phase for determination of D_3, 25[OH]D_3, 1,25[OH]$_2D_3$, and 24,25[OH]$_2D_3$. Metabolism ratios (MR) were defined by the area under the plasma concentration-time curve (AUC) of pre-cursor to a subsequent metabolite. Analyses for differences were assessed by ANOVA with a Tukey-Kramer post-hoc test.

Results: Metabolism was differentially altered by VitD status and CKD. Significant differences in assessment of MR were determined in both an immediate precursor to the next metabolite in the sequence and by the parent compound (D_3) to the final metabolite in the metabolism sequence. The metabolism of D_3 to 25[OH]D_3 and of 25[OH]D_3 to 1,25[OH]$_2D_3$ were significantly decreased by CKD severity, with differences more pronounced after VitD repletion.

Conclusions: CKD severity decreased metabolism by the cytochrome 2R1 and 27B1 sequential pathways resulting in reductions in the D_3 to 25[OH]D_3 and 25[OH]D_3 to active VitD (1,25[OH]$_2D_3$), respectively. Daily dosing leading to repletion appears to decrease the overall conversion of cholecalciferol to its metabolites in HC and CKD patients, possibly due to saturation of metabolism pathways. Future research will evaluate the influence of daily vs. intermittent dosing on metabolism efficiency.

Funding: Other NIH Support - NIGMS

		Immediate Precursor to Sequential Metabolite			Parent Compound to Final Metabolite	
	Patient Group	D_3:25[OH]D_3	25[OH]D_3:1,25[OH]$_2D_3$	25[OH]D_3:24,25[OH]$_2D_3$	D_3:1,25[OH]$_2D_3$	D_3:24,25[OH]$_2D_3$
Phase 1	Healthy	0.0024 ± 0.0045 (11)	188 ± 42 (11)	16 ± 5.8 (11)	0.40 ± 0.71 (11)	0.032 ± 0.056 (11)
	CKD Stage 1-3	0.016 ± 0.024 (20)	214 ± 47 (20)	19 ± 6.2 (20)	3.4 ± 5.1 (20)	0.33 ± 0.56 (20)
	CKD Stage 4-5	0.021 ± 0.040 (10)	243 ± 56 (10)	22 ± 7.4 (10)	5.0 ± 9.5 (10)	0.38 ± 0.70 (10)
Phase 2	Healthy	0.031 ± 0.045 (9)	209 ± 53 (9)	14 ± 8.6 (9)	6.2 ± 9.0 (9)	0.40 ± 0.55 (9)
	CKD Stage 1-3	0.061 ± 0.079 (17)[a]	252 ± 54 (17)[a]	16 ± 4.9 (17)	15 ± 19 (17)[a,b]	1.1 ± 1.4 (17)[a]
	CKD Stage 4-5	0.062 ± 0.065 (7)	283 ± 60 (7)[a,b,c]	22 ± 7.2 (7)	17 ± 17 (7)	1.4 ± 1.4 (7)[a]
	P-value	0.017	0.0008	0.032	0.0052	0.0067

Data reported as mean ± SD (n); p-values calculated using one-way ANOVA.a: p<0.05 vs. phase 1, HC.

b: p<0.05 vs. phase 1, CKD 1-3.

c: p<0.05 vs. phase 2, HC.

PO0384

Long-Term Safety and Efficacy of Tenapanor for the Control of Serum Phosphorus in Patients with CKD on Dialysis

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Background: Tenapanor (TEN) is an investigational, first-in-class, non-binder therapy that targets the primary pathway of phosphate absorption, providing a novel approach to treating hyperphosphatemia. TEN blocks the paracellular absorption of phosphate in the GI tract by local inhibition of the sodium-hydrogen exchanger (NHE3) and is dosed as one small pill (<12x7 mm) twice daily. Two previously conducted pivotal trials of TEN met their primary efficacy endpoint.

Methods: A 52-week study consisting of a 26-week, open-label, randomized treatment period (RT) with a 12-week placebo-controlled randomized withdrawal period (RW), followed by a 14-week open label safety extension period (SE). Patients on maintenance dialysis with serum phosphorus (sP) ≥ 6.0 mg/dL and <10.0 mg/dL and a 1.5 mg/dL increase in sP following washout were randomized 3:1 to receive one 30 mg TEN tablet BID or sevelamer carbonate (SEV; a safety control) dosed per package insert. At end of RT all patients in the TEN arm were re-randomized 1:1 to either TEN or placebo for the RW. Primary endpoint was the mean change in sP from the end of RT to the end of the RW and was compared between TEN and placebo for the efficacy analysis set, defined as patients demonstrating a ≥ 1.2 mg/dL decrease in sP at the end of RT.

Results: The study achieved its primary endpoint demonstrating a statistically significant difference in least squares (LS) mean sP change (-1.4 mg/dL, p<0.0001), between TEN and placebo. For the efficacy analysis set (n=131), the mean sP decreased from 7.7 mg/dL at baseline to 5.1 mg/dL at the end of the 26-week TEN treatment, with a mean reduction of 2.6 mg/dL. During the 26-week treatment period, 77% of TEN-treated patients in the intent-to-treat population (n=407) had a decrease in sP, with a mean reduction from baseline of 2.0 mg/dL. TEN was generally well tolerated; the only AE with incidence >5% during RT was loose stools/diarrhea (53.0%), the majority of which were mild-to-moderate and transient in nature. In the RT, 17.4% of tenapanor-treated patients compared to 23.4% of sevelamer-treated patients experienced a serious adverse event.

Conclusions: The trial results suggest that among patients on maintenance dialysis with hyperphosphatemia, TEN dosed one tablet twice daily is safe and efficacious as monotherapy.

Funding: Commercial Support - Ardelyx, Inc.

PO0385

Diagnostic Accuracy of Static Bone Histomorphometry Parameters to Define Low Bone Turnover

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Background: Tetracycline labeling for bone biopsy allows pathologists to measure the pace of new bone production, which is critical to defining bone pathology in CKD. In the setting of clinical fractures, bone tissue is available, but tetracycline labeling is not possible. Therefore, we sought to determine the diagnostic accuracy of static measures of bone turnover relative to that measured by tetracycline in CKD patients undergoing iliac crest biopsy and histomorphometry.

Methods: We evaluated 147 individuals ages 12.4 ±8.9 who had undergone iliac crest bone biopsy with tetracycline labeling for clinical indications of CKD-MBD. Using the tetracycline labels under florescence, we defined bone formation rate relative to bone surface (BFR/BS) < 8 (normal range 8-73) as our gold standard to define low bone turnover. A blinded investigator used light microscopy without fluorescence to measure static bone turnover parameters. We then compared the area under the ROC curve (AUC), sensitivity, and specificity of each bone turnover parameter with low turnover based on tetracycline using the Youden J Index, which is the point on the ROC curve farthest from line of equality that maximizes sensitivity and specificity.

Results: Among the 147 biopsies, 35 (24%) had low bone turnover based on tetracycline. Weevaluated 5 parameters available by static bone microscopy, among which Osteoblast Surface relative to Bone Surface (Ob.S/BS), Osteoclast Surface relative to Bone Surface (Oc.S/BS), and Osteoid Volume to Bone Volume (OV/BV) had the highest AUCs for low bone turnover based on tetracycline labeling. Using the best cut-offs from the AUC curves, a %Ob.S/BS of 82% had a sensitivity and specificity of 80% and 75% for low bone turnover.

Conclusions: Static measures of bone turnover have high sensitivity and specificity for identifying low bone turnover defined by tetracycline labeling at the iliac crest in CKD patients. Bone tissue without tetracycline labeling may be useful clinically to define bone turnover.

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Table. Criteria for defining low bone turnover using static histomorphometry measures

	AUC	Sensitivity	Specificity	Youden J	Cutpoint
Ob.S/BS	0.8245	0.80	0.75	0.55	2.30
Oc.S/BS	0.7753	0.91	0.60	0.49	1.70
OV/BV	0.7212	0.49	0.91	0.40	1.38
O.Th	0.6969	0.80	0.51	0.31	1.61
Ob.S/BS + Oc.S/BS	0.8252	0.75	0.78	0.52	NA
Ob.S/BS + Oc.S/BS + OV/BV	0.8487	0.71	0.86	0.57	NA

PO0386

Acid-Base Status More Than Dietary Acid Intake Determines Urine Citrate Excretion in CKD

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Background: Lower urine excretion of the pH-sensitive metabolite citrate (UcitV) might be a clinically useful biomarker of steady-state acid (H^+) retention not evident by plasma acid-base parameters in patients with CKD. Ongoing dietary H^+ intake might also be an important determinant of UcitV and possibly confound its utility as a biomarker of underlying H^+ retention.

Methods: We examined the influence on 8-hour UcitV (UcitV), its plasma citrate concentration (Pcit) and kidney clearance (UcitV/Pcit) components, and 8-hour urine net acid excretion (8h NAE) of 1) ongoing dietary acid addition assessed by potential renal acid load (PRAL) and 2) steady-state acid-base status assessed by plasma total CO_2 ($PTCO_2$) and by H^+ retention [estimated by comparing observed to expected $PTCO_2$ increase in response to retained HCO_3 (administered minus $UHCO_3V$) 2 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body wt HCO_3 apparent space of distribution] in 224 patients with CKD stages 1-3 due to macroalbuminuric, non-diabetic, hypertension-associated nephropathy.

Results: Because Pcit, UcitV, UcitV/Pcit, and $PTCO_2$ each directly associated with eGFR ($p<0.01$) and because H^+ retention inversely associated with eGFR ($p<0.01$), we adjusted reported associations for eGFR. PRAL associated directly with 8h NAE ($p<0.01$, $R^2=0.05$) and inversely with UcitV/Pcit ($p=0.03$, $R^2=0.13$) but not with $PTCO_2$ ($p=0.15$), H^+ retention ($p=0.85$), UcitV ($p=0.21$) or Pcit ($p=0.49$). $PTCO_2$ associated inversely with H^+ retention ($p<0.01$, $R^2=0.06$) but not with 8h NAE ($p=0.14$), UcitV ($p=0.59$), Pcit ($p=0.11$) or with UcitV/Pcit ($p=0.79$). By contrast, H^+ retention associated inversely with UcitV ($p<0.01$, $R^2=0.55$), Pcit ($p<0.01$, $R^2=0.52$) and with UcitV/Pcit ($p<0.01$, $R^2=0.20$) but not with 8h NAE ($p=0.12$).

Conclusions: Ongoing dietary acid intake assessed by PRAL associated inversely with UcitV/Pcit, although quantitatively less than did H^+ retention (R^2 0.13 vs. 0.20), but did not associate with the remaining measures of citrate homeostasis. By contrast, steady-state acid-base status assessed by H^+ retention associated inversely with each measure of citrate homeostasis. The data show that steady-state acid-base status is a more important determinant of UcitV than dietary acid intake and support continued exploration of UcitV as a biomarker of underlying H^+ retention in CKD.

PO0387

Calciphylaxis (Calcific Uremic Arteriolopathy) in a Predominantly African-American Urban US Patient Population

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Background: Calcific Uremic Arteriolopathy (CUA) which is commonly called calciphylaxis is a rare and serious condition characterized by painful skin ulcerations due to ischemia with necrosis of the skin. The disorder carries a mortality rate > 50% in the first year, and death is often due to recurrent infections. Risk factors for calciphylaxis includes end-stage renal disease (ESRD), a history of diabetes, obesity, female gender, Caucasian race, and the use of medications such as warfarin. We present clinical characteristics of CUA patients admitted to a large academic medical center which serves as a CUA referral center due to the presence of a wound center with hyperbaric oxygen therapy available.

Methods: Retrospective chart review of CUA patients from 2001-2019 in our single center academic hospital. Baseline data reported included age, calcium, phosphorus, PTH, albumin, hemoglobin, creatinine, BUN, the use of medications such as warfarin or steroids, and treatment options.

Results: There were 110 patients included. Patient identified racial (n=108) make-up included African-American (n=89), Caucasian (n=18), and Asian (n=1). Average age was 56±14 years and 80% of patients were female (n=88). Also, 59% (n=65) of patients were diabetic. Dialysis modalities included hemodialysis (n=82) and peritoneal dialysis (n=24). Also 4 patients with CKD not yet on dialysis at the time of diagnosis. Average calcium levels of 8.9±1.1 mg/dL and phosphorus of 5.1±1.9 mg/dL. The average PTH was 569.6±714.9 pg/mL, albumin 2.5±0.7 g/dL, and hemoglobin 9.8±1.7 g/dL. Approximately 50% of patients received hyperbaric oxygen therapy as inpatient, 25% received sodium thiosulfate therapy, and 20% received a surgical intervention during the admission. Approximately 33% of patients were currently or recently on warfarin therapy, and approximately 25% were currently or recently exposed to high dose steroids.

Conclusions: We reported the largest single center and predominantly African-American (81%) calciphylaxis case series. In comparison to other reported calciphylaxis series our average PTH was lower and a high percentage of our patients were using warfarin or steroids. The PTH levels were higher in the African American group compared to others. Also, with a lower than expected parathyroidectomy rate which is likely due to our lower than average PTH.

PO0388

Citric Acid-Containing Dialysate (CD) Attenuates Vascular Calcification in Hemodialysis Patients (HD)

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Background: The main causes of death in patients with CKD, especially in HD, are heart failure, cardiovascular, and cerebrovascular disease, which are due to a high degree of systemic vascular calcification. Progression of aortic calcification, simply evaluated by chest radiography, was reported to be significantly associated with overall and cardiovascular mortality in HD. Recently, it was reported that the use of CD reduced blood calciprotein particles (CPPs) associated with arteriosclerosis and inflammation in HD. Therefore, we investigated the effect of using CD on blood CPPs and vascular calcification in HD in a retrospective observational study.

Methods: The subjects were 262 HD who were visiting the Joban Hospital in Japan. These patients were divided into two groups, those who continued to use acetate-containing dialysate (AD) or switched to CD from October 2017. A one-year retrospective observational study was conducted on the association with blood, laboratory test values, and AoACS (aortic arch calcification score) evaluated by chest X-ray. At baseline, patients with AoACS>50%, bisphosphonate, and warfarin use were excluded. Univariate, multivariate, subgroup analyses were used for statistical analysis. The main outcome was the presence or absence of AoACS exacerbation of 5% or more in one year.

Results: A total of 115 patients with AD and 102 patients with CD matched to the criteria were included. As a result, the use of CD (HR 0.53, [95% confidence interval (CI) 0.30-0.92], P = 0.026), ALP (HR 0.97, 95 %CI 0.94-0.99, P = 0.013), and AoACS (HR 1.36, 95% CI 1.15-1.63], P = 0.0004) were significantly associated with an exacerbation of AoACS. Subgroup analyses showed the characteristics of patients who benefit from using CD are those older than 75 years old, those with non-diabetes as the underlying disease, low nPCR(normalized protein catabolic rate), high blood CRP, and not severe calcification. In other words, patients with MIA syndrome can benefit from the use of CD.

Conclusions: Among patients with mild to moderate vascular calcification, HD with CD had a significantly reduced progression of AoACS compared with AD. The results indicate that the dialysis method using CD in HD may be a useful therapeutic method for suppressing vascular calcification.

Funding: Government Support - Non-U.S.

PO0389

Vascular Calcifications in Renal Transplantation

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Background: The aim of this study was to analyse the progression of vascular calcifications (VC) in a cohort of renal transplanted patients.

Methods: Prospective cohort study of de *novo* renal transplant patients. All patients were submitted to X-ray of the pelvis and hands (Adragão score); bone biopsy; laboratorial and echocardiographic evaluation at baseline and after 12 months (time 0 and 1). At the end of the study, bone densitometry and non-contrast cardiac CT (Agatston score) were performed. Associations between variables were performed using Wilcoxon rank sum test and Spearman correlation test. STATA software was used and $p < 0.05$ was considered statistically significant.

Results: We recruited 85 patients during 29 months and 69 were included in the study (6 patients refuse to perform the 2nd evaluation, 5 had primary non-function of the kidney graft, 1 had no sample on bone biopsy in time 0 and 4 patients died). Mean age 50.1±12.7 years, 59 men (69.4%), 66 caucasian (77.6%), median BMI 25.1±3.4. The median baseline and 12 months Adragão score had no differences. The median coronary artery calcium score (CACS) was 48.5 (0 – 535) and median percentile was 80 (0 – 92.5). Valvular calcifications were present in 15 and 16 patients at baseline and after 1 year ($p>0.05$). CACS were correlated with age ($p<0.001$), both Adragão score ($p<0.001$), presence of valvular calcification in time 1 ($p=0.004$), baseline calcium ($p=0.02$), baseline and 1-year sclerostin ($p=0.01$; $p=0.04$). CACS were higher in patients with highest values of FGF23 at baseline ($p=0.04$). Using a pairwise correlation, vitamin D levels ($r=0.4$, $p=0.0004$), iPTH ($r=0.6$, $p<0.001$) and total cholesterol levels ($r=-0.3$, $p=0.01$) were correlated with the score. Coronary calcium percentile was correlated with Adragão score in the two time points ($p=0.0001$; $p=0.002$), with presence of valvular calcifications in time 1 evaluation ($p=0.02$), baseline and 1-year calcium levels ($p=0.004$; $p=0.02$) and baseline sclerostin ($p=0.01$).

Conclusions: VC stabilize after renal transplantation. Adragão score can assess VC in renal transplanted patients. Calcium and sclerostin correlated with Agatston scores.

PO0390

Vascular Calcification and Progression of CKD

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Background: Vascular calcification, particularly the medial form, is common in advanced chronic kidney disease (CKD) and leads to poor outcomes. However, the extent to which medial calcification affects the kidneys and could exacerbate CKD is unknown. To this end, progression of CKD was compared in women with and without breast arterial calcification (BAC), a marker of systemic medial arterial calcification, and the prevalence of renal arterial calcification was assessed radiologically and histologically in patients undergoing nephrectomy.

Methods: Women with CKD (eGFR <60 ml/min/m2) were identified from previous studies of breast arterial calcification, and those with a subsequent measurement of serum creatinine at least 1 year later were included. Consecutive patients with CKD and nephrectomies were identified from a computerized search of medical records. Computed tomography (CT) scans were reviewed for aortic and renal artery calcification, and histology (hematoxylin and eosin staining) was reviewed for calcification of main renal arteries and parenchymal arteries. Current or past warfarin use was an exclusion in all cohorts.

Results: Women with (n=51) and without (n=67) breast arterial calcification had similar yearly eGFR declines (1.55 vs. 1.60 ml/min/1.73 m^2) despite a greater age (75.4 ± 1.3 vs 70.4 ± 1.5) and lower baseline eGFR (33.8 ± 1.8 vs. 39.2 ± 1.6) in women with BAC. There was no correlation between the quantity of BAC and the decline in eGFR ($r = 0.10$). Of 246 patients with nephrectomies who were screened, 50 had an eGFR < 30. End-stage renal disease was present in 82% and 36% had diabetes. CT scans were available in 34 patients and showed aortic and renal artery calcification in 59% and 38%. Prevalences of histologic calcification of renal artery and intraparenchymal arteries were 16% and 15%. When present, calcification of parenchymal arteries was usually very mild, and was severe in only 3 cases and limited to large arteries. In patients with CT scans, only those with renal artery calcification had parenchymal artery calcification (4 of 11 vs. 0 of 17 without, $p=0.016$).

Conclusions: Vascular calcification does not contribute to the progression of CKD. This is explained by the surprisingly low prevalence and severity of calcification in intrarenal arteries. Patients without renal artery calcification on imaging are at low risk for parenchymal artery calcification.

Funding: Clinical Revenue Support

PO0391

Clinical Outcomes in Patients with Calcifications on Kidney Biopsy

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Background: Calcification is often noted on kidney biopsies, but the consequences of this finding is not known.

Methods: We searched a biobank for specimens with at least two years of linked clinical data and identified those which had calcification on report. Biopsy specimens were further classified to be described as calcium oxalate (CO), calcium phosphate/ dystrophic (DC), or both. Linked clinical data was examined in 3 month intervals before and after index date of kidney biopsy. Cox proportional hazard analysis was performed using a split time model to evaluate relationships between presence of calcification, type of calcification, and clinical outcome endpoints. Linked clinical data was examined in 3 month intervals before and after index date of kidney biopsy. Cox proportional hazard analysis was performed using a split time model to evaluate relationships between presence of calcification, type of calcification, and clinical endpoints.

Results: Patients with any calcification (n=429) vs. without (n= 3936) were ($p < 0.05$) older, more likely to be white, have diabetes, lower eGFR and higher AKI/ATN on kidney biopsy specimen (31 vs. 13%). Patients with COX (n = 126) vs. DC (n = 260) were older, less diabetes, lower eGFR, more likely to have malabsorption or gastric bypass, and used more vitamin D. By univariate analyses, patients with any calcification were more likely to have a decline in the slope of creatinine at 6 months, 1 year, and 2 years; these changes persisted even after adjustment for baseline eGFR, htn, proteinuria, negative biopsy findings, CAD (for 1 year beta 0.029, $p < 0.001$). When adjusted for age, diabetes, and baseline eGFR, patients with any calcification were less likely than those without calcification to advance to ESKD (HR 0.59; 95%CI 0.38-9.82; $p < 0.05$) but not to meet the outcome of death.

Conclusions: The presence of calcification on kidney biopsy specimen is associated with lower progression to ESKD and decrease in rate of decline of eGFR over time at 6 months, 1 year, and 2 years. This paradoxical finding may be due to increased AKI with recovery, rather than progressive chronic disease but requires further analyses.

PO0392

Urine Phosphate Excretion and Microvascular Function in a Population-Based Cohort

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Background: Higher serum phosphate is associated with cardiovascular events and all-cause mortality. While these associations have largely been attributed to an increased risk of large vessel calcification, our previous work demonstrated a higher morning serum phosphate is associated with microvascular dysfunction. However, the relationship between 24-hour urinary phosphate excretion ([(UPE) a surrogate for dietary phosphate] and microvascular function has not been explored.

Methods: We performed a cross-sectional analysis of 3,116 community-living participants that underwent a 24-hour urine collection and skin capillaroscopy, laser-Doppler flowmetry, and flicker-light induced retinal vessel responses as part of the Maastricht Study. The primary outcome was post-occlusive finger skin capillary recruitment. Secondary outcomes included capillary recruitment during venous congestion, heat-induced skin hyperemic response, and flicker-light induced retinal arteriolar and venular dilation.

Results: The mean age of the cohort was 60 years, 48% were women, 7% had an eGFR< 60ml/min/1.73 m^2, and the mean serum phosphate concentration was 3.2mg/dl. The mean UPE was 874 ± 315 mg/day. UPE was not associated with any of the microvascular outcomes (**Table 1**) and there were no significant interactions between UPE and sex, diabetes status or eGFR on any of the outcomes (P>0.43). We found an inverse relationship between UPE and serum phosphate ($r=-0.26$, $p<0.001$)

Conclusions: We found no relationship between UPE and microvascular function in community-living individuals predominantly with normal kidney function. Relationships between urine phosphate, serum phosphate and microvascular function require further exploration.

Funding: NIDDK Support, Private Foundation Support

Table 1: Association of 24 Hour Urine Phosphate Excretion and Serum Phosphate Concentration with Microvascular Measurements*

Measurement Technique	Per 100 mg/day Higher (Urine)	P	Per 1 mg/dl Higher † (Serum)	P
% Capillary Recruitment during Post-Occlusive Reactive Hyperemia	0.01 (-0.4, 0.8)	0.82	-5.0(-10.0, -0.1)	0.04
% Capillary Recruitment during Venous Congestion	0.2 (-0.6, 1.0)	0.65	-4.5 (-9.8, 0.7)	0.09
% Heat-Induced Skin Hyperemic Response	-9 (-24, 5)	0.20	- 25 (-113, 63)	0.57
% Retinal Arteriolar Dilation	0.00 (-0.04, 0.04)	0.88	-0.12 (0.3, 0.15)	0.39
% Retinal Venular Dilation	0.00 (-0.03, 0.04)	0.94	-0.23 (-0.44, -0.02)	0.03

*Relationships are adjusted for age, sex, body mass index, smoking status, blood pressure, use of antihypertensive medications, use of lipid modifying medications, glucose metabolism status, eGFR, and serum calcium.

† Data for serum phosphate analysis from prior study, Ginsberg et al., CJASN 2019

PO0393

Complete Resolution of Calciphylaxis in a Renal Transplant Patient with Calcifediol

Mohankumar Doraiswamy,[1] Priyamvada Singh,[1] Shumei Meng,[2] Todd E. Pesavento.[1] *[1]Comprehensive Transplant Center, The Ohio State University Wexner Medical Center, Columbus, OH; [2]Division of Endocrinology, The Ohio State University Medical Center, Columbus, OH.*

Introduction: Calciphylaxis is a rare but lethal disorder (mortality 60-80%) characterized by occlusion of microvasculature in the subcutaneous adipose tissue and dermis, resulting in excruciating painful, ischemic skin lesions. It commonly occurs in dialysis patients but only few cases in transplants reported. Treatment options are meager, and a multidisciplinary approach (dermatology, nephrology, nutrition, pain, palliative medicine, plastic surgery, and wound care), with surgical debridement, antimicrobial therapy, optimization of calcium-phosphorus product, dialysis adequacy, sodium thiosulfate, and hyperbaric oxygen been suggested.

Case Description: A 62-year-old female with a LDKT (2008) complicated with CKD III, lupus nephritis, hypothyroidism, presented with painful, bilateral, medial calf ischemic ulcerations, which on punch biopsy revealed calciphylaxis. Her baseline iPTH, calcium, phosphorus, and 25-hydroxy-vitamin D, was 372 pg/mL, 9.4 mg/dL, 3.8 mg/dL, and 17.4 ng/mL, respectively. She was on calcitriol 0.75 mg/daily, ergocalciferol 50,000 units weekly and cinacalcet 30 mcg every other day. We started her on Calcifediol 30 mg, which increased to 60 mg daily. Her calcitriol and ergocalciferol doses were reduced slowly, while cinacalcet remained the same. This led to gradual increase in 25-hydroxyvitamin D and reduction in iPTH levels without effect on the calcium-phosphorus product. Over 1-year follow-up, her ulcers completely resolved as shown in the images with marked improvement in the pain.

Discussion: Treatment of hyperparathyroidism is limited as calcitriol and ergocalciferol worsen the calcium-phosphorus product while calcimimetics cause hypocalcemia, which hinders the attempt to lower calcitriol. Calcifediol is well tolerated and causes a progressive increase in serum 1,25-dihydroxy vitamin D and reductions in plasma iPTH without a significant effect of serum calcium and phosphorus levels. This led to remarkable clinical improvement with resolution of calciphylaxis in this case. Large clinical trials mandated to test these findings

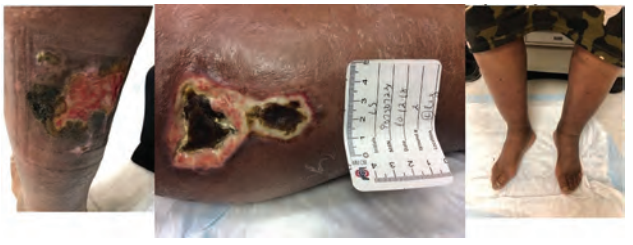

Image 1 & 2: Calciphylaxis wound in the Lower ExtremityImage 3: Resolution of wound after Calcefediol

PO0394

Rapidly Growing "Calcified Cauliflower" in the Lung of an Orthotopic Heart Transplant (OHT) Recipient on Hemodialysis (HD)

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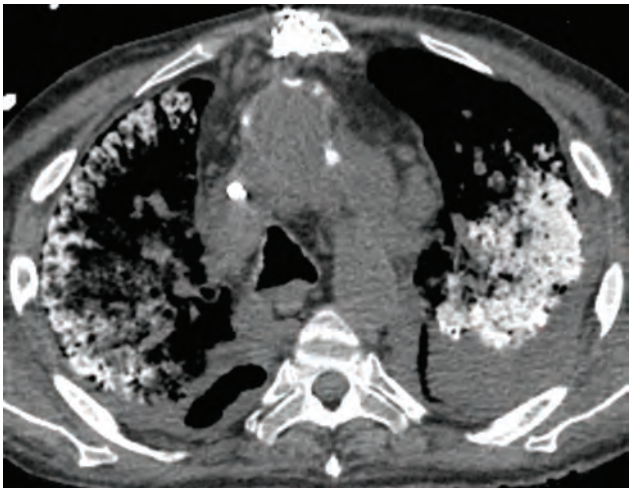
Introduction: Pulmonary calcinosis is commonly seen in ESRD patients but rarely in OHT recipients. We report a rare case of an OHT recipient who developed AKI requiring RRT. CT chest was noted for rapid progressive calcifications of lungs with both dystrophic and metastatic features.

Case Description: A 48-year old male with non-ischemic cardiomyopathy who underwent OHT. The post-transplant course was complicated by biventricular failure requiring VA/ECMO and IABP support, aortic anastomotic bleeding, multiple surgeries, recurrent bacterial and viral pneumonia dependent on mechanical ventilation, and ischemic acute tubular injury requiring CRRT then switched to HD. The imaging was noted for cardiac calcification, followed by rapidly progressive lung calcification. CT chest showed diffuse ground-glass opacity and "calcified cauliflower" signs with a mixture of dystrophic and metastatic lung calcifications. Work up for hyperparathyroidism, vitamin D toxicity, malignancy was negative. Contributing factors for pulmonary calcinosis included multiple surgeries, infections of the lungs, massive transfusion with subsequent IV calcium repletion, calcium concentration in replacement fluid of CRRT, use of calcium acetate. Subsequently, the patient was put on the lowest calcium bath and longer HD hours.

Discussion: Dystrophic pulmonary calcification occurs in the injured lung due to inflammation, infection, or hemorrhage. While metastatic calcification is more common in ESRD patients, primary and secondary hyperparathyroidism, or malignancy. Our case report emphasizes the importance of bone mineral disease as an underlying etiology for pulmonary calcinosis in dialysis-dependent OHT patients. The supportive approach includes avoidance of massive transfusions, IV calcium infusion, and calcium-based phosphorus binder, use of low calcium bath in HD.



CT chest: cauliflower calcification bilaterally

PO0395

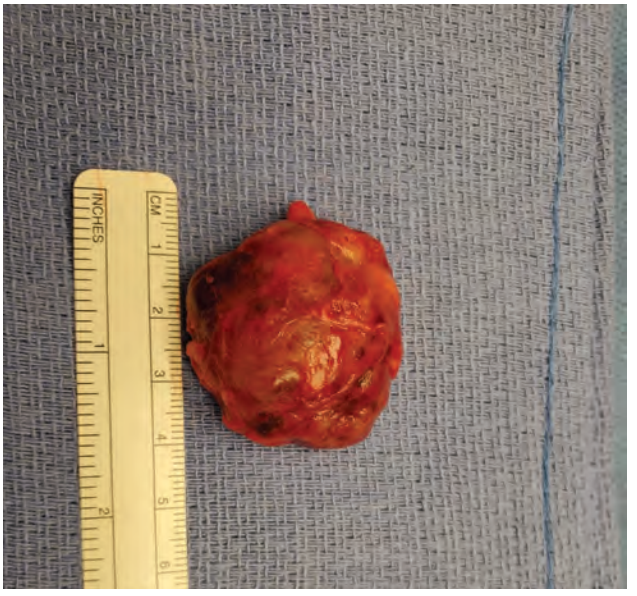
Calciphylaxis and Ectopic Parathyroid Gland: Chicken or the Egg?

Jonathan Berry, Carissa Wilkins, Tauseef A. Sarguroh, Habeeb S. Amatul. *Franciscan Health Inc, Mishawaka, IN.*

Introduction: Calciphylaxis is a vascular calcification disorder that is clasically seen in patients(pts) with end stage renal disease on hemodilaysis. It is most common in caucasian females and risk factors include hypercalcemia, hyperphosphatemia, hyperparathyroidism, coumadin use and iron therapy. This is a case of a patient with severe calciphylaxis, ectopic primary hyperparathyroidism with chronic kidney disease(CKD) not yet on dialysis.

Case Description: 64 year old female with CKD-4, obesity, HTN, pulmonary embolism not on anticoagulation, undiagnosed mediastinal mass came with lower extremity pain and a non-healing ulcer over the left anterior shin. Initial labs showed BUN:68mg/dl, Creatinine:5.4mg/dl, Calcium:11.3mg/dl, PTH:3,059 pg/ml. She underwent punch biopsy of the skin lesion that was consistent with calciphylaxis and was subsequently initated on hemodialysis and sodium thiosulphate infuson. A nuclear uptake scan showed an anterior mediastinal mass that was consistent with ectopic parathyroid adenoma after surgical excision.

Discussion: This case highlights a rare cause of calciphylaxis in a pt. with undiagnosed ectopic primary hyperparathyroidism and CKD. Our pt. had hypercalcemia and a mediastinal mass which upon work-up was found to be a hypersecretory ectopic parathyroid adenoma that likely triggered her calciphylaxis in the setting of concomitant secondary hyperparathyroidism due to chronic kidney disease as evident by hypercellularity of the reamaining three parathyroid glands. Only 12 known cases of calciphylaxis are attributed to primary hyperparahtyroidism and none due to an ectopic adenoma. Our pt. underwent hemodialysis, parathyroidectomy of the adenomatous gland and sodium thiosulphate infusion after which her PTH and calcium levels significantly improved and her skin lesions healed with no recurrence.



PO0396

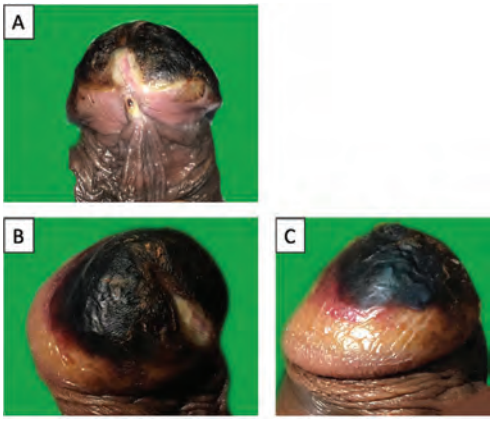
Penile Calciphylaxis: Challenges in Its Diagnosis and Management

Isabelle Dominique V. Tomacruz, Carl Arenos, Sachiko S. Estreller, Blythe N. Ke, Shahara Abalos-Babaran, Elizabeth Montemayor. *Philippine General Hospital, Manila, Philippines.*

Introduction: Penile calciphylaxis is an uncommon presentation of a rare systemic disorder.

Case Description: We discuss 2 cases of penile calciphylaxis in patients with end stage kidney disease on hemodialysis presenting with painful ulcerations and eschar formation on their penile shaft. Diabetes mellitus, hyperphosphatemia and vascular calcifications on radiographs were common in both patients. A multidisciplinary approach to management involved wound care with irrigation followed by application of petrolatum-impregnated wet-to-dry dressing, antibiotic therapy, intensification of hemodialysis and use of intravenous sodium thiosulfate. Both patients showed good wound healing on discharge.

Discussion: Skin biopsy may aid in confirmation, but should be weighed against the risks of provoking nonhealing wounds & secondary infection. A high index of suspiscion and multidisciplinary management are key components; but, prognosis is poor with survival rates reported to be less than a year upon diagnosis.



Case 1. Penile ulcer

Case 2. A&B. Penile and lower extremity lesions. **C.**Vascular calcifications on radiograph. **D.**Punch biopsy of the leg ulcer consistent with calciphylaxis(H&E stain,40x). **E.**Thready calcium deposits in the lobular panniculus together with calcification of a medium-sized vessel(H&E stain,10x)

PO0397

High Turnover Bone Disease After Successful Parathyroidectomy in a Dialysis Patient

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Introduction: We report a patient with end stage renal disease (ESRD) on hemodialysis (HD) with history of successful near-total parathyroidectomy (PTX) and normal to low parathyroid hormone (PTH) levels, found to have high-turnover/hyperparathyroid (HPT) bone disease on biopsy (bx).

Case Description: 54-year-old female with ESRD on HD for 10 years presented with declining bone density and osteoporosis (left radial T-score of -2.7). She had a near-total PTX in 2014 for secondary hyperparathyroidism and bx proven severe HPT bone disease, complicated by calciphylaxis treated with wound care and sodium thiosulfate. Patient also has history of focal segmental glomerular sclerosis of her native kidneys, gastric bypass, uterine cancer requiring radiation, and psoriatic arthritis and gout requiring steroids. Labs showed corrected calcium 9.4 mg/dL, serum phosphorus 7.9 mg/dL, 25-OH-vitamin D3 16.9 ng/mL, bone specific alkaline phosphatase 12.8 ug/L, intact PTH level 34 pg/mL (consistent with past values), PTH-(1-84)/-(7-84) ratio 1.1 (Scantibodies CA). She was started on weekly ergocalciferol. Bone bx showed persistent high-turnover/HPT bone disease with normal mineralization and low bone volume (2019, Figure 1). Relative to her prior bx, however, there was a demonstrable decrease in bone turnover and volume.

Discussion: Bone bx studies showing the evolution of bone disease after PTX in ESRD patients are limited. Development of adynamic bone disease is often presumed, but not established. In this patient, osteoporosis was related to high bone turnover, despite near-total PTX and successful reduction of serum PTH. These observations suggest that more research is needed into mechanisms other than PTH that contribute to bone turnover and loss in ESRD patients.

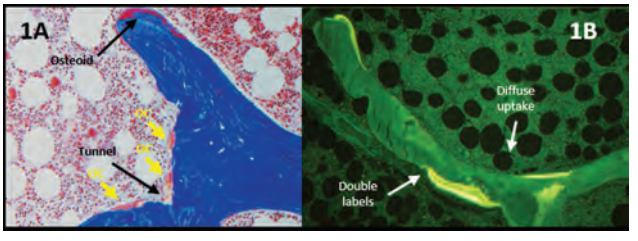


Figure 1: Anterior iliac crest bone biopsy: 1A – Trichrome stain 10x showing osteoclastic activity with tunneling in trabecular bone and increased osteoid volume and surface 1B – Fluorescent microscopy for tetracycline labeling 10x showing double labels and diffuse uptake in woven bone

PO0398

Successful Treatment of Severe Osteoporosis with Romosozumab in a Patient Undergoing Combined Peritoneal Dialysis and Hemodialysis: A Case Report

Hyeryong Lee, Kazuhito Fukuoka, Shinya Kaname. Kyorin University School of Medicine, Department of Rheumatology and Nephrology *Kyorin Daigaku, Mitaka, Japan.*

Introduction: Recently osteoporosis is becoming a bigger problem as aging of dialysis population progresses. However, the use of anti-osteoporotic drugs is limited because of concerns for increased rates of adverse events associated with decreased drug clearance and comorbidities such as CKD-MBD in dialysis patients. Here we present a case of severe osteoporosis that was successfully treated with romosozumab.

Case Description: A 57-year-old woman ESKD patient due to lupus nephritis had been on peritoneal dialysis (PD) combined with hemodialysis for the last 4 years. She has been suffering from systematic lupus erythematosus and complicated by severe osteoporosis probably due to long-term use of glucocorticoids and renal dysfunction. Although she was treated with vitamin D3 analogues, bisphosphonates, and denosumab, severe pains continued and had pelvic bone and vertebral fractures, followed by repeated pathological bone fractures of the ribs. Thus, we decided to use romosozumab. After administration of romosozumab, bone pains dramatically improved and fragile bone fractures became less frequent, without progression of bone destruction. Four months later levels of tartrate-resistant acid phosphatase-5b decreased, total type 1 procollagen N-terminal propeptide increased, and bone mineral density significantly improved. Serum calcium and inorganic phosphate levels slightly decreased, and intact PTH slightly increased, but no overall adverse effects were noted.

Discussion: Romosozumab is a humanized anti-sclerostin monoclonal antibody that has recently been introduced for the treatment of osteoporosis. While it demonstrates strong effects on osteogenesis and bone reabsorption, it also raises concerns about increased cardiovascular events. Our case suggests that romosozumab can be safely and effectively used for the treatment of osteoporosis, at least for a short period, in patients undergoing dialysis, although further study is clearly required to evaluate the efficacy of the agent.

PO0399

Bone Fractures and Antihypertensive Drugs in CKD Patients: The Fukuoka Kidney Disease Registry (FKR) Study

Tomoya Shukuri,[1] Kentaro Nakai,[1] Yoshiki Sato,[1] Nao Yamaoka,[1] Yukiko Ishimatsu,[1] Megumi Inoue,[1] Chiaki Kohara,[1] Koji Mitsuiki,[1] Shigeru Tanaka,[2] Toshiaki Nakano,[3,5] Kazuhiko Tsuruya,[4] Takanari Kitazono.[3] *[1]Japanese Red Cross Fukuoka hospital, Fukuoka, Japan; [2]Division of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Department of Medicine and Clinical science, Graduate school of Medical Sciences, Kyushu University, Fukuoka, Japan; [4]Department of Nephrology, Nara Medical University, Nara, Japan; [5]Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.*

Background: Patients with chronic kidney disease (CKD) are known to be at high risk for bone fractures. Bone fractures are serious complication that causes inactivity, hospitalization, and premature death. Some reports showed the association between bone fractures and antihypertensive drugs in elderly persons, but there are few reports in CKD patients. The aim of this study is to elucidate the relationship between bone fractures and antihypertensive drugs in CKD patients.

Methods: The Fukuoka Kidney disease Registry (FKR) Study is a prospective, multicenter cohort study of approximately 5000 patients with CKD. This is a cross-sectional study that investigated the relationship between antihypertensive drugs and bone fractures. The odds ratio (OR) of bone fractures in each risk factors was calculated by performing a logistic regression model analysis with adjustment factors, such as age, sex, body mass index(BMI), smoking history, presence of diabetes mellitus, eGFR levels, serum levels of albumin, sodium, calcium, phosphate, parathyroid hormone(intact assay).

Results: A total of 4474 patients were included in this study (age 63.9 years, men 56.0%, BMI 23.4 kg/m^2, diabetes mellitus 27.5%, and smoking history 52.0%). The average eGFR was 44.0ml/min/1.73 m^2, with 60.0 ml/min/1.73 m^2 or more at 24.2%, 30.0-60.0 ml/min/1.73 m^2 at 39.5%, and less than 30.0 ml/min/1.73 m^2 at 36.3%. Bone fractures were found in 282 patients(6.3%). Loop diuretics were independently associated with bone fractures (OR: 1.75, 95% confidence interval [CI]: 1.24-2.49), and angiotensin II receptor blockers (ARB) had significantly fewer bone fractures (OR: 0.64, CI: 0.49-0.85). Angiotensin-converting enzyme inhibitors, calcium channel blockers, alpha blockers, beta blockers, and thiazide diuretics were not showed significant association with bone fractures.

Conclusions: It is suggested that loop diuretics may be associated with higher bone fractures risk and ARB may be associated with lower bone fractures risk in CKD patients. The results are being verified in this prospective cohort by future.

PO0400

Differences in Bone Biomarkers by Renal Osteodystrophy Pathology

Marciana Laster, Renata C. Pereira, Isidro B. Salusky. *University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.*

Background: The gold standard for the diagnosis of Renal Osteodystrophy (ROD) remains the iliac crest bone biopsy. Given its limited availability, it is important to consider whether serum markers of bone metabolism will allow the ability to predict ROD type. Here we assess how major markers of bone metabolism differ by ROD category.

Methods: 93 pediatric patients with CKD underwent measurement of calcium, phosphate, alkaline phosphate (ALP), PTH, intact and c-terminal FGF23, sclerostin and TRAP5B at the time of bone biopsy. Patients were categorized by ROD diagnoses and biomarker comparisons were made according to turnover and mineralization status. Comparisons of bone markers within each category were made using the Wilcoxin Rank Sum test.

Results: Cohort characteristics are presented in Table 1. Of the ROD categories, 30.1% had normal bone, 30.1% adynamic bone disease, 11.8% mixed uremic osteodystropy, 14% osteitis fibrosa cystica, 4.3% osteomalacia and the remainder unknown disease. Those with high turnover disease had greater ALP ($p<0.0001$) and PTH ($p=0.001$) and lower calcium ($p=0.04$) than those with non-high turnover disease. Of those with low turnover bone disease, TRAP5B ($p=0.01$) and ALP ($p=0.0003$) were significantly lower and calcium ($p=0.03$) higher as compared to those with non-low turnover disease. In those with a mineralization defect, ALP ($p=0.001$) was higher and sclerostin ($p=0.02$) lower than those without a defect (Figure 1).

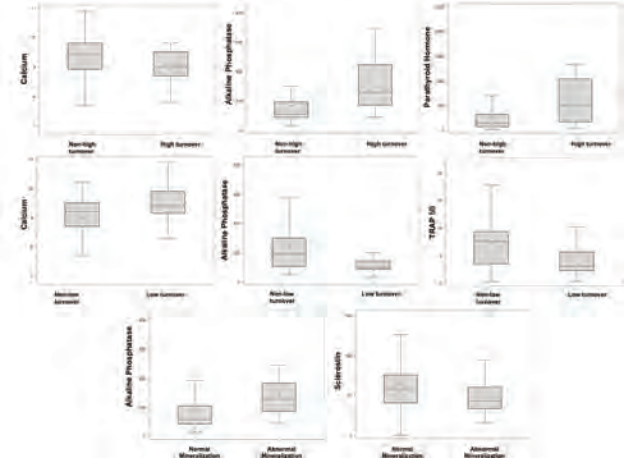
Conclusions: Comparisons within ROD categories demonstrate differences in serum biochemical markers. With further study, these differences may help to predict the type of CKD-related bone lesion without the need for bone biopsy. Promising markers such as TRAP5B, which is unaffected by renal function, may be valuable in distinguishing low turnover disease but this requires further investigation.

Funding: NIDDK Support

Table 1: Cohort Characteristics

N	93	CKD Stage, n (%)	
Age, mean (SD)	16.4 (3.3)	Stage 2	10 (10.8)
Gender, n (%)		Stage 3	16 (17.1)
Male	65 (69.9)	Stage 4	4 (4.3)
Female	28 (30.1)	Stage 5	1 (1.1)
Race, n (%)		unknown	4 (4.3)
Black	8 (8.6)	HD	29 (31.2)
White	21 (22.6)	PD	29 (31.2)
Hispanic	60 (64.5)	Disease, n (%)	
Asian	3 (3.2)	CAKUT	40 (43)
Unknown	1 (1.1)	GN	34 (36.6)
		Unknown	19 (20.4)

Figure 1: Comparison of serum biomarkers by turnover and mineralization



PO0401

Ethnic Differences in the Association of Kidney Function and Low Bone Density

Joshua Chang, Malini Chandra, Jeanne A. Darbinian, Nirmala D. Ramalingam, Joan C. Lo, Sijie Zheng. *Kaiser Permanente Oakland Medical Center, Oakland, CA.*

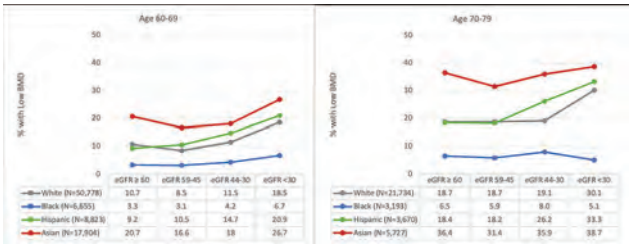
Background: Chronic kidney disease (CKD) is an important risk factor for bone disease and fracture. Here, we examined the relationship between reduced kidney function (RKF) and bone mineral density (BMD) in women. We also examined PTH and calcium levels among a subset of patients with advanced CKD and low BMD (osteoporosis range).

Methods: We examined femoral neck BMD in 118,484 women age 60-79 with an ambulatory creatinine/eGFR within 1 year of the BMD scan and compared the proportion with low BMD (T-score ≤ -2.5) by kidney function. Presence of hyperparathyroidism (PTH > 65 and > 130 pg/mL) and hypercalcemia (Ca ≥ 10.5 mg/dL) was examined in a subset of 257 patients with low BMD and advanced CKD G3B (eGFR < 45) and G4/G5 (eGFR < 30) who had PTH, calcium, and confirmatory eGFR measured within 2 years of BMD scan.

Results: Among 118,484 women, 83% had eGFR ≥ 60, 12% had eGFR 59-45, 4% had eGFR 44-30, and 1% had eGFR < 30. Overall, 12% of women age 60-69 and 21% of women age 70-79 had low BMD, but this varied by race/ethnicity. Asians had the highest burden of low BMD. Within each race/ethnicity group, the burden of low BMD varied by RKF/eGFR (Figure). In the subset with low BMD, advanced CKD, and measured PTH and calcium, 9.7% of G3B (n = 145) and 5.4% of G4/G5 (n = 112) patients were hypercalcemic. Of these hypercalcemic patients, 57% with G3B had PTH > 65 pg/mL (28.6% had PTH > 130 pg/mL), and all with CKD G4/G5 (n = 6) had PTH > 65 pg/mL (n = 4 > 130 pg/mL). Of the remainder with normal/low calcium, 57% with G3B and 84% with G4/G5 had PTH > 65 pg/mL (19% of G3B and 53% of G4/G5 had PTH > 130 pg/mL).

Conclusions: The burden of low BMD and the association of RKF with low BMD varied by race/ethnicity. The majority of patients with advanced CKD and low BMD also had evidence of hyperparathyroidism when laboratory data were assessed. Our findings support guidelines for PTH and BMD screening in advanced CKD patients to optimize bone health.

Funding: Private Foundation Support



Low BMD and RKF by Race/Ethnicity

PO0402

Serum Biomarkers, but Not Dual-Energy X-ray Absorptiometry, Predict Cortical Bone Mineral Density in Children and Young Adults with CKD

Alexander D. Lalayiannis,[1,2] Nicola J. Crabtree,[3] Charles Ferro,[9] Varvara Askiti,[4] Andromachi Mitsioni,[4] Lorenzo Biassoni,[1] Amrit Kaur,[10] Manish Sinha,[5] David C. Wheeler,[6] Neill D. Duncan,[7] Joyce Popoola,[11] David Milford,[3] Jin Long,[8] Mary B. Leonard,[8] Mary Fewtrell,[1,2] Rukshana Shroff.[1,2] *[1]Great Ormond Street Hospital For Children NHS Foundation Trust, London, United Kingdom; [2]University College London Institute of Child Health, London, United Kingdom; [3]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, GB, Birmingham, United Kingdom; [4]Children's Hospital "P. & A. Kyriakou", Athens, Greece; [5]Evelina London Children's Hospital, London, United Kingdom; [6]University College London, London, United Kingdom; [7]Imperial College Healthcare NHS Trust, London, London, United Kingdom; [8]Stanford University, Stanford, CA, US, Stanford, CA; [9]University Hospitals Birmingham NHS Foundation Trust, Birmingham, Birmingham, GB, Birmingham, United Kingdom; [10]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [11]St Georges Healthcare Trust, London, United Kingdom.*

Background: Currently available serum biomarkers and Dual-energy X-ray Absorptiometry(DXA) are thought to be poor predictors of bone mineral density(BMD). We set out to determine the clinical utility of DXA and routine clinical biomarkers in the young CKD population, by comparing them with tibial cortical BMD measured by peripheral Quantitative Computed Tomography(pQCT).

Methods: A multi-centre cross-sectional study with 77 patients on dialysis and 26 in CKD4-5 (n=103 total, ages 5-30 years). Participants underwent hip and lumbar spine (LS) DXA, tibial pQCT [for cortical (cortBMD) and trabecular BMD (trabBMD)] and measurement of routine serum biomarkers. All bone measures were expressed as Z-scores adjusted for age, sex, race and height. Tibial cortical BMD Z-scores was used as the gold standard to evaluate the predictive value of other measures.

Results: Bone pain was present in 58%, hindering activities of daily living. 10% had suffered at least one previous low-trauma fracture. DXA LS Z-scores were higher in the CKD compared to the dialysis population, with a corresponding higher trabBMD Z-score on pQCT (p=0.006 & p=0.02). pQCT cortBMD and cortical mineral content Z-scores were significantly lower in dialysis compared to CKD patients (p=0.01 & p=0.05 respectively). Hip and LS DXA Z-scores did not correlate with any biomarkers or cortBMD. CortBMD Z-scores were negatively associated with PTH (r=-0.44, p<0.001) and alkaline phosphatase (ALP)(r=-0.22, p=0.03) and positively with calcium (r=0.33, p=0.001). None of the patients with PTH levels less than three times the upper limit of normal had a cortBMD below -2 SD (OR 95%CI 7.331 to infinity). Multivariable linear regression analysis showed the independent predictors of cortBMD Z-scores were PTH (β -0.43, p<0.001), ALP (β -0.36, p<0.001) and serum calcium (β 0.21, p=0.005), which together predicted 57% of variability in cortBMD. DXA imaging did not improve this model.

Conclusions: Routinely used biomarkers are moderate predictors of tibial cortical BMD. DXA is not a clinically useful tool and should not be performed routinely in children and young adults with CKD4-5 and on dialysis.

Funding: Other NIH Support - UK NIHR, Kidney Research UK, Kids Kidney Research

PO0403

Advanced Glycation End Products Are Related with Cortical Bone Quality and Increased Risk for Fractures in CKD Patients

Noemi A. Roza,[2] Kelcia Rosana da Silva Quadros,[2] André B. Esteves,[2] Renata A. Franca,[2] Wagner Dominguez,[1] Luzia N. Furukawa,[1] Rodrigo B. de Oliveira.[2] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Universidade Estadual de Campinas, Campinas, Brazil.*

Background: The risk of bone fractures is higher in chronic kidney disease (CKD) patients than general population. We aim to investigate the relationships between advanced glycation end-products (AGEs) and cortical bone in a cohort of CKD patients.

Methods: 86 CKD patients (stages 3-4, N=26; hemodialysis, N=32; peritoneal dialysis, N=28) were included. AGEs levels were measured in serum (pentosidine and glycated hemoglobin), in skin (by AGE-Reader device) and in cortical bone by immunohistochemistry; receptor activator of nuclear factor kappa-B (RANK) and its

ligand (RANKL) and SOST mRNA expression were evaluated by real-time PCR. Bone histomorphometry was performed to measure cortical porosity, thickness and volume. Fracture risk was predicted using FRAX tool.

Results: Age was 51±13 years; 48 (56%) were male, 41 (48%) Caucasian and 16 (19%) diabetics; dialysis vintage was 21 (10-44) months. AGEs levels in skin were 3.0±0.7 AU (reference: <2.0 AU), serum pentosidine 71 (44–121) pmol/mL and glycated hemoglobin 5.4 (5-6)%; cortical bone volume, thickness and porosity were 22.3±9.8 μm², 619±213 μm and 1.55 (0.9-2.7)%, respectively. AGEs levels in skin were correlated with age (R=0.538; P=0.0001), risk for major osteoporotic fracture (R=0.562; P=0.0001) and hip fractures (R=0.49; P=0.0001). The mean area of AGEs deposits in the cortical bone was 5.4 (3-12.1)%; cortical thickness were negatively correlated with serum pentosidine levels (R=-0.27; P=0.02) and age (R=-0.235; P=0.04); cortical porosity were positively correlated with glycated hemoglobin (R=0.278; p=0.02), SOST mRNA expression (R=0.321; p=0.03), RANKL mRNA expression (R=0.414; p=0.004). Finally, RANK mRNA expression was correlated with serum pentosidine levels (R=0.304; p=0.045).

Conclusions: AGEs were detected in cortical bone and skin of CKD patients and correlates with their risk for osteoporotic fractures. Serum pentosidine levels were associated with low thickness of cortical bone. Cortical porosity was associated with serum glycated hemoglobin levels, SOST and RANKL mRNA expression. RANK was positively influenced by serum pentosidine levels. Together these data point to a direct relationship between AGEs and fractures in patients with CKD.

Funding: Government Support - Non-U.S.

PO0404

Low Bone Turnover and Increasing Calcification with Lower Trabecular Bone Score in Early CKD Patients

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Background: Little information is available on turnover abnormalities early during the development of loss of kidney function. Vascular calcifications may develop in association with bone turnover abnormalities. This study was designed to evaluate bone changes and cardiovascular calcification in early CKD patients without clinically known bone or cardiovascular disease.

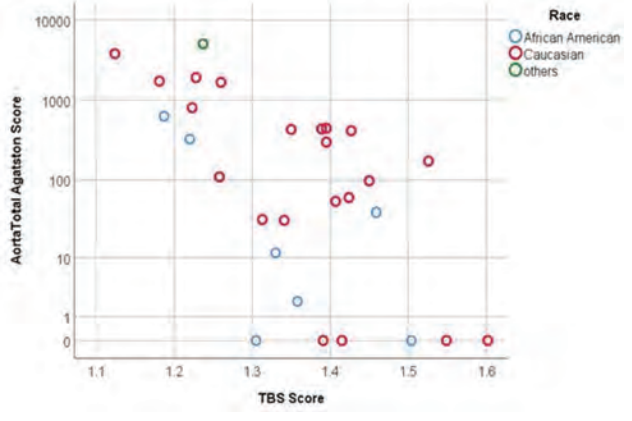
Methods: This is a cross-sectional analysis of 32 adult volunteers with CKD stage 2-4. All patients underwent 1) dual energy x-ray absorptiometry including trabecular bone score (TBS). 2) Non-contrast CT for cardiovascular calcium scoring, and 3) anterior iliac crest bone biopsy after double tetracycline-labelling and mineralized bone histology with histomorphometry.

Results: The mean age of the patients was 61±11 years. Patients tended to be obese (75%), white (72%), and female (59%). The mean eGFR was 44±16 ml/min/1.73 m². On bone histology low turnover was found at the higher eGFR levels in 78% and normal or high turnover at lower eGFR levels. Mineralization was normal in all. Bone volume was normal in 75% and slightly low in the others. Correlation between bone parameters and eGFR are shown in Table 1. Coronary artery calcium (CAC) score was above 400 in 31%, between 100 and 400 in 24%%, and less than 100 in 45% of patients. TBS correlated negatively with CAC-scores (rho -0.43, p=0.023), and with aortic calcium scores (rho -0.62, p <0.001) (Figure 1)

Conclusions: Low bone turnover, normal total bone volume and absence of mineralization defect are seen in early stages of CKD. There are increased vascular calcifications with low TBS pointing to a relationship between bone quality and vascular calcifications.

Table 1

		Linear regression adjusted for age		
Dependent Variable	**rho with eGFR**	**B**	**95% CI**	**p-value**
Osteoid surface /Bone surface	-0.58**	-0.06	-0.33 to -0.07	0.006
Osteoid volume/Bone volume	-0.48*	-0.03	-0.06 to -0.003	0.032
Bone formation rate/Bone surface	-0.50*	-0.02	-0.04 to -0.002	0.033
Activation Frequency	-0.47*	-0.008	-0.016 to 0.000	0.044



PO0405

Bone-Derived Hormones, Mineral Metabolism, Cardiovascular Disease, and Patient Survival in ESRD

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Background: The aim of this study was to analyse the associations between chronic kidney disease-mineral and bone disorder (CKD-MBD) players [alpha-klotho, fibroblast grow factor (FGF) 23, sclerostin, parathyroid hormone (PTH), bone alkaline phosphatase (bAP), vitamin D (vitD), phosphorus (Pi), Calcium (Ca) and Magnesium (Mg)], and echocardiographic findings [left ventricular mass index (LVMI) measured by Devereux formula, valvular calcifications], vascular calcifications and patients (pts) outcomes.

Methods: We performed a prospective cohort study of a sample of ESRD pts listed for renal transplant. All pts were submitted to renal transplant and were followed for 12 months. Patient and graft survival were recorded. At inclusion, demographic and clinical data were collected, laboratory evaluation, bone biopsy and X-ray of the pelvis and hands (Adragão score) were performed. Associations between variables were performed using Wilcoxon rank sum test and Spearman correlation test. STATA software was used and $p < 0.05$ was considered statistically significant.

Results: We included 85 pts. Mean age 50.1±12.7 years, 59 men (69.4%), 66 caucasian (77.6%). The median LVMI was 108.5 (92 – 129) g/m², with 32 patients presenting LVH and 19 valvular calcifications. Median Adragão score was 1 (0 – 2). At the end of 12 months, 4 pts died and 5 had graft failure (non-primary function). Alpha-klotho correlated with bAP (p=0.0006) and marginally with PTH and absence of valvular calcifications (p=0.05). FGF23 correlated with Pi (p<0.001), Ca (p=0.004), PTH (p=0.003), Mg (p=0.002), and inversely with bAP (p=0.003), and presented a marginal association with Adragão score (p=0.06). We didn't find correlations between FGF23 and alpha-klotho or dialysis vintage or echocardiographic characteristics. Sclerostin correlated negatively with bAP (p=0.007) and PTH (p=0.04). The 3rd sclerostin tertile was associated with high scores of vascular calcifications (p=0.02). Lower levels of sclerostin were associated with pt survival at the end of 12 months (p=0.02).

Conclusions: Sclerostin, a bone formation inhibitor, seems to act as a risk factor for vascular calcifications and worse outcomes.

PO0406

Bone Mineral Density Is Not Associated with Coronary Artery Calcification in Children and Young Adults with CKD

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Background: Coronary artery calcification(CAC) has been linked with bone demineralization in older adults with CKD, but there are no studies examining this relationship in children and young adults. We studied bone mineral density(BMD) by tibial peripheral quantitative CT(pQCT) and measures of vascular health to examine the association between bone demineralization and vascular calcification in a young CKD population.

Methods: Patients with CKD4-5 & on dialysis aged 5-30 years underwent tibial pQCT [for cortical(cortBMD) and trabecular BMD(trabBMD)], cardiac CT for CAC, ultrasound for carotid intima-media thickness(cIMT), carotid-femoral pulse wave velocity(cfPWV) and measurement of routine serum biomarkers. All measures were expressed as Z-scores and adjusted for age, and height. CAC was expressed as Agatston score(AS).

Results: One hundred participants [median 13.82 years(IQR 10.7 to 16.5), 20% above 18 years, 44% female, 77% on dialysis] were included. The median cIMT-SDS was 2.17(IQR 1.14 to 2.86). On multivariable regression analysis TrabBMD-SDS was the only independent predictor of cIMT-SDS(R^2 0.17, β 0.29, p=0.02). The median cfPWV-SDS was 1.45(IQR -0.16 to 2.57) and correlated with systolic (r=0.32, p=0.001) and diastolic (r=0.36, p<0.0001) BP. There were no independent predictors of cfPWV-SDS. 10% of all participants had CAC(AS range 0.8 to 413). CAC correlated with vitamin D doses(r=0.34, p=0.04) but there were no independent predictors. Patients above 18 years had a higher prevalence of CAC(25% vs 6.5% in children, p=0.006) and higher PTH levels(58.5 vs 12.8 pmol/L, p<0.0001), although children had a greater Ca intake from P-binders(median 18.75 vs 0 mmol/day, p=0.03) and superior cortBMD Z-scores (-0.23 vs -2.43, p<0.0001).

Conclusions: Despite a high prevalence of bone and cardiovascular disease(CVD), there was no correlation between bone mineral density and CAC or surrogate measures of CVD in this cohort of children and young adults with CKD4-5D. The skeleton accrues calcium until the third decade of life, perhaps allowing a buffering effect that protects against vascular calcification. Confirmation through longitudinal studies is required.

PO0407

A Randomized, Double-Blind, Placebo-Controlled Trial Assessing Efficacy of Standard and Low-Dose Hydrochlorothiazide Treatment for Prevention of Recurrent Calcareous Nephrolithiasis (NOSTONE Trial)

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Background: Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8 % in men and 9.4 % in women. Without specific treatment, 5- and 20-year recurrence rates are 40 % and 75 %, respectively. Given the high cost of medical treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Efficacy of thiazides for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial with the purpose to assess the dose-response relationship for three different dosages of hydrochlorothiazide (placebo, 12.5mg, 25.0mg, 50.0mg) in kidney stone prevention. The primary outcome is incidence of stone recurrence (a composite of symptomatic or radiologic recurrence) at 3 years, a low-dose CT will be performed at the beginning and the end of the trial. Patients from 12 hospitals throughout Switzerland were included in the trial.

Results: NOSTONE received all necessary approvals by the end of February 2017. Recruitment started in Bern on the 9th of March 2017, all study sites are operative since June 30th 2017. As of October 31st 2019, the target number of 416 patients randomized in the trial was reached and therefore recruitment stopped (www.nostone.ch). In March 2020 the first patient randomized in the trial completed the treatment phase. All patients are expected to reach end of treatment by the end of August 2021.

Conclusions: The NOSTONE study will provide critical information to physicians for the treatment of kidney stones. The impact of the results of this study will affect many patients currently treated with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

PO0408

Roux-en-Y Gastric Bypass and Kidney Stones

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Background: Roux-en-Y gastric bypass (RYGB) is a bariatric surgical procedure that is highly effective in the management of morbid obesity but also associated with higher risk of kidney stone formation after surgery. It is not known why RYGB is associated with higher kidney stone risk but it may be due to changes in urine composition, such as high urine calcium oxalate supersaturation (CaOx SS) and calcium phosphate supersaturation (CaP SS). It is not known who is at risk for high urine CaOx SS after surgery. We examined 24-hour urine composition in 18 men and women before and after RYGB to look for predictors of urine high CaOx SS and CaP SS.

Methods: Patients were recruited from a bariatric surgery clinic prior to scheduled laparoscopic long-limb RYGB. Three consecutive 24-hour urine collections performed in a Clinical Research Center both before and 1 year after surgery. We performed Welch's 2-sample and paired t-tests to compare mean urinary values for pre- to post-RYGB collections and to compare men to women in the post-RYGB collections. We used linear regression to evaluate predictors of urine CaOx SS and CaP SS.

Results: Seven men and eleven women completed pre- and post-RYGB urine collections. Post-RYGB, women had a significantly higher urine CaOx SS (13.1 vs. 4.6, p=0.002), CaP SS (0.59 vs. 1.04, p=0.05), and lower urine volumes (1.7 vs. 2.7L, p<0.001) compared with men. There were no differences by sex in CaOx SS or urine volume pre-RYGB. Both men and women had high oxalate in the pre- and post-RYGB collections. Urine volume was most strongly associated with urine CaOx SS with a difference in urine CaOx SS of -6.4 (-8.7 to -4.0) for every 1 liter of urine volume excretion. Citrate was also associated with change in -0.01 (-0.01 to -0.002) per mg of citrate. Calcium and oxalate were not significantly associated. For CaP SS, higher urine calcium and pH (1.3, 0.8 to 1.7) were associated with higher CaP SS (Calcium 0.01mg, 0.008 to 0.12mg; pH 1.3, 0.8 to 1.7). Higher urine volume (-0.4 -0.6 to -0.1) was associated with lower CaP SS and citrate was not significant.

Conclusions: There are important differences in urinary parameters by sex that may contribute to differences in kidney stone risk after RYGB. Women may be at higher risk for kidney stone formation after RYGB compared with men.

Funding: Clinical Revenue Support

PO0409

Nephrocalcinosis at Baseline Did Not Increase the Risk of Nephrocalcinosis Progression After Long-Term Burosumab Treatment in Adults and Children with X-Linked Hypophosphatemia (XLH)

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Background: In patients with XLH, excess FGF23 induces hypophosphatemia, leading to musculoskeletal impairments. In two Phase 3 trials (NCT02526160, NCT02915705), burosumab significantly improved serum phosphorus concentrations in adults and children with XLH. We examined subject characteristics and long-term safety of burosumab by the absence or presence of nephrocalcinosis (NC) at baseline (BL) from these trials.

Methods: Adults were randomized (1:1) to burosumab 1.0 mg/kg every 4 weeks or placebo for 24 weeks; after 24 weeks, adults received burosumab through 96 weeks. Children were randomized (1:1) to burosumab 0.8 mg/kg every 2 weeks or oral phosphate and active vitamin D (Pi/D) for 64 weeks. NC was determined at BL and during study by ultrasound and graded by central readers from 0 (normal) to 4 (stone formation).

Results: In adults, NC was found in 73/134 patients (54%) at BL. Age, sex, and duration of treatment with Pi/D as adults did not differ by baseline NC group. Compared with adults without NC at BL, those with NC had longer duration of treatment with Pi during childhood (mean [SD] 13.2 [3.2] vs 11.3 [4.9] years) but not with D. After 96 weeks in adults, median 24-hr urine calcium increased by 35% overall but remained within the normal range. NC scores increased by +1 in 5/73 adults with NC at BL and 5/61 adults without NC at BL. In children, NC was found in 14/61 (23%) at BL. Compared with children without NC at BL, children with NC were older (7.6 [2.8] vs 5.7 [3.4] years), more likely to be male (71% vs 36%), treated longer with Pi/D pre-enrollment (4.8 [3.3] vs 3.6 [3.0] years), and had higher 24-hr urine calcium (4.4 [5.4] vs 2.3 [1.9] mg/kg/day [normal <4.0 mg/kg/day]). After 64 weeks in children, median urine calcium decreased by 50% overall. At week 64, NC scores did not increase in any child and decreased by 1 in 8 children. Serum creatinine and estimated GFR did not change in adults or children.

Conclusions: In adults with XLH, NC at BL was associated with longer duration of Pi during childhood. In children with XLH, NC was associated with longer duration of Pi and D pre-enrollment and with BL hypercalciuria. With long-term burosumab, the presence of NC at BL did not increase the risk of NC progression.

Funding: Commercial Support - Ultragenyx Pharmaceutical Inc.

PO0410

Proton-Pump Inhibitors Are Associated with Decreased Urinary Citrate Excretion

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Background: Proton-pump inhibitors (PPIs) may increase the risk of kidney stone formation, but the mechanism(s) has not been elucidated. PPI-associated hypomagnesemia is due to impaired intestinal magnesium absorption thought to result from changes in intestinal pH that decrease binding of magnesium to its transporters. Citrate is a tricarboxylic acid with pKa values of 2.9, 4.8, and 5.6. Since citrate is transported primarily in the divalent form ($citrate^{2-}$) by the intestinal sodium dicarboxylate transporter (NaDC1), changes in intestinal pH by PPIs might decrease the amount of the divalent form, thus reducing intestinal absorption of citrate, thereby decreasing alkaline load and urinary citrate excretion.

Methods: We performed a retrospective review of nephrolithiasis patients treated at our institution and compared patients who were taking PPIs or not at the time of their 24-hour urine collections. Hierarchical multivariate linear regression was used to evaluate the independent relationship between PPI use and urinary composition.

Results: We identified 301 consecutive patients, 88 (29%) of whom were taking PPIs at the time of their 24-hour urine collections. Patients taking PPIs were older and more likely to have medical comorbidities associated with metabolic syndrome such as hypertension, diabetes, and dyslipidemia (p<0.01). Controlling for these factors, patients taking PPIs were found to have lower 24-hour urine citrate excretion (β=-0.12, ΔF=4.24, p=0.04). 24-hour urine magnesium excretion was numerically but not significantly lower in patients taking PPIs. There were no other differences in urinary composition between the groups.

Conclusions: Our findings suggest that patients who take PPIs regularly may be at risk for decreased urinary citrate excretion, which is a known risk factor for kidney stone formation. It is possible that the decrease in urinary citrate with PPIs may have clinical significance, particularly in patients with idiopathic hypocalciuria or other conditions associated with hypocitraturia such as genetic polymorphisms of the renal sodium-citrate transporter, chronic metabolic acidosis, use of carbonic anhydrase inhibitors, high animal protein diet intake, and incomplete distal RTA.

PO0411

Dietary Intake and Risk of Incident and Recurrent Kidney Stones

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Background: Dietary factors associated with recurrent kidney stones (KS) may differ from those associated with incident KS.

Methods: We recruited adult incident symptomatic KS formers and controls from local residents surrounding the Mayo Clinics in Minnesota and Florida between 2009 and 2018. Participants were administered a Viocare Food Frequency Questionnaire, a KS survey, and completed a 24h urine chemistry evaluation at a baseline study visit. Medical records of stone formers were reviewed for symptomatic recurrence with a visually confirmed stone through May 2019. Analyses compared baseline dietary factors between incident symptomatic stone formers and controls and assessed whether these same dietary factors predicted symptomatic recurrence.

Results: There were 416 incident symptomatic KS formers (74 had a recurrence during follow-up) and 384 controls. Higher dietary potassium, calcium and phytate were associated with lower odds of an incident symptomatic KS adjusting for age, race, BMI, underlying diseases, family history of KS, education status, fluid and energy intake. During median follow-up time of 4.1 years, higher dietary calcium and lower oxalate intake predicted a lower risk of symptomatic KS recurrence (Hazard ratio for highest tertile vs lowest tertile = 0.53, 95%CI [0.28, 0.99] and 2.09, 95%CI [1.18, 3.69], respectively) adjusting for BMI, fluid and energy intake, and Recurrence of Kidney Stone score. **(Table)**

Conclusions: Certain dietary factors may differ in their association with incident and recurrent KS. In particular, dietary oxalate intake may be more important for preventing recurrence than for preventing a first KS episode.

Funding: NIDDK Support

Table Association of nutrient intake with incident KS and recurrent KS.

Nutrient intake	Adjusted odds ratio for incident symptomatic stone (stone formers vs controls)	95% confidence interval	Adjusted hazard ratio for symptomatic recurrence (stone formers with vs without symptomatic recurrence)	95% confidence interval
Sodium intake (mg/d)				
<3,278	1.00	ref	1.00	ref
3,278-3,727	0.79	(0.54, 1.15)	**1.90**	**(1.08, 3.35)**
>3,727	0.85	(0.58, 1.24)	1.12	(0.61, 2.08)
P-trend	0.38		0.38	
Potassium intake (mg/d)				
<3,073	1.00	ref	1.00	ref
3,073-3,636	**0.54**	**(0.36, 0.80)**	1.09	(0.62, 1.91)
>3,636	**0.53**	**(0.35, 0.82)**	0.64	(0.32, 1.27)
P-trend	0.003		0.20	
Calcium intake (mcg/d)				
<1,078	1.00	ref	1.00	ref
1,078-1,416	0.70	(0.48, 1.03)	0.84	(0.48, 1.47)
>1,417	**0.64**	**(0.43, 0.95)**	**0.53**	**(0.28, 0.99)**
P-trend	0.02		0.05	
Oxalate intake (mg/d)				
<170	1.00	ref	1.00	ref
170-238	0.90	(0.61, 1.35)	1.19	(0.64, 2.22)
>238	0.93	(0.63, 1.37)	**2.09**	**(1.18, 3.69)**
P-trend	0.71		0.01	
Phytate intake (mg/d)				
<759	1.00	ref	1.00	ref
759-988	**0.63**	**(0.43, 0.92)**	1.44	(0.81, 2.58)
>988	**0.61**	**(0.42, 0.90)**	1.52	(0.85, 2.72)
P-trend	0.01		0.16	
Caffeine intake (mg/d)				
<81	1.00	ref	1.00	ref
81-222	1.07	(0.73, 1.57)	1.04	(0.61, 1.78)
>222	0.67	(0.43, 1.04)	1.09	(0.57, 2.10)
P-trend	0.08		0.82	
Animal Protein (g/d)				
<55	1.00	ref	1.00	ref
55-68	0.94	(0.64, 1.37)	0.78	(0.43, 1.43)
>68	0.90	(0.61, 1.31)	1.15	(0.65, 2.02)
P-trend	0.58		0.47	
Vegetable Protein (g/d)				
<27	1.00	ref	1.00	ref
27-31	0.68	(0.46, 1.01)	1.36	(0.77, 2.39)
>31	0.86	(0.59, 1.25)	1.15	(0.64, 2.08)
P-trend	0.41		0.61	

Adjusted odds ratios and hazard ratios in bold denote significance at the 0.05 alpha level.
Multivariate logistic regression model was adjusted for age, race, BMI, hypertension, chronic diarrhea, history of urinary tract infection, family history of stone, education status, fluid intake and energy intake (using residual method)
Multivariate Cox regression model was adjusted for BMI, ROKS score, fluid intake and energy intake (using residual method)

PO0412

Cross-Sectional Study of Metabolomic Profiles and the Association with Kidney Stone Disease in the Nurses' Health Studies I and II

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Background: Kidney stone disease is a painful and expensive health condition with a high recurrence rate and substantial morbidity; however, the mechanisms underlying the disease remain incompletely understood. Metabolomics is one novel approach that might provide important insights into the etiology of stone disease.

Methods: In a subset of participants from the Nurses' Health Study I and II cohorts (NHSI and NHSII), subjects were divided into stone and non-stone former groups. Data from existing mass-spectrometry based plasma metabolomic profiling that had been performed in multiple case-control studies of other diseases were used. Multivariable logistic regression models were employed to identify metabolites which were associated with kidney stone history after adjusting for multiple comparisons using false detection rate correction.

Results: We included 230 prevalent kidney stone cases among 5380 NHSI participants and 114 cases among 2283 NHSII participants. 277 metabolites were measured and passed the 10% missing threshold. In NHSI, one metabolite was significantly inversely associated with kidney stones (p=0.01) and passed the false-detection rate correction for multiple testing. The identified metabolite was cinnamoylglycine (HMDB0011621), which is a metabolite in the carboxylic acids and derivatives class. There were no significant metabolites in NHSII. When the cohorts were combined, HMDB0011621 was significantly inversely associated with stone history (p<0.01). The odds ratio per standard deviation increase in the metabolite for the combined cohorts was 0.87 (0.81, 0.95).

Conclusions: We identified one plasma metabolite associated with a history of kidney stones. The metabolite has been recently identified as one of the potential biomarkers of proximal tubule function, colonization of antibiotic resistant gut microbiome, and diabetes, which are also known to correlate with kidney stone disease. Larger studies are needed to identify other potential metabolites that may be involved in kidney stone formation.

Funding: NIDDK Support, Private Foundation Support

Table of results

		P-value	Odds Ratio (95% CI)
NHS I	HMDB0011621	0.01	0.87 (0.80, 0.93)
NHS II	HMDB0011621	0.80	0.96 (0.83, 1.12)
Combined	HMDB0011621	0.005	0.87 (0.81, 0.95)

CI, confidence interval

PO0413

Type 3 Renal Tubular Acidosis in Association with a Pelvic Kidney

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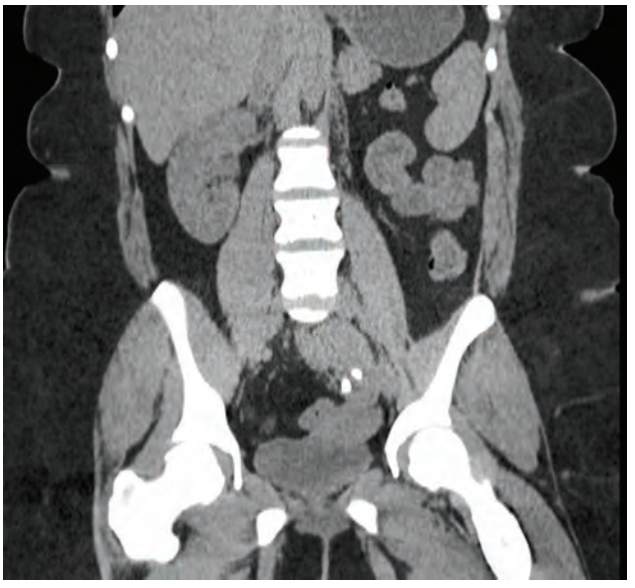
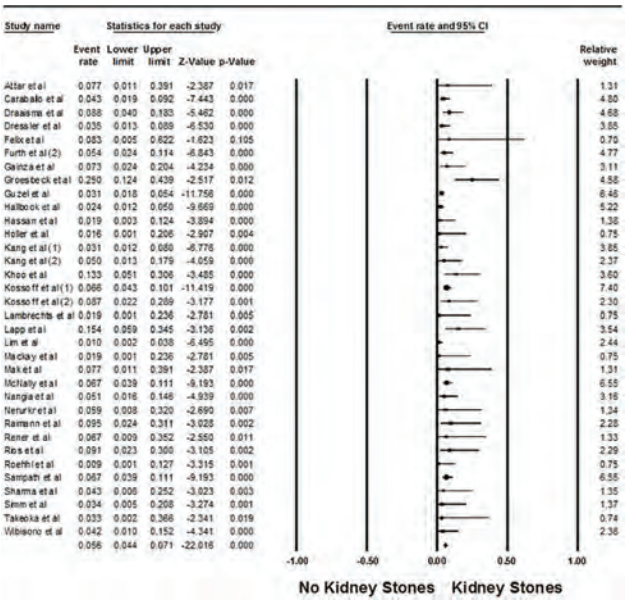
Introduction: The association of renal tubular acidosis (RTA) from carbonic anhydrase isoenzyme II (CA II) deficiency, cerebral calcifications and osteopetrosis is known as *marble brain disease*

Case Description: 21-year-old woman with a medical history of multiple fractures since childhood, recurrent episodes of nephrolithiasis and, renal tubular acidosis (RTA), presented to establish care at our clinic. Genetic testing had revealed she had CA II gene mutation. Her brother had the same condition but her sisters were healthy. Her medication included potassium citrate and vitamin D3. Laboratory assessment revealed the following: serum Na+ 143 mmol/L, K+ 3.9 mmol/L, Cl- 109 mmol/L, HCO3 21 mmol/L, creatinine 0.73 mg/dl, Ca2+ 9 mg/dl, PO43- 4.4 mg/dl, vitamin D 7.6 mg/dl. Urine pH was 6. CT urogram revealed a normal right kidney and an ectopic left kidney with numerous small stones. (Figure 1). Spine X rays showed osteopetrosis of vertebral endplates and MRI brain showed calcifications in basal ganglia. Pyelolithotomy of the pelvic stone was performed and stone analysis revealed 90% calcium phosphate and 10% calcium oxalate. 24-hour urine showed a low urine citrate with low urine volume. Thus the findings were consistent for RTA with low serum bicarbonate, low urine citrate and calcium phosphate predominant stones.

Discussion: CA II deficiency syndrome is a rare autosomal recessive disorder that results in Type 3 RTA (combined proximal and distal RTA). Pelvic kidneys, which result from a failure of mesonephros to ascend normally during early gestation, are prone to urolithiasis due to poor urinary drainage. In our patient RTA, along with altered urine flow due to pelvic kidney predisposed to nephrolithiasis.



Ectopic (pelvic) left kidney with multiple stones with a normal looking right kidney



PO0414

Incidence and Characteristics of Kidney Stones in Patients on a Ketogenic Diet: A Meta-Analysis

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Background: Very-low-carbohydrate diets or ketogenic diets have frequently been used for weight loss in adults and as a therapy for epilepsy in children. The incidence and characteristics of kidney stones in patients on ketogenic diets are not well studied.

Methods: A systematic literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from the databases' inception through April 2020. Observational studies or clinical trials that provide data on the incidence and/or types of kidney stones in patients on ketogenic diets were included. We applied a random-effects model to estimate the incidence of kidney stones.

Results: A total of 36 studies with 2,795 patients on ketogenic diets were enrolled. The estimated pooled incidence of kidney stones was 5.6% (95%CI, 4.4%-7.1%) in patients on ketogenic diets at mean follow-up time 3.7+/- 2.9 years. Subgroup analyses demonstrated the estimated pooled incidence of kidney stones of 5.6% (95%CI, 4.3%-7.2%) in children and 5.6% (95%CI, 2.3%-12.6%) in adults, respectively. Within reported studies, 48.7% (95%CI, 33.2%-64.6%) of kidney stones were uric stones, 36.5 % (95%CI, 10.6%-73.6%) were calcium based (CaOx/CaP) stones, and 27.8% (95%CI, 12.1%-51.9%) were mixed uric acid and calcium based stones, respectively.

Conclusions: The estimated incidence of kidney stones in patients on ketogenic diets is 5.6%. Its incidence is comparable among adults and children. Uric acid stones are the most prevalent kidney stones in patients on ketogenic diets followed by calcium based stones. These findings may impact the prevention and clinical management of kidney stones in patients on ketogenic diets.

PO0415

Association of Urine Findings with Metabolic Syndrome (met-s) Traits in Patients with Nephrolithiasis

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Background: Met-s is a health concern related to lifestyle habits including acidogenic and high protein diets. The odds of nephrolithiasis increases with an increasing number of met-s traits. Prior studies have shown relationships among the number of met-s traits and decreasing urine pH and other acid excretion markers. We evaluated associations of urine factors including acid excretion and stone composition with the number of met-s traits in a large cohort of stone-forming patients.

Methods: A retrospective review was performed of 24-hour urine studies (Litholink, Chicago, Il) from patients seen in Urology and Nephrology divisions, UVMMC July 2009 to December 2018. Patients <18 years and those with improper collections based on creatinine/kg were excluded. Patient variables, laboratory values, associated diagnoses, and medications were identified within 6 months of urine collection and 1 year of kidney stone composition. Four groups based on the number (0, 1, 2, 3-4) of met-s traits (hypertension, obesity, dyslipidemia, diabetes) were evaluated. Trends across groups were tested using linear contrasts in analysis of variance.

Results: 1250 unique patients, 49% F, 703 with stone composition met criteria for inclusion. Met-s groups n were 0=509, 1=381, 2=203, 3+4=157. There was no difference or trends among the groups for urine volume, calcium or citrate. There was a significant trend p<0.001 for increasing number of met-s traits with decreasing urine pH and SS calcium phosphate (CaP) and increasing age, weight, protein intake, urine uric acid (UA), SS UA, oxalate, sodium, potassium, phosphorus, urea nitrogen, chloride, estimated net acid excretion and p<0.05 for sulfate (S), ammonium, magnesium. When adjusted for age and protein intake the trend remained significant only for urine pH and a reversed trend for S. There was a significant trend for more UA and fewer predominately CaP stones in those with more met-s traits.

Conclusions: High protein intake accounted for most of the difference in urinary markers of stone risk except low urine pH. The latter facilitates more UA and less CaP contribution to stone composition. Future studies could determine if changing diet can reduce risk for stones in met-s

Funding: Clinical Revenue Support

PO0416

Primary Hyperoxaluria (PH) Types 1 and 2 with Kidney and/or Liver Transplant Achieve Best Health-Related Quality of Life (HRQoL)

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Background: Our previous study showed that PH without a transplant (tx) had worse HRQoL compared to the US Standard Population and worsened with increased stone frequency. We now show the first longitudinal HRQoL profiles for PH patients with transplants.

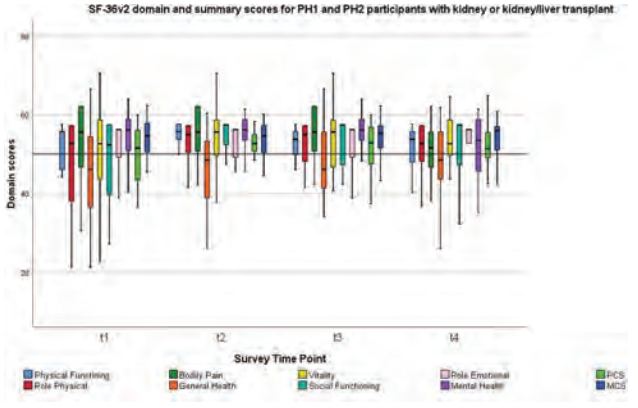
Methods: PH participants were enrolled from the Rare Kidney Stone Consortium registry. HRQoL was measured with a generic non-disease specific instrument (SF-36v2). Results were calculated as norm-based scores (NBS) based on US Standard Population

(Mean domain score = 50). We created three groups based on the time of last stone event (<= 30 days, 31 – 365 days, >366 days). The study compared HRQoL for participants with a kidney and/or liver transplant over 5 different time points.

Results: This sub-sample included 100 surveys of 32 PH participants (16 males and 16 females) with a tx. The mean age was 47 years for both males and females. This sub-sample includes 24 participants with liver/kidney tx (75%) and 8 with kidney tx only (25%). Participants with only a kidney tx reported significantly more stone events within a year (26% vs 13%, X^2 =0.028). Two way ANOVA did not find a change in HRQoL profiles over time for PH participants with kidney or kidney/liver tx (figure). Most mean domain scores are 50 or above, except for the domain of General Health which was less. Participants with only a kidney tx scored significantly lower in role physical, bodily pain, general health, social function, and physical component score (data not shown) than participants with kidney/liver tx. There was no difference between male and female participants over time.

Conclusions: PH participants with kidney/liver tx achieve better HRQoL, measured with a non-disease specific generic instrument, than those with kidney alone; both are better when compared to the US Standard Population. The majority of PH participants with a tx are stone-free, with a direct beneficial impact on their HRQoL.

Funding: NIDDK Support



PO0417

Assessment of Blood Oxalate Concentrations in Patients with CKD

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Background: Alterations in oxalate homeostasis are associated with kidney stone disease and progression of chronic kidney disease (CKD). However, accurate measurement of plasma oxalate (P_{Ox}) concentration is challenging as prompt processing and acidification of samples has been deemed necessary. In the present study we examined the effects of variations in sample handling on P_{Ox} results. Subsequently, a standardized analytical protocol was established, and P_{Ox} concentrations were measured in a large cohort of patients with CKD.

Methods: We tested the effects on P_{Ox} results of storage time at room temperature (RT), storage on dry ice and maintenance of samples at -80°C. P_{Ox} was measured in 1826 patients enrolled in the German Chronic Kidney Disease (GCKD) study, an ongoing multicenter, prospective, observational cohort study.

Results: P_{Ox} concentrations increased rapidly when samples were maintained at RT. This was most relevant for P_{Ox} < 10 µM as concentrations more than doubled within a few hours. Immediate freezing on dry ice and storage at -80°C provided stable results and allowed postponement of acidification for > 1 year. In the GCKD study, mean (SD) eGFR at the time of P_{Ox} measurement was 44.0 (17.9) ml/min/1.73 m². More than half of the patients had a P_{Ox} concentration below 2.0 µM. P_{Ox} correlated positively with urinary albumin to creatinine ratio and inversely with eGFR (P <0.001). In the lowest eGFR quartile, median eGFR was 25.1 ml/min/1.73 m² (IQR 20.3 - 28.1) with a median P_{Ox} of 2.7 µM (IQR 1.9 – 4.2).

Conclusions: We conclude that immediate freezing and maintenance of plasma samples at -80°C facilitates the sample collection process and allows accurate P_{Ox} assessment in large patient cohorts. Our study presents a critical and useful modification of the complex preanalytical procedure. Moreover, we demonstrate that P_{Ox} concentrations in patients with CKD are substantially lower than previously reported. The present study may serve as a reference for sample handling to assess P_{Ox} in clinical trials and to determine its role in CKD progression.

Funding: Commercial Support - Dicerna Pharmaceuticals, Cambridge, USA, Private Foundation Support, Government Support - Non-U.S.

PO0418

Safety and Efficacy of Reloxaliase in Enteric Hyperoxaluria (EH): An Aggregate Review of Completed Studies

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Background: EH occurs when excess oxalate is absorbed from the gastrointestinal (GI) tract due to underlying fat malabsorption, increasing renal oxalate load and as a result, risk of both kidney stones and chronic kidney disease. Reloxaliase is a first-in-class oral enzyme that specifically targets and degrades oxalate within the GI tract to treat EH. An aggregate safety and efficacy assessment of reloxaliase in subjects with EH across completed clinical trials was performed.

Methods: There were a total of four Phase 2 and 3 trials that enrolled EH subjects; 2 were single-arm and 2 were randomized, placebo (PBO) controlled. Subjects took reloxaliase orally (7,500 units/dose) 3 to 5 times/day, for 4 days to 12 weeks. The efficacy endpoint in all trials was change in 24-hour urine oxalate (UOx) excretion (mg/d). For this aggregate analysis, percent change from baseline was calculated using the average of all values obtained during treatment.

Results: There were a total of 168 randomized subjects with EH (94 reloxaliase and 74 PBO), most with bariatric surgery as the cause of malabsorption. Baseline estimated glomerular filtration rate (eGFR) ranged from normal to as low as 33 mL/min/1.73m². In subjects with baseline UOx ≥ 50 mg/d, reloxaliase treatment consistently reduced 24-hr UOx by a mean of 23 to 35% across the studies, despite differences in dosing frequency and duration of treatment. Efficacy appeared to be unrelated to baseline eGFR. Adverse events (AEs) were reported in 67% of reloxaliase subjects compared to 51.4% on PBO, with GI AEs most common in both groups. There were no treatment-related serious AEs or deaths, and none of the reloxaliase treated subjects withdrew from the study due to a related AE.

Conclusions: Reloxaliase reduces 24-hr UOx excretion and is well tolerated in EH patients independent of eGFR, dosing frequency, or duration of treatment. Further studies are ongoing to assess the long-term benefits of reloxaliase and its potential to decrease kidney stone events and preserve kidney function.

Funding: Commercial Support - Allena Pharmaceuticals

PO0419

Trends in Treatment of Secondary Hyperparathyroidism and Association with Post-Transplant Outcomes

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Background: Secondary hyperparathyroidism(SHPTH) affects nearly all patients with kidney failure on maintenance dialysis and has been independently associated with increased mortality and cardiovascular disorders. Treatment includes vitamin D analogs, calcimimetics, or parathyroidectomy. However, treatment choice for SHPTH on outcomes after kidney transplantation(KT) is not well understood. The primary objectives of our study were to understand treatment trends in SHPTH and their association with post-transplant outcomes.

Methods: Using SRTR and Medicare claims data, we identified 12,372 adults(age≥18) who received KT in 2007-2016 and had a diagnosis of SHPTH during dialysis. We examined the association between treatment method for SHPTH and development of tertiary hyperparathyroidism, delayed graft function, graft failure, and death using adjusted Cox proportional hazards models.

Results: Of 12,372 patients with a diagnosis of SHPTH, 4,554(36.8%) received cinacalcet, 205(1.7%) underwent parathyroidectomy, and 7,613(61.5%) had no treatment prior to KT. Cinacalcet use increased throughout the duration of the study period with 18.4% of patients receiving it 2007 versus 46.2% in 2017(p<0.001). Utilization of parathyroidectomy increased from 0.8% in 2007 to 3.1% in 2016(p=0.005). Compared to patients treated with cinacalcet, those treated with parathyroidectomy had a lower risk of developing tertiary hyperparathyroidism(aHR=0.49,95%CI:0.29-0.82) at 3 years post-KT and those who received no treatment had lower odds of delayed graft function(aOR=0.87,95%CI:0.78-0.96). There was no association between treatment of SHPTH and post-transplant death-censored graft failure, all-cause graft failure or death.

Conclusions: The use of calcimimetics and parathyroidectomy to treat SHPTH has been steadily increasing since 2007. Importantly, patients who underwent parathyroidectomy for SHPTH had lower risk of developing tertiary hyperparathyroidism post-transplant. Therefore, patients treated with cinacalcet pre-transplant may need closer surveillance post-transplant for development of tertiary hyperparathyroidism.

Funding: Other NIH Support - NIA

PO0420

A Combined MicroRNA and Target Protein-Based Panel for Predicting the Probability and Severity of Uremic Vascular Calcification

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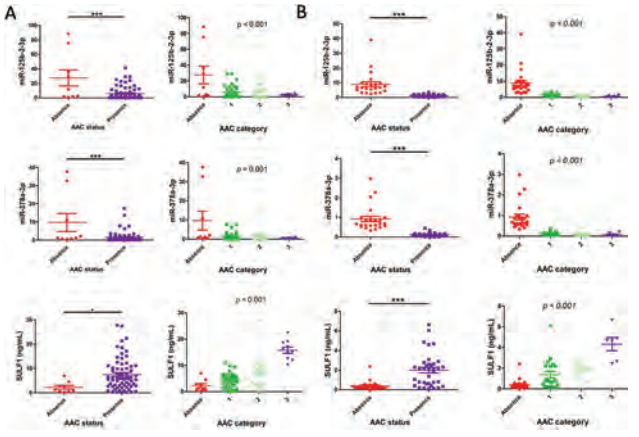
Background: Vascular calcification (VC) increases the future risk of cardiovascular events in uremic patients, but effective therapies are still unavailable. Accurate identification of those at risk of developing VC using pathogenesis-based biomarkers is of particular interest and may facilitate individualized risk stratification. We aimed to uncover miRNA-target protein-based biomarker panels for evaluating uremic VC probability and severity.

Methods: We created a 3-tiered *in vitro* VC model and an *in vivo* uremic rat model receiving high phosphate diet to mimic uremic VC. RNAs from the *in vitro* and *in vivo* models underwent miRNA and mRNA microarray, with results screened for differentially expressed miRNAs and their target genes as biomarkers. Findings were validated in all models and human cells, followed by functional assays of identified miRNAs, and tests of sera from end-stage renal disease (ESRD) and non-dialysis dependent chronic kidney disease (CKD) patients without and with VC.

Results: Totally 122 down-regulated and 119 up-regulated miRNAs during calcification progression were identified initially; further list-narrowing based on miRNA-mRNA pairing, anti-correlation, and functional enrichment left 16 and 14 differentially expressed miRNAs and mRNAs. Levels of 4 miRNAs (miR-10b-5p, miR-195, miR-125b-2-3p, and miR-378a-3p) were shown to decrease throughout all models tested, while 1 mRNA (SULF1, a potential target of miR-378a-3p) exhibited the opposite trend concurrently. Among 77 ESRD (88.3% with VC) (Figure A) and 59 CKD patients (61% with VC) (Figure B), serum miR-125b2-3p and miR-378a-3p decreased with greater VC severity, while serum SULF1 levels increased. Adding serum miR-125b-2-3p, miR-378a-3p, and SULF1 into regression models for VC substantially improved performance compared to using clinical variables alone.

Conclusions: Using a translational approach, we discovered a novel panel of biomarkers for gauging the probability/severity of uremic VC based on miRNAs and their target proteins, which improved the diagnostic accuracy.



PO0421

Clinical Characteristics and eGFR and Urine Albumin-to-Creatinine Ratio Distribution According to the 2012 KDIGO CKD Classification: A Report from the DISCOVER CKD International Retrospective Cohort

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Background: Contemporary studies describing the prevalence and characteristics of patients with CKD categorised according KDIGO 2012 are scarce. We describe patient characteristics and the prevalence of CKD according to the 2012 KDIGO categories in patients with CKD.

Methods: The DISCOVER-CKD retrospective cohort of patients was extracted using real-world data from the integrated Limited Claims and Electronic Health Record (LCED) data and TriNetX. Patients were aged ≥18 years, with ≥1 UACR measure and required first diagnostic coding of CKD (Stages3A to ESRD) or two estimated glomerular filtration rate (eGFR) measurements of <75 mL/min/1.73 m² recorded at least 90 days apart (max 730) between January 2008 and March 2020. Index date was date of diagnostic coding or 2nd eGFR. UACR closest to index was used to categorise patients. Descriptive analyses were used to summarise prevalence and patient characteristics.

Results: Preliminarily, among 22229 included patients, 63.6% (n=10979, TriNetX) and 76.6% (n=3813, LCED) had normal to mildly increased albuminuria, 26.6% (n=4581, TriNetX) and 17.9% (n=889, LCED) had moderately increased albuminuria and 9.8% (n=1694, TriNetX) and 5.5% (n=273, LCED) had severely increased albuminuria (Figure 1). Hypertension and type 2 diabetes were the most common comorbidities (prevalence >60%) and their prevalence increased with albuminuria.

Conclusions: This study, utilising real-world data, fills an important knowledge gap regarding the characteristics of patients with CKD in different eGFR and UACR strata according to the KDIGO 2012 definitions.

Funding: Commercial Support - AstraZeneca

Figure 1: Prevalence of CKD included in DISCOVER CKD, according to the 2012 KDIGO definition.

Overall TriNetX

eGFR (mL/min/1.73m2)	KDIGO 2012 eGFR & UACR Categories	UACR (mg/g)		
		0-29	30-299	≥300
	60-75	7208 (65.7%)	2277 (49.7%)	561 (33.1%)
	45-59	2651 (24.1%)	1259 (27.5%)	448 (26.4%)
	30-44	862 (7.9%)	697 (15.2%)	342 (20.2)
	15-29	176 (1.6%)	256 (5.6%)	261 (15.4)
	0-14	82 (0.7%)	92 (2.0%)	82 (4.8%)
	Total	10979 (63.6)	4581 (26.6)	1694 (9.8)

Overall LCED

eGFR (mL/min/1.73m2)	KDIGO 2012 eGFR & UACR Categories	UACR (mg/g)		
		0-29	30-299	≥300
	60-75	2210 (58.0%)	369 (41.5%)	68 (24.9%)
	45-59	1161 (30.4%)	384 (43.2%)	114 (41.8%)
	30-44	198 (5.2%)	108 (12.1%)	56 (20.5%)
	15-29	40 (1.0%)	21 (2.4%)	25 (9.2%)
	0-14	204 (5.4%)	7 (0.8%)	10 (3.7%)
	Total	3813 (76.6%)	889 (17.9%)	273 (5.5%)

PO0422

The DAPA-CKD-Like Population in a Contemporary US Healthcare System: Cohort Characteristics and Clinical Outcomes

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Background: The DAPA-CKD Trial is the first SGLT-2i renal outcome trial to test the efficacy and safety of an SGLT-2i, dapagliflozin, in patients with diagnosed CKD with and without T2D. To appropriately evaluate future results and aid clinical interpretation of the DAPA-CKD trial, the present study assessed the renal and CV outcomes of a "DAPA-CKD-like population" (eGFR 25-75ml/min/1.73m² and UACR 200-5000mg/g) in a contemporary US healthcare system.

Methods: Administrative data from the Henry Ford Health System was used to identify patients with CKD stages 2 through 4 between 2006 and 2016 based on eGFR lab reading (n=38,376). Exclusions included no confirmatory eGFR > 90 days from index date, death within 30 days, history of renal transplant, and evidence of renal replacement therapy, or progression to CKD stage 5 during the baseline period (6 months pre or post index date). Within that cohort, 17,742 had eGFR (25-75ml/min/1.73m²) and 9,177 had a UACR (0-5000 mg/g) within 12 months of index date. Additional exclusions were type 1 diabetes, lupus nephritis and polycystic kidney disease. Patients were followed through December 31st, 2018.

Results: Of the 6,557 patients that met the eligibility criteria and were included in the study cohort, the mean age was 62.9 years and 46.2% were male. The population was stratified by UACR (0-<30, 30–199, 200–5,000mg/g). Across all outcomes assessed, incidences were highest in the DAPA-CKD-like cohort (UACR 200-5000mg/g) (HF 36.1%; MI 11.3%, Stroke 8.9%; ESKD 18.6%; Mortality 18.5%; see Table 1). The greatest increase was observed for renal outcomes particularly ESKD, increasing from 0.9% (UACR 0-<30mg/g) to 3.4% (UACR 30-199mg/g) to 18.6% (UACR 200-5000mg/g).

Conclusions: In a contemporary US healthcare system, there remains significant adverse renal, CV and mortality outcomes among patients fitting the DAPA-CKD study inclusion criteria. These results highlight the unmet need existing for additional therapies to delay disease progression and improve outcomes and survival in this high risk population.

Funding: Commercial Support - AstraZeneca

Table 1. 5-year CV, renal and mortality outcomes across the 3 UACR categories analysed.

	UACR 0-<30mg/g N= 4331		UACR 30-199mg/g N = 1354		UACR 200-5000mg/g N= 873		Total		p - value
	n	%	n	%	n	%	n	%	
All-cause mortality	243	6.0	146	11.7	139	18.5	528	8.7	< 0.0001
Renal outcomes									
ESKD (composite of 3 below)	37	0.9	42	3.4	140	18.6	219	3.6	< 0.0001
Progression to CKD stage 5	28	0.7	38	3.0	118	15.7	184	3.0	< 0.0001
Dialysis onset	7	0.2	16	1.3	83	11.0	106	1.8	< 0.0001
Renal transplant	9	0.2	3	0.2	7	0.9	19	0.3	< 0.001
CV Outcomes									
Myocardial infarction (MI)	191	4.7	92	7.4	85	11.3	368	6.1	< 0.0001
Stroke	161	4.0	71	5.7	67	8.9	299	4.9	< 0.0001
Heart failure (HF)	561	13.9	307	24.6	272	36.1	1140	18.9	< 0.0001

PO0423

NSAID Use Is Not Associated with Kidney Injury or Dysfunction in Ambulatory Older Adults

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Background: NSAIDs cause AKI and may worsen CKD, especially in vulnerable populations such as older adults. We hypothesized that NSAID use would be associated with markers of both tubular and glomerular damage in older adults.

Methods: In the multicenter Health ABC cohort of ambulatory older adults, prescription and OTC NSAID use was self-reported. Estimated GFR by cystatin C, and urine albumin (ACR), KIM-1, and IL-18 were measured in 2,999 participants; urine a1m, NGAL, PIIINP, and UMOD were measured in a random subset of 500 participants. We evaluated cross-sectional associations between NSAID use and these biomarkers with separate linear regression models. The association between time-updated NSAID use and eGFR decline over 10 years was estimated with linear mixed models.

Results: Participants had a mean age of 74 years, 51% were female, and 41% African-American. No eGFR differences were detected between NSAID users (n=655) and non-users (n=2344) at baseline (72 mL/min/1.73m^2 in both groups). Compared to non-users, NSAID users had 33% (95% CI: 11%-49%) lower adjusted odds of having ACR >30 mg/g and 11% (95% CI: 4%-18%) lower mean urine IL-18 concentration at baseline. No significant differences in baseline concentrations of the remaining urine biomarkers were detected. NSAID users and non-users did not differ significantly in the rate of eGFR decline (-2.2% vs. -2.3% per year).

Conclusions: Among ambulatory older adults, NSAID use was not associated with kidney dysfunction or injury based upon eight measures of kidney health, and NSAIDs were associated with significantly lower urine albumin and IL-18 concentrations. These findings illustrate the potential for NSAID use without kidney harm, even in a presumably high-risk population.

Table: Association of NSAID use with annual change in eGFR

All (n = 2999)	Mean eGFR change, % per year (95% CI)	Adjusted β (95% CI)
NSAID users (n = 655)	-2.21 (-2.49, -1.92)	-0.06 (-0.39, 0.28)
NSAID non-users (n = 2344)	-2.31 (-2.47, -2.16)	0 (reference)
eGFR ≥60 (n = 2249)		
NSAID users (n = 496)	-2.36 (-2.62, -2.11)	-0.001 (-0.31, 0.31)
NSAID non-users (n = 1753)	-2.42 (-2.56, -2.29)	0 (reference)
eGFR <60 (n = 750)		
NSAID users (n = 159)	-1.74 (-2.52, -0.96)	-0.29 (-1.19, 0.61)
NSAID non-users (n = 591)	-2.00 (-2.41, -1.59)	0 (reference)

Adjusted for age, gender, race, education, BMI, osteoarthritis, osteoporosis, diabetes, SBP, antihypertensive medications, prevalent heart failure, gait speed, and grip strength.

PO0424

The Prevalence of CKD Among First-Degree Relatives of Saudi Hemodialysis Patients and Associated Factors

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Background: In Saudi Arabia, there are currently over 20,000 patients on dialysis and 9810 patients followed up for functioning renal transplantation. The combined prevalence of renal replacement therapy (stage 5 CKD) in Saudi Arabia is estimated to 1294.3 PMP. There are no local data or registry about stages 1 to 4 CKD in the Kingdom. Objective: To assess the prevalence of CKD among first degree relatives of Saudi hemodialysis patients and evaluate the associated characteristics

Methods: 1st degree relatives of all hemodialysis patents in Diaverum clinics in Saudi Arabia were screened for CKD. Demographic data were collected as well as history of hypertension or diabetes mellitus. Serum creatinine, urinalysis and a single Blood pressure reading were measured. eGFR was calculated using EPI formula. For the index cases, the cause of CKD, age and gender were recorded. The prevalence rates of CKD stages among relatives were calculated and the association between different variables and CKD stages assessed

Results: Out of 4500 dialysis patients, 20258 1st degree relatives were approached of whom 5177 responded. The cause of CKD among the index cases was DM in 52.5% followed by hypertension (20.6%). The eGFR was < 90 mls /min in 39.6% and < 60 mls/ min in 5.8% of the screened cases. Proteinuria was present in 8%, making the combined prevalence of CKD of 13.8%. In the screened group, the prevalences of glycosuria, hematuria and proteinuria were 9.5%, 17.9% and 26.5% respectively and systolic hypertension (>130 mmHg) was observed in 28.1% and diastolic hypertension in 8.6%. Screened relatives in stages 0-1 were significantly younger than those in stages 2-5 (31.3 ±12.8 versus 40.9± 15 years (p=0.0001). The relationship of the screened persons to the index patients among those in stages 2-5 were offspring (35.8%), sibling (41.6%) and parent (50.0%) (p=0.0005). The prevalences of the primary renal diseases in the index cases did not differ between screened relatives in CKD stages 0-1 and those in stage 2-5.

Conclusions: The overall combined prevalence of CKD was 13.8% and is highest in the Southern region of Saudi Arabia. The presence of CKD in the screened relatives was not associated with identifiable cause of CKD in the index cases or use of analgesics. Many relatives were discovered to have undiagnosed hypertension and undiagnosed diabetes.

Funding: Private Foundation Support

PO0425

Sex Differences in CKD Prevalence in Asia: A Systematic Review and Meta-Analysis

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Background: Individual studies reporting sex-specific chronic kidney disease (CKD) prevalence in Asia have shown inconsistent sex differences in CKD prevalence. We sought to synthesise available sex-disaggregated data to better define and compare CKD prevalence in women and men in Asia.

Methods: We systematically searched the literature for observational studies of ≥500 adults reporting sex-disaggregated CKD prevalence data in Asia. We calculated the women-to-men prevalence ratio (PR) for each study and pooled these using random-effects meta-analysis. Subgroup analyses were performed to explore potential sources of heterogeneity in the PR.

Results: Sex-disaggregated CKD prevalence data were available for 12 of the 26 Asian countries (109 studies; 1,452,308 women and 1,391,995 men). Most studies (83%) came from China, Taiwan, Japan and South Korea. Sex-specific CKD prevalence estimates varied substantially between studies (median [IQR] reported prevalence was 19% [9-35%] in women and 17% [8-28%] in men). Overall, CKD prevalence was higher in women compared to men (pooled PR 1.14; 95%CI 1.07-1.21), with evidence of significant heterogeneity (I^2=99%). In subgroup analyses, prevalence was higher in women among studies with a younger mean age, a higher proportion of diabetes and that defined CKD using eGFR only (Table 1). The pooled PR varied considerably by country.

Conclusions: Existing sex-disaggregated data suggest a higher overall prevalence of CKD in women compared to men in Asia. However, adequate assessment of sex differences in CKD prevalence is limited by the absence of sex-disaggregated data for a large part of the region. Standardised reporting of sex-disaggregated CKD prevalence data in Asia is needed.

Variable	No. of studies	Pooled women-to-men PR (95% CI) by subgroup	I^2 (%)
Number			0
<5000	59	1.11 (1.02-1.21)	
≥5000	50	1.16 (1.06-1.27)	
Mean age (years)			77.01
<65	75	1.14 (1.04-1.24)	
≥65	22	1.02 (0.97-1.08)	
Prop. with diabetes			20.63
<Median	41	1.07 (0.98-1.18)	
≥Median	36	1.16 (1.05-1.29)	
Country			78.67
Bangladesh	1	1.17 (0.83-1.63)	
China	32	1.21 (1.05-1.39)	
India	3	0.86 (0.64-1.14)	
Indonesia	1	0.75 (0.53-1.08)	
Iran	4	1.79 (1.28-2.50)	
Japan	32	1.06 (0.94-1.18)	
Nepal	2	2.35 (0.84-6.60)	
Singapore	3	1.16 (0.65-2.06)	
South Korea	9	1.26 (0.80-1.96)	
Taiwan	18	0.92 (0.83-1.03)	
Thailand	3	1.17 (1.08-1.28)	
Vietnam	1	2.73 (1.81-4.12)	
eGFR equation			0
CKD-EPI	26	1.13 (1.00-1.27)	
Others	72	1.16 (1.08-1.26)	
CKD definition			92.92
eGFR	80	1.21 (1.13-1.30)	
eGFR or albuminuria	29	0.95 (0.86-1.06)	

Table 1 Subgroup analyses of the pooled PR.

PO0426

Increased Circulating suPAR Levels in African Patients with HIV

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Background: Decline in kidney function associated with APOL1 risk alleles is dependent on circulating suPAR levels in African American (AA) patients. Yet, little is known among HIV infected persons in sub-Saharan Africa, and epidemiological data from

this region regarding APOL1 risk status is scarce. We aimed to determine APOL1 risk variants, plasma suPAR levels and estimated kidney function in HIV patients in Zambia.

Methods: We performed a cross-sectional study with 480 adult HIV infected persons on anti-retroviral treatment (ART) (women, 64.8%) in Lusaka, Zambia. APOL1 genotyping was done to determine the prevalence of the risk alleles; plasma suPAR levels were assayed and estimated GFR (eGFR) was calculated by CKD-EPI creatinine-based formula.

Results: Plasma suPAR levels were increased and were negatively correlated to eGFR, whether less than 60 or not (r=-0.15, p=0.001). Women while younger (42 vs 46 years old for men, p=0.0003), had higher suPAR than men (3.68 ng/ml vs 3.07 ng/ml, p<0.0001). Ten out of 480 patients (2.1%) had CKD, and their suPAR levels were higher than patients without CKD (5.6 ng/ml vs 3.44 ng/ml, p<0.0001). Fifty patients (10.4%) had 2 APOL1 risk alleles (35 for women vs 15 for men); among those, 3 (6%) developed CKD (p=0.07). No difference in suPAR levels or eGFR was observed between patients who carried 2 APOL1 risk alleles and those with 1 or 0 risk allele.

Conclusions: HIV infected persons in Zambia on ART have increased suPAR levels. The prevalence of two APOL1 risk alleles is similar as with AA HIV patients. A longitudinal study with a bigger cohort should reveal the relationship between suPAR, APOL1 risk alleles and kidney function.

Funding: NIDDK Support

PO0427

Kidney Tubular Injury and Dysfunction Relate to Frailty and Cognitive Function in Persons with CKD in SPRINT

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Background: The association of markers of kidney disease (eGFR and albuminuria) with frailty and cognition is well established. However, these markers do not specifically evaluate kidney tubule injury or dysfunction.

Methods: We measured 8 biomarkers of kidney tubule dysfunction and injury among 2,282 SPRINT participants with eGFR < 60 and evaluated their associations with frailty and cognitive function. Frailty was defined with a previously validated frailty index (FI), categorized as fit (FI < 0.10), less fit (0.10 < FI < 0.21), and frail (FI > 0.21). Global cognitive function was measured using the Montreal Cognitive Assessment (MoCA). Models were adjusted for, demographic, behavioral, and clinical variables including urine creatinine, eGFR and albuminuria.

Results: Higher urine concentrations of MCP-1 & α1M were independently associated with frailty (Figure). These associations were independent of demographics, other CKD risk factors, eGFR and albuminuria, and were comparatively stronger than associations of albuminuria with frailty (Figure). Higher urine β2M was associated with lower cognitive function (β: -0.09; 95% CI -0.17, -0.01), whereas albuminuria was not (β: -0.03; 95% CI -0.13, 0.08).

Conclusions: Urine markers of tubulointerstitial fibrosis (captured by MCP-1) and diminished proximal tubule reabsorptive capacity (captured by α1M and β2M) were associated with frailty and worse cognition independent of eGFR and albuminuria in hypertensive trial participants with CKD.

Funding: NIDDK Support, Other NIH Support - NIA, NINDS, NHLBI, Veterans Affairs Support

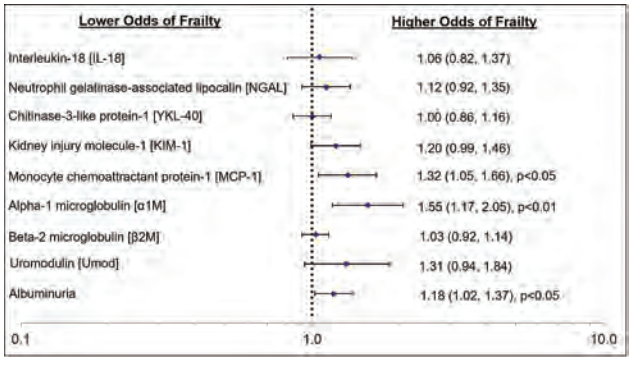

Figure. Multinomial regression showing the baseline association between biomarkers of kidney tubule dysfunction and injury with frailty compared with fit older adults (less fit group omitted). Models were adjusted for age, sex, race, BMI, alcohol use, years of education, SBP and DBP, smoking status, urine creatinine, eGFR, and albuminuria.

PO0428

Association of Kidney Tubule Injury and Dysfunction with Cognitive Function in the Health, Aging and Body Composition Study

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Background: The association of lower levels of eGFR and higher levels of albuminuria with poor cognition is well established. However, these markers do not specifically evaluate kidney tubule injury or dysfunction.

Methods: We measured 5 urinary biomarkers of kidney tubule injury and dysfunction (alpha-1 microglobulin [α1m], kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18], uromodulin [Umod], and neutrophil gelatinase-associated lipocalin [NGAL]) among a random sample of 502 participants, and serum bicarbonate [sHCO3] among 2,288 community-living elders aged 70-79. We evaluated the cross-sectional associations with cognitive function using the Modified Mini-Mental State Exam (3MSE) and the Digit Symbol Substitution Test (DSST), where higher scores represent better cognitive function.

Results: None of the urine kidney tubule markers were associated with 3MSE, whereas higher urine NGAL was associated with lower scores of 3MSE but not DSST (table). These associations were independent of demographics, eGFR, and albuminuria.

Conclusions: Among urine markers of tubule injury and dysfunction, only higher NGAL was associated with lower cognitive function testing by DSST. Similarly sHCO3 was associated with worse cognitive function by 3MSE independent of eGFR, albuminuria, or other risk factors

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Cross-sectional association between biomarker of kidney tubule dysfunction with cognitive function.

	Modified Mini-Mental State Exam (0-100)	Digit Symbol Substitution Test (0-90)
Year 1	β Coefficient (95% CI)	
Log 2 α1M, mg/dL	0.11 (-0.72, 0.93)	-0.79 (-2.52, 0.94)
Log 2 KIM-1, pg/dL	-0.10 (-0.60, 0.40)	-0.25 (-1.25, 0.76)
Log 2 IL-18, pg/mL	-0.08 (-0.52, 0.36)	-0.29 (-1.18, 0.60)
Log 2 Umod, ng/mL	0.35 (-0.16, 0.86)	0.40 (-0.63, 1.43)
Log 2 NGAL, ng/mL	0.03 (-0.17, 0.23)	-0.41 (-0.81, -0.01)*
Year 3	β Coefficient (95% CI)	
sHCO3, mmol/L	0.22 (0.07, 0.37)**	0.26 (-0.02, 0.53)

*P<0.05, **P<0.01

All models were adjusted for age, sex, race, years of education, clinic site, BMI, smoking status, Center for Epidemiologic Studies Depression Scale score, SBP, any antihypertensive medication, diabetes, stroke, cystatin C and creatinine-based eGFR, albuminuria, and urine creatinine. sHCO3 was additionally adjusted for spirometry (horizontal dry rolling seal spirometer).

PO0429

Risk of Pneumonia Hospitalization Associated with Serum Triglycerides Across CKD Stages in US Veterans

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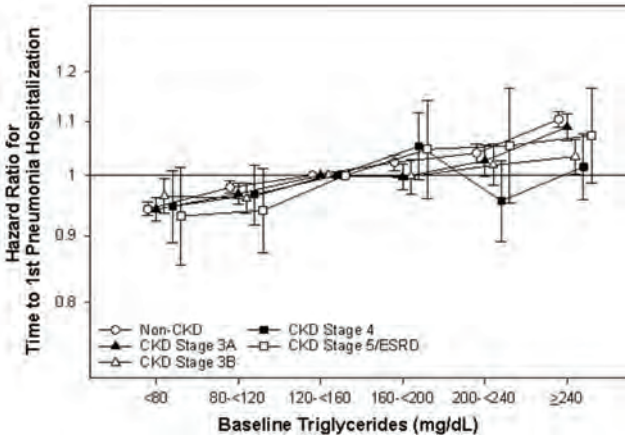
Background: Small studies have suggested that chronic kidney disease (CKD) is an independent risk factor for pneumonia hospitalization. Although lipid modulating therapies are known for atherosclerotic cardiovascular disease risk reduction, they have been shown to also lower risk of pneumonia. Cholesterols were recently identified as having important roles in lung physiology and maintenance, yet the relationship of another lipid, serum triglycerides (TG) with pneumonia across CKD stages is relatively unknown.

Methods: Our cohort comprised 2,963,176 US veterans who received care from 2004-2006 (baseline) and were followed until 2014. Primary diagnosis ICD-9 codes identified inpatient pneumonia events. Using Cox proportional hazards models, we evaluated the association between baseline TG and time to first pneumonia hospitalization, stratified by CKD stage at the time of the TG measurement. Models were adjusted for demographics, comorbidities, use of lipid modulating therapies, and other biomarkers including serum lipids.

Results: Our patient cohort was on average 63±14 years old, had a median [IQR] TG of 127[87, 189] mg/dL and 23% had CKD at baseline. After full adjustment, TG <160 mg/dL were generally associated with a lower time to first pneumonia event (ref: TG 120-<160 mg/dL) for all CKD stages (Figure). Conversely, high TG ≥240 mg/dL were associated with higher risk of a pneumonia hospitalization in non-CKD and CKD stage 3A-3B patients. Notably, elevated TG >200 mg/dL were not associated with a higher risk of pneumonia among CKD stage 4, 5 and end-stage renal disease patients.

Conclusions: We observed that elevated TG were associated with higher risk of pneumonia hospitalization in non-CKD and CKD stage 3A-3B patients, but this relationship was not observed in late-stage CKD patients. While use of statins and cholesterol levels have been studied in the context of pneumonia and lung function, future studies are warranted to also investigate the role of triglycerides in pneumonia risk especially among early stage CKD patients.



PO0430

The Reference Interval and Risk Factors of NT-ProBNP in CKD Patients Without Heart Failure

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Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP), a diagnostic marker of heart failure (HF), as well as the specific and sensitive biomarker of HF is been demonstrated to be affected by renal function. NT-proBNP is significantly associated with the severity of GFR loss. However, the reference interval (RI) of NT-proBNP in non-dialysis chronic kidney disease (CKD) patients without HF remains unclear. The aim of our study was to establish the threshold value of NT-proBNP which could help to early recognition, prevention and treatment for HF.

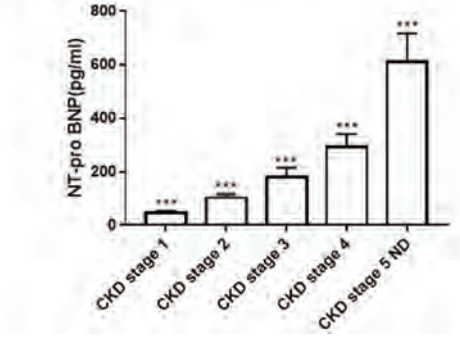
Methods: All patients diagnosed with CKD aged more than 18 years old in our hospital from Jan 01, 2014 to Dec 31, 2019 were recruited into this study. Individuals who diagnosed with HF were excluded. The RI for NT-proBNP was defined by nonparametric method and risk factors were analyzed by linear regression analysis.

Results: A total of 1260 CKD patients without HF were included in this study. Of them, 588(46.67%) were female. NT-proBNP were increased with the advanced stage of kidney function in CKD patients without HF. The median level of NT-proBNP in CKD stage 5 ND (non-dialysis) patients without HF were the highest, as 610.25 pg/ml. The RIs for NT-proBNP in CKD patients without HF with respect to kidney function stage (ranges of stage 1, stage 2, stage 3, stage 4, stage 5 ND) were 8.15-536.32, 12.38-811.90, 16.62-1411.05, 33.14-2945.05, 88.58-5533.73pg/ml. We also demonstrated that NT-proBNP was significantly correlated with the serum levels of Hb (β=-0.174, P<0.001), Ca (β=-0.214, P<0.001), P (β=0.111, P<0.001), hs-CRP (β=0.140, P<0.001), and eGFR(β=-0.243, P<0.001).

Conclusions: Our study proved that NT-proBNP was increased with the advanced stage of GFR in CKD patients without HF. The RI of NT-proBNP varied among the different stages of CKD without HF and multiple factors contributed to NT-proBNP, which could help clinicians to prevent and take actions against the occurrence of HF.

Funding: Government Support - Non-U.S.

Figure 1. The NT-pro BNP levels in different stage of chronic kidney disease patients without heart failure



PO0431

Soluble Urokinase Plasminogen Activation Receptor and Major Adverse Cardiac Event Morbidity in CKD Patients in the German Chronic Kidney Disease (GCKD) Cohort

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Background: Soluble urokinase plasminogen activation receptor (suPAR) is supposed as risk factor for both chronic kidney disease (CKD) and biomarker for major adverse cardiac events (MACE) disease. A long-term longitudinal analysis in a large cohort of patients suffering from both diseases simultaneously, CKD and cardiovascular (CV) disease including MACE criteria, to analyze suPAR as a predictive biomarker has not been performed, yet.

Methods: SuPAR was studied in the GCKD Study Group with a follow-up time of 4 years. Association of suPAR with CKD (estimated glomerular filtration rate, eGFR) and overall risk of all-cause death, CV death, and MACE (three-point MACE, MACE3; four-point MACE, MACE4) was estimated by Cox proportional hazards regression according to quintiles of suPAR.

Results: Altogether, 4994 participants were enrolled (60.1 ± 12.0 years; eGFR of 49.4 ±18.3 mL/min/1.73m^2). Median suPAR concentration was 1771 pg/mL (25th-75th percentile, 1447-2254 pg/mL). Hazard ratio for CV mortality was 1.58 (95%CI 0.62-4.00) in the second, 2.15 (95%CI 0.87-5.26) in the third, 3.48 (95%CI 1.53-7.93) in the fourth, and 5.30 (95%CI 2.34-12.0) in the fifth quintile. If additionally adjusted for eGFR, UACR, NT-proBNP, hsCRP results were confirmed.

Conclusions: In the GCKD study cohort suPAR predicts all-cause death, cardiovascular death, and MACE independent of NT-proBNP, renal function and of markers of systemic inflammation.

PO0432

Incidence and Racial Disparities in Cardiovascular Disease and CKD Progression in Young Adults with CKD

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Background: Cardiovascular disease (CVD) is a major source of morbidity and mortality in adult CKD patients; yet is not well elucidated in young adults with CKD. Furthermore, racial and ethnic disparities in CVD and CKD progression has been found in research of pediatric and older-adult CKD populations, but has not been investigated specifically in young adults.

Methods: We studied 317 participants aged 21-40yrs of age with mild to moderate CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, of whom, 174 were black or Hispanic. We calculated incidence rates for CV events (heart failure [HF], MI, stroke, and death) and CKD progression (50% decline in eGFR or ESRD) for all young adult participants and as stratified by race and ethnicity. Cox proportional hazards regression models were constructed to test the association between race/ethnicity and CV events and CKD progression, adjusting for age, sex, eGFR, UACr, baseline SBP, and APOL1 status.

Results: HF, mortality and CKD progression had the highest incidence rates amongst young adults with CKD (**Figure 1**). Rates of these events were higher among Black and Hispanic participants: HF (17.5 vs. 5.1/1000 person-years), all-cause mortality (15.2 vs. 7.1/1000 person-years), and CKD progression (125 vs. 59/1000 person-years). Lastly, in adjusted models, black or Hispanic status was significantly associated with higher risk of CV events (HR: 1.25, 95%CI: 1.12-1.41) and CKD progression (HR: 1.38, 95%CI: 1.21-1.57).

Conclusions: Young adults with CKD in the CRIC study experience high incidence rates of cardiovascular disease. The burden of disease is even higher for black and Hispanic participants with CKD. Further research is required to better understand the factors underlying racial disparities in young adults with CKD.

Funding: NIDDK Support

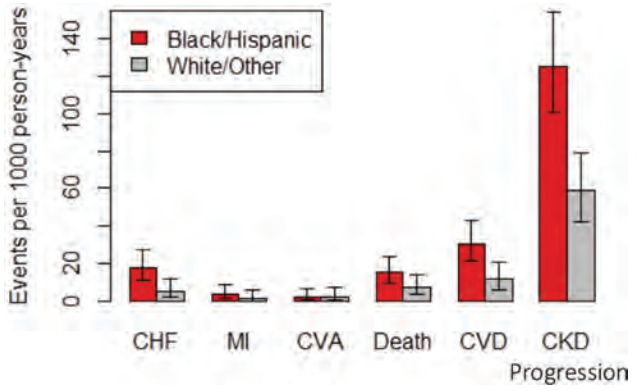

Figure 1

PO0433

Trends in the Transition to ESRD Among Native Hawaiians and Pacific Islanders Across the United States

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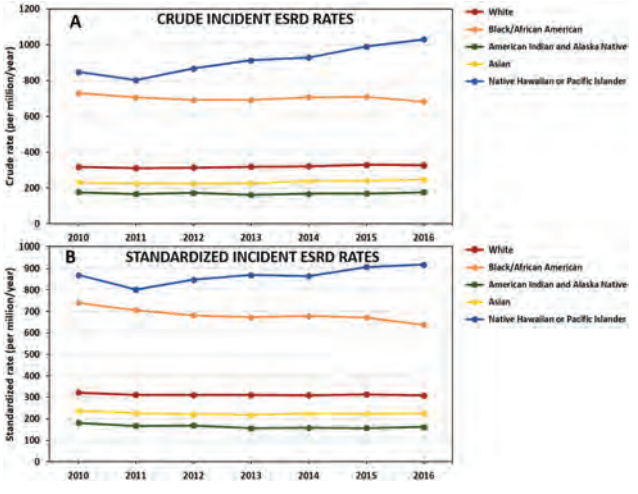
Background: Census data indicate there are >1.5 million Native Hawaiians and other Pacific Islanders (NHOPIs) in the US. While growing data show NHOPIs have a high prevalence of kidney disease risk factors (diabetes, obesity, hypertension, limited healthcare access), there are major knowledge gaps regarding the burden of end-stage renal disease (ESRD) in this population. We examined trends in the transition to ESRD in NHOPIs.

Methods: Using United States Renal Data System (USRDS) and Census Bureau data, we compared annual incident ESRD rates among NHOPI, African Americans (AA), and other racial subgroups over 2010-16. Rates were calculated as the observed incident ESRD count divided by the race-specific Census population size of that year. Multiple race designations were considered by utilizing Census categorizations that incorporated primary race in combination with one or more other races (alone or combination). We estimated crude rates and rates standardized to the age-sex distribution of 2011 race-specific Census population data.

Results: Over 2010-16, NHOPIs and AAs demonstrated the highest crude incident ESRD rates over time (**Fig 1A**). A similar pattern was observed for standardized incident ESRD rates (**Fig 1B**): 918, 638, 308, 226, and 162 incident ESRD patients per million (population)/year in 2016 for NHOPI, AA, Caucasian, Asian, and American Indian/Alaska Native subgroups, respectively. While standardized incident ESRD rates among AAs gradually declined, there was a steady rise in NHOPIs' incident ESRD rates over time.

Conclusions: NHOPIs demonstrated the highest incident ESRD rates over time. Further studies are needed to determine sociodemographic, biologic/genetic, cultural, and health care related ESRD risk factors among NHOPIs to inform targeted interventions in this population.

Funding: NIDDK Support



PO0434

Association Between eGFR-Cystatin C/eGFR-Creatinine Ratio and Fat Weight

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Background: The ratio of eGFR-cystatinC/eGFR-creatinine less than 0.7 is a condition that demonstrates different filtration for small and large molecules and is associated with accumulation of atherosclerosis-promoting proteins, higher cardiovascular event and mortality risk. Though, we hypothesize that this ratio could also be an indirect reflection of certain body composition. For example creatinine/cystatin C ratio has been used as a marker for sarcopenia, whereas cystatin C is highly expressed in human adipose tissue and might be increased in obesity. So the aim was to explore whether eGFR-cystatinC/eGFR-creatinine ratio is valid independently on body composition measures.

Methods: Data were extracted from the population based Malmö Diet and Cancer (MDC) study (n= 28 449) cardiovascular cohort (MDC_CC) that enrolled a random sample of study subjects invited to participate in carotid artery disease epidemiological analysis (n = 6103) during the year 1991-1994. Our study sample consisted of 5061 subjects who had body composition measurements and cystatin C available. Estimated glomerular filtration rate (eGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2012 creatinine-cystatin C equation was calculated. Bioimpedance analysis of body composition was estimated by following procedures provided by manufacturer (BIA-103 RJL Systems, Detroit, MI, single frequency (50kHz))

Results: In our study sample 11% (n=564) of subjects, mainly women (n=562), were classified as with eGFR-cystatinC/eGFR-creatinine ratio lower that 0.7. Therefore, we applied logistic regression analysis explicit in women and compared 2430 women without SPS with the rest of 562. We found that the ratio adjusted for age was associated with obesity (OR 3.49, p<0.001) and in multivariate analysis only with fat weight (OR 1.19, p<0.001). Lower lean weight showed also significant relationship with lower eGFR-cystatinC/eGFR-creatinine ratio, but not after adjustment to other cofounders.

Conclusions: The ratio of eGFR-cystatinC/eGFR-creatinine lower than 0.7 is dependent on fat weight in females from population based study.

PO0435

Discovery of Obesity and Adiposity-Related CKD Subgroups and Preliminary Metabolomics Findings: The CRIC Study

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Background: Obesity/adiposity perturbs the plasma metabolome, as does chronic kidney disease (CKD). Understanding the complex relationships across CKD patient subphenotypes, obesity, and the metabolome may shed light on finding novel risk factors and the mechanisms for CKD progression.

Methods: Among 1,529 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study for whom metabolomics data (Broad Institute) were generated, we first applied consensus clustering with K-means on 20 baseline clinical adiposity-obesity-related attributes to identify patient subgroups. We individually examined the association of 634 known metabolites with the identified subgroups using separate multivariable linear models. Finally, Cox model was used to examine the prospective association of the adiposity-obesity subgroups (the biggest subgroup as reference) with CKD progression, ESRD, a composite cardiovascular disease outcome, and death.

Results: We identified four distinct adiposity-obesity-related CKD subgroups: Subgroup 1 (N=429) - favorable obesity/diabetes profiles and elevated lipid levels; Subgroup 2 (N=349) - favorable diabetes profiles, but slightly obese; Subgroup 3 (N=357) - less favorable diabetes profile, lower lipid levels and severe obesity; and Subgroup 4 (N=394) - less favorable diabetes profiles, but less obese. Among the 634 known metabolites, after adjusting for demographics, health history, eGFR and UACR, 260 were significantly associated with CKD subgroups at Bonferroni-adjusted $p<7.9\times10^{-5}$. Survival analyses showed that compared to Subgroup 1 (ref), Subgroup 4 had the highest risk for CKD progression (HR 1.78, 95% CI 1.40, 2.26) and ESRD (HR 1.92, 95% CI 1.45, 2.52), and Subgroup 3 had the highest risk for the composite CVD outcome (HR 1.87, 95% CI 1.40, 2.50) and death (HR 1.51, 95% CI 1.09, 2.10).

Conclusions: With consensus clustering and metabolomics analysis, we discovered four distinct adiposity-obesity-related subgroups of CKD patients that were associated with numerous metabolites and different risks of clinical endpoints. Novel biomarkers that co-segregate with patient subgroups of high risk could reveal new insights into the obesity related biology of CKD progression and subsequent CVD events, and potentially suggest tailored therapeutic targets among CKD patients.

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PO0436

Defining the Excess Risk of Adverse Kidney Outcomes in CKD Patients with Type 2 Diabetes in the DISCOVER-CKD Cohort

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Background: Chronic Kidney Disease (CKD) patients with type 2 diabetes (T2D) are considered at a high risk of cardiovascular events. However, the excess risk of major kidney events in T2D patients compared to patients without T2D is unknown.

Methods: DISCOVER-CKD is an international observational study of patients with CKD that encompasses large retrospective electronic medical records (EMR) and claims data between 2008 and 2020. Preliminarily, data from US-based Limited Claims and Electronic Health Record (LCED) data (IBM Health, Armonk, NY) and TriNetx (hospital-based EMR) were analysed. CKD patients (eGFR <75 mL/min/1.73m^2) aged ≥18 years with ≥1 record of urine albumin to creatinine ratio (UACR) were identified. T2D status was ascertained any time before the index date (2nd eGFR measurement). The risk of kidney outcomes (sustained ≥50% eGFR decline or end-stage kidney disease) was compared between patients with and without T2D at 5 years' follow-up.

Results: Compared to non-T2D patients, T2D patients had a slightly higher incidence rate of adverse renal outcomes (LCED: 2.7% versus 2.3% per year; TriNetX: 1.8% versus 1.2% per year). After adjusting for all confounding factors (Figure 1) we observed no increased risk of adverse renal outcomes in patients with T2D compared to non-T2D patients in LCED (hazard ratio (HR): 1.08: 95%CI 0.81-1.43) and a 34% increased risk in TriNetX database (HR:1.34; 95%CI 1.11-1.62).

Conclusions: There is an excess risk of adverse renal outcomes in CKD patient with T2D compared to those without T2D. This is explained to a large extent by conventional risk markers in LCED but not completely in TriNetX. Both groups (T2D and non-T2D) should be managed proactively to reduce the risk of poor clinical outcomes.

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Table 1: Cox regression analysis for adverse renal outcome (sustained ≥50% reduction in eGFR, or ESKD [composite chronic dialysis, renal transplant or sustained eGFR<15mL/min/1.73^2]) in patients with T2D versus without T2D

	Hazard Ratio (95% CI)			
	Model 1 (Age, gender, race†, index year)	Model 2 (Model 1 + systolic BP, diastolic BP, BMI, LDL, CV history)	Model 3 (Model 2 + baseline eGFR)	Model 4 (Model 3 + UACR)
LCED CKD with T2D = 4,156 CKD without T2D (unexposed) = 1,189	1.48 (1.12-1.95)	1.07 (0.80-1.42)	1.11 (0.83-1.47)	1.08 (0.81-1.43)
TriNetX CKD with T2D = 13,405 CKD without T2D (unexposed) = 4,615	1.40 (1.17-1.69)	1.33 (1.10-1.61)	1.43 (1.18-1.74)	1.34 (1.11-1.62)

†Only available in TriNetX

Note: patients with CKD were identified based on two eGFR measures of <75 mL/min/1.73 m^2 recorded at least 90 days apart (max 730)

PO0437

Increased Risk of Progression to ESRD or Death in CKD Patients with Symptoms of Depression: A Systematic Review and Meta-Analysis of Cohort Studies

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Background: Comorbid symptoms of depression are common psychiatric disorder in patients with chronic kidney disease (CKD). It remains unclear whether it is an independent risk factor for progression of patients with CKD not requiring dialysis. We conducted a systematic review to assess the association of depressive symptoms with poor clinical outcomes in patients with CKD not requiring dialysis.

Methods: PubMed, Embase and CINAHL were searched (up to February 15th, 2020) for cohort studies assessing the association of depression with progression to end-stage renal disease (ESRD), defined as requiring maintenance dialysis, or all-cause mortality in patients with CKD not requiring maintenance dialysis. Two independent researchers extracted data, assessed risk of bias and evidence certainty.

Results: Seven cohort studies of 6145 patients were included. Methodological quality of studies was generally low risk of bias. Compared with non-depression or low depressive symptoms, high depressive symptoms increased the risk of progression to ESRD (HR, 2.09 95%CI 1.43 to 3.07, I^2=37%), all-cause mortality (HR, 1.51 95%CI 1.13 to 2.01, I^2=57%) and hospitalization (HR, 1.52 95%CI 1.20 to 1.93, I^2=32%).

Conclusions: Depressive symptoms in CKD are independent risk factors of poor clinical outcomes, including ESRD, all-cause death, and hospitalization. There is necessary to design high quality studies to assess the effects of treating depressive symptoms in patients with CKD.

PO0438

Association of the Creatinine-to-Cystatin C Ratio with Overall Survival with and Without CKD

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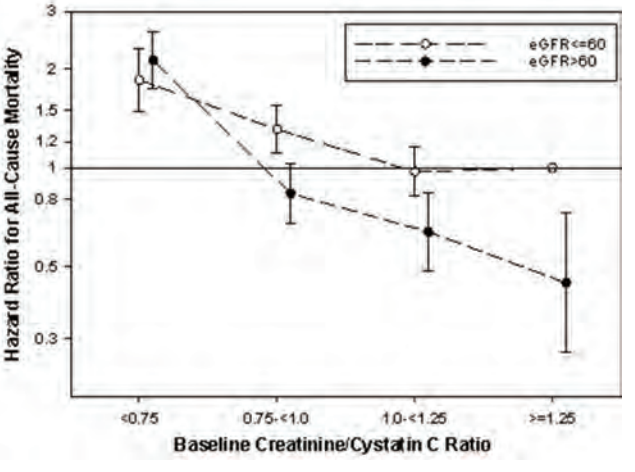
Background: Creatinine and Cystatin C are measured as glomerular filtration markers. Creatinine is highly correlated with skeletal muscle mass, whereas Cystatin C is not. We hypothesized that persons, in whom serum Cystatin C is lower than creatinine level, i.e., creatine to Cystatin C ratio (CrCCR) >1.00 (regardless of measurement units) have incrementally greater survival chance, likely due to a larger muscle mass.

Methods: We examined a cohort of 7,849 Veterans with baseline measured Cystatin C and creatinine data between 2004-2015. Veterans were divided into 0.25 increments of CrCCR, i.e., <0.75, 0.75-<1.0,1.0-<1.25,≥1.25. They were further stratified into groups based on normal vs. low eGFR (>60 vs. ≤60 mL/min/1.73 m^2, and the associations of CrCCR with survival across two eGFR strata were examined.

Results: The mean age (±SD) in the Veterans' cohort was 69±12 years. There were 4% female, 77% white, and 15% African American. The median (IQR range) for cystatin C was 1.28 (0.99,1.71) mg/L, for creatinine 1.24 (0.92,1.68) mg/dl, and for the CrCCR was 0.99 (0.81,1.17). Compared to the reference (CrCCR≥1.25 and eGFR≤60 mL/min/1.73 m^2) the multivariable adjusted model showed that those with a lower CrCCR <0.75 (suggesting lowest muscle mass) had the highest mortality risk for both eGFR strata, with the normal eGFR group having higher death risk than the low eGFR group (HR(95%CI): 1.86(1.49,2.31) and 2.13(1.75,2.59), respectively). In the highest CrCCR group (≥1.25) indicating more muscle mass, the normal eGFR group had the best overall survival than those with low eGFR (HR(95%CI):0.45(0.27,0.73)).

Conclusions: A lower CrCCR indicating higher cystatin C relative to creatinine levels are strongly associated with worse overall survival in Veterans regardless of kidney function level. Future studies should examine the clinical utility of this potential surrogate of muscle mass and overall health over creatinine or Cystatin C alone in evaluating risk stratification in patients with and without kidney disease.



PO0439

CKD by Previous Diabetes or Hypertension: A Longitudinal Outcomes Study in Primary Care

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Background: To compare mortality and progression to end-stage-renal-disease (ESRD) in patients with new chronic kidney disease (CKD) by previous occurrence of type 2 diabetes (DM) and/or arterial hypertension (HT) in Catalonia

Methods: We designed a longitudinal retrospective study of adults with new CKD between 2007 and 2017 identified using electronic medical records from primary care

in Catalonia, Spain. New CKD was considered the index event and defined as a first occurrence of an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2, a urine albumin-creatinine ratio ≥ 30 mg/g or albuminuria ≥ 20mcg for 90+ days, or a diagnostic code for CKD. Variables were extracted from the SIDIAP research database and the Spanish hospital basic minimum dataset. Patients were classified according to previous occurrence of DM, HT, both or none. The resulting mutually exclusive cohorts, DM-CKD, HT-CKD, DM/HT-CKD and unspec-CKD, were followed until ESRD and death within the study period. We defined ESRD as an eGFR<15 mL/min during 90+ days or renal replacement therapy. Fine and Grey regression models were used to assess differences in incidence of ESRD among the four CKD groups, considering mortality as a competing risk, and Cox regression for mortality. Both models were adjusted for multiple confounders

Results: In total, 467,802 persons were included (median age 75 years; 46.8% men]. At baseline, 51% had HT-CKD, 4% had DM-CKD, 33% had HT/DM-CKD and 12% had unspec-CKD. The DM-CKD group were the youngest in average, more likely to be men, had the highest proportion of persons with an eGFR below 60 mL/min/1.73m2 and the highest proportion of altered albuminuria. Compared to unspecific-CKD, DM- and HT-CKD had lower risk of ESRD -adjusted subdistribution hazard ratio (SHR) and 95% confidence interval (CI): 0.68 (0.54-0.84) and 0.71 (0.65-0.79), respectively, but HT/DM-CKD had a higher risk: SHR(CI) 1.11 (1.06-1.15). In turn, the risk for death was higher in DM-CKD, HR (CI): 1.19 (1.11-1.27) and lowest in the HT-CKD group, 0.84 (0.79-0.88), as compared to unspec-CKD. For the group HT/DM-CKD the HR(CI) was 0.92 (0.87-0.97)

Conclusions: According to these results, there are no differences in ESRD risk among CKD patients by prior DM or HT, but there is a synergistic effect. Mortality is different in CKD patients with HT vs with DM.

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PO0440

Elderly Patients Are Likely to Have Faster CKD Progression if Plasma Brain Natriuretic Peptide (BNP) Is Elevated

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Background: Elderly CKD patients have been mostly believed that they have slower decline in eGFR than younger individuals. However, this is not the case, especially when the patient has well-known factor(s) that accelerate(s) CKD progression, such as cardiac dysfunction. Plasma concentration of brain natriuretic peptide (BNP) is often elevated in patients with cardiac dysfunction and is known to be associated with higher mortality. This study was conducted to find out whether plasma BNP level can be used to predict future decline in eGFR.

Methods: A hospital-wide study with all the laboratory data for a period of 4 years and 2 months was performed. Non-dialysis CKD patients (median eGFR <60 mL/min/1.73m2) with an age 65 or more in whom the eGFR slope was obtained over 731 days or more with BNP measured at least three times were retrieved. An eGFR slope per each patient was calculated and its relationship with plasma BNP level and other factors was assessed. Statistical analysis was done with R 3.6.0 on Ubuntu.

Results: A total of 339 patients (M:F = 154:185, age 65-102 (median 84) years) were included whose initial BNP was 130.0+-184.2 (0-1,641.5, median 75.6) pg/mL. A "random forest" analysis, one of the multivariate analyses, was performed using an R package {randomForest}, in order to elucidate risk factors associated with faster decline in GFR; factors with the highest importance, i.e., with the highest change in Gini indices, were found to include initial eGFR, initial BNP and variability of BNP. With linear regression analysis, the eGFR slope was significantly associated with initial eGFR and initial BNP (P<0.0001). Patients with higher-than-average initial BNP (>130.0 pg/mL and higher-than-average initial eGFR (>49.1 mL/min/1.73m2) had significantly faster decline in eGFR than the rest of the population (-3.83+-4.62 vs -1.72+-3.57, P=0.0001). A combination of initial eGFR and initial BNP correctly differentiated the fastest quartile from the rest in 72.9% of the population.

Conclusions: Elevated plasma BNP might predict faster decline in eGFR in the elderly CKD patients.

PO0441

Proton-Pump Inhibitors (PPIs) vs. H2 Blockers (H2B) Users and Overall Risk of CKD Progression

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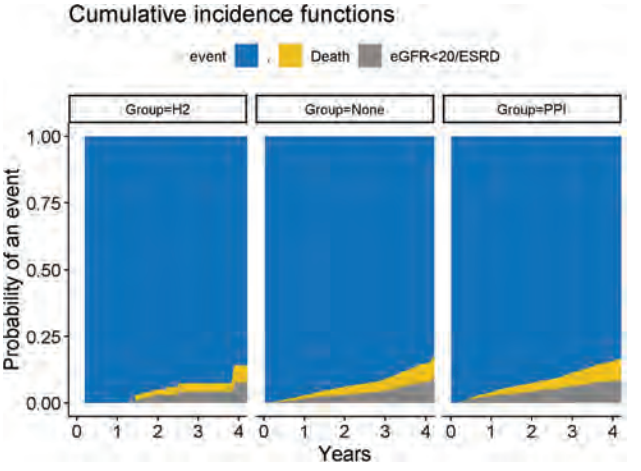
Background: PPI use is associated with adverse kidney events. The relationship between PPI use and the development of acute interstitial nephritis (AIN) is well established. However, the relationship between PPI use and CKD progression is less clear. Notably, there is a lack of data concerning renal outcomes in established CKD patients. The aim of our study is to determine the risk of CKD progression amongst CKD patients on PPI, H2B, or no anti-acid therapy.

Methods: Using our CKD registry, we evaluated the relationship between the use of PPI and H2B and outcomes among patients with CKD stage 3 and 4 with at least 2 PCP visits in the year prior. We evaluated the relationship between medication group and overall mortality using a Cox proportional hazards model while adjusting for demographics and comorbidities, and the relationship between medication group and progression to eGFR<20 or ESKD with death as a competing risk using regression models as described by Fine and Gray.

Results: Among 3,930 patients, 1,374 were in PPI group, 119 were in H2 blocker group, and 2,437 were on no medication. Average age was 72.8±11.1, and 42.5% male. Among PPI 28% had Coronary Artery Disease compared to 22% among H2B and 19% among no medication (P<0.001). Congestive Heart Failure was 13%, 8% and 7% for each group respectively (P < 0.01). Overall mortality was not different amongst the three groups (PPI vs. none HR 0.94, 95% CI: 0.80, 1.10, and PPI vs. H2B HR 0.80, 95% CI: 0.52, 1.24). The cumulative incidence of ESKD/eGFR<20 with death as a competing risk was also not different across groups in univariate (Fig. 1) or adjusted models (PPI vs. none SHR 0.99, 95% CI: 0,74, 1.34, PPI vs. H2B SHR 1.82, 95% CI: 0.91, 3.63).

Conclusions: Use of PPI in a CKD population was not associated with increased mortality or CKD progression to ESKD when compared to the use of H2 blockers and to no acid suppressing therapy.



PO0442

Renin-Angiotensin-Aldosterone System (RAAS) Blockade Does Not Affect Kidney Progression in Patients with CKD Without Diabetes and Without Proteinuria

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Background: Non-proteinuric CKD contributes to about 80% of end stage kidney disease and is poorly studied in terms of risk factors & pathogenesis. RAAS blockers such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) have been shown to be renoprotective in CKD progression in patients with diabetes and proteinuria. There is a paucity of data on effect of ACEI/ARB in non-diabetic non-proteinuric CKD patients.

Methods: This is a retrospective observational study of insurance claim database from 1/1/07 to 12/31/17 examining the effect of ACEI or ARB use on CKD progression. Inclusion criteria: adults at least 18 years of age, with CKD stage 3 or higher [based on at least 2 serum creatinine (SCr) values 90 days apart] with at least 2 urinalyses with dipstick urine protein with negative or trace, follow-up (FU) period of at least 3 yrs. Patients with diabetes or proteinuria were excluded. Primary outcomes were doubling of SCr, or reaching CKD stage 5. Mortality data was not available. Duration of ACEI/ARB exposure is defined as number of prescribed days. The eGFR was calculated based on CKD-EPI equation. Analysis are performed with 2 models: time varying Cox regression, and mixed model (which included time-period fixed effect and random effects). A greedy 1:1 propensity score matching scheme was applied.

Results: Of 20,000 CKD patients, there were 2,853 with CKD stage 3 or higher without proteinuria, with 301 on ACEI/ARB during mean FU 6 yrs. Percentage of patients with HTN or CHF, mean age, gender, and eGFR did not differ between ACEI/ARB *vs.* non-ACEI/ARB groups. The eGFR decrease per year was not statistically different between those on ACEI/ARB *vs.* non-ACEI/ARB group (matched cox model, p = 0.2285; mixed model, p = 0.4346 respectively). Age and ACEI/ARB duration of exposure have no effect. ACEI/ARB patients had lower rate of developing diabetes during the study (OR 0.57, p = 0.0044), and higher rate of proteinuria at the end of study (OR 1.59, p = 0.0048), though these associations were not observed in the matched sample.

Conclusions: This study suggests ACEI/ARB does not affect CKD progression in non-diabetic & non-proteinuric patients, irrespective of age. Further studies are needed to confirm those findings.

PO0443

Biomarkers of Immune Activation and ESKD: Results from AASK

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Background: Immune activation is fundamental to the pathogenesis of many kidney diseases, and innate immune molecules such as soluble urokinase-type plasminogen activator receptor (suPAR) have been linked to incidence and progression of CKD.

Whether other biomarkers of immune activation are associated with ESKD in African Americans with non-diabetic kidney disease is unclear.

Methods: Utilizing baseline serum samples from AASK, we measured 4 biomarkers of immune activation (soluble tumor necrosis factor receptors 1 and 2 [sTNFR1, sTNFR2], tumor necrosis factor alpha [TNF-α], interferon gamma [IFN-γ]) and examined their associations with ESKD and all-cause mortality. Covariates included age, sex, systolic BP, BMI, smoking, baseline GFR and urine PCR. We also considered interactive effects of each biomarker with *APOL1* risk status.

Results: Among 500 participants with available samples, mean GFR was 44.7 ml/min/1.73 m^2 and median urine PCR was 0.09 g/g at baseline. Over a median follow-up 9.6 yrs, there were 161 (32%) ESKD and 113 (23%) death events. In fully adjusted models, each two-fold higher baseline level of sTNFR1, sTNFR2, and TNF-α was associated with 3.66, 2.29, and 1.35-fold greater risks of ESKD, respectively (**Table**). In comparison, the association between suPAR and ESKD was 1.39 (95% CI: 1.04, 1.86). These three biomarkers were also significantly associated with death (up to 2.2-fold higher risks per 2-fold higher baseline level; p≤0.01). IFN-γ was not associated with either outcome. None of the biomarkers modified *APOL1*-associated risks for ESKD (p-interaction>0.05). The C-statistic for the fully adjusted clinical model in predicting ESKD was excellent at 0.849 (95% CI: 0.820, 0.878). Adding sTNFR1, the biomarker with the strongest association, to the clinical model led to a small but statistically significant improvement in the C-statistic at 0.860 (95% CI: 0.833, 0.887; difference of 0.011; 95% CI: 0.001, 0.021).

Conclusions: Among African Americans with CKD attributed to hypertension, baseline levels of sTNFR1, sTNFR2, and TNF-α but not IFN-γ were associated with ESKD and mortality.

Funding: NIDDK Support

Table: Associations of biomarkers of immune activation with end-stage kidney disease in AASK.

Model	n	events	sTNFR1		sTNFR2		TNF-α		IFN-γ	
			Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Unadjusted	500	161	8.10 (6.15, 10.66)	<0.001	5.09 (4.03, 6.43)	<0.001	1.88 (1.54, 2.29)	<0.001	1.11 (0.98, 1.25)	0.10
Adjusted for age and sex	500	161	7.44 (5.59, 9.89)	<0.001	4.63 (3.63, 5.91)	<0.001	1.69 (1.39, 2.07)	<0.001	1.08 (0.96, 1.22)	0.19
Further adjusted for systolic BP, BMI, and current smoking	500	161	8.30 (6.06, 11.35)	<0.001	4.96 (3.62, 6.80)	<0.001	1.69 (1.39, 2.07)	<0.001	1.08 (0.96, 1.22)	0.19
Further adjusted for GFR	500	161	4.80 (3.18, 7.62)	<0.001	2.76 (1.97, 3.86)	<0.001	1.31 (1.05, 1.64)	0.02	1.09 (0.96, 1.23)	0.18
Further adjusted for log$_2$urine PCR)	500	161	3.66 (2.31, 5.80)	<0.001	2.29 (1.60, 3.29)	<0.001	1.35 (1.07, 1.71)	0.01	1.03 (0.91, 1.16)	0.69
Further adjusted for APOL1 risk status and European ancestry	333	112	3.83 (2.21, 6.61)	<0.001	2.53 (1.63, 3.95)	<0.001	1.28 (0.97, 1.70)	0.09	1.02 (0.88, 1.18)	0.81

Hazard ratios are per 2-fold higher baseline level of each biomarker.
Abbreviations: BP=blood pressure; GFR=glomerular filtration rate; PCR=protein-to-creatinine ratio; sTNFR1=soluble tumor necrosis factor receptor 1; sTNFR2=soluble tumor necrosis factor receptor 2; TNF-α=tumor necrosis factor alpha; IFN-γ=interferon gamma.

PO0444

Novel Fibrosis Biomarker Development and Validation in Human Kidney Disease

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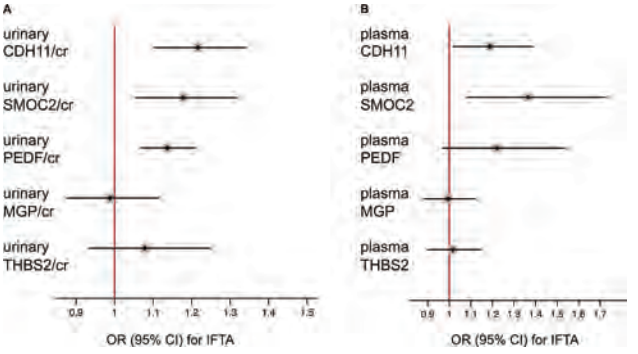
Background: Biomarkers for non-invasive assessment of kidney fibrosis are not available. This study illustrates the characterization of five novel candidate biomarkers of kidney fibrosis—Cadherin-11 (CDH11), Sparc-related modular calcium binding-2 (SMOC2), Pigment epithelium-derived factor (PEDF), Matrix-gla protein (MGP), and Thrombospondin-2 (THBS-2)—which were selected from transcriptomic findings in animal models of fibrosis.

Methods: We developed Luminex-based assays and measured proteins in plasma and urine samples of two independent prospective cohort studies, the Boston Kidney Biopsy Cohort (BKBC, n=801), a cohort of individuals with biopsy-confirmed semi-quantitative assessment of kidney fibrosis, and the Seattle Kidney Study (SKS, n=252). Ordinal logistic regression and Cox proportional hazard models tested associations of biomarkers with interstitial fibrosis and tubular atrophy (IFTA) in the BKBC and progression to end-stage kidney disease (ESKD) in both cohorts, respectively. snRNA datasets of human kidneys assessed cell-specific gene expression profiles.

Results: In the BKBC, higher levels of urinary PEDF and plasma and urinary SMOC2 and CDH11 were independently associated with more severe IFTA (Figure 1). In both cohort studies, higher levels of plasma and urinary SMOC2 and urinary CDH11 associated with progression to ESKD (HR-range 1.27 to 1.89) after adjustment for age, sex, race, proteinuria, and eGFR. Higher levels of urinary PEDF were associated with ESKD in the SKS (HR=1.29, 95% CI 1.14 to 1.45), with consistent signals in the BKBC, although the latter narrowly missed statistical significance. snRNA-sequencing data demonstrated expression of all biomarkers in human fibroblasts.

Conclusions: Novel plasma and urine biomarkers of kidney fibrosis, developed from animal models, are associated with higher levels of human kidney fibrosis and subsequent progression to ESKD.

Funding: Private Foundation Support



PO0445

Urinary Fibrosis Markers and Risk for ESKD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Connective tissue growth factor (CCN2) and amino-terminal peptide of procollagen type III (PIIINP) are both correlated with kidney fibrosis. However, it is unclear if these markers are independently associated with the risk for ESKD.

Methods: We measured CCN2 and PIIINP in baseline urine and standardized to urine creatinine (Cr) in a multi-center cohort study of men and women with chronic kidney disease (CKD), the CRIC Study (N=3727). ESKD was defined as initiation of kidney replacement therapy (N=1118 events). Cox proportional hazards models were adjusted hierarchically as indicated (Table).

Results: The mean age of the study population was 58 years; mean eGFR: 45 mL/min/1.73m2; and 48% had diabetes. After multivariable adjustment and median follow-up of 10 years, the highest quartiles of CCN2/Cr and PIIINP/Cr were associated with a 1.8-fold and 1.7-fold higher risk for ESKD compared to the lowest quartiles, respectively (Table). The association was no longer statistically significant after adjustment for proteinuria.

Conclusions: Urinary CCN2 and PIIINP are strongly associated with risk for ESKD, an association that may be mediated through proteinuria. Future studies should investigate if these markers add to the identification of those at highest risk for progression to ESKD.

Funding: NIDDK Support

	Model 1	Model 2	Model 3	Model 4
CCN2/Cr, ng/g	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Q1: <1403	reference	reference	reference	reference
Q2: 1404-3291	1.5 (1.2-1.8)	1.4 (1.1-1.8)	1.4 (1.1-1.8)	1.0 (0.8-1.3)
Q3: 3292-8125	2.8 (2.2-3.4)	2.5 (2.0-3.1)	1.6 (1.2-2.0)	1.0 (0.8-1.3)
Q4: >8126	7.0 (5.7-8.6)	5.4 (4.4-6.7)	1.8 (1.4-2.3)	0.9 (0.7-1.2)
PIIINP/Cr, ng/g				
Q1: <733	reference	reference	reference	reference
Q2: 733-1886	1.3 (1.0-1.6)	1.2 (0.9-1.5)	1.3 (1.0-1.6)	0.9 (0.7-1.1)
Q3: 1889-3974	2.2 (1.8-2.7)	1.8 (1.5-2.2)	1.3 (1.1-1.7)	0.8 (0.6-1.0)
Q4: >3975	5.5 (4.5-6.6)	3.7 (3.0-4.5)	1.7 (1.3-2.1)	0.7 (0.5-0.9)

Abbreviations: CI: confidence interval; HR: hazard ratio.

Model 1: unadjusted; Model 2: stratified by clinical site and adjusted for age, gender, race/ethnicity, education, BMI, SBP, Hgb, smoking, diabetes, and history of CVD; Model 3: Model 2 + urine Na, urine K, serum phosphate, FGF-23, serum bicarbonate, hsCRP, IL-1β, IL-6, TGF-β, TNF-α, hs-Troponin T, NTproBNP, urine NGAL, eGFR; Model 4: Model 3 + proteinuria.

PO0446

Urinary Retinol-Binding Protein Is Associated with the Risk of Kidney Replacement Therapy in CKD

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Background: Urinary Retinol-Binding Protein (uRBP), a biomarker of proximal tubular injury, is used in clinical practice as a risk factor for CKD in tubular diseases, such as Dent's disease and cystinosis, and in renal transplantation. However, its role as a biomarker of CKD progression outside these conditions is less clear. The aim of our study was to evaluate the association of uRBP with the risk of mortality and kidney replacement therapy (KRT) in CKD of multiple etiologies.

Methods: The Progredir Cohort is composed of 454 older adults with CKD (predominantly G3 and G4) recruited from the outpatient services of a tertiary hospital in Sao Paulo, Brazil. Baseline uRBP was measured using an immunoenzymatic assay with monoclonal antibody and expressed as mg/g urinary creatinine, and those with missing values were excluded (n=22). Events of death (n=184) and KRT (n=60) were ascertained

(median follow-up of 6 years, with 5 participants lost to follow-up). Uni and multivariable Cox and Competitive Risk models (R package "cmprsk") were computed.

Results: Mean age was 67(12)y, mean eGFR was 38(15) mL/min/1.73m^2, 64% were male and 58% were diabetic. Median (P25, P75) for uRBP were: 0.29 (0.08, 1.47) in all; 0.24 (0.06, 0.84) vs. 0.46 (0.10, 2.87) in those who remained alive vs. those who died (p=0.001); and 0.26 (0.08, 0.90) vs. 2.98 (0.21, 17.5) in those without and with KRT, respectively (p<0.0001). In Cox models, RBP was not related to mortality. However, competitive models showed that uRBP was related to the risk of KRT, even after adjustments (Table). This association was also present when only normoalbuminuric participants (CKD A1) were included.

Conclusions: URBP is significantly associated with the risk of KRT in the setting of CKD, and may be particularly useful as a biomarker in CKD patients with normoalbuminuria (CKD A1).

Funding: Government Support - Non-U.S.

Competing risk models for the risk of KRT.

	SHR (95%CI)	p-value
uRBP (mg/g creatinine) - unadjusted	1.03 (1.01 to 1.04)	<0.0001
uRBP (mg/g creatinine) - adj. 1	1.01 (1.00 to 1.02)	0.015
uRBP (mg/g creatinine) - adj. 2	1.01 (1.00 to 1.02)	0.03

Adj.1= age, sex, eGFR; adj.2 = same as 1 + SBP, DM, MI, ACR, smoking. Models for KRT were computed considering the competing risk of death. SHR, subdistribution hazard ratio.

PO0447

Tubular Secretion of Creatinine and Risk of Kidney Failure: The Modification of Diet in Renal Disease Trial

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Background: Whether tubular secretion is associated with clinical outcomes beyond glomerular filtrate rate (GFR) or proteinuria is unknown. By using measured GFR and creatinine clearance, we evaluate the association of tubular secretion of creatinine with long-term kidney and mortality outcomes.

Methods: The Modification of Diet in Renal Disease (MDRD) Study was a randomized controlled trial conducted to examine the effects of strict blood pressure control and dietary protein restriction on progression of stages 3 to 4 CKD. This prospective analysis included 838 participants with baseline measures of iothalamate glomerular filtration rate (mGFR) and 24-hour urine creatinine clearance (CrCl). Tubular secretion of creatinine (TS_{cr}) was calculated as the difference between CrCl and mGFR. The primary outcome was incident end-stage kidney disease (ESKD) and secondary outcomes were cardiovascular disease (CVD) related and all-cause mortality.

Results: At baseline, mean mGFR was 33 ml/min/1.73 m^2 and the mean CrCl was 42 ml/min/1.73 m^2. Over 21 years of follow up there were 626 ESKD, 202 CVD-related mortality, and 444 all-cause mortality events. Each 10 ml higher TS_{cr} was associated with a lower risk of ESKD (HR 0.74, 95% CI 0.66-0.84)) after adjustments for mGFR, proteinuria, and other potential confounding factors [Image]. Higher TS_{cr} was associated with lower risk of CVD related mortality (HR 0.78, 95% CI 0.65, 0.95) and all-cause mortality (HR 0.86, 95% CI 0.75, 0.97) in unadjusted models but these associations were no longer statistically significant after adjusting for confounders (HR 0.82, 95% CI 0.66, 1.02 and HR 0.92, 95% CI 0.79, 1.06 respectively).

Conclusions: Higher TS_{cr} is associated with lower risk of ESKD, independent of mGFR, proteinuria, and other kidney disease factors. Tubular secretion provides prognostic information above and beyond GFR and proteinuria.

Funding: NIDDK Support

TS_{cr} ml/min/1.73m^2	Events/N	Unadjusted Incidence rate Per 100-py	Unadjusted OR (95% CI)	Demographic Adjusted* OR (95% CI)	Multivariable Adjusted** OR (95% CI)
Per 10 higher	626/838	9.2	**0.68 (0.61, 0.76) p<0.001**	**0.78 (0.70, 0.88) p<0.001**	**0.74 (0.66, 0.84) P<0.001**
≤4.9	168/209	12.9	**2.22 (1.77, 2.79) p<0.001**	**1.55 (1.22, 1.97) P=0.0003**	**1.69 (1.31, 2.17) p<0.001**
>4.9 to 9.0	170/210	12.1	**2.03 (1.62, 2.55) p<0.001**	**1.45 (1.15, 1.83) P=0.002**	**1.55 (1.21, 1.98) p=0.005**
>9.0 to 13.5	150/210	7.9	**1.30 (1.03, 1.64) p=0.025**	1.08 (0.86, 1.37) p=0.504	1.22 (0.96, 1.55) p=0.106
>13.5	138/209	6.2	1.00 (ref)	1.00 (ref)	1.00 (ref)

*adjusted for age, sex and race
**adjusted for age, sex, race, mGFR, MDRD study A/B, blood pressure target, randomization arm, cause of kidney disease, smoking status, history of CVD, proteinuria, transferrin and urine urea nitrogen
Values in bold indicate p value <0.05

PO0448

Clinical Significance and Related Factors of GFR Slope in a Large Multicenter Observational Study in Japan

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Background: Recently, GFR slope has attracted attention as an important surrogate marker for the prognosis of CKD, with a reduction in slope of GFR decline by 0.75 mL/min/1.73 m^2 per year reportedly having clinical significance. This investigation addresses the clinical significance of GFR slope and its related factors on Japanese CKD patients.

Methods: CKD patients in 15 general hospitals between January and March 2014 were surveyed using medical records. The selection criteria were age ≥20 years, eGFR <60 mL/min/1.73 m^2, and receiving medical treatment for CKD. Baseline patient characteristics, eGFR changes, and hard endpoints (death or ESKD requiring RRT) were analysed. We calculated GFR slope using GFR data of 2 years by 2 calculation methods, the linear mixed model and least squares linear regression, and examined the relationship of GFR slope with the hazard ratio (HR) of the endpoints. The factors related to GFR slope were also assessed by multiple regression analysis.

Results: Among a total of 11233 patients, we analyzed the data of 7490 CKD G3 and G4 patients (60% male, mean age: 71 years, CKD G3a: 55%, G3b: 30%, G4: 15%, mean eGFR: 44 mL/min/1.73 m^2, urine protein positive: 51%, diabetes mellitus: 49%, use of RAS-I: 57%). The mean observation period was 1040 days. Hard endpoints after the GFR slope measurement period occurred in 301 subjects. The GFR slope of the cohort was -0.948 mL/min/1.73 m^2 per year (95% confidence interval [CI] -1.016, -0.880) in the linear mixed model and -0.982 mL/min/1.73 m^2 per year (95% CI -1.075, -0.889) according to least squares linear regression. Both calculated GFR slopes were significantly related to the HR of the composite hard endpoints. HR decreased by 0.85 (linear mixed model) and 0.9 (least squares linear regression) times in case of a reduction in slope of GFR decline by 0.75 mL/min/1.73 m^2 per year. Multiple regression analysis revealed strongly significant associations for GFR slope with urine protein and CKD stage and undetectable relationships for GFR slope with diabetes and age.

Conclusions: This study demonstrated the clinical significance of GFR slope as a surrogate marker for renal prognosis in Japanese CKD patients. In order to reduce slope of eGFR decline, active intervention for proteinuria before the progression to an advanced CKD stage appears to be effective.

PO0449

The Kidney Failure Risk Equation: Testing Previous eGFR Slopes, Clinical Variables, and Novel Populations

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Background: The 4-variable kidney failure risk equation (KFRE) is a well-validated tool that accurately predicts the 2- and 5-year risk of kidney failure in patients with eGFR <60 ml/min/1.73 m^2 using baseline eGFR, ACR, age, and sex. The aim of this study was two-fold: to assess whether KFRE can be improved using previous eGFR slope or other variables; and to evaluate whether the KFRE can be used in patients with eGFR ≥60 ml/min/1.73 m^2.

Methods: We used 36 cohorts in development and 17 cohorts in validation to accomplish these aims; all cohorts participate in the CKD-Prognosis Consortium and had data on the four variables, previous 2-year eGFR slope, and at least 25 ESKD events.

Results: There were 205,004 participants with eGFR <60 ml/min/1.73 m^2 (12,794 ESKD events) and 441,915 participants with eGFR ≥60 ml/min/1.73 m^2 (1,220 ESKD events). In the eGFR <60 group, previous 2-year eGFR loss >3 ml/min/1.73 m^2/year was associated with ESKD (meta-analyzed HR 1.36, 95% CI: 1.19-1.56) with a small improvement over the 4-variable model (baseline c-statistic in validation cohorts, 0.87-0.95; meta-analyzed difference in c-statistic in validation cohorts when adding slope, 0.001, 95% CI: 0.000-0.002). Using previous 5-year slope resulted in slightly better c-statistic compared to the model using 2-year slope (meta-analyzed difference in c-statistic in validation cohorts, 0.003, 95% CI: 0.001-0.005). Other approaches, such as using 1-year average eGFR or 1-year average ACR as inputs in the 4-variable KFRE, or incorporating black race, heart failure, or atrial fibrillation, did not result in meaningful improvements. The KFRE had poor discrimination and calibration in the eGFR ≥60 ml/min/1.73 m^2 population. In a model that instead predicted 40% decline in eGFR and included age, sex, ACR, diabetes, hypertension, heart failure, and coronary heart disease, previous eGFR loss > 3 ml/min/1.73 m^2/year over 2- and 5-years were associated with greater risk (HR, 1.43, 95%CI: 1.19-1.70; 1.84, 95%CI: 1.40-2.42).

Conclusions: In summary, the KFRE was improved only slightly by the inclusion of previous eGFR slope. For populations with eGFR >60, a more relevant and predictable outcome may be percent eGFR decline.

Funding: NIDDK Support, Private Foundation Support

PO0450

Comparison of Predicted Risk of Renal Replacement Therapy vs. eGFR for Arteriovenous Fistula Placement in CKD: A Retrospective Analysis

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Background: The complexity in predicting which and when patients with chronic kidney disease (CKD) will progress to renal replacement therapy (RRT) contributes to 80% of patients starting hemodialysis without a functioning permanent access. Studies suggest AVF referral at eGFR of 15-20 ml/min increases the likelihood of starting dialysis with an AVF. We were interested in whether a prediction model developed at Kaiser Permanente Northwest better predicted progression to RRT at 1 year compared to eGFR.

Methods: We retrospectively followed 613 patients with stage 4 CKD between ages of 18 to 89 from May 2013 to May 2018 followed by nephrology who had a nephrology visit with an eGFR and a calculatable 2-yr risk for RRT around 12 months before end of follow up (defined as death, initiation of RRT, or 2 years from initial enrollment date). We calculated sensitivity, specificity, and area under the curve (AUC) based on a range of 2-yr risk for RRT (20%, 40%, 60%, and 80%) and compared them to eGFR threshold of 15 ml/min and 20 ml/min at the 12 month visit prior to end of follow up. We compared 2-yr risk for RRT vs. eGFR using a decision curve analysis.

Results: At end of follow up, 12% had died and 14% had progressed to RRT (69% hemodialysis, 22% peritoneal dialysis, 9% transplant). Compared to eGFR threshold of 20 ml/min, specificity and specificity was greater at 2-yr RRT risk of 40% (73% and 49% for eGFR threshold of 20 ml/min respectively compared to 85% and 54% respectively for 2-yr RRT risk threshold of 40%). Compared to eGFR threshold of 15 ml/min, specificity and specificity was greater at 2-yr RRT risk of 80% (97% and 11% for eGFR threshold of 15 ml/min respectively compared to 98% and 18% respectively for 2-yr RRT risk threshold of 80%). The AUC was greater between 2-yr RRT of 20% to 40% (0.73 to 0.70) compared to eGFR between 15 ml/min to 20 ml/min (0.54-0.61). Decision curve analysis showed better net benefit using 2-yr risk >40% compared to eGFR of 20 ml/min above a 1 year threshold of 25%.

Conclusions: In patients with CKD stage 4, 2-yr risk for RRT better predicted progression to RRT at 1 year compared to eGFR alone. Our study suggests that use of prediction model for RRT may be an important tool for determining optimal timing for AVF referral.

PO0451

Risk Factors of Renal Replacement Therapy in Hospitalized Patients with CKD Stage 4

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Background: Data on risk factors of renal replacement therapy (RRT) in hospitalized patients with CKD4 may help nephrologists to delay dialysis. The study was designed to describe the risk factors of RRT in CKD4 inpatients.

Methods: Medical records of CKD4 inpatients in Guangdong Provincial Hospital of Chinese Medicine during January, 2010 - January, 2020 were collected. Related indicators such as demography characteristics, laboratory and echocardiography test results, treatments, comorbidities and primary diseases were collected. Patients were followed up till they reached clinical outcomes (RRT) or the end of the study (January, 2020). Patients who were followed up for less than one year were excluded. Descriptive statistics and survival analysis were performed with Cox regression, with 95% CI, considered a value of $p < 0.05$ as statistically significative.

Results: 222 CKD4 inpatients [age, 60.00(47.75-72.25) years); female, 55.9%] were enrolled. In a median follow-up of 2.41 years, 199 inpatients (10.6%) started RRT. Among those patients, the median time progression to RRT was 2.10 (1.20-3.58) years. All patients were divided into two groups according to whether progressed to RRT within 2.41 years. For those received RRT within 2.41 years, they had heavier urine protein, urine occult blood and account for a higher proportion of inpatients with diabetes mellitus(63.6%), chronic heart failure (43.6%), diabetic kidney disease (55.5%). Their serum albumin and ejection fraction(EF) were lower(P<0.001). The multivariate Cox proportional hazards models showed that age[hazard ration (HR): 0.986; 95% confidence interval(CI): (0.976-0.995); P=0.004], diabetic kidney disease(DKD) [HR:1.727,95%CI: (1.274-2.391), P=0.001], urinary protein [HR:1.148, 95% CI: (1.094-1.205), P<0.001], serum albumin [HR:0.971,95%CI: (0.949-0.994), P=0.013], LVMI [HR:1.010,95%CI: (1.004-1.016), P=0.002], left ventricular dimension systolic(LVDs) [HR:0.948, 95%CI: (0.910-0.986), P=0.008] and EF [HR:0.970, 95%CI: (0.950-0.990), P=0.004] were independently associated with factors for progression to RRT in CKD4 inpatients.

Conclusions: DKD, urinary protein, LVMI were risk factors that were significantly associated with CKD4 progression to RRT in inpatients. Whereas, serum albumin, LVDs, and EF are protective. The urinary protein, serum albumin and echocardiographic parameters need to be taken seriously for patiens with CKD4.

PO0452

Development and Validation of a Predictive Model to Identify Patients with Undiagnosed CKD

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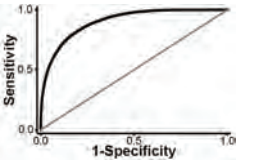
Background: Chronic kidney disease (CKD) is a common condition and often goes undiagnosed. Unmanaged CKD can progress rapidly, resulting in poor clinical outcomes and increased health care costs. Identification of individuals who may have undiagnosed CKD would allow for implementation of CKD management practices in order to slow progression, potentially improving outcomes and reducing health care costs. Here, we report the development and validation of a claims-based algorithm to identify CKD.

Methods: This model was developed using Medicare Part A and Part B claims from calendar year 2017. Data from 378,460 unique patients with no evidence of end-stage kidney disease or claims for dialysis through April 2017 were split into derivation (n = 189,203) and validation (n = 189,257) sets. The predicted outcome was the presence of a diagnosis code for CKD stages 3 to 5, which occurred in 4.4% of patients within the data. To simulate the use case, codes for kidney disease were not eligible as predictors in the model. Area under the curve (AUC) of the receiver operating curve and positive predictive value (PPV) were used to assess the performance of candidate models.

Results: The best model was a logistic regression algorithm based on 94 input terms derived from 13 clinical constructs. The model demonstrated an excellent ability to discriminate (AUC = 0.90), which was stable when tested in the validation set (AUC = 0.90). The PPV in the top 1% and top 2% of patients identified by the model was approximately 72% and 59%, respectively.

Conclusions: We developed an algorithm that uses medical claims to identify patients who are most likely to have unrecognized CKD. If the algorithm were applied to a population of 10,000 patients, it could identify the 100 patients at highest risk, among whom 72 would have CKD if tested.

	Derivation Set	Validation Set
Patients	189,203	189,257
CKD 3-4 Prevalence	4.3	4.4
AUC	0.90	0.90
PPV (1% Threshold)	71.80%	72.20%
PPV (2% Threshold)	58.9%	59.1%



PO0453

Predicting Progression to ESKD: Application of Novel Statistical Methodologies

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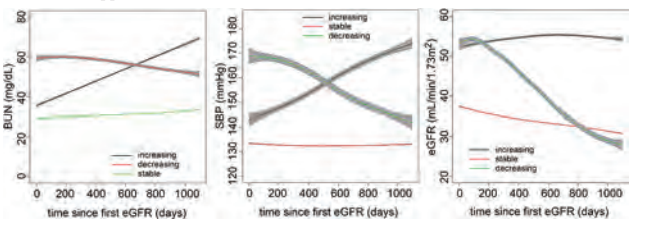
Background: Estimating time to end-stage renal disease (ESRD) in chronic kidney disease patients (CKD) is important in preparing patients for a smooth transition to dialysis. In this analysis we explored patterns in trajectories of blood urea nitrogen (BUN), systolic blood pressure (SBP), and estimated glomerular filtration rate (eGFR) in patients with CKD and associated them to time to ESRD.

Methods: We used data from a registry of CKD patients from practices using Acumen electronic medical records, obtaining 8,572 patients with CKD 3 from 2003 to 2018 based on their first eGFR value. BUN, SBP, and eGFR were observed for 3 years after first eGFR measurement. Time to ESRD is calculated from the start of the follow-up period to when eGFR < 15 mL/min/1.73m2. Functional data for each patient was generated by fitting cubic splines to BUN, SBP, and eGFR, respectively. Trajectories of each variable were grouped into 3 clusters using principle component analysis (PCA) scores; time to ESRD was compared between them by Kaplan-Meier analysis. We fit Cox proportional hazards model with eGFR, SBP, BUN clusters and age, sex, and race as predictors of ESRD onset.

Results: BUN, SBP, and eGFR have stable, increasing, and decreasing trajectory clusters (Figure). In a Cox model with these clusters as well as age, gender, and race, trajectories of eGFR, BUN, and SBP were significant predictors of ESRD onset.

Conclusions: Since BUN, SBP, and eGFR trajectories were all significant predictors of progression to ESRD, it is important to consider all three to ascertain CKD progression.

Funding: NIDDK Support, Other NIH Support - This work was partially supported by a grant from the Chronic Kidney Disease Biomarkers Consortium (RFA-DK-14-011)., Commercial Support - Fresenius Medical Care



PO0454

Indexing Proteinuria to Renal Function Improves Prediction for Renal Events in Individuals with CKD

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Background: Identifying the optimal measurement of proteinuria in clinical settings has been challenging. To determine the potential consequence of varied measures of proteinuria, we contrasted their clinical significance primarily in relation to renal events and secondarily to cardiovascular (CVD) and mortality events.

Methods: We compared the predictive ability of four measures of proteinuria and albuminuria, among 3592 CKD participants from the Chronic Renal Insufficiency Cohort (CRIC) Study, for incident renal events (halving of glomerular filtration rate [GFR] or end-stage renal disease), CVD events (myocardial infarction, congestive heart failure, stroke and peripheral arterial disease) and mortality over 3 years. The four measures included timed urinary albumin and protein excretion rates (AER, PER), albumin/protein: creatinine ratios (ACR, PCR), albumin/protein: adjusted creatinine (accounting for creatinine production) ratios (eAER, ePER), and lastly albuminuria/proteinuria indexed to GFR (ACR-G, PCR-G), as an estimation of glomerular permeability. We used Harrell's C-Statistics to measure model discrimination.

Results: Predictive performance for renal events was lowest for AER and PER. Results were generally similar for ACR vs eAER and PCR vs ePER. Notably, PCR-G showed significant improvement in predicting renal outcomes and performed better than albuminuria-based measures. C-statistics for renal events were 0.831, 0.840, 0.841, 0.846 and 0.862 for AER, eAER, ACR, PCR and PCR-G, respectively. Trends were similar for CVD and mortality events, except that ACR performed better than PCR for CVD events, but not as well as PCR-G or ACR-G. Results were overall consistent across diabetes, gender and race strata, and were validated in an additional 1443 participants from the third phase of CRIC.

Conclusions: Indexing proteinuria to GFR is a simple and economical measure, compared to albuminuria, that significantly enhances the prediction of CKD progression and associated outcomes.

Funding: NIDDK Support

PO0455

The Phosphate-to-Urinary Urea Nitrogen Ratio (P/UUN): A Tool to Evaluate Phosphate Intake and Excretion in CKD Patients

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Background: Phosphate (P) restriction is crucial in CKD patients. Classically, P intake has failed to correlate with 24-h phosphaturia. Organic or inorganic P have different intestinal absorption rates, which might explain the lack of correlation between P intake and phosphaturia. Thus, we aimed to evaluate if the source of dietary P rather than the total P ingested determines phosphaturia, and to what extent inorganic P intake modifies phosphaturia

Methods: A 3-day dietary survey was performed in 71 stages G2-3 CKD patients to estimate the amount and source of P intake. 24-h urine samples were collected. Total phosphaturia, the FeP(%), and P/UUN, which reflect intestinal absorption of P relative to proteins absorbed and metabolized), were evaluated. P/UUN ratio tertiles were contrasted with the other variables analyzed (T1<58.9mg/g, T2=58.9-71.1mg/g, T3>71.1mg/g). Statistics were performed using Rv3.6.2

Results: The P intake was 1086.5±361.3 mg/day. P intake was 64.0%,22.1%, and 14.1% from animal, vegetables, and inorganic sources respectively. Total P intake did not correlate with urinary P (p=0.12), nor FeP. Patients ingesting more P ingested more inorganic P (Fig1). P intake correlated with P/UUN ratio(p=0.008). Patients in the upper P/UUN tertile showed the highest daily P intake (p=0.04) from inorganic sources (p=0.03), and the highest phosphaturia (p=0.04)

Conclusions: P/UUN reflects the total P intake and provides information about the amount of inorganic P, and could be used to guide the appropriate nutritional advice for CKD patients.

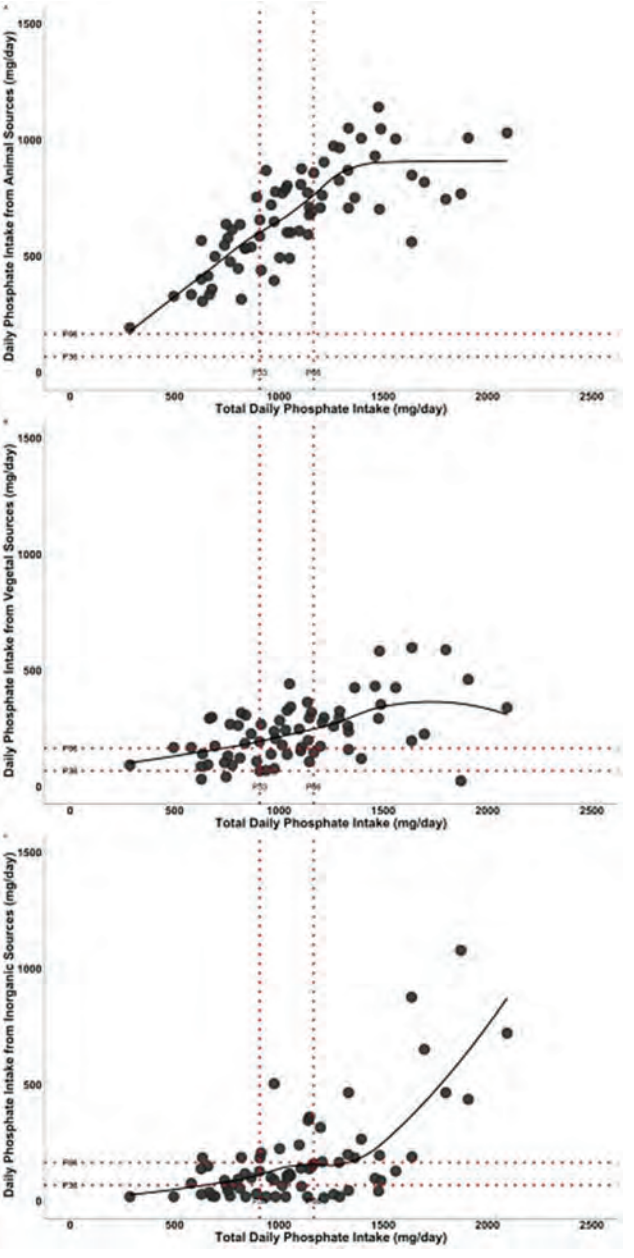

Fig1 Correlation between P intake and the different sources. A. Animal, B. Vegetal, C. Inorganic

PO0456

Hypophosphatemia as a Surrogate Marker of Renal Outcome in Chronic Hepatitis B Patients Receiving Antiviral Therapy

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Background: Antiviral therapy is crucial for the treatment of chronic hepatitis B (CHB). Although hypophosphatemia has been known to be an important adverse effect of antiviral agents, the clinical significance is yet to be revealed. In this study using a large cohort of CHB patients, the incidence and clinical significant of hypophosphatemia was investigated.

Methods: CHB patients who started antiviral therapy between 2005 and 2015, and had received at least one year of therapy, were included after excluding liver cirrhosis, diabetes mellitus, hypertension, concomitant administration of diuretics, and ESRD. Hypophosphatemia was defined as serum phosphorous level ≤ 2.5mg/dL. The primary outcome was changes in renal function. Secondary outcomes included the incidence of infection and changes in serum potassium, uric acid, and total carbon dioxide (tCO2)

Results: Of the 4,335 patients, hypophosphatemia developed in 75 patients (1.7%). When patients were categorized depending on the change of serum phosphate level, median phosphate level of 728 patients (16%) decreased by more than 0.5mg/dL from the baseline. During the 2-year follow-up period, patients with hypophosphatemia showed lower eGFR compared to the control group. Also, patients whose serum phosphate level decreased by more than 0.5mg/dL showed significantly lower eGFR compared to the control group at all time points. The incidence of infection and changes in serum potassium, uric acid, and tCO2 were similar between groups.

Conclusions: Hypophosphatemia was associated with renal function decline in CHB patients receiving antiviral therapy. Although the incidence of hypophosphatemia during antiviral therapy was relatively low, our results support the clinical significance of hypophosphatemia as a surrogate marker of adverse renal outcome in CHB patients.

PO0457

Dietary Phosphorus Restriction Improves Renal Function, Blood Pressure, FGF-23, and Klotho Levels in CKD Stages 1 and 2

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Background: To evaluate Impact of dietary education and intervention (phosphorus restriction) on creatinine, eGFR, FGF23, Klotho and blood pressure.

Methods: 105 subjects (CKD stages 1, 2 N 70; 35controls) evaluated for eGFR, creatinine, phosphorus, calcium, FGF-23, soluble α-Klotho iPTH FGF 23, blood pressure and 3 days dietary intake, using standard methodology on first visit, 6 and 12 months. CKD patients were grouped based on dietary phosphorus intake:Group 1 (n 42): phosphorous intake <1000mg/day and Group 2 (n=37; 17 in CKD 1; 20 CKD 2): high phosphorous intake (>1000mg/d). Patients in Group 2 were counselled for low phosphorus diet.

Results: Parameters of controls and CKD patients differed significantly. Dietary, serum and urinary phosphorus (0.001) had significant association. Systolic and diastolic BP, protein intake, dietary phosphorus, iPTH, FGF23 were significantly high (p 0.001) and Klotho significantly low(p 0.001) in Group 2 compared to Group 1. Impact of dietary intervention was seen at 6 and 12 months as reduction in protein intake from 0.64±0.95 to 0.58±0.11 (CKD 1) and 0.71±0.074 to 0.64±0.095 (p 0.012 CKD 2); decline in creatinine from 1.13±0.14 to 1.07±0.14 (CKD 1) and 1.06±8.56 (p 0.009 CKD 1); serum phosphorus from 3.57±0.19 to 3.23±0.58 (CKD 1) and 4.32±0.42 to 3.35±0.85 mg/dL (p 0.001 CKD 2), FGF-23 from 55.01±1.65, to 51.27±11.17 (CKD 1); 65.42±4.80 to 56.60±11.23 (p 0.010 CKD 2); **systolic BP** from **127.95±3.14 to 121.05±14.40**(CKD 1); **134.22±3.54 to 118.38±9.08** (p 0.001 CKD 2) and **diastolic BP** from **85.14±3.40 to 83.29±8.03**(CKD 1); **89.11±4.74 to 80.33±8.02** (p 0.003 CKD 2) and a significant increase in **eGFR** ml/min from **95.17±5.50 to 97.75±20.26** (CKD 1); **69.82±8.56 to 74.08±11.07** (p 0.019 CKD 2)was observed. sKlotho increased from 700.79±27.82 to 897.39±168.37 (p0.001 CKD 1); from 633.52±60.56 to 823.37±156.67 (p 0.001 CKD 2). Ca x P product declined from 36.10±4.84 to 29.48±7.63 (p0.001). **eGFR can predicted using dietary protein, creatinine systolic BP, haemoglobin, cholesterol (r^2 0.868).**

Conclusions: Dietary counselling had significant effect on all the parameters in early CKD stages. Dietary intervention can preventrise in FGF23, reduce blood pressure and prevent decline in renal function as demonstrated by significant increase in eGFR with phosphorus restriction in early stages of CKD.

PO0458

Baseline Serum Magnesium and Risk of CKD Progression in the Chronic Renal Insufficiency Cohort (CRIC) Study

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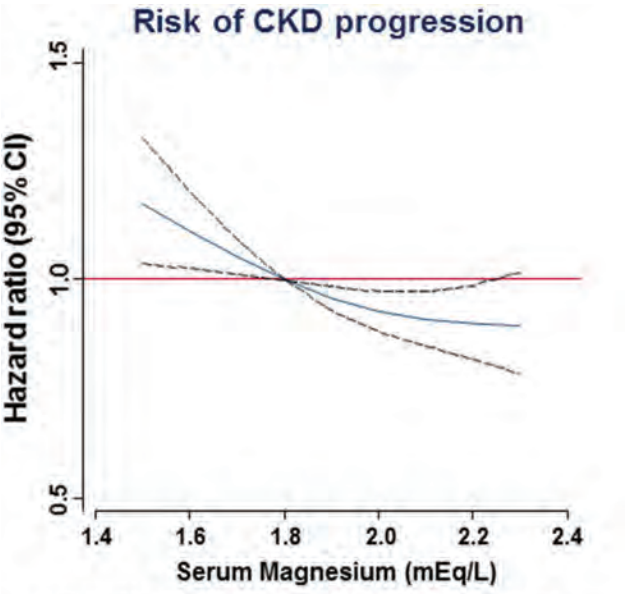
Background: Serum magnesium (sMg) concentration is regulated by intestinal absorption and renal handling which are impaired in CKD. While Mg has been implicated in blood pressure regulation and sMg has been associated with the risk of hypertension, the association of sMg with long-term risk of CKD progression remains unclear.

Methods: Adjusted cox-proportional hazard regression models were fit to determine the association of baseline sMg with CKD progression in CRIC. CKD progression was defined as 1) development of end-stage renal disease (renal transplantation or dialysis initiation) or 2) a 50% decline in baseline eGFR (CKD-EPI). All models were stratified by clinical site and adjusted for demographics, BMI, DM, CV comorbidities, hematocrit, baseline eGFR CKD-EPI, serum albumin, 24-hour urine protein, serum and urine electrolytes, total-PTH, CV biomarkers associated with CKD progression, antihypertensive medications and diuretics. Adjusted splines were also fit.

Results: We analyzed data from 3,866 participants from CRIC who had sMg assessed at baseline. Median sMg was 2.0 mEq/L (25^{th}-75^{th} percentile 1.9 to 2.1 mEq/L). After multivariate adjustment, higher baseline sMg was associated with a 27% lower hazard of CKD progression (aHR 0.73, 95% CI 0.58-0.92; P<0.01, per 1 mEq/L). Compared to the lowest quartile (Q1), sMg concentration in the top quartile (Q4) was associated with a 23% lower hazard of CKD progression (aHR Q1:Q4 0.78, 95% CI 0.65-0.94; P<0.01). The adjusted relationship of sMg with CKD progression appeared to be linear (Fig 1).

Conclusions: In patients with CKD, higher sMg is associated with a lower risk of CKD progression independent of clinical and biochemical data. Whether correction of hypomagnesemia prevents CKD progression deserves future prospective studies.



Adjusted for age, sex, race, BMI, diabetes, hypertension, coronary artery disease, peripheral vascular disease, heart failure, hematocrit, baseline eGFR CKD-EPI, serum albumin, 24-hour urine protein, serum sodium, serum potassium, serum calcium, serum phosphate, urine sodium, urine potassium, total-PTH, hsTnT, BNP, CRP, FGF-23, ACE-I, ARB, aldosterone antagonist, diuretics. Stratified by clinical site. Plotted serum magnesium values between 5th and 95th percentile.

PO0459

The Effects of Intermittent Fasting on the Progression of CKD

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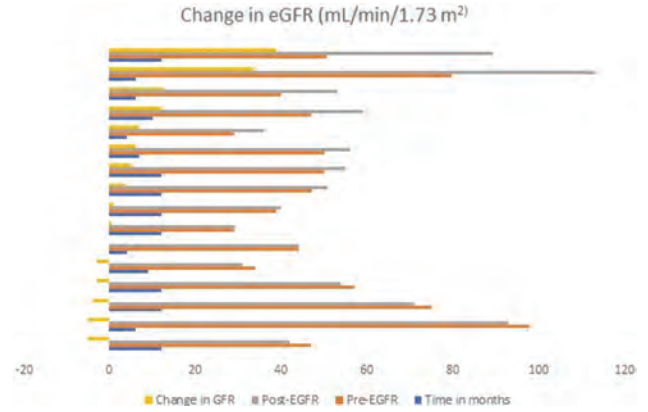
Background: Intermittent fasting (IF) refers to the practice of restricting food intake to a short period of the day alternating with a prolonged period of fasting. Preclinical studies and clinical trials have shown that IF has broad-spectrum benefits for many health conditions, such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurologic disorders. There are currently few studies suggesting a decrease in the progression of chronic kidney disease (CKD) with IF.

Methods: Retrospective chart review was done on patients from outpatient nephrology clinic with CKD stage I to IV who were self-reported to practice intermittent fasting. Patients with ESRD on dialysis, hospital admission during the study period, and reported poor compliance with fasting regimens were excluded. The primary outcome was the change in eGFR at the end of the period of intermittent fasting.

Results: Here we report current findings from 16 patients practicing IF regimen with continued ongoing enrolment. 75% of these patients were diabetic. Duration of the IF regimen ranged from 4 months to 12 months, 50% of patients had completed 12 months of IF regimen. 62.5% of patients were found to have an improvement in eGFR at the end of the period of IF. The change in eGFR was found to range from 0.4 ml/min/1.73 m^2 to 38.8 ml/min/1.73 m^2 (1.4-76.5%). The median increase in eGFR was 6.5 ml/min/1.73 m^2 (18.1%) during an average period of 8.8 months of IF (p-value = 0.04). There was no significant correlation between change in eGFR and change in weight or hemoglobin A1C during this period.

Conclusions: A significant increase in eGFR was seen in a small population of patients with CKD practicing intermittent fasting for four months or more. Previous studies report an average annual decline in GFR of 1.5-2 ml/min/1.73 m^2 in the general CKD population, with a more rapid decline in certain subsets. Intermittent fasting as a preventive measure for the progression of CKD needs to be studied further.



Change in eGFR after the period of IF

PO0460

The Association Between Dietary Fiber Intake and Clinical Outcomes in CKD: A Report from the Chronic Renal Insufficiency Cohort (CRIC)

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Background: Standard dietary interventions for individuals with chronic kidney disease (CKD) consist of reductions in salt, phosphorus, potassium, and protein intake, with no specific guidance regarding dietary fiber intake. In animal models of kidney disease, a diet high in amylose resistant starch has been found to trigger a reduction in inflammation and CKD progression. It is unclear whether low dietary fiber intake is associated with a higher risk of incident kidney disease progression, cardiovascular disease, and overall mortality in individuals with CKD.

Methods: A total of 3791 participants with chronic kidney disease and information on dietary fiber intake at the baseline visit in the Chronic Renal Insufficiency Cohort (CRIC) Study were included in the analyses. Cox proportional hazards models adjusted for sociodemographic, comorbidities, medications and laboratory data, including eGFR and proteinuria were used to analyze the association between dietary fiber intake and clinical outcomes.

Results: The mean age was 59±11 years, 46% were female, 47% had diabetes, and the average eGFR was 48±17 ml/min/1.73m^2. The average dietary fiber intake was 17.3±9.6 g. After a median follow up of 8.8±4.5 years, there was an inverse association between crude death rates and baseline dietary fiber intake: increasing from 3.1 per 100 person-years (PY) for the highest to 3.4 per 100 PY for the lowest fiber tertile. After multivariable adjustments, individuals in the middle and low fiber tertiles were at greater risk of death compared to those in the highest fiber tertile (HR[95%CI], 1.18 [1.01, 1.38], p =0.04 and 1.10 (0.94, 1.29), 0.24, respectively). We found no significant association between dietary fiber intake and kidney and cardiovascular disease outcomes. Results were similar in sensitivity analyses by subgroups defined by age, gender, ethnicity, diabetes, eGFR (< and >/= 45 ml/min/1.73m^2), and proteinuria.

Conclusions: Dietary fiber intake may be associated with the risk of death, but not with cardiovascular outcomes or kidney disease progression in individuals with CKD. Future intervention trials should investigate whether a diet enriched in fibers would influence mortality and other clinical outcomes.

Funding: Other NIH Support - NHLBI

PO0461

Changes in Dietary Protein Intake and Outcomes Among Patients with CKD

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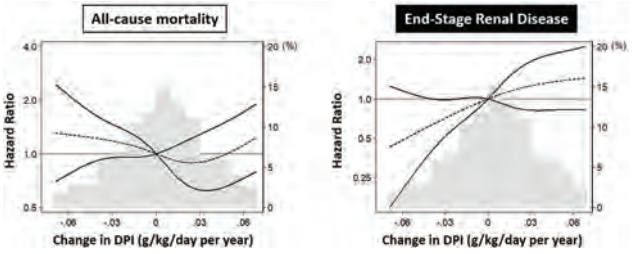
Background: Protein energy wasting is common and associated with poor outcomes in CKD while low protein diet is recommended to delay the development of ESRD. However, the clinical relevance of the temporal change in dietary protein intake (DPI) in real-world data remains unclear in this population.

Methods: We performed repeated collections of morning spot urine in a prospective cohort of non-dialysis dependent veterans with CKD at a single institution. We assessed urine urea nitrogen-to-creatinine ratio to estimate 24-hour urine urea excretion and then estimated DPI using the Maroni formula. Among 345 patients who had data on DPI between 6-12 months from the initial measurement, we estimated the slope of DPI in mixed effects models and examined its association with subsequent ESRD and all-cause mortality in cause-specific hazard models with adjustment for demographics, Charlson Comorbidity Index, eGFR, urinary protein, smoking status, body mass index, and baseline DPI.

Results: Patients were 68±10 years old, 97% were male, 36% were African American, and their baseline eGFR was 34±12 ml/min/1.73m^2. Baseline DPI was median 0.55 (IQR, 0.45–0.67) g/kg/day and its slope was 0.01±0.04 g/kg/day per year. During a median follow-up of 4.2 years, 129 died (104/1000 PY) and 87 developed ESRD (83/1000 PY). Decrease in DPI was associated with lower risk of ESRD (HR 0.94 [95%CI, 0.89-0.99] per 0.01 g/kg/day per year; P=0.025), but not with mortality risk (P=0.84). Non-linear regression models confirmed these findings (**Figure**). Compared to patients who had no change in DPI, the hazard ratio (95%CI) of death and ESRD in those with a change of -0.03 g/kg/day per year were 1.12 (0.95-1.47) and 0.71 (0.52-0.98), respectively.

Conclusions: In patients with CKD, DPI showed a relatively small intraindividual temporal variation, but decrease in DPI was significantly associated with lower risk of ESRD, without an association with mortality.



PO0462

Effect of Zinc Deficiency on CKD Progression and Effect Modification by Hypoalbuminemia

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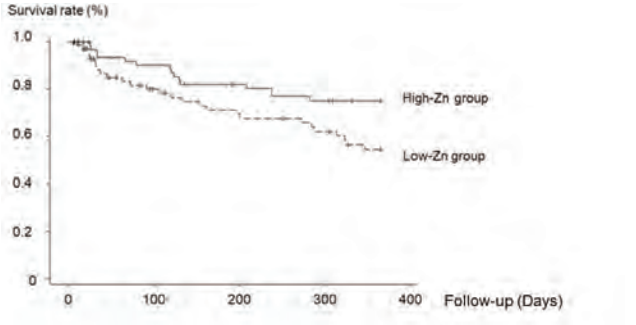
Background: Serum zinc (Zn) levels tend to be low in chronic kidney disease (CKD) patients. However, it has not been shown whether zinc deficiency itself leads to poor renal prognosis. The purpose of this study was to investigate the relationship between zinc deficiency and CKD progression.

Methods: This is a retrospective cohort study using the CKD patient database of electronic medical records (n=325). The study patients were classified into two groups: Zn levels<60μg/dl (low-Zn group, n=163) and Zn levels≥60μg/dl (high-Zn group, n=162). The primary outcome was defined as end-stage kidney disease (ESKD) or death, and the observation period was one year. The relationship between low Zn levels and the outcome was assessed using Cox proportional hazard model and by competitive risk analysis. Furthermore, the propensity score-matched analysis for low Zn level was also conducted.

Results: Among the subjects, 51.7% were male; mean age, 69.3years; mean Zn level, 59.9μg/dl; and median eGFR, 20.4ml/min/1.73 m^2. The incidence of the primary outcome was higher in the low-Zn group than in the high-Zn group (42.3% vs 19.1%, p<0.001). The risk of the primary outcome was higher in the low-Zn group [adjusted hazard ratio (HR) 1.88 (95% CI 1.08, 3.28; p=0.025)]. The analysis using competitive risk models showed that low Zn levels were associated with ESKD, but not with death. Moreover, in the propensity score-matched analysis, the low-Zn group showed a high risk of the primary outcome [HR 2.05 (95%CI, 1.09, 3.86; p=0.026)]. Furthermore, the relationship between the low Zn levels and the primary outcome was aggravated in the hypoalbuminemia patients (interaction p=0.011).

Conclusions: This study indicated that zinc deficiency is a risk factor for ESKD among CKD patients. Hypoalbuminemia affects the CKD progression due to zinc deficiency.



Kaplan-Meier curves for the primary outcome in the propensity score-matched population

PO0463

Association of Plasma Selenium with Renal Function in Hypertensives: Modification by Folate

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Background: We aimed to investigate the association between plasma selenium (Se) and renal function decline in adults with hypertension and to explore the possible modifiers.

Methods: This was a prospective study, including a total of 935 hypertensive adults from a folic-acid intervention trial (CSPPT) with baseline plasma Se measurements and renal outcome data available. The primary outcome was rapid decline in renal function, defined as an average decline in eGFR ≥5 mL/min/1.73m^2 per year.

Results: Over a median follow-up of 4.4 years, the primary outcome occurred in 72 participants. After multivariate-adjusted, there was an inverse association between plasma Se and rapid decline in renal function (per 10-unit increment; OR, 0.85; 95% CI: 0.72, 0.99). Consistently, compared to the lowest tertile of baseline plasma Se (<74.5 μg/L), the highest tertile (89.4~<150 μg/L) was significantly associated with a 60%(0.40; 0.21, 0.79) reduction in the odds of the outcome. A stronger inverse plasma Se-renal function decline association was observed in those received folic acid treatment (per 10-unit increment: OR, 0.70; 95% CI: 0.54, 0.90; *P*-interaction=0.036) or with a higher baseline folate concentration (≥9.0 ng/mL: 0.59; 0.43, 0.82; *P*-interaction=0.004).

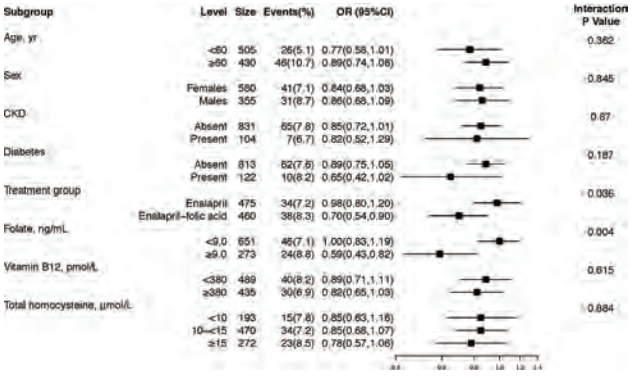
Conclusions: In China hypertensives with plasma Se <150 μg/L, there was an inverse relationship of plasma Se with the renal function decline, especially in those with folic-acid supplementation or a higher folate level.

Funding: Government Support - Non-U.S.

Association between plasma Se and the outcome

Plasma selenium, μg/L	Events (%)	Adjusted OR (95%CI)*	P
Per 10-unit increment	72(7.7)	0.85(0.72-0.99)	0.04
Tertile 1 (<74.5)	35(11.2)	Ref (1.0)	
Tertile 2 (74.5~<89.4)	22(7.1)	0.59(0.33-1.07)	0.081
Tertile 3 (89.4~<150)	15(4.8)	0.40(0.21-0.79)	0.008

*Adjusted for age, sex, eGFR, treatment group, BMI, MTHFR C677T polymorphisms, proteinuria, SBP, TC, glucose, smoking status at baseline, and averaged SBP during follow-up period.



Subgroup analyses on plasma Se (per 10-unit increment) and the outcome.

PO0464

Association Between CKD and New Onset of Dyslipidemia: Results from a Longitudinal Nationwide Survey

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Background: Dyslipidemia is a significant risk factor of CVD and seems to be associated with CKD onset and progression. On the contrary, CKD patients have dyslipidemia more frequently than non-CKD patients, but it is unclear whether CKD affects new onset of dyslipidemia.

Methods: This is a longitudinal study based on data obtained from the Japanese Specific Health Check and Guidance System. Among 664,926 individuals who participated in this program from 2008 to 2014, we excluded participants who met the following criteria: 1) health check only one time, 2) missing values for creatinine or proteinuria, 3) dyslipidemia at baseline, or 4) medication for dyslipidemia at any point. We evaluated new onset of dyslipidemia according to each factor; hypertriglyceridemia (High-TG), hyper-LDL cholesterolemia (High-LDL), or hypo-HDL cholesterolemia (Low-HDL), defined as triglycerides ≥150 mg/dL, LDL cholesterol ≥140 mg/dL, or HDL cholesterol <40 mg/dL, respectively, and compared between participants with and without CKD. These associations were analyzed using Kaplan-Meier methods and Cox regression analysis after adjustment for clinically relevant factors.

Results: During a median follow-up period of 3.1 years, the cumulative incidences of High-TG, High-LDL, and Low-HDL were 45,300, 51,940, and 13,313 participants, respectively, among 305,893 participants (non-CKD: 254,884; CKD: 51,009). In the univariable analyses, hazard ratios (HRs) [95% confidence intervals (CIs)] in CKD vs non-CKD participants were 1.31 [1.27-1.34], 1.02 [0.99-1.05], and 1.70 [1.63-1.77] for High-TG, High-LDL, and Low-HDL, respectively. After adjustment for clinically relevant confounders, adjusted HRs [95% CIs] in CKD participants were 1.10 [1.07-1.13], 0.99 [0.96-1.02], and 1.16 [1.11-1.22] for High-TG, High-LDL, and Low-HDL, respectively.

Conclusions: CKD was associated with new onset of High-TG and Low-HDL, but not High-LDL among general population in Japan.

PO0465

Relationship of Serum Triglycerides with Incident Albuminuria Among 114,817 US Veterans

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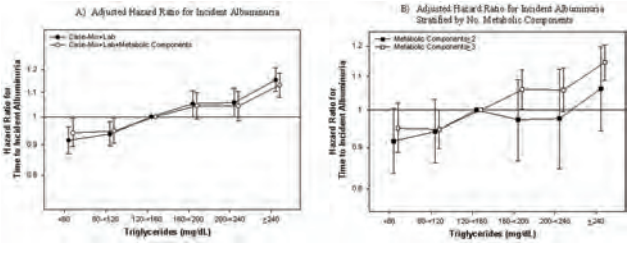
Background: The association of metabolic syndrome (MetS) components of impaired glucose, obesity, low high-density lipoprotein, hypertension, and serum triglycerides (TG), with renal endpoints such as incident chronic kidney disease (CKD) have been previously studied individually. Urine albumin to creatinine ratio (UACR) remains an integral part of CKD staging and incidence, yet it remains understudied. Thus, we sought to examine the relationship of TG with incident albuminuria among normal UACR patients with consideration for other MetS components.

Methods: Our cohort comprised 114,817 veterans with albuminuria stage A1 (<30 mg/g) and data on TG and MetS components. Incident albuminuria was defined as at least two UACR measurements of >30 mg/g at least 90 days apart. We used Cox proportional hazards models to evaluate the association of TG with incident albuminuria, adjusted for case-mix characteristics, laboratory values and individual MetS components, as well as stratified by ≤2 and ≥3 MetS components.

Results: The mean±SD age was 65±11, with a median[IQR] of TG, UACR and eGFR of 144[97, 214] mg/dL, 7[4, 13] mg/g, and 75[61, 89] mL/min/1.73m^2 respectively, and 70% had at least 3 MetS components. We observed a linear association between TG and incident albuminuria after adjustment for case-mix and laboratory variables (ref: TG 120-<160 mg/dL). The association did not differ after adjustment for MetS components (Figure A). Moreover, stratification by number of MetS components showed similar linear associations between TG and incident albuminuria, especially in patients with ≥3 MetS components. In patients with ≤ 2 MetS components, the linear relationship of TG and incident albuminuria was attenuated (Figure B).

Conclusions: Higher TG are associated with incident albuminuria independent of other components of MetS. Further study is needed to understand the drivers of this association, with a specific focus of how to best manage TG levles in addressing albuminuria development.



PO0466

Short-Term Associations of Triglycerides with Atherosclerotic and Non-Atherosclerotic Cardiovascular Disease Hospitalizations Across CKD Stages

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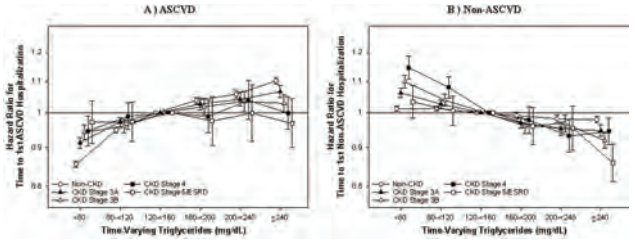
Background: In chronic kidney disease (CKD) patients, we showed that the risk of atherosclerotic cardiovascular disease (ASCVD) and non-ASCVD events with high baseline triglycerides (TG) incrementally attenuated across worse CKD stages, where high TG was associated with lower risk of non-ASCVD events in late-stage CKD. TG levels can change with CKD progression, but associations of time-varying TG with ASCVD or non-ASCVD hospitalizations is unknown.

Methods: We examined time-varying TG with time to first ASCVD or non-ASCVD hospitalization in 2,963,176 US veterans who received care in 2004-2006 (baseline) and were followed to 2014. Events were classified by primary ICD-9 codes. Using time-varying Cox models, we evaluated associations of time-varying TG with first ASCVD or non-ASCVD events stratified by baseline CKD stage, with adjustment for demographics, and time-varying comorbidities and laboratory values.

Results: The cohort was 63±14 years old with a median[IQR]TG 127[87,189] mg/dL, and 23% had CKD 3A or higher at baseline. TG <80 mg/dL was associated with a lower risk of time to first ASCVD event (ref: TG 120-<160 mg/dL) for all baseline CKD stages (Fig A). There was a linear association between time-varying TG and ASCVD events. High TG≥240 mg/dL had the highest risks for ASCVD, for baseline non-CKD, and CKD 3A-3B. Among late-stage CKD patients, the association of high TG and ASCVD was null. We observed an inverse association between time-varying TG with time to first non-ASCVD event (Fig B). Patients with low TG had faster times to first non-ASCVD event for non-CKD and CKD 3A-4, while high TG were associated with slower times in all stages. CKD stage 5/end-stage renal disease patients with TG ≥240 mg/dL had the lowest risk of non-ASCVD event.

Conclusions: Short-term risk of higher TG with ASCVD or non-ASCVD events incrementally decreased across CKD stages, where risk was lower to null in late stage patients. High TG were associated with lower risks of non-ASCVD across all CKD stages. Investigation is needed to evaluate the pathways involving TG and cardiac events as CKD severity progresses in order to best manage health.



PO0467

Metabolic Acidosis and Progression to Renal Replacement Therapy

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Background: Metabolic acidosis is common in advanced chronic kidney disease (CKD) and is associated with its progression (Kraut J, *Adv Chronic Kidney Dis*. 2017).

Methods: De-identified electronic health records (Optum® EHR), 2007 to 2017 were queried to identify patients with non-dialysis CKD Stages 3-5 with ≥2 serum bicarbonate tests 28–365 days apart, ≥3 eGFR values <60 mL/min/1.73 m² and ≥2 years of post-index data or who died during that period. Cohorts with metabolic acidosis and normal serum bicarbonate were established based on the index serum bicarbonate (< 22 mEq/L or 22 - 29 mEq/L). Progression to RRT was defined as initiation of dialysis or kidney transplantation, identified in EHR data by diagnosis or procedure codes, or eGFR ≤ 9 mL/min/1.73 m². We evaluated the impact of baseline serum bicarbonate on RRT initiation, adjusted for age, sex, race, diabetes, hypertension, heart failure, Charlson Comorbidity Score (index of comorbidity burden), and baseline eGFR and log albumin-to-creatinine ratio (ACR) using logistic regression models (2-year outcome period) and Cox proportional hazards models (up to 10 years).

Results: 51,558 patients qualified for analysis; 17,350 with metabolic acidosis, 34,208 with normal serum bicarbonate at baseline. Unadjusted rates of progression to RRT within 2 years were higher among patients with metabolic acidosis vs. normal serum bicarbonate overall (19.6% vs. 5.5%, respectively, p< 0.001) and at all baseline CKD stages (p< 0.001) except stage 5 (p=0.4). Each 1 mEq/L increase in serum bicarbonate between 12 and 29 mEq/L was associated with a 2.5% decrease in the 2-year risk of initiating RRT, (OR: 0.975, 95% CI: 0.965, 0.985), and a 4.5% decrease in risk up to 10 years (HR: 0.955, 95% CI: 0.948, 0.963).

Conclusions: The presence of metabolic acidosis was associated with an increased risk of CKD progression to dialysis or kidney transplantation. This finding was independent of age, sex, race, pre-existing comorbidities, and baseline eGFR and ACR.

Funding: Commercial Support - Tricida, Inc.

PO0468

Relationship Between Metabolic Acidosis and CKD Progression Is Evident Across US Racial and Ethnic Groups

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Background: Metabolic acidosis is a known risk factor for CKD progression, but little is known about the impact of race and ethnicity on this relationship. We used a large electronic medical record (EMR) database of >100 million patients from all 50 states and insurance types to evaluate the relationship between metabolic acidosis and adverse renal outcomes and death by race and ethnicity.

Methods: De-identified electronic medical records (Optum® EHR), 2007–2019 were queried to identify patients with non-dialysis CKD Stages 3-5, ≥2 years of post-index data or death within 2 years, and grouped by baseline metabolic acidosis (12 to < 22 mEq/L) vs normal serum bicarbonate (22 to < 30 mEq/L). Patients (N = 136,067) were classified as Asian (N=1,328), Black (N=15,248), Hispanic (N=4,137), White (N=111,953) or Other (N=3,401). The primary endpoint was the composite outcome of death, kidney dialysis or transplant, or 40% decline in eGFR from baseline (DD40). Cox proportional hazards models examined the impact of serum bicarbonate on DD40 within each racial/ethnic group, adjusted for age, sex, eGFR, log albumin-to-creatinine ratio, diabetes, hypertension, heart failure, Charlson Comorbidity Score.

Results: Overall, 47,032 patients (34.6%) experienced DD40 events within 2 years: Asian, 35%; Black, 44%; Hispanic, 48%; White, 32%; Other, 48%. Serum bicarbonate independently predicted DD40 in all racial/ethnic groups. Adjusted Hazard Ratios for DD40 per 1 mEq/L increase in serum bicarbonate (median 4.2 yrs, max 11.5 yrs follow-up) were as follows: Asian, 0.942 (CI: 0.917- 0.968); Black, 0.976 (CI: 0.969-0.983); Hispanic, 0.970 (CI: 0.956-0.984); White, 0.960 (CI: 0.957-0.963); *P*< 0.0001 for all groups.

Conclusions: In a large community-dwelling US population, serum bicarbonate was independently associated with adverse kidney outcomes and death in Asians, Blacks, Hispanics and Whites with CKD. Since race and ethnicity are associated with other sociodemographic factors that affect health, further exploration of the potential reasons for the observed range of hazard ratios across these groups is warranted.

Funding: Commercial Support - Tricida, Inc.

PO0469

Metabolic Acidosis Is Associated with CKD Progression: A Longitudinal Analysis of >100,000 US Community-Based Patients

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Background: To delay the progression of CKD, it is imperative to identify modifiable risk factors and then to evaluate efficacy of interventions. Here we assess the role of metabolic acidosis as an independent risk factor for CKD progression in patients (pts) with non-dialysis-dependent CKD Stages 3-5.

Methods: De-identified electronic medical records (Optum® EMR), 2007–2019 were queried to identify pts with non-dialysis CKD Stages 3-5, (2 consecutive eGFR values >10 and <60 mL/min/1.73m² 90-365 days apart) followed by 2 consecutive serum bicarbonate values 28–365 days apart, both 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) and ≥2 yrs of post-index data or death within 2 yrs. Pts (N = 136,067) were followed for up to 11.5 yrs for evidence of CKD progression, measured as a ≥40% decline in eGFR from baseline and as progression of ≥ 1 CKD stage from baseline using laboratory data. We describe outcomes at 2 yrs and used Cox proportional hazards models over the entire follow-up period to examine potential confounders: age, sex, race/ethnicity, eGFR, log albumin-creatinine ratio, diabetes, hypertension, heart failure, and weighted Charlson Comorbidity Index.

Results: 75,127 pts (55%) progressed 1 or more CKD stages within 2 yrs. The incidence of CKD progression within 2 years was significantly higher in pts with metabolic acidosis compared to pts with normal serum bicarbonate, irrespective of the endpoint (≥40% decline in eGFR: 38.3% vs. 20.4%, *P*< 0.0001; progression of ≥ 1 CKD stage: 66.7% vs. 54.5%, *P*< 0.0001). During the up to 11.5-yrs of follow-up (median 4.2 yrs), serum bicarbonate was independently associated with CKD progression; hazard ratios per 1 mEq/L increase in serum bicarbonate were 0.969, CI: 0.965-0.973 for a ≥40% decline in eGFR and 0.975, CI: 0.972-0.977 for progression ≥1 CKD stage.

Conclusions: In pts with non-dialysis CKD, serum bicarbonate levels below 22 mEq/L were independently associated with increased risk of CKD progression. Large randomized trials targeting treatment of metabolic acidosis to slow CKD progression are needed. There was a 2.5–3.0% risk reduction for a ≥40% decrease in eGFR or progression by ≥1 CKD stage for every 1 mEq/L increase in serum bicarbonate.

Funding: Commercial Support - Tricida, Inc.

PO0470

Lower Urine Citrate Excretion Associated with Advanced CKD Stage Is Mediated by Reduced Plasma Citrate and Decreased Kidney Citrate Clearance

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Background: Lower urine citrate excretion (UcitV) might be a biomarker of covert acid (H^+) retention in patients with CKD but without metabolic acidosis and so mechanisms that mediate UcitV differences among patients with CKD would help assessment of its biomarker utility. Because longitudinal eGFR decreases in patients with CKD associated with decreasing UcitV (Goraya, et al. AJP 317:F502, 2019), we examined cross-sectional differences in UcitV across CKD stages and mechanisms that mediate such differences.

Methods: We measured 8-hour UcitV (8h UcitV), plasma citrate concentration (Pcit), and kidney citrate clearance citrate (UcitV/Pcit) in 52 patients with CKD 1 (eGFR=99.5±7.7 ml/min/1.73 m^2), 120 with CKD 2 (eGFR=73.4±6.1 ml/min/1.73 m^2), and 52 with CKD 3 (eGFR=40.1±7.6 ml/min/1.73 m^2) with macroalbuminuric, non-diabetic, hypertension-associated nephropathy. We assessed ongoing dietary H+ intake as potential renal acid load (PRAL) and steady-state acid-base status with plasma total CO_2 ($PTCO_2$) and H^+ retention, the latter estimated by comparing observed to expected $PTCO_2$ increase in response to retained HCO_3 (administered minus $UHCO_3V$) 2 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body weight HCO_3 apparent space of distribution.

Results: Although PRAL was not different among CKD 1, CKD 2, and CKD 3 groups (62.4±11.9, 62.9±14.7, and 65.2±7.9 mmol/day, respectively, p=0.47), $PTCO_2$ was progressively lower (26.4±0.7, 25.9±0.6, and 21.6±1.9 mM, respectively, p<0.01) and H^+ retention progressively higher (3.9±12.9, 18.2±14.0, and 25.1 ±13.4 mmol, respectively, p<0.01) with advancing CKD stage. 8h UcitV was progressively lower with advancing CKD stage (1.14±0.03, 1.00±0.25, and 0.86±0.10 mmol/1.73m^2, respectively, p<0.01) as was Pcit (0.16 ± 0.01, 0.15 ± 0.02, and 0.14 ± 0.01 mM, respectively, p<0.01) and UcitV/Pcit (0.015 ± 0.001, 0.014 ± 0.003, and 0.013 ± 0.001 ml/min/1.73 m^2, respectively, p<0.01).

Conclusions: Cross-sectional advanced CKD stage was associated with greater H^+ retention and lower UcitV, the latter mediated by lower Pcit and lower UcitV/Pcit. The data support that reduced UcitV associated with decreased eGFR reflects underlying H^+ retention with reduced body citrate stores and increased citrate conservation through reduced kidney citrate clearance.

PO0471

Urinary Calcium Excretion and Risk of CKD Progression: The CRIC Study

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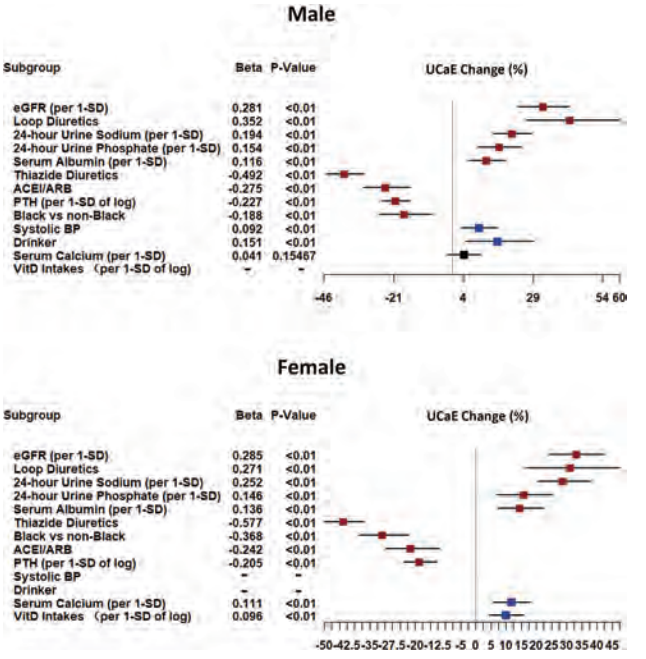
Background: Hypercalciuria is implicated in nephrolithiasis and nephrocalcinosis, conditions associated with chronic kidney disease (CKD). We aimed to study the determinants of urinary calcium excretion (UCaE) and its association with adverse clinical outcomes in CKD.

Methods: 24-hour UCaE was measured in 3,768 Chronic Renal Insufficiency Cohort (CRIC) participants. We used multivariable linear regression models to determine independent predictors of UCaE in CKD. Weighted Cox regression analyses tested the associations of UCaE with incident end stage kidney disease (ESKD), CKD progression (50% eGFR decline or incident ESKD), atherosclerotic cardiovascular disease (ASCVD) events, and death.

Results: Estimated glomerular filtration rate (eGFR) correlated most strongly with UCaE (r=0.417, P<0.001). In both males and females, determinants of UCaE included eGFR, African American race, iPTH, 24-hour urine sodium and phosphate, serum albumin and the use of diuretics and angiotensin receptor blockers (Figure 1). Certain predictors of UCaE differed between sexes: systolic blood pressure and alcohol drinker were associated with UCaE in males, while serum calcium and vitamin D intakes were significantly associated with UCaE in females. Higher UCaE was significantly associated with lower risk of ESKD, CKD progression, death and ASCVD events in unadjusted models. These associations were attenuated after adjusting for baseline characteristics, and for most outcomes the associations became insignificant after adjusting for eGFR.

Conclusions: Predictors of UCaE in CKD differed between males and females. eGFR is extremely strongly associated with UCaE and greatly confounds the associations between UCaE and all the outcomes.



β is from the linear model setting ln (UCaE) as dependent variable. UCaE Change= Exp(β)-1.

PO0472

Neighborhood Socioeconomic Status and Patterns of Kidney Care: Data from Electronic Health Records

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Background: Electronic health records (EHR) can be leveraged to assess quality of care measures in patients with CKD. Neighborhood socioeconomic status (SES) could be a potential barrier to receiving appropriate evidence-based therapy and follow up. Our goal was to examine whether neighborhood SES is independently associated with quality of care received by CKD patients.

Methods: EHR data for patients seen at a healthcare system in the 7-county Minneapolis/St Paul area and linked census tract data were used. Census tract SES measures used were: median value of owner occupied housing units (wealth), percentage of residents >25 years with ≥ Bachelor's degree (education), and median household income (income). A patient was considered to be living in low and high SES tracts if they belong to the first and fourth quartile of each SES measures, respectively. CKD quality of care indicators used were: prescription for ACEi/ARB in patients with moderate to severe CKD or mild CKD+UACR >300 mg/day; UACR measurement; and CKD identified on the problem list or coded for at an encounter among patients with CKD (eGFR<60 ml/min/1.73 m^2). We used a multilevel Poisson regression with robust error variance with a random intercept at the census tract level to estimate the association between each quality of CKD care measure and neighborhood SES.

Results: Of the 16,776 patients who should be on ACEi/ARB, 65% were prescribed these medications. In patients with CKD (n=25,097), UACR was measured in 27% of patients and only 55% of patients with CKD had CKD identified in their EHRs. Belonging to low neighborhood SES compared to high neighborhood SES was not associated with ACEi/ARB prescription compliance after adjusting for demographics and clinical characteristics (prevalence ratio (PR): wealth-0.96[0.91,1.03], education-1.01[0.97,1.05], income-0.97[0.94,1.02]). Neighborhood SES was not associated with UACR measurement after adjustment (PR: wealth-1.01[0.91,1.12], education-1.07[0.98,1.17], income-0.96[0.87,1.06]). Similarly, neighborhood SES was not associated with CKD identification in the EHR after adjustment (PR: wealth-1.02[0.98,1.06], education-1.03[0.98,1.07], income-1.01[0.97,1.06]).

Conclusions: Neighborhood SES is not associated with quality of CKD care received. However, adherence to CKD guidelines is low, indicating an opportunity to improve care for all patients, regardless of SES.

PO0473

Neighborhood Socioeconomic Status, Health Insurance, and CKD Prevalence: Findings from a Large Healthcare System

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Background: The association of neighborhood characteristics and insurance status with chronic kidney disease (CKD) remain unclear. Therefore, we investigated the association of neighborhood socioeconomic (SES) and insurance type with CKD prevalence.

Methods: We utilized electronic health record (EHR) data of patients seen at a healthcare system in the 7-county metropolitan area in Minnesota and linked census tract data. Census tract measures [median value of owner occupied housing units (wealth), percentage of residents >25 years with ≥ Bachelor's degree (education), and median household income (income)] and individual level insurance status (<65 years: Medicaid vs. other insurance; ≥65 years: Medicare vs. supplemental insurance plan) were obtained from the American Community Survey (2008-2012) and the EHR, respectively. A patient was considered to be living in low and high SES tracts if they belong to the first and fourth quartile of each SES measures. CKD prevalence was defined as having an estimated glomerular filtration rate (eGFR) <60/mL/min/1.73m^2 or proteinuria. We used a multilevel Poisson regression with robust error variance with a random intercept at the census tract level to estimate the association between tract SES [low (first quartile) vs. high (fourth quartile)], insurance, and CKD.

Results: We included 185,269 patients. Tract SES (wealth and education) and insurance are independently associated with CKD prevalence. After adjusting for demographic and clinical characteristics, patients (<65 and ≥ 65 years) living in low vs. high SES tracts had higher CKD prevalence (Prevalence Ratio PR, 95%CI of low vs. high tract SES for education among patients <65 years: 1.11 [1.05, 1.18] and 1.08 [1.04, 1.12] for ≥65 years). Patients (<65 years) on Medicaid vs. other insurance had higher CKD prevalence (PR, 95%CI: 1.51 [1.43, 1.60]). For patients ≥65 years, insurance type was not associated with prevalence of CKD in the fully adjusted model.

Conclusions: In conclusion, we found that patients from low SES tracts and Medicaid recipients (among patients <65 years) have greater rates of CKD compared to patients from high SES tracts and patients with other insurance. These may be two of several socioeconomic and individual factors influencing the complexity of identification, management, and treatment of CKD.

PO0474

Social Determinants of CKD in the Military Health System

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Background: A growing body of evidence suggests that negative social determinants of health—or social risks—contribute to socioeconomic and racial disparities in chronic kidney disease (CKD). One mechanism through which social risks appear to produce disease is by impeding access to healthcare. The Military Health System (MHS) provides an opportunity to assess CKD disparities in the context of universal healthcare.

Methods: We identified all MHS beneficiaries aged 18 to 64 who received care through the MHS from October 1, 2015 to September 30, 2018. CKD was identified by ICD-10 code and/or a validated laboratory value-based electronic phenotype for CKD. Directed acyclic graphs were developed to understand potential confounding or mediating roles of covariates. Multivariable logistic regression models were used to compare the prevalence of CKD by race, rank, zip code level median household income, and marital status, controlling separately for suspected confounders (age, sex, active duty status, service branch, and depression) and mediators (hypertension, diabetes, HIV and BMI). For family beneficiaries, the sponsor's rank and zip code were used.

Results: Of the 3,330,893 MHS beneficiaries in this analysis, 105,504 (3.2%) were identified as having CKD. In confounder-adjusted models, CKD prevalence was statistically elevated in beneficiaries of black vs white race, lower vs higher rank (as a proxy for socioeconomic status), lower vs higher income, and married vs single status (p <.0001). As expected, associations were partially or fully mitigated when further adjusting for suspected mediators, indicating the mediators may indeed be on the causal pathway between social risks and CKD.

Conclusions: Racial and socioeconomic disparities persist in CKD under the conditions of universal healthcare coverage provided by the MHS. While racial disparities may result in part from underlying genetic differences, the presence of disparities by rank and area income suggest social factors remain pertinent despite access to universal healthcare coverage.

Funding: Other U.S. Government Support

PO0475

Low Documentation of Social Determinants of Health Among US Veterans and Medicare Patients with CKD

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Background: The implementation of ICD-10 codes in 2015 included new codes (Z-codes) to identify social determinants of health (SDOH). We sought to identify differences in SDOH-related Z-code (SDOH-ZC) utilization in Veterans Health Administration (VHA) and Medicare patients identifying differences in SDOH-ZC utilization in those with and without chronic kidney disease (CKD).

Methods: We used 5% sample of Medicare claims data (2015-2018) and 100% VA health data (2015-2019). A list of SDOH-ZCs were grouped into 17 categories (education and literacy, employment status, occupational risk factors, housing, economic circumstances, lifestyle factors, etc.). Proportion of claims assigned a SDOH-ZC were measured quarterly across different healthcare encounters and described by patient characteristics including age, sex, race, and hypertension, diabetes, and CKD. Use of SDOH-ZC were compared between those with and without CKD.

Results: SDOH-ZCs appeared more frequently in the VA health system than in Medicare data (Fig 1.a-b). Tobacco use was the most common SDOH-ZC in both the Medicare and VA data. More SDOH-ZCs were evident in the VA employment, environment, housing and economic, and family circumstances. Compared to those without CKD, use of SDOH-ZC was higher in individuals with CKD in outpatient settings but lower among those with inpatient visits, observation stays, and emergency department visits (Fig 1.c-d).

Conclusions: We observed lower recording of SDOH overall and among those with CKD in health care settings. Additional efforts might consider increasing SDOH documentation to help assess need for social services, which could potentially reduce disparities in health outcomes by socioeconomic status.

Funding: Other U.S. Government Support

PO0476

Association of Health-Related Social Needs with Kidney Protective Measures in an Urban Population

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Background: Health-related social needs are individual-level social determinants of health, such as food insecurity and housing insecurity. Maintaining blood pressure ≤130/80 mmHg, hemoglobin a1c ~7%, sodium intake <2 g/day, regular physical activity, BMI 20-25 kg/m^2, and smoking cessation reduce risk of CKD and CKD progression. We evaluated whether having unmet needs was associated with achieving kidney protective measures.

Methods: We performed a cross-sectional analysis of data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (Baltimore, MD) during study visit 4. We used multivariable regression to quantify associations between having and least one unmet social need (food insecurity or housing insecurity), and the number of protective measures met (BP ≤130/80 mmHg, a1c 6.5-7.5%, daily sodium intake <2g, BMI 20-25 kg/m^2, physical activity, non-smoker), and each measure independently.

Results: Among 1805 HANDLS participants, 899 (49.8%) reported at least one unmet health-related social need. Compared to those without unmet needs, those with unmet needs were younger (mean age 55.0 versus 57.8 years), more likely to be black (63.7% versus 58.5%), report income <125% of federal poverty level (46.8% versus 31.9%), and had higher eGFR (mean 90.0 versus 85.8 ml/min/1.73m^2). The likelihood of achieving a higher number of protective measures was significantly lower for those with unmet needs compared to those without unmet needs (**Table**). Having unmet needs was significantly associated with lower likelihood of being a non-smoker and engaging in physical activity.

Conclusions: Individuals with unmet social needs may be less likely to achieve measures to prevent incident CKD and CKD progression.

Association Between Unmet Health-related Social Needs and Kidney Protective Measures

	Total # measures	BP ≤130/80 mmHg	HgbA1c 6.5-7.5%	Sodium <2g/day	BMI 20-25 kg/m2	Physical activity	Non-smoker
	IRR (95%CI)	IRR (95%CI)	RR (95%CI)	IRR (95%CI)	IRR (95%CI)	RR (95%CI)	IRR (95%CI)
Unadjusted	0.87 (0.82-0.93)	0.99 (0.94-1.05)	0.90 (0.68-1.19)	0.81 (0.42-1.54)	1.13 (0.94-1.36)	0.72 (0.63-0.83)	0.73 (0.68-0.79)
Adjusted*	0.90 (0.84-0.96)	1.00 (0.95-1.05)	0.97 (0.73-1.28)	0.92 (0.46-1.86)	1.11 (0.92-1.35)	0.72 (0.63-0.83)	0.79 (0.73-0.86)

*Fully adjusted models adjusted for age, race, sex, income above/below 125% federal poverty level, urine albumin-creatinine ratio, estimated glomerular filtration rate.

**BP – blood pressure; HgbA1c – hemoglobin A1c; BMI – body mass index; IRR – incidence rate ratio; RR – risk ratio; CI – confidence interval

PO0477

Association Between Air Pollution and Renal Outcomes: A Systematic Review and Meta-Analysis

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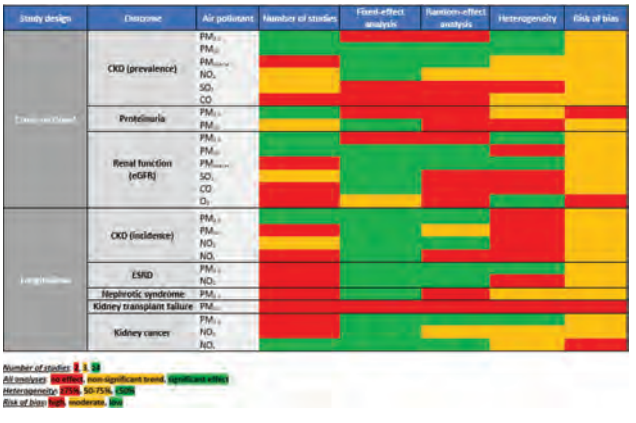
Background: Although several risk factors of chronic kidney disease (CKD) have been well-established, mainly diabetes and hypertension, many remain less studied, such as chronic exposure to air pollution. Our purpose is to exhaustively summarize the current evidence on the association between air pollution and various renal outcomes.

Methods: We searched EMBASE, Pubmed, Web of Science, Cochrane library, and CINAHL database, for relevant records using a combination of keywords related to the type of exposure (O_3, CO, NO_x, NO_2, SO_2, $PM_{2.5}$, PM_{coarse}, and PM_{10}) and outcome (CKD, end-stage renal disease -ESRD-, proteinuria/albuminuria, renal function, kidney transplant failure, nephrotic syndrome, and kidney cancer). Using random-effects meta-analyses, we pooled summary statistics (hazard ratios, odds ratios, or beta-coefficients with their respective 95% confidence intervals) associated with a standardized increased level of each pollutant and presented the results by air pollutant and outcome. Heterogeneity has been assessed using the $\chi 2$ test on Cochran's Q statistic and quantified I2 calculation.

Results: Within 1214 eligible studies, 42 articles fulfilling the selection criteria were included in this work (11 cross-sectional, 15 prospective, and 16 retrospective cohort studies). The most significant associations are for $PM_{2.5}$ exposure and higher risks of CKD, ESRD, and kidney cancer incidence (HR=1.24 [1.15; 1.34]; 1.27 [1.18; 1.36]; 1.26 [1.02; 1.57] respectively, per 10µg/m^3 increased level); NO_2 exposure and higher risks of CKD and ESRD incidence; PM_{10} /PM_{coarse} exposure and higher CKD prevalence, as well as lower renal function (see details in Figure 1). These results should however be interpreted with caution, due to significant between-studies heterogeneity and risks of methodological bias.

Conclusions: Chronic exposure to particulate matter and nitrite dioxide seems to be associated with poorer renal outcomes. Further studies are warranted to confirm these results.



PO0478

Living Kidney Donors from a Hotspot for CKD of Unknown Origin

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Background: Tierra Blanca region has been identified as a Chronic Kidney Disease of unknown origin (CKDu) hotspot. At the National Heart Institute 52 young patients with CKDu from Tierra Blanca have been transplanted from living kidney donors from the same area The objective of the study was to determine the prevalence of decreased kidney function in living kidney donors from Tierra Blanca

Methods: Medical records from 1995 to 2019 were reviewed in order to obtain anthropometric measurements, occupation, past medical history and family history Laboratory data included serum creatinine (SCr), albumin-creatinine ratio (ACR), 24 hour urinary protein-creatinine ratio (PCR), at baseline and at 1,3,5, and 10 years. Time zero kidney biopsies were obtained in a subset of the cohort. eGFR ACR and PCR were used as indicators of kidney function

Results: 32 patients were included the mean age was 36 ± 10 y and mean eGFR at donation was 95.1±15.5 mL/min. 35% worked in agriculture 50% in household 6% in construction 6% in a storage company 3% unemployed. The mean change in eGFR at 1, 3, 5, and 10 years was - 18.2 ± 12.4, -7.5 ± 19.8, -6.9 ± 19, -8.1 ± 11.9ml/min. There was a significant difference between agriculture and domestic workers in eGFR decrease at 5 and 10 years. 50% underwent time zero biopsy and 69 % had some evidence of histological damage 62% showed glomerular abnormalities 40% had glomerular sclerosis, tubulointerstitial infiltrates 31% interstitial fibrosis 50% and either medial hypertrophy or intimal fibrosis 69 % These findings were not associated to occupation In multivariate analysis using a lineal model of repetitive measurements, working in agriculture was the most important risk factor associated to eGFR decrease (p= .023)

Conclusions: Baseline histological changes were observed in the majority of the kidney donors, Agricultural work was the most important risk factors for eGFR decline

Table 1. Demographic characteristics, and difference in eGFR between groups

VARIABLE	TOTAL (N = 32)	AGRICULTURE (N = 11)	DOMESTIC WORKERS (N = 16)	P
Age (years)	35.8 ± 10.3	35 ± 10	35 ± 11	NS
Genre (N, M/F)	16 / 16	10 / 1	1/ 15	***0.000***
Basal eGFR (ml/min)	95.1 ± 15.5	93 ± 17	96 ± 17	NS
eGFR 1st year (ml/min)	76.7 ± 14.9	71 ± 16	81 ± 14	NS
eGFR 3 years (ml/min)	83.3 ± 17.9	74 ± 9	89 ± 19	NS
eGFR 5 years (ml/min)	81.2 ± 17.8	78 ± 16	87 ± 18	NS
eGFR 10 years (ml/min)	79 ± 12.4	78 ± 15	83 ± 3	NS
Mean eGFR change 1st year (ml/min)	-18.2 ± 12.4	-22.6 ± 1.7	-14.7 ± 13.8	NS
Mean eGFR change 3 years (ml/min)	-7.5 ± 19.8	-14.5 ± 20.5	-3.6 ± 20.8	NS
Mean eGFR change 5 years(ml/min)	-6.9 ± 19	-22.8 ± 2.6	2.4 ± 16.4	***0.035****
Mean eGFR change 10 years (ml/min)	-8.1 ± 11.9	-16.9 ± 10.8	-0.45 ± 1	***0.005****

PO0479

Prevalence and Severity of Hyperkalemia in Patients Referred to Nephrology Consultation: Epidemiologic Data from 1106 Mexican Patients at a National Reference Hospital

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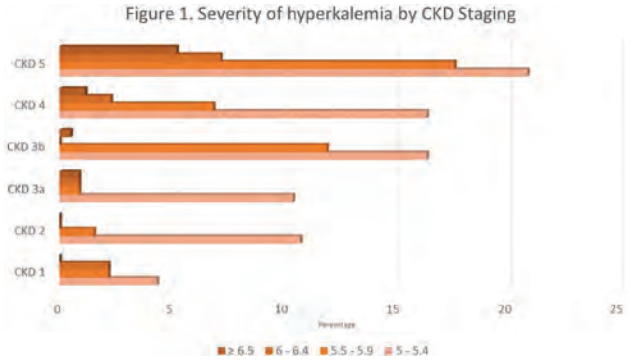
Background: Hyperkalemia (HK, serum K > 5 mEq / L) is an electrolyte disorder that occurs frequently in patients with chronic kidney disease (CKD), heart failure. In CKD, the ability to excrete K+ is reduced, impairing quality of life and increasing morbidity and mortality

Methods: Cross-sectional retrolective, observational study. Records of adult patients who attended an outpatient Nephrology consultation in the period from February 2019 to February 2020 were included, with laboratory reports from the last 15 days prior to the date of the medical consultation. Descriptive statistics were performed, with a 95% CI and a p-value ≤0.05

Results: 1106 patient records were included. 51% (563) were women. The mean age was 55.8 ± 15.6 years. 47% of the population had Diabetes mellitus and / or hypertension as their main comorbidity and 61% were overweight or obese. HK was identified in 29% of the study population. Figure 1 shows the frequency of HK by stage of CKD. 13% of the patients who entered the study were on renal replacement therapy, of which 54% had HK. 54% of the subjects with HK were diabetic, 56% hypertensive, 25% consumed ACE inhibitors and 13% consumed NSAIDs on a regular basis and 48% had proteinuria.

Conclusions: The presence of HK is a risk factor that increases the risk for cardiovascular complications and accelerates the progression to more advanced stages of CKD. It is important to intentionally search for this alteration in all stages of CKD and implement measures that help correct and mitigate its impact on patients with CKD

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.



PO0480

Serum Potassium and Survival Among Advanced CKD Patients Transitioning to Dialysis

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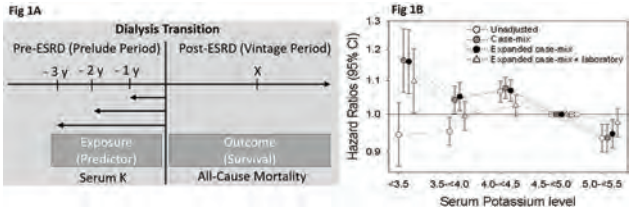
Background: Most laboratories designate a wide reference range for "normal" serum potassium levels (3.5-<5.5 mEq/L), yet the precise concentrations associated with favorable outcomes in chronic kidney disease (CKD) remain uncertain. While dietary potassium is commonly restricted in CKD patients to mitigate hyperkalemia, there may be ill effects of this strategy by restricting healthy potassium-rich foods (fruits, vegetables). We hypothesized that high-normal serum potassium levels are associated with better long-term survival in advanced non-dialysis dependent (NDD) CKD patients transitioning to dialysis.

Methods: Among 43,798 US Veterans with NDD-CKD transitioning to end-stage renal disease (ESRD) over 10/2007-3/2015, we examined the association of serum potassium levels averaged over the one-year pre-dialysis transition period (pre-ESRD prelude period) with post-ESRD mortality (**Fig 1A**) using national Veterans Affairs (VA) data linked to United States Renal Disease System data. Associations of serum potassium levels (categorized as <3.5, 3.5-<4.0, 4.0-<4.5, 4.5-<5.0, and 5.0-<5.5mEq/L) with all-cause mortality were estimated using adjusted Cox models.

Results: In adjusted Cox analyses, high-normal serum potassium levels ranging from 5.0-<5.5mEq/L were associated with greater survival (ref: 4.5-<5.0mEq/L): HR (95%CI): 0.95 (0.91-0.98) (**Fig 1B**). In contrast, serum potassium concentrations at or below low-normal serum potassium ranges were associated with higher death risk (ref: 4.5-<5.0mEq/L): HRs (95%CIs) 1.07 (1.04, 1.10), 1.05 (1.01, 1.09), and 1.16 (1.06, 1.27) for serum potassium levels 4.0-<4.5, 3.5-<4.0, and <3.5mEq/L, respectively.

Conclusions: In NDD-CKD patients transitioning to dialysis, serum potassium levels in the high-normal range were associated with greater long-term survival, whereas serum potassium levels at or below low-normal ranges were associated with higher long-term death risk. Further studies are needed to determine whether dietary factors may be a potential mechanistic link underlying these relationships.

Funding: NIDDK Support



PO0481

Hyperkalemia, CKD, and RAAS Inhibition: A Triad with a Fine Balance to Prevent Mortality

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Background: Hyperkalemia (HK) is a common and dangerous complication of CKD. HK is also a complication of beneficial therapeutic agents acting on the RAAS. Our goal was to investigate incidence, prevalence and clinical outcomes of at least one episode of HK in a CKD population outpatient setting. Additionally, we investigated the association of HK with changes in RAAS inhibition and mortality risk.

Methods: Retrospective analysis of all adult patients referred to a nephrology clinic over a 6 years period. We included CKD stage 3 patients with at least 24 months of follow up and 3 or more serum potassium determinations. The prevalence of HK at first consultation and incidence during follow up were accessed. Patients were spited in two groups prior to analysis: A) Patients without any HK episode and B) Patients with at least one HK episode.

Results: Out of the 3008 patients referred, 575 (19.1%) met the inclusion criteria (mean age: 70.4 years; 63.7% male and 94.0% white color). Mean follow-up was 4.1±1.8 years. The prevalence of HK at first consultation was 8.7% and follow up incidence 21.7%. From this cohort, 164 (28.5%) had at least on episode of HK (Group B) and 101 (17.6%) died. During the follow up, RAAS inhibition drugs was removed or not started in 200 (34.8%) and diuretic was initiated in 165 (28.7%). At least one HK episode was associated with Diabetes (65.9 vs 42.3%, p<0.001), Heart failure (36.6 vs 28.0%, p=0.007), Macroalbuminuria (34.1 vs 21.2%, p=0.001), CKD progression (33.5 vs 16.3. p<0.001) higher frequency of diuretic initiation (38.4 vs 24.8%, p<0.001) and higher mortality (27.6 vs 13.7%, p<0.001). The independent predictors of mortality were: At least one HK episode (OR 1.82, 95% CI 1.08-3.04); Heart Failure (OR 1.97, 95% CI 1.16-3.35); Older age (OR per 1 year increase 1.04, 95% CI 1.02-1.07); CKD progression (OR 4.18, 95% CI 2.43-7.19); Patients who maintained RAAS inhibition during follow up (OR 0.50, 95% CI 0.26-0.96); Patients who started RAAS inhibition during follow up (OR 0.38, 95% CI 0.16-0.88).

Conclusions: Our study confirms that RAAS inhibition had and protector and independent impact in mortality when prescribed in CKD early stages. Patients with at least one episode of HK have a higher risk of mortality. All efforts should be made to maintain these therapeutic agents, looking for other ways to control hyperkalemia rather than stop it.

PO0482

High Serum Alkaline Phosphatase Predicts CKD Progression: Effect Modification by GFR

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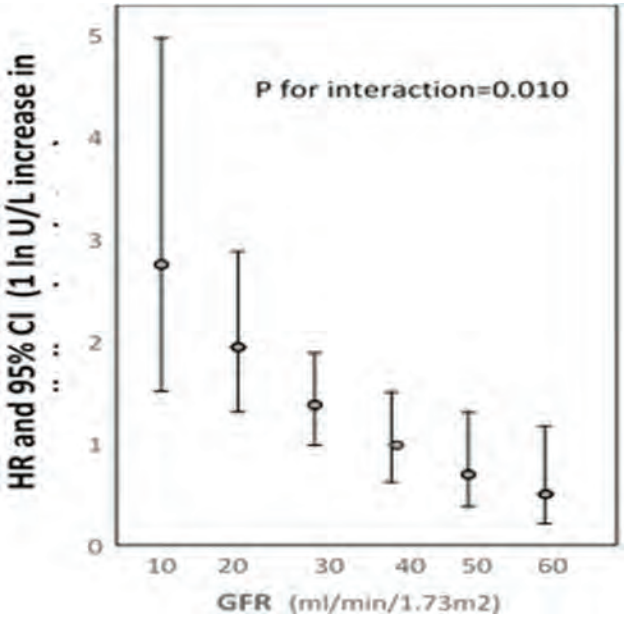
Background: In the post-hoc analyses of SUSTAIN/ASSURE trials, Apabetalone, an epigenetic modulator which lowers alkaline phosphatase (AlkPhos), stabilized the GFR in patients with CV disease and GFR <60/ml/min/1.73m2. Analyzing the relationship between AlkPhos and renal outcomes in patients with CKD is useful to explore the biological hypothesis that AlkPhos is implicated in CKD progression.

Methods: We investigated the relationship between AlkPhos and the risk of a combined end-point (30% GFR loss or dialysis/renal transplantation) in 609 stage 3-5 CKD patients (mean GFR: 34.8±12.1ml/min/1.73 m2).

Results: Median AlkPhos was 91 IU/L and in the majority of patients had values below 147 IU/L (the upper limit of the normal range). Over a median follow up of 3 yrs, 200 patients had the combined end-point. In an unadjusted analysis, 1 ln increase in AlkPhos entailed a 49% risk excess for the renal end-point (HR:1.49, 95% CI 1.11-2.01, P=0.008). Adjusting for age, gender, smoking, diabetes, cholesterol, BMI, systolic BP, CV comorbidities, hemoglobin, albumin, phosphate, and hs-CRP, did not modify this association (HR:1.48, 95% CI 1.08-2.02, P=0.016). In a fully adjusted analysis testing the GFR as an effect modifier of the AlkPhos - combined renal end point link showed a GFR-AlkPhos interaction (Figure). Indeed, the risk for the combined end-point was gradually more pronounced at progressively more severe degrees of renal dysfunction (see Figure).

Conclusions: In stage 3-5 CKD patients, AlkPhos within the normal range is associated with the progression to ESRD and the GFR is an effect modifier of this relationship. These findings are compatible with the hypothesis that within the normal range of this biomarker, the risk for CKD progression by AlkPhos is amplified by CKD severity. These data are in keeping with post-hoc analyses of SUSTAIN/ASSURE trials and support the hypothesis that interventions lowering AlkPhos may mitigate CKD progression.

Funding: Government Support - Non-U.S.



PO0483

The Association Between Fibroblast Growth Factor 23 (FGF-23) and Pulse Pressure (PP) in CKD Stage G5 Patients

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Background: FGF23 is associated with increased cardiovascular events and mortality in CKD patients. Non-classical biological effects of FGF23, such as left ventricular hypertrophy and vascular remodeling, may potentially explain this association. Experimental models suggest that FGF23 stimulates renal tubular sodium reabsorption and volume overload. It is plausible that FGF23 also increases blood pressure. The linking of FGF23 increment with blood pressure control may help identify novel risk factors of mortality in CKD patients. Therefore, we aimed to evaluate the relationship between FGF23, blood pressure control, and indirect signs of arterial stiffness in subjects with CKD G5

Methods: Clinical and analytical variables were analyzed in 159 CKD G5 patients immediately before starting kidney replacement therapy. The association between these variables and the levels of intact FGF23 (iFGF23) was evaluated with linear regression models. PP was used as an indirect surrogate of arterial stiffness. Statistics were performed using R v3.6.2

Results: The mean SBP was 158.8±21.3 mmHg, whereas the mean DBP was 87.2±12.3 mmHg, and the mean PP was 76.6±20 mmHg. The median iFGF23 was 468.3 (268.8—904.9) pg/ml. iFGF23 was positively correlated with serum phosphate (p<0.001), plasma sodium (p=0.02), C-reactive protein (p<0.01), SBP (p<0.001), DBP (<0.01) and PP (p=0.02). Linear multivariable analysis (Table1) showed that iFGF23 was independently associated with the increase in SBP, DBP, and PP, suggesting that for each 10 pg/ml increase in iFGF23, the SBP increased 3.7 mmHg, the PAD increased 3.0 mmHg, and PP increased 2.1 mmHg. By every ten years of increment in age, PP increased 2.4 mmHg (p<0.01).

Conclusions: The increase in FGF23 is associated with higher SBP, DBP, and PP. These data suggest that iFGF23 may increase the risk of cardiovascular events in patients with CKD G5 through increasing blood pressure and arterial stiffness.

	SBP (mmHg)		DBP (mmHg)		PP (mmHg)	
	Beta	p*	Beta	p*	Beta	p*
iFGF23 (pg/ml)	0.37	<0.0001	0.30	0.003	0.21	0.04
Age (yr)	—	—	0.28	0.003	0.24	<0.01

Table1. Determinants of SBP, DBP, and PP. *SBP: Systolic Blood Pressure DBP: Diastolic Blood Pressure. PP: Pulse Pressure. * Model adjusted by serum phosphate, serum calcium, parathyroid hormone, and C-reactive protein*

PO0484

Pulse Mass Index and Pulse Mass Pressure Product in CKD Patients

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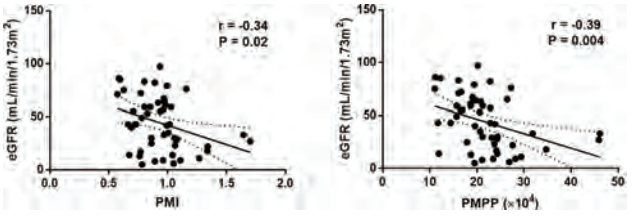
Background: Recent studies have conflicting findings on the association between obesity and the risk of chronic kidney disease (CKD). The body mass index (BMI) by itself is an imperfect marker of metabolically unhealthy obesity. The pulse mass index (PMI) and the pulse mass pressure product (PMPP) show strong correlations with the risk of cardiovascular disease and may reflect an individual's metabolic energy state. However, it is still unclear whether PMI and PMPP can be useful parameters for the risk of CKD.

Methods: We retrospectively identified 51 subjects who underwent ambulatory blood pressure monitoring and kidney biopsy simultaneously at the Jikei University Hospital, Tokyo, from 2017 to 2019. All subjects were diagnosed as primary or secondary glomerular diseases by kidney biopsy. The PMI and the PMPP were calculated from the following formula: PMI = BMI × resting heart rate (RHR) /1730. PMPP = BMI × RHR × systolic blood pressure. We evaluated the clinicopathological findings associated with PMI and PMPP.

Results: Of 51 subjects, the age was 50.3 ± 16.1 years (mean ± standard deviation), and 60.8% were male. The eGFR was 44.4 ± 25.3 mL/min/1.73m^2. The median glomerulosclerosis index (GS) was 18.3 (interquartile range, 4.7-44.4) %, and the tubular injury level was 17.5 (5.0-36.3) %. The PMI was 0.94 ± 0.23, the PMPP was 21.6 ± 7.3 ×10^4, and the BMI was 22.9 ± 4.47 kg/m^2. Both PMI and PMPP were positively associated with GS, HbA1c, and triglyceride, whereas negatively associated with eGFR (P = 0.02 and 0.004; respectively), CKD stages (P = 0.04 and 0.02; respectively) and HDL. Of note, each parameter such as BMI, RHR, and blood pressure was not correlated with either eGFR or CKD stages.

Conclusions: We observed correlations between both PMI and PMPP and kidney function. This study indicates that PMI and PMPP may be possible makers of the relative risk of unhealthy obesity with CKD.



PO0485

Thyroid Status and Mortality Among CKD Patients Transitioning to Dialysis

Jia Li,[1] Amy S. You,[1] Gregory Brent,[2] Elani Streja,[1] Dorsa F. Maryska,[3] Monica Thornhill-Joynes,[3] Yoko Narasaki,[1] Jui-Ting Hsiung,[1] Cachet Wenziger,[1] Christina Park,[1] John J. Sim,[4] Danh V. Nguyen,[1] Csaba P. Kovesdy,[5] Kamyar Kalantar-Zadeh,[1] Connie Rhee.[1] *[1]University of California Irvine, Irvine, CA; [2]University of California Los Angeles, Los Angeles, CA; [3]Kidney Specialists Medical Corporation, Los Angeles, CA; [4]Kaiser Permanente Southern California, Pasadena, CA; [5]The University of Tennessee Health Science Center, Memphis, TN.*

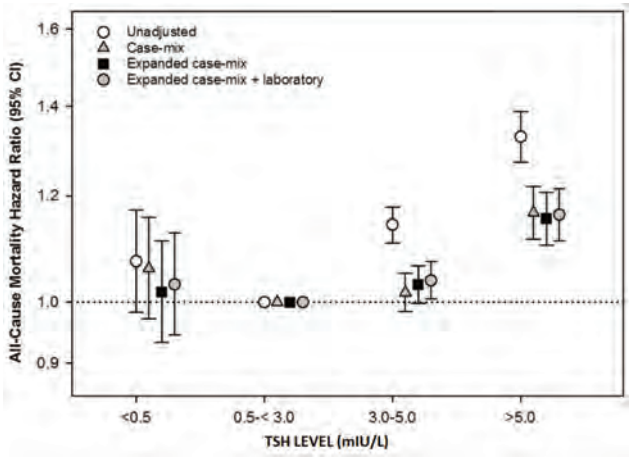
Background: Hypothyroidism has been associated with higher death risk in non-dialysis dependent chronic kidney disease (NDD-CKD) and end-stage renal disease (ESRD) patients, presumably due to cardiovascular pathways. We examined whether pre-ESRD thyroid status is a predictor of survival in NDD-CKD patients transitioning to dialysis.

Methods: Among US Veterans with NDD-CKD transitioning to dialysis from 10/2007-3/2015, we examined the association of serum thyrotropin (TSH) levels averaged over a three-year pre-ESRD transition period ("pre-ESRD prelude period") with post-ESRD mortality. Patients were followed for the outcome for up to three-years, and HRs for all-cause mortality were estimated using expanded case-mix+laboratory adjusted Cox models. In sensitivity analyses, we examined varying pre-ESRD prelude and post-ESRD mortality intervals.

Results: Among 43,161 patients in the primary cohort (three-year pre-ESRD prelude cohort), increasingly higher TSH levels >3.0mIU/L were associated with incrementally higher mortality (ref: TSH 0.5-<3.0mIU/L): adjusted HRs (95%CI) 1.04 (0.95-1.13), 1.04 (1.00-1.07), and 1.16 (1.11-1.22) for TSH levels of <0.5, 3.0-5.0, and >5.0mIU/L, respectively. A similar pattern of findings was observed for patients whose TSH levels were examined over one-year and two-year pre-ESRD prelude periods, with follow-up for the outcome of interest for up to one and two years, respectively.

Conclusions: There was a dose-dependent relationship between higher pre-ESRD TSH levels exceeding 3.0mIU/L and higher post-ESRD mortality in NDD-CKD patients transitioning to dialysis. Further studies are needed to determine the underlying determinants of thyroid dysfunction in CKD, and whether reduction of TSH levels with thyroid hormone supplementation ameliorates mortality in this population.

Funding: NIDDK Support



PO0486

Baseline Characteristics of Non-Dialysis CKD Patients with and Without Anemia: A Report from the Retrospective Cohort from DISCOVER CKD

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Background: Anemia is a frequent complication of chronic kidney disease (CKD), associated with adverse clinical outcomes and reduced quality of life. This analysis describes baseline characteristics of non-dialysis dependent (NDD) CKD patients with and without anemia in DISCOVER CKD.

Methods: The DISCOVER CKD retrospective cohort of patients in this analysis were extracted from the TriNetX health research network, Japan Medical Data Vision (JMDV) and integrated Limited Claims and EHR (LCED) databases. Patients were aged >18 years with 2 estimated glomerular filtration rate (eGFR) measures <60 mL/min/1.73m2 >90 days apart between January 2008 and March 2020. The index date was the first Hb measure (regardless of value) or an anemia therapy (iron, ESA or blood transfusion) prescription after the 2nd eGFR measure. Exclusion criteria included: <1-year registration/medical history prior to index, active bleeding, a Hb value (only) within 30 days from transfusion or bleeding and no Hb measure within a year after CKD diagnosis. Anemia was defined as <12 g/dL [females], <13 g/dL [males] per WHO criteria. Baseline characteristics were summarized and stratified by presence of anemia.

Results: Preliminarily**,** of 709183 CKD patients meeting our I/E criteria, 67% were not anemic at baseline. In patients with anemia (33%): 191451 (81%) had a baseline Hb of 10-12(female)/10-13(male)g/dL, 36889 (16%) 8-10g/dL and 6906 (3%) <8g/dL. Compared to patients without anemia: patients with anemia were older, more likely to be female, to have more advanced CKD, and more likely to have comorbidities.

Conclusions: In routine clinical care, the presence and severity of anemia increases as CKD advances and is associated with a higher comorbidity burden.

Table 1 - Prevalence and baseline characteristics of CKD patients with and without anemia.

	Patients with Anemia by Severity						Patients Without Anemia	
	Hb < 8 g/dL		Hb 8-10 g/dL		Hb 10-12/10-13 g/dL			
Database	LCED	JMDV+TriNetX	LCED	JMDV+TriNetX	LCED	JMDV+TriNetX	LCED	JMDV+TriNetX
N (%)	458	6448	2701	34188	14684	176767	36722	437215
Demographics								
Age, Mean (SD)	71.0 (14.0)	64.3 (15.6)	72.8 (14.2)	66.1 (15.1)	73.4 (13.1)	67.5 (13.8)	68.9 (13.3%)	64.3 (13.4%)
Female N (%)	265 (57.9%)	3750 (58.2%)	1648 (61.0%)	21278 (62.2%)	7707 (52.5%)	94879 (53.7)	22101 (60.2%)	262412 (60.0%)
BMI, Mean (SD)	28.1 (6.8)	27.5 (5.9)	28.8 (7.2)	28.1 (5.9)	29.2 (6.8)	28.6 (5.7)	30.0 (6.5)	29.0 (5.3)
Baseline (Index) Comorbidities N (%)								
Hypertension	368 (80.3%)	4517 (70.1%)	2238 (82.9%)	24145 (70.6%)	12579 (85.7%)	123809 (70.0%)	28202 (76.8%)	261926 (59.9%)
Heart Failure	138 (30.1%)	1707 (26.5%)	953 (35.3%)	9459 (27.7%)	3818 (26.0%)	36230 (20.5%)	4833 (13.2%)	45277 (10.4%)
Stroke	121 (26.4%)	1047 (16.2%)	798 (29.5%)	5519 (16.1%)	4023 (27.4%)	27667 (15.7%)	7101 (19.3%)	49427 (11.3%)
Type 2 diabetes	205 (44.8%)	2426*37.6%)	1269 (47.0%)	13845 (40.5%)	6708 (45.7%)	64741 (36.6%)	11110 (30.3%)	99897 (22.8%)
Baseline (Index) Labs, Mean (SD)								
eGFR	42.3 (15.8)	41.8 (25.0)	43.4 (16.5)	41.1 (22.3)	47.4 (15.4)	47.0 (20.2)	49.6 (17.9)	53.5 (22.2)
LDL Cholesterol	2.2 (1.1)	2.2 (1.0)	2.2 (1.0)	2.3 (1.2)	2.3 (1.0)	2.4 (1.0)	2.6 (1.0)	2.7 (1.0)
Hb	7.1 (0.8)	7.0 (0.8)	9.2 (0.6)	9.1 (0.7)	11.6 (0.8)	11.5 (0.9)	14.0 (1.2)	14.1 (1.3)

Non-anemic patients includes all patients fulfilling the I/E criteria. For anemia severity, this included patients with eligible Hb values only.

PO0487

Incidence of and Risk Factors for Incident eGFR <60 in the REasons for Geographic and Racial Differences in Stroke Study

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Background: Few contemporary US cohorts examined the incidence of and risk factors for developing a low estimated glomerular filtration rate (eGFR) or whether these factors vary by race, sex or region of US residence.

Methods: We studied 11,814 black or white participants with an eGFR> 60 ml/min/1.73m^2 at baseline and who had 10-year follow-up eGFR. Low eGFR was defined as incident eGFR<60 ml/min/1.73m^2 at the second visit and ≧40% decline from baseline. Incidence rates were calculated overall and by age, sex and race groups. We used Poisson regression to calculate the risk of incident low eGFR, adjusting for demographics, socioeconomic status and clinical factors, and across race, sex and region strata.

Results: At baseline, mean age was 62 (±8.1) years, 54% were female, 36% black and 56% resided in the US stroke belt. The overall incidence of low eGFR was 9% and ranged from 4% in those aged 45-54 to 18% in those 75 years and older. Age, systolic blood pressure, diabetes, heart disease, BMI, smoking, lower income, higher education, and residence in the US stroke belt were independent risk factors for incident low eGFR. Blacks had higher risk, accounting for sociodemographic risk factors, but this was fully attenuated after adjusting for clinical factors. Low eGFR risk factors did not differ substantially by race, sex or region.

Conclusions: The higher incidence of low eGFR in black compared to white participants was accounted for by modifiable clinical risk factors. Residence in the US stroke belt was independently associated with incident low eGFR in REGARDS participants.

Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke, National Institute on Aging

Risk factors for incident low eGFR (Relative risk and 95% confidence interval)

Risk factor	Model 1	Model 2	Model 3
Age, per SD increase	1.46 (1.39, 1.54)	1.42 (1.33, 1.49)	1.44 (1.36, 1.54)
Male sex, vs female	0.87 (0.78, 0.97)	0.97 (0.86, 1.09)	0.88 (0.78, 1.00)
Black race, vs white	1.30 (1.16, 1.46)	1.22 (1.08, 1.39)	0.97 (0.85, 1.10)
High school or above, vs less		0.71 (0.59, 0.85)	0.82 (0.68, 0.99)
Income ≥$35,000/yr or more, vs lower		0.74 (0.65, 0.84)	0.85 (0.74, 0.97)
US stroke belt, vs rest of the US		1.16 (1.03, 1.31)	1.15 (1.02, 1.29)
Current smoking, vs former or never		1.19 (0.99, 1.43)	1.30 (1.08, 1.50)
Systolic blood pressure, mmHg, per SD higher			1.21 (1.15, 1.28)
BMI, kg/m^2, per SD higher			1.20 (1.13, 1.27)
Diabetes, vs none			2.30 (1.02, 2.63)
History of heart disease, vs none			1.33 (1.15, 1.55)

PO0488

High Prevalence of CKD Among Individuals Living with HIV in the United States

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Background: Chronic kidney disease (CKD) is an important comorbidity among people living longer with human immunodeficiency virus (HIV). We report the prevalence, trends and characteristics of individuals with HIV in the US, with the aim of better understanding this understudied, but important risk factor for CKD.

Methods: Data from 22,626 adults aged 20-59 who had consented for HIV testing in the National Health and Nutrition Examination Survey (NHANES; 1999-2014), were analyzed. Those with HIV + vs. - serology were compared with respect to demographics, comorbidities, and social determinants of health in the full sample and those with CKD, as defined by either eGFR<60 ml/min/1.73m^2 or urine albumin to creatinine ratio of >30 mg/g. Logistic regression was used to assess the odds of CKD by HIV status. Comparisons were assessed using survey weights for all analyses.

Results: Prevalence of HIV+ remained stable, from 0.4% to 0.6% during this time period. Individuals HIV+ were older than those HIV- in both the full sample and among those with CKD. A higher proportion of HIV+ than HIV- individuals were black, current smokers, had < high school education, with income <$45k, and reported either Medicare or other government insurance (Table). Among individuals with CKD, those HIV+ had almost twice the prevalence of diabetes (30% vs. 19%, p=NS) and over 4 times higher awareness of their CKD (28% vs. 6%, p=0.002) compared to HIV-. HIV+ vs. HIV- individuals had more than twice the prevalence of CKD (15.3% vs. 7.1%, p=0.002). CKD was associated with HIV + status [unadjusted odds ratio (OR) = 2.37; 95% CI: 1.36-4.17]. Adjusting for other covariates, attenuated the association only slightly (adjusted OR=2.17; 95% CI: 1.21-3.89).

Conclusions: CKD was associated with HIV+ status among younger adults living with the disease in the US. However, larger, longitudinal studies among individuals living with HIV and CKD are needed to increase awareness of this complication among survivors of the disease.

Measure	All Tested (mean or %, 95% CI)			With CKD (Mean or %, 95% CI)		
	HIV + (n=130)	HIV – (n=22,262)	P-value + vs. -	HIV + (n=22)	HIV – (n=1,783)	P-value + vs. -
Age (years)	40.4 (39.0-41.7)	36.9 (36.6-37.3)	0.005	43.1 (41.8-44.9)	39.1 (38.3-39.8)	0.004
Male (%)	79.5 (74.2-84.8)	49.1 (48.5-49.7)	<0.0001	61.5 (45.0-77.9)	40.4 (37.3-43.5)	0.08
Black Race (%)	49.8 (42.7-56.9)	11.5 (10.2-12.7)	<0.0001	49.4 (34.9-63.9)	14.9 (12.7-17.1)	0.003
Current Smoker (%)	50.0 (42.2-57.9)	26.1 (25.0-27.2)	<0.0001	48.9 (38.2-59.7)	28.4 (25.6-31.1)	0.07
Diabetes (%)	5.6 (2.0-9.2)	5.0 (4.6-5.3)	0.80	30.4 (0-69.9)	18.7 (16.4-20.9)	0.36
Hypertension (%)	24.1 (18.0-30.2)	18.2 (17.4-19.0)	0.22	45.0 (28.8-61.3)	51.5 (48.3-54.7)	0.59
Education < HS (%)	24.0 (17.4-30.7)	16.5 (15.5-17.5)	0.05	28.8 (0-68.7)	21.0 (18.8-23.1))	0.51
Income < $45k	73.3 (66.3-80.3)	43.9 (42.2-45.5)	<0.0001	86.1 (73.0-99.3)	51.1 (47.6-54.5)	0.04
Insured: (%)	72.7 (66.6-78.7)	75.7 (74.6-76.8)	0.47	83.1 (57.8-100)	74.7 (72.1-77.4)	0.42
Medicare	8.8 (4.0-13.6)	1.6 (1.4-1.9)	0.0001	19.5 (13.7-25.2)	4.3 (3.1-5.5)	0.02
Private	41.2 (35.5-46.9)	64.4 (63.0-65.7)	<0.0001	33.5 (0-73.6)	56.2 (53.2-59.1)	0.16
Other government	19.4 (14.4-24.3)	8.1 (7.5-8.7)	0.0001	19.8 (13.9-25.7)	12.6 (10.6-14.5)	0.19
Low eGFR* (%)	2.8 (0.5-5.0)	1.0 (0.8-1.2)	0.02	18.0 (0-41.1)	13.5 (11.0-16.0)	0.51
Albuminuria (%)	14.9 (11.2-18.5)	6.5 (6.0-6.9)	0.0008	97.3 (96.4-98.1)	91.5 (89.5-93.4)	0.24
Any CKD (%)	15.3 (11.6-19.0)	7.1 (6.6-7.5)	0.002	100	100	-
Aware of CKD (%)	-	-	-	27.9%	5.5%	0.0017

* eGFR < 60 ml/min/1.73m^2

PO0489

Oxygen Kinetics and Microvascular Function in CKD

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Background: Patients with chronic kidney disease (CKD) have reduced cardiorespiratory fitness levels that are associated with reduced quality of life and mortality. Impaired oxygen uptake kinetics create a larger oxygen deficit that promotes fatigue. CKD related microvascular dysfunction may contribute to impaired oxygen uptake kinetics by hampering oxygen delivery to the working muscle. The purpose of this study is to investigate the relationship between oxygen kinetics and a measure of microvascular function in CKD.

Methods: 13 patients with stage 3-5 CKD (Mean±SD, Age 60±14 years; eGFR 48.5±10.3 ml/min/1.73m^2) were included in the analysis. Peak oxygen consumption (VO_{2peak}) was measured via breath by breath expired respiratory gas analysis during a symptom limited graded cycle ergometry test. Oxygen kinetics were quantified as mean response time (MRT), the exponential time constant to reach 63% of steady state VO_2. MRT was analyzed from three minutes of steady state submaximal cycling (<60% VO_{2peak}). Microvascular function was assessed as cutaneous vasodilation during local heating coupled with intradermal microdialysis, measured by laser Doppler flowmetry.

Results: VO_{2peak} was 20.36±6.87ml/kg/min. A moderate inverse correlation was shown between oxygen uptake kinetics and microvascular function (Figure 1; r=-0.56, p=0.02).

Conclusions: Microvascular dysfunction may contribute to a larger oxygen deficit in CKD patients. Following further studies, microvascular function could serve as a potential treatment target to improve exercise tolerance in these patients.

Funding: Other NIH Support - Grant number: 17GRNT33670462

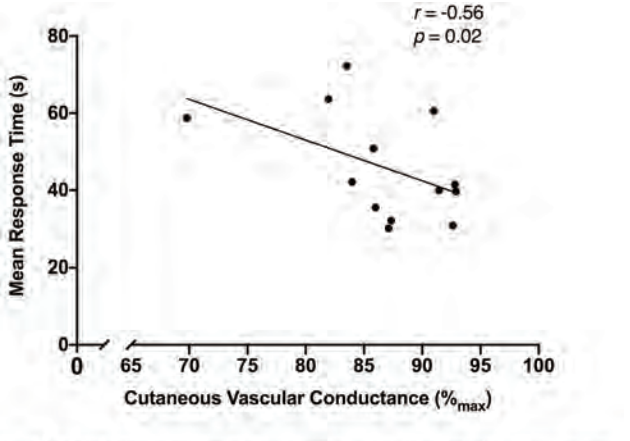

Figure 1. Reduced microvascular function (cutaneous vascular conductance) is associated with slower oxygen uptake kinetics (mean responsne time) in non-dialysis CKD patients. Cutaneous blood flow response to standardized local heating is expressed as percentage of maximal dilatory capacity obtained with local infusion of sodium nitropruisside via intradermal microdialysis.

PO0490

Trends, Prevalence, and Predictors of Illicit Drug Use in CKD Patients

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Background: Illicit drugs use is an important problem in general populations and chronic kidney disease (CKD) patients. Since 2012, marijuana has been legalized in several parts of United States, however, the trend and prevalence of illicit drug use in CKD patients in the current era remains unknown.

Methods: We conducted a cross-sectional analysis using the data from the National Health and Nutrition Examination Survey between 2007 and 2018. We calculated the trend of self-reported illicit drug use (marijuana, cocaine, heroin, methamphetamine, and intravenous drug use) and defined current use if the last use was within 1 year of the survey. We then assessed whether the use of illicit drugs is associated with CKD (defined by estimated glomerular filtration rate ≤ 60 ml/min/1.73 m^2 and/or urine albumin-creatinine ratio (UACR) ≥ 30 mg/g), microalbuminuria (UACR≥ 30 mg/g) and macroalbuminuria (≥ 300 mg/g). Lastly, we assessed any predictors for drug use in CKD patients.

Results: Between 2007 to 2018, there were 22,214 adult patients between 18-59 years old. Of these, 2,148 had CKD as defined above. CKD patients were significantly older, more likely to be female, obese, cigarette smoker, alcohol drinker, and to have diabetes, and hypertension. We found that prevalence of marijuana (21.9% vs 21.9%, p=0.23), cocaine (4.9 vs 3.6, p=0.95) and methamphetamine (1.5% vs 1.3%, p=0.52) did not differ between CKD and non-CKD. However, heroin use (0.2% vs 0.5%, p=0.02) were significantly lower in CKD compared to non-CKD. Interestingly, there is significant trend towards increasing marijuana use in CKD patients overtime as prevalence increase from 17.3% in 2007-2010 to 21.7% in (2011-2014), and up to 26.5% in 2015-2018 (p trend 0.02). Recent Illicit drug use was not associated with CKD, microalbuminuria or macroalbuminuria. Age, black race, current smoker and alcohol drinking were significant predictors of drug use within 1 year in CKD patients.

Conclusions: In a national sample, marijuana was the most common illicit drug use among CKD patients and the trend of marijuana use in CKD patients is increasing, likely due to marijuana legalization. Age, black race, current smoker and alcohol drinking increase the odds of illicit drug use in CKD patients.

PO0491

Evaluating the Longitudinal Association of Marijuana Use and Adverse Kidney Outcomes

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Background: Marijuana use has increased for recreational and medicinal purposes, however, its long-term effects on the kidneys remain uncertain. We examined the longitudinal association of marijuana use and adverse kidney outcomes among adults living in Baltimore, MD.

Methods: We used data from the prospective Healthy Aging in Neighborhoods of Diversity across the Life Span study. Baseline exposure, defined as self-reported never, former, or current marijuana use, and covariates were obtained between 2004 and 2009. The primary outcome was incident reduced kidney function, defined as an eGFR<60 ml/min/1.73m^2. Rapid kidney function decline (defined as ≥3% eGFR decline per year) among those with a baseline eGFR>=15 and incident albuminuria (albumin-to-creatinine ratio (ACR) >= 30 mg/g) at follow-up was also assessed. Participant characteristics were evaluated using ANOVA or χ^2 tests. Multivariable-adjusted logistic regression was used to evaluate associations of marijuana use with kidney outcomes. Covariates included baseline eGFR, age, sex, race, education, poverty status; current cigarette, opiate, cocaine use; hypertension, diabetes, and body mass index (BMI).

Results: Among 1,529 participants, 54.5%, 31.8% and 13.7% reported never, former, or current marijuana use, respectively. Participants with current marijuana use were more likely to be younger, male, African American, have lower BMI and concurrently use cigarettes, opiates and/or cocaine; but were less likely to have hypertension or diabetes. Mean follow-up time was 8.6 years. 337 deaths occurred in this cohort, but there was no significant difference in deaths between marijuana exposure groups (Pearson χ^2, p= 0.524). After adjustment, marijuana use was not significantly associated with incident reduced kidney function (OR 1.08 [95% CI, 0.49-2.36] among those with current use, and OR 0.90 [95% 0.49-1.61] for former use). Marijuana use was not significantly associated with rapid kidney function decline (OR 0.73 [95% CI, 0.42-1.27] for current use) or incident albuminuria (OR 0.63 [95% CI, 0.11-3.48] for current use).

Conclusions: In this Baltimore-based cohort, there was no independent association of marijuana use and longitudinal adverse kidney outcomes.

Funding: Other NIH Support - National Institute on Aging

PO0492

Life's Simple 7 and CKD Progression: Results from the Mexico Chronic Renal Insufficiency Cohort (MCRIC) Study

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Background: The American Heart Association developed the Life's Simple 7 metric to promote cardiovascular health. We evaluated the association of this metric with chronic kidney disease (CKD) progression among individuals with CKD living in Mexico.

Methods: MCRIC is an ongoing, prospective observational cohort study of adults with CKD recruited in Mexico City, with entry estimated glomerular filtration rate (eGFR) 20-70 ml/min/1.73 m^2. Using data from 371 participants, we conducted Cox proportional hazards regression analysis to evaluate the association between Life's Simple 7 (score range 0-14) and CKD progression (30% decline in eGFR from baseline).

Ideal cardiovascular health was defined as nonsmoker; body mass index <25 kg/m^2; ≥150 minutes/week of physical activity; healthy dietary pattern (high in fruits and vegetables, fish, and fiber-rich whole grains; low in sodium and sugar-sweetened beverages); total cholesterol <200 mg/dL; blood pressure <120/80 mm Hg; and fasting blood glucose <100 mg/dL).

Results: At study entry, mean age was 57 years, 71% were male, and 57% had diabetes. The mean baseline eGFR was 47 ml/min/1.73m^2, and the median urine protein excretion 633 mg/24 hours. Nine percent met all seven criteria for ideal cardiovascular health. During a median follow-up of 2.9 years, there were 78 CKD progression events. In sex- and age-adjusted analysis, each point higher Life's Simple 7 score was associated with 13% lower risk of CKD progression (HR, 95% CI, 0.87, 0.78-0.96). This association attenuated after adjusting for baseline eGFR and proteinuria (0.94, 0.83-1.05).

Conclusions: In this cohort of adults with CKD in Mexico, the prevalence of ideal cardiovascular health as measured by Life's Simple 7 was low. The protective effect of Life's Simple 7 on CKD progression was explained by baseline kidney function.

Funding: NIDDK Support, Other NIH Support - Fogarty International Center, Private Foundation Support

PO0493

Facilitators and Barriers to Self-Management of CKD

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Background: Self-management is integral for the treatment of chronic kidney disease (CKD). Despite low adherence to self-management behaviors, few studies provide insight into barriers and facilitators of self-management from the perspective of patients.

Methods: Semi-structured interviews were conducted with 30 participants who were purposively recruited for representation by CKD stage (3 or 4), age (<65, ≥65 yrs), race (white, non-white), and sex. Interviews focused on patient experiences with CKD and efforts to follow treatment recommendations. They were recorded, transcribed, and entered into NVivo 12.0 for coding and analysis. Transcripts were coded inductively and analyzed thematically.

Results: We identified three key phases of CKD self-management behavior engagement: prioritization, participation, and maintenance. Facilitators and barriers were organized according to these phases. Participants needed to **prioritize** the behavior to consider engagement, which was favorably influenced by optimism, stress management, and effective patient-provider communication. Prioritization was impeded by fatalism and competing priorities. One of the most widely reported impediments to behavior **performance** was comorbid conditions that caused treatment burden and adverse symptoms. Notable facilitators of behavior performance included the presence of motivating factors, self-efficacy, social support, low cost, and convenience. For **maintenance**, participants' ability to integrate and sustain behaviors in their lives was influenced by the aforementioned behavior performance factors, but also by behavior-specific factors, such as pets and physical therapy (for physical activity) and pharmacy assistance (for medication adherence). Key elements of effective maintenance included the use of memory aids, goal-setting, self-monitoring, and proactive preparation.

Conclusions: Individuals who adhered to CKD self-management behaviors viewed them as a priority, and developed strategies that fit their life to allow for behavior performance and maintenance. To increase self-management behavior prioritization, performance, and maintenance, we need to assess patients' attitudes and beliefs, improve patient-provider communication, help patients overcome barriers such as high costs and conflicting treatment regimens, and leverage facilitators such as memory aids and goal-setting.

Funding: NIDDK Support

PO0494

Relationship Between Renal Function and Quality of Life in Patients with CKD at the Pre-Dialysis Stage

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Background: There have been several studies evaluating the effect of kidney function on health-related quality of life (HRQOL). However, the association between kidney function and the burden of kidney disease, symptoms, and the effects of kidney disease among patients with advanced-stage kidney disease remains unclear.

Methods: The nationwide prospective Reach-J cohort study was successfully conducted. Of these patients, 2,248 with advanced chronic kidney disease (CKD) stage G3b (n = 632), G4 (n = 1010), and G5 (n = 606) were included in our study. A questionnaire regarding the kidney-disease-specific domains of quality of life (QOL) including burden, symptoms, and the effects of kidney disease at the baseline was cross-sectionally evaluated. Moreover, factors influencing the QOL were studied.

Results: Patients' characteristics were as follows: age, 69.1±12.6 years; male, 64.6%; estimated glomerular filtration rate, 23.2 ± 10.4 mL/min/1.73m^2; and serum creatinine level was 2.64 ± 1.49 mg/dL. The rates of comorbidities were as follows: diabetes, 33.6%; hypertension, 87.3%; ischemic heart disease, 8.2%; and chronic obstructive pulmonary disease (COPD), 2.3%. Crude scores in CKDG4 and CKDG5 as comparison to CKDG3b were as follows: burdens, -8.7 and -17.5; symptoms; -2.1 and -4.5; effects of kidney disease, -4.4 and -8.1, respectively. After adjusting for age, sex, body mass index (BMI), diabetes, hypertension, ischemic heart disease, COPD, and CKD stage; multivariate analysis to identify independent factors that caused reduced QOL scores revealed that age (β = 0.053, p = 0.024), BMI (β = 0.091, p < 0.001), diabetes (β = –0.058, p = 0.014), and CKD stage (β = –0.25, p < 0.001) were significant factors for burden; that age (β =–0.153, p < 0.001), diabetes (β =–0.093, p < 0.001), and CKD stage (β =–0.11, p < 0.001) were significant factors for symptoms; and that age (β = –0.128, p < 0.001), BMI (β = 0.067, p = 0.005), diabetes (β = –0.066, p = 0.006) and CKD stage (β = –0.196, p < 0.001) were significant factors for the effects of kidney disease.

Conclusions: This study suggests that the progression of CKD stage could be associated with a reduction in some aspects of HRQOL in advanced-stage CKD patients.

PO0495

Patterns of Hospital Admissions Among Patients with CKD

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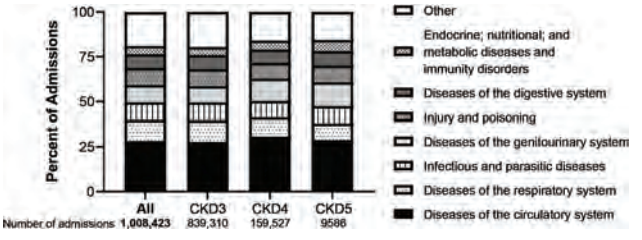
Background: Although chronic kidney disease (CKD) is relatively common in the United States, an understanding of the frequency, causes, and costs of hospital admissions among patients with CKD at the national level is lacking.

Methods: Study data were derived from the Centers for Medicare & Medicaid Services 100% claims sample (2017-2018). Included patients were adults enrolled in Medicare Parts A and B who had a claim including a diagnosis code for CKD stage 3, 4, or 5 during 2017; exposure was ascribed as the most severe observed stage. Patients with evidence of commercial insurance, diagnosis of end-stage kidney disease, dialysis treatment, or death, prior to 31 Dec 2017 were excluded. Hospital admissions and paid costs were considered from 01 Jan 2018 through the first of 31 Dec 2018 or censoring for loss of Medicare Part A, dialysis initiation, or death. Hospitalization causes were ascribed on the basis of ICD-10 codes, grouped using Clinical Classification Software Level 1 categories.

Results: A total of 1,352,401 patients with CKD3, 208,963 patients with CKD4, and 16,159 patients with CKD5 met eligibility criteria. Annual hospitalization rates were 0.66, 0.87, and 0.77 admissions/patient-year among patients with each CKD stage, respectively. Across all 3 stages, admissions for "Diseases of the Circulatory System" accounted for approximately 25% of hospitalizations, with "hypertension with complications and secondary hypertension" contributing approximately half of the hospitalizations in this category. Considerable regional variation was observed with respect to annual hospitalization costs among this population, with the Southwest, Northeast, and Mid-Atlantic regions tending to have higher costs than other parts of the country.

Conclusions: Patients with CKD are frequently hospitalized, with associated costs that display marked regional variation. Clinically and regionally targeted programs may result in improved patient outcomes and lower health care costs.



PO0496

Critical Care Resource Use in CKD in the Safety-Net Setting

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Background: Chronic kidney disease (CKD) is associated with adverse outcomes among patients with critical illness. There is limited data on the extent of critical care resource use among patients with CKD in safety-net settings.

Methods: We conducted a retrospective cohort study of patients in a safety-net healthcare system with non-dialysis-dependent CKD and critical illness, defined as admission or transfer to the intermediate or intensive care unit. Poisson regression was used to identify risk factors for critical illness based on sociodemographic factors, comorbidities, and baseline stage of CKD. Critical care resource use was extracted from the medical record, including dialysis initiation, ventilatory support, blood products, and vasoactive medications. Results were stratified by baseline stage of CKD.

Results: Out of 1,298 patients with CKD who were hospitalized during a three-year period (stage 3a- 43%, stage 3b- 35%, stage 4- 22%), 495 patients required intermediate or intensive care. In the multi-adjusted model [IRR (95% CI)], critical illness was associated with stage of CKD [stage 3a- 1 (referent), stage 3b- 1.24 (1.10,1.40), stage 4- 1.99 (1.72, 2.30)]. Hispanic and non-Hispanic black race, congestive heart failure, and moderate/severe anemia were also associated with risk of receiving critical care (Table 1).

Conclusions: We report a high burden of hospitalizations requiring critical care resources in a safety-net setting. Notably, a third of patients with CKD stage 4 and critical illness required hemodialysis initiation. Further research is needed to prevent critical illness and the need for critical care resources in patients with CKD.

	CKD Stage 3a	CKD Stage 3b	CKD Stage 4
Number of patients hospitalized, n			
Any hospitalization	554	456	288
Hospitalization with critical illness	193	173	129
Risk of hospitalization with critical illness, IRR (95% CI)[1]			
Female Sex	0.67 (0.57, 0.78)[t]	0.81 (0.67, 0.99)[t]	1.01 (0.75, 1.35)
Hispanic Race	1.64 (1.25, 2.16)[t]	2.38 (1.63, 3.48)[t]	1.50 (0.89, 2.52)
Non-Hispanic black race	1.18 (0.89, 1.55)	1.71 (1.17, 2.49)[t]	1.78 (1.07, 2.98)[t]
Congestive Heart Failure	3.75 (3.13, 4.49)[t]	1.51 (1.20, 1.91)[t]	1.45 (1.03, 2.04)[t]
Moderate/Severe Anemia	3.61 (2.85, 4.57)[t]	4.07 (2.90, 5.73)[t]	2.02 (1.21, 3.37)[t]
Critical care resource use, n (%)			
Dialysis	18 (9.4%)	22 (12.7%)	43 (33.3%)
Ventilatory Support	62 (32%)	46 (26.6%)	34 (26.4%)
Blood Products	56 (29.0%)	68 (39.3%)	43 (33.3%)
Vasoactive Medication	26 (13.5%)	27 (15.6%)	14 (10.9%)

Table 1. Critical care resource use and factors associated with outcomes in those with different stages of CKD.[1] *Multi-adjusted model for baseline characteristics*

[t] *p<0.001*

PO0497

Usual Source of Care and Clinical Outcomes in Adults with CKD: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: In general populations, having a usual source of care (USOC) increases use of preventive care and is associated with higher survival. However, there are limited data in adults with chronic kidney disease (CKD).

Methods: In the CRIC Study, we categorized participants' self-reported USOC as follows: 1) clinic/doctor's office, 2) emergency room (ER)/urgent care, and 3) other. Using multivariable regression analyses, we evaluated the association between USOC and incident end stage renal disease (ESRD), cardiovascular events (myocardial infarction, heart failure, stroke and peripheral arterial disease), hospitalizations, and all-cause death.

Results: Among 3,140 participants, mean age was 65 years, 45% were non-Hispanic white, 43% non-Hispanic black, 9% Hispanic, and mean estimated glomerular filtration rate (eGFR) was 50 mL/min/1.73m^2. 90% identified clinic/doctor's office as USOC, 9% ER/urgent care, and 1% other. Over a median follow-up time of 3.6 years, there were 288 deaths, 181 incident ESRD events, 444 cardiovascular events, and 7,957 hospitalizations. In multivariable analyses, compared to clinic/doctor's office as USOC, ER/urgent care was associated with higher risk for death and hospitalizations (**Table**). No significant association was seen with incident ESRD or cardiovascular events.

Conclusions: ER/urgent care as USOC was associated with higher risk for adverse outcomes in this large and diverse adult cohort with CKD. Further studies are needed to identify barriers to accessing appropriate preventive care to reduce negative health outcomes in this population.

Funding: NIDDK Support

Association between usual source of care (ER/urgent care vs. clinic/doctor's office) and outcomes

Outcome	HR (95% CI)
Incident ESRD	0.86 (0.49-1.52)
Cardiovascular Events	1.28 (0.94-1.75)
All-Cause Death	1.53 (1.05-2.23)*
	RR (95% CI)
Hospitalizations	1.41 (1.32-1.51)*

*p<0.05; Results adjusted for clinical center, age, sex, race, education, income, smoking status, physical activity, HbA1c<7%, statin, aspirin, ACEI/ARB, eGFR, urine protein.

PO0498

Healthcare Resource Utilisation and Costs of CKD According to the 2012 KDIGO CKD Classification: A Report from the DISCOVER CKD Retrospective Cohort

Juan Jose Garcia Sanchez,[1] Juan J. Carrero,[2] Supriya R. Kumar,[3] Hiddo J. L Heerspink,[4] Glen James,[1] Stephen Nolan,[1] Lam S. Carolyn,[5,6] Hungta (tony) Chen,[3] Alyshah Abdul Sultan,[1] Carol A. Pollock,[7] Roberto Pecoits-Filho.[8,9] *[1]AstraZeneca, Cambridge, United Kingdom; [2]Karolinska Institutet, Stockholm, Sweden; [3]AstraZeneca, Gaithersburg, MD; [4]Rijksuniversiteit Groningen, Groningen, Netherlands; [5]National Heart Centre Singapore, Singapore, Singapore; [6]Duke-NUS Medical School, Singapore, Singapore; [7]Royal North Shore Hospital, St Leonards, NSW, Australia; [8]Pontificia Universidade Catolica do Parana Escola de Medicina Campus Londrina, Londrina, Brazil; [9]Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: The DAPA-CKD trial finished early due to overwhelming efficacy. Real-world data reporting healthcare resource utilization (HCRU) and cost associated with CKD categorized according to the 2012 KDIGO recommendations are scarce. We assessed HCRU and costs in a "DAPA-CKD-like population" (eGFR 25-75ml/min/1.73m^2 and UACR 200-5000mg/g) compared to patients categorized according to KDIGO 2012 recommendations.

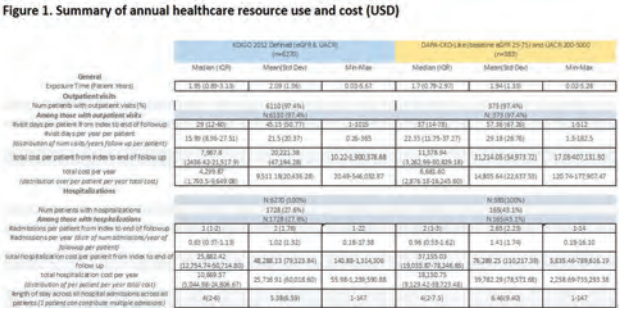
Methods: DISCOVER CKD is an observational study in patients with CKD, data was extracted using the integrated Limited Claims and Electronic Health Record data. Patients were aged ≥18 years, with ≥1 UACR measure and two eGFR measures of 0-75ml/min/1.73m^2 recorded at least 90 days apart between January 2008 and September 2018. Index date was 2nd eGFR. We calculated total and annualized number of encounters and estimated annualized per-patient and total costs. Incidence rates per 100 person-years (PY) were estimated for outpatient and hospitalization events.

Results: Preliminarily, 6270 patients met the KDIGO 2012 definition (mean[SD] age 64.0(10.9) years, 51.0% female) and 383 patients met the DAPA-CKD-like criteria (mean[SD] age 64.0(11.9) years, 38.9% female). The rate of hospitalizations almost doubled for the DAPA-CKD-like population vs the KDIGO 2012 defined population (Rate 100-PY[95CI] 59.0[53.7-64.8] vs 26.4[25.5-27.3]) and length of stay was also higher (Mean[SD] 6.5[9.4] vs 5.4[6.6] days). The DAPA-CKD-like population incurred substantially higher annualized per patient hospitalization costs (mean[SD] USD39782[78572] vs USD25717[60019]); Figure 1.

Conclusions: This analysis demonstrated that the DAPA-CKD-like population is associated with a higher HCRU and cost burden. These results highlight the need for innovative therapies to improve patient outcomes in this population.

Funding: Commercial Support - AstraZeneca

Figure 1. Summary of annual healthcare resource use and cost (USD)



PO0499

Healthcare Resource Utilization and Costs in a DAPA-CKD-Like Population Using a Contemporary US Healthcare Cohort

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Background: The DAPA-CKD Trial is the first SGLT-2i renal outcome trial to test the efficacy and safety of an SGLT-2i, dapagliflozin, in patients with diagnosed CKD with and without T2D. The objective of this study is to assess the healthcare resource utilization and cost in a "DAPA-CKD-like population" (eGFR 25-75ml/min/1.73m^2 and UACR 200-5000mg/g) using a contemporary US healthcare system.

Methods: Data from the Henry Ford Health System (HFHS) were used to identify patients with CKD stages 2 through 4 between 2006 and 2016 (based on eGFR labs) and patients were followed through 2018. Patients with no confirmatory eGFR > 90 days from index date, death within 30 days, history of renal transplant, and evidence of renal replacement therapy, or progression to CKD stage 5 during the baseline period (6 months pre or post index date) were excluded. Cumulative primary and secondary utilization was evaluated for all patients during the follow-up time. Annual utilization rates are the total observed utilization divided by follow-up time. Billing records with HFHS were used to estimate costs.

Results: 6,557 patients (mean age 62.9 years, 46.2% male) met the eligibility criteria and are included in the study cohort. The population was stratified by UACR (0-<30, 30–199, 200–5,000mg/g). The DAPA-CKD-like population (200-5000mg/g) was associated with significantly higher annualized per-patient healthcare costs, $39,222/yr (UACR

200-5000mg/g) vs. $19,547/yr (UACR <30mg/g). Persons in the highest UACR category were almost three times more likely to have a hospital admission compared to the lowest (rates 0.55/year vs. 0.20/year, respectively; see Table 1).

Conclusions: This analysis of a contemporary US healthcare system demonstrated that there exists a high disease burden in the DAPA-CKD-like population as seen by the substantial increase in healthcare resource utilization and costs compared to other cohorts of patients with a lower UACR. These results highlight the need for innovative therapies to improve patient outcomes in this high risk population.

Funding: Commercial Support - AstraZeneca

Table 1. Summary of healthcare resource utilization and costs by UACR category

	UACR 0-<30mg/g N= 4331	UACR 30-199mg/g N = 1354	UACR 200-5,000mg/g N= 873	p - value
Acute care				
Hospital admissions (rate/year)	0.20	0.36	0.55	< 0.0001
Inpatient days (length of stay)	1.00	2.25	3.27	< 0.0001
Emergency department visits (rate/year)	0.30	0.40	0.60	< 0.0001
Ambulatory care				
Outpatient primary care visits (rate/year)	5.81	5.93	5.21	< 0.01
Outpatient specialist visits (rate/year)	6.74	7.02	7.55	< 0.05
Total outpatient visits (rate/year)	12.55	12.95	12.77	NS
Costs of care				
Annualized charges ($)	$19,547	$28,338	$39,222	< 0.0001

PO0500

Understanding Patterns of Medical Spend Informs Design of Upstream Intervention in CKD

Titte Srinivas. *University Hospitals, Cleveland, OH.*

Background: Despite ease of diagnosis based on laboratory testing, CKD is often unrecognized and comorbid decompensation results in delayed diagnosis in acute care settings. The purpose of our inquiry was to inform the design of systems of care that would prevent escalation of total cost of care (TCOC) of CKD through minimization of acute care spend.

Methods: Unrecognized CKD was defined as CKD that was evident by laboratory data in the EHR but not captured by an ICD10 code or DRG for chronic kidney disease. Recognized CKD or ESRD had both ICD10 and DRG data and laboratory evidence of CKD. We then compared inpatient and total medical spends as well as the density of preventive measures such as wellness visits among these groups. The data respository was built on the MS Power BI platform and machine learning and high throughput analyses were conducted using Alteryx utilities.

Results: A total of 217,125 patients were included that had eGFR and spend data in 2019. Annual wellness visits occurred on average among 38 percent (n=142,373) of those with no CKD diagnosed or evident by lab values vs. 19.1 percent of those with unrecognized Stage 3b to 4 CKD (n=31,435) vs. 18 percent among those with recognized Stage 3-5 CKD or ESRD (n= 52,242; P < 0.001). No statistical difference was observed between wellness rates and stage 1 and stage 2 unrecognized CKD cohorts. Of annual spend in 2019, those with recognized CKD/ESRD, incurred 61.9 percent of spend in the inpatient setting vs. 25 percent among those with unrecognized CKD. The number of chronic condition increased from an average of 3.5 among those with Stage 3-5 unrecognized CKD to 10 among those with recognized CKD/ESRD. Average 12 mo spend was $ 6500 among those with unrecognized CKD stage 3b-5 and $ 22,978 among those with recognized CKD/ESRD (p<.0001). A diagnosis of CHF was recorded in 13.1 %, 20.5 %, and 24.3 % of those with undiagnosed CKD stage 3a-5 vs. 46.9 percent of those with diagnosed CKD/ESRD (Chi square for trend <0.001).

Conclusions: CKD is often unrecognized clinically despite eGFR support of its existence in the medical record Decompensation of unrecognized heart disease likely contributes to increased inpatient utilization and costs with clinical recognition of CKD Wellness measures are unfortunately deficient in this population and systems of care triggered by eGFR values could inform care upstream of CKD decompensation to capture value.

Funding: Clinical Revenue Support

PO0501

Abstract Withdrawn

PO0502

Treatment Pathways of CKD Patients Defined by the 2012 KDIGO CKD Classification: A Report from the DISCOVER CKD Retrospective Cohort

Juan Jose Garcia Sanchez,[1] Juan J. Carrero,[2] Supriya R. Kumar,[3] Roberto Pecoits-Filho,[4,5] Glen James,[1] Hiddo J. L Heerspink,[6] Stephen Nolan,[1] Lam S. Carolyn,[7,8] Hungta (tony) Chen,[3] Eiichiro Kanda,[9] Alyshah Abdul Sultan,[1] Naoki Kashihara,[9] Mikhail Kosiborod,[10] David C. Wheeler,[11] Carol A. Pollock.[12] *[1]AstraZeneca, Cambridge, United Kingdom; [2]Karolinska Institutet, Stockholm, Sweden; [3]AstraZeneca, Gaithersburg, MD; [4]Arbor Research Collaborative for Health, Ann Arbor, MI; [5]Pontificia Universidade Catolica do Parana Escola de Medicina Campus Londrina, Londrina, Brazil; [6]Rijksuniversiteit Groningen, Groningen, Netherlands; [7]National Heart Centre Singapore, Singapore, Singapore; [8]Duke-NUS Medical School, Singapore, Singapore; [9]Kawasaki Ika Daigaku, Kurashiki, Japan; [10]Saint Luke's Mid America Heart Institute, Kansas City, MO; [11]University College London, London, United Kingdom; [12]Royal North Shore Hospital, St Leonards, NSW, Australia.*

Background: Treatment strategies to delay the progression of CKD focus on use of RAASi, anti-hypertensive and, for patients with type 2 diabetes, anti-diabetic therapy. Data describing treatment pathways in patients defined according to the 2012 KDIGO classification are scarce.

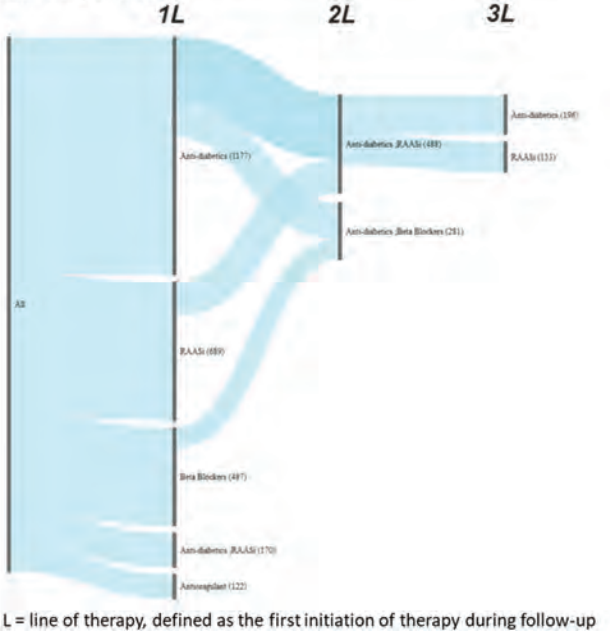
Methods: The DISCOVER CKD retrospective cohort of patients was extracted using the integrated Limited Claims and EHR data. Patients were aged ≥18 years, with ≥1 UACR measure and two measures of eGFR 0-75 mL/min/1.73 m^2 recorded at least 90 days apart between 2008-2018. Sankey Plots were used to visualize chronological treatment pathways (1st-3rd line) post-index, of key treatments commonly prescribed to these CKD patients including: RAASi, anti-diabetic therapy, beta-blockers and anticoagulants. We also describe median time to 1st line therapy initiation.

Results: Preliminarily, 4283 patients were prescribed key treatments during follow-up with anti-hyperglycaemic therapy and RAASi therapy being the most common 1st-line therapy, Figure 1. Median time to 1st-line therapy initiation was: 34 days for anti-diabetic therapy, 45 days for beta-blockers, 49 days for RAASi therapy and 50 days for anticoagulants. Anti-diabetic therapy and RAASi therapy accounted for the highest proportion of time in which treated patients remained on therapy during follow-up (68% and 61%, respectively).

Conclusions: We observed a high proportion of time on therapy for key pharmacological treatments during the follow-up period. However, it is well established that a substantial residual risk and unmet need exists with current standard of care.

Funding: Commercial Support - AstraZeneca

Figure 1: Treatment pathways of key treatments in CKD patients defined by the 2012 KDIGO classification (eGFR & UACR)



L = line of therapy, defined as the first initiation of therapy during follow-up

PO0503

Treatment Pathways of Patients with CKD: A Report from the DISCOVER CKD Retrospective Cohort

Glen James,[1] Juan J. Carrero,[2] Supriya R. Kumar,[3] Steven Fishbane,[4] Carol P. Moreno Quinn,[1] Hiddo J. L Heerspink,[5] Eric T. Wittbrodt,[3] Eiichiro Kanda,[6] Katarina Hedman,[7] Naoki Kashihara,[6] Hungta (tony) Chen,[3] Mikhail Kosiborod,[8] Lam S. Carolyn,[14,15] Carol A. Pollock,[9] Peter Stenvinkel,[10] Roberto Pecoits-Filho,[11,12] David C. Wheeler.[13] *[1]AstraZeneca UK Ltd, Cambridge, United Kingdom; [2]Karolinska Institutet, Stockholm, Sweden; [3]AstraZeneca, Gaithersburg, MD; [4]Northwell, Manhasset, NY; [5]University of Groningen, Groningen, Netherlands; [6]Kawasaki Medical School, Kurashiki, Japan; [7]AstraZeneca, Gothenburg, Sweden; [8]Saint Luke's Hospital of Kansas City Health Sciences Library, Kansas City, MO; [9]University of Sydney, Sydney, NSW, Australia; [10]Karolinska Universitetssjukhuset, Stockholm, Sweden; [11]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [12]Arbor Research Collaborative for Health, Ann Arbor, MI; [13]University College London, London, United Kingdom; [14]National Heart Centre Singapore, Singapore, Singapore; [15]Duke-NUS Medical School, Singapore, Singapore.*

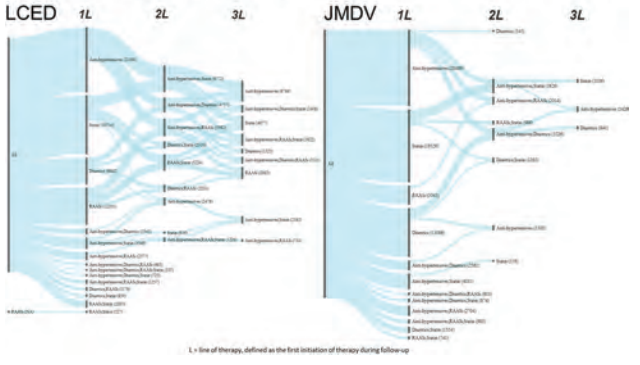
Background: Chronic kidney disease (CKD) is a global health problem associated with clinical complications. Gaps exist in real-world data to understand treatment pathways of CKD patients. We describe treatment pathways of key medications prescribed to CKD patients in DISCOVER CKD.

Methods: The DISCOVER CKD retrospective cohort of patients were extracted using Japan Medical Data Vision (JMDV) and integrated Limited Claims and EHR (LCED) data. The study included patients aged ≥18 years with a diagnostic CKD code (stage 3A through end stage renal disease or renal replacement therapy) or 2 estimate glomerular filtration rate (eGFR) measures <75 mL/min/1.73m^2 at least 90 days apart between January 2008 and October 2018. The index date was the date of first diagnostic code or 2nd eGFR. Sankey Plots were used to visualize chronological treatment pathways (1st to 3rd line) post-index of key treatments (including combinations) commonly prescribed to at least 500 CKD patients including: RAASi, statins, diuretics and anti-hypertensives. We also describe median time to first line therapy initiation.

Results: Preliminarily, in the study cohort (N=159849) anti-hypertensives were the most common first-line therapy prescribed. Median time to first-line therapy initiation for LCED and JMDV was: 48 days and 168 days for anti-hypertensives, 39 days and 89 days for diuretics, 51 days and 259 days for RAASi and 56 days and 133 days for statins, respectively. In both databases patients remained on anti-hypertensives the most (33.7%) during follow-up.

Conclusions: Patients with CKD have high therapy burden, with varying time to initiation of therapies.

Figure 1 – Treatment Pathways of Key Treatments



L = line of therapy, defined as the first initiation of therapy during follow-up

PO0504

Increased Urinary Albumin Creatinine Testing in CKD Stage 3 and Effect on Quality Metrics

Ken J. Park, Micah L. Thorp, Robert Unitan. *Kaiser Permanente Northwest, Portland, OR.*

Background: One of the goals of Advancing American Kidney Health Initiative is "reducing the number of Americans developing End Stage Renal disease by 25% by 2030." An important part in achieving this goal is increased use of interventions backed by high quality evidence including use of ACE inhibitors or ARBs, control of hypertension, and diabetes (DM) control. Albuminuria has been clearly linked to CKD progression, but evidence is lacking as to whether more frequent monitoring slows CKD progression. We were interested in whether more frequent monitoring of albuminuria via automated testing improved CKD quality metrics.

Methods: This was a cross sectional study using a CKD registry in Kaiser Permanente Northwest. The CKD registry was population-based which did not require patient consent. We compared urinary albumin creatine (ACR) testing, filled ACE inhibitor and ARB prescriptions, DM control (hgba1c < 8%), and hypertension control (blood pressure <140/90) at one time point before and after implementing a quality improvement project targeting patients with stage 3 CKD based on eGFR criteria or ICD-10 codes. A web-based tool examined the registry and ordered an ACR in those patients that did not have an ACR checked within the past year. Primary care providers received an received an alert in the electronic health record (EHR) for those patients not on an ACE inhibitor or ARB who had a renal indication. Renal indications for an ACE inhibitor or ARB were hypertension and an ACR > 30 mg/g with DM or an ACR > 300 mg/g without DM.

Results: There were 10,335 patients in the CKD registry on 12/5/2017 and 10,515 on 12/5/2019. Average age was 73, 81% had hypertension, 38% had DM, and 44% were male. Automated ACR testing in patients with stage 3 CKD was implemented on 5/23/2018. One and half years after implementation of ACR testing, ACR testing increased from 26% to 61% (p < 0.001). ACE inhibitor or ARB use among patients with renal indication did not increase significantly (79% vs. 81%, p = 0.08). Control of DM increased (78% vs. 81%, p < 0.001) while control of hypertension worsened (76% vs. 74%, p = 0.001).

Conclusions: In patients with stage 3 CKD, increased albuminuria testing via automated testing linked with EHR alerts did not results in an overall improvement in CKD quality metrics. However, our study was limited by the cross-sectional design as well as the short follow up.

PO0505

Albuminuria Testing and Prevalence and Incidence of Elevated Albuminuria

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Background: Guidelines recommend an annual evaluation of urine albumin creatinine ratio (ACR) in patients with diabetes (DM) or hypertension (HTN) for early identification and close monitoring of kidney damage. The aim of this study was to inform ACR testing strategies by 1) evaluating the frequency of ACR testing, 2) determining the prevalence and incidence of ACR≥30 mg/g, and 3) developing and validating a risk prediction model for incident ACR≥30 mg/g.

Methods: We analyzed 28 cohorts from the CKD Prognosis Consortium including 1,909,350 persons with DM or HTN from 5 countries. Analysis was performed separately for persons with DM and those with HTN but without DM. We selected a two-year baseline period for administrative cohorts and used the baseline visit for research cohorts to assess frequency of testing and prevalence of a single ACR≥30 mg/g. Confirmed incident ACR≥30 mg/g (elevated twice) was assessed 5 years after baseline in those with baseline ACR<30 mg/g. Development of prediction models for incident ACR≥30 mg/g used logistic regression and age, sex, baseline systolic blood pressure, HTN and DM medication use, coronary heart disease, heart failure, BMI, A1c, and eGFR as covariates. Models were validated in 5 DM cohorts and 4 HTN only cohorts.

Results: The median frequency of ACR testing across administrative cohorts was 48.9% (IQI, 32.5-58.3%) and 4.3% (IQI, 3.2-7.1%) in DM and HTN only. Among those tested at baseline, the median prevalence of ACR≥30 mg/g was 32.7% (IQI, 28.4-37.0%) and 21.9% (IQI, 18.6-29.6%) in DM and HTN only. Among 107,754 persons with DM and 15,676 persons with HTN only who had baseline ACR<30 mg/g, the median incidence of ACR≥30 mg/g at 5 years was 23.3% (IQI, 18.6-28.5%) and 21.7% (IQI, 15.7-26.3%) in DM and HTN only. Risk prediction models for 5 year incidence of ACR≥30 mg/g had only modest accuracy in DM (median C statistic: development cohorts 0.629, IQI: 0.600-0.655; validation cohorts 0.635, IQI: 0.619-0.641) and in HTN only (median C statistic: development cohorts 0.649, IQI: 0.621-0.695; validation cohorts 0.663, IQI: 0.638-0.671).

Conclusions: ACR testing in DM or HTN is low in clinical practice. The risk prediction models for incident ACR≥30 mg/g performed only modestly, suggesting focused efforts based on risk stratification may not be a viable strategy. Universal albuminuria testing for individuals with DM or HTN is likely necessary.

Funding: NIDDK Support, Private Foundation Support

PO0506

Urine Albumin and Serum Creatinine Dual Testing in US Veterans: Trends and Associations with Subspecialty Care

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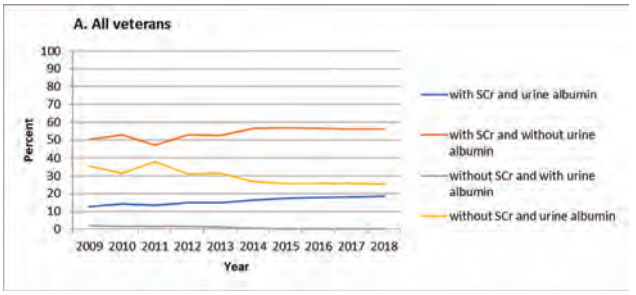
Background: Urine albumin and serum creatinine (SCr) help define chronic kidney disease (CKD). Despite the fact that urine albumin and SCr are multiplicatively associated with cardiovascular and all-cause mortality, dual testing remains limited. We sought to characterize trends in dual testing in all veterans and those seen by nephrologists.

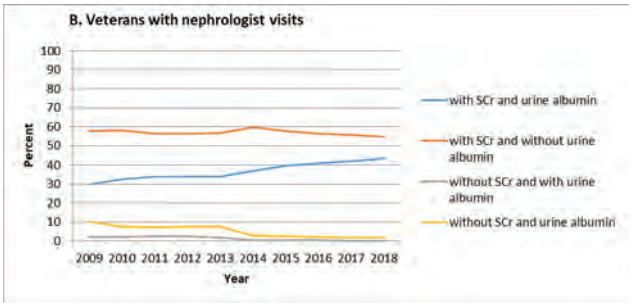
Methods: We used Veterans Health Administration (VA) data (2009-18). VA patients with any inpatient or outpatient visit in a given calendar year were included. Time trend of dual testing and patient characteristics including age, sex, race, hypertension, diabetes, CKD, and cardiovascular diseases (CVD) were noted.

Results: The study population included 58,508,942 patients (90.3% male). Overall, 12.5% of VA patients had both Scr and urine albumin testing in 2009 as compared with 18.6% in 2018 (Fig.A, p_{trend}<0.001). Among patients seen by nephrologists, 30.1% had both SCr and urine albumin testing in 2009, increasing to 43.3% in 2018 (Fig.B, p_{trend}<0.001). Compared to VA patients with SCr testing only, those with both SCr and urine albumin testing were older, more likely to be male, and more likely to have diabetes, hypertension, and CKD, but less likely to have CVD (p<0.001).

Conclusions: Dual SCr and urine albumin testing among VA nephrology patients is more common than among all VA patients and has increased over time, However, in a given year, less than half of nephrology patients undergo dual testing. Efforts to encourage screening for albuminuria among patients at high risk for CKD and CVD might be considered.

Funding: Other U.S. Government Support





PO0507

Dipstick Urinalysis Can Identify Patients with Early CKD Who Lack a Quantified Proteinuria Measurement

Meredith McAdams, Duwayne L. Willett, Yu-Lun Liu, Vaishnavi Kannan, L Parker Gregg, Susan Hedayati. *University of Texas Southwestern Medical Center at Dallas, Dallas, TX*.

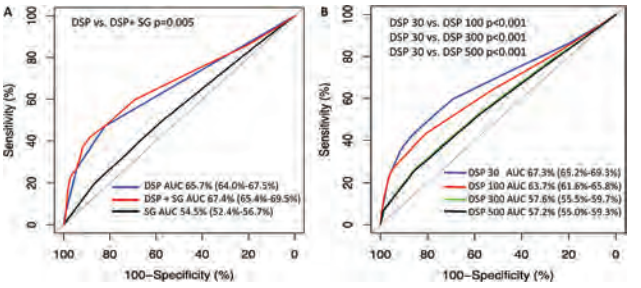
Background: Urine protein-to-creatinine ratio (UPCR)>0.15 g/g or albumin-to-creatinine ratio (UACR)>30 mg/g is the gold standard for identifying patients with stages 1-2 CKD with eGFR>60 mL/min/1.73m^2, but are not routinely obtained. Dipstick urinalysis semi-quantitative protein (DSP) is widely available and commonly measured.

Methods: To develop a pragmatic EHR tool to identify patients with stages 1-2 CKD, we investigated diagnostic utility of various DSP cutoffs (negative/trace, 30, 100, 300, or ≥500 mg/dL) against gold-standard proteinuria (UPCR>0.15 g/g or UACR>30 mg/g) using logistic regression. We also investigated whether addition of SG improved the diagnostic utility of DSP by comparing areas under the receiver-operating characteristic curves (AUC) for DSP with and without addition of SG. DSP was obtained from the EHR in 3,897 individuals with UPCR or UACR measured on the same date. A development model was created in a random sample of 2,728 (70%) using a bootstrap method and validated in the remaining 1,169 individuals.

Results: Mean age was 57.6±16.9 years, 51.7% were female, 25.6% Black, and 42.8% had an eGFR≤60 mL/min/1.73m^2. Gold-standard proteinuria was present in 1,775 (45.5%). DSP cutoff=30 had specificity 81.1 (95% CI 79.0, 83.1), +LR=2.43 (95% CI 2.15, 2.75), -LR=0.67 (95% CI 0.63, 0.71). The combination of DSP and SG, taken continuously, performed better than DSP alone (**Figure A**). When including SG, a DSP cutoff of 30 had the best diagnostic accuracy vs. other cutoffs (**Figure B**). In the validation cohort, addition of SG to DSP also yielded a higher AUC than DSP alone, P=0.03. For DSP ≥30 as a screening test, an SG of at least ≥1.025 is needed. A more dilute urine, with a SG of 1.020, would be allowed if DSP ≥100. A DSP cutoff of 30 had an AUC of 0.652 (0.621, 0.684), P<0.001, vs. a cutoff of 300 or 500. Using DSP≥30 identified an additional 141 individuals with CKD than use of eGFR<60 alone.

Conclusions: Combining DSP and SG from a dipstick urinalysis can identify patients with early CKD who do not have a measured UPCR or UACR.

Funding: NIDDK Support



PO0508

Prevalence of Coded and Uncoded CKD in the Military Health System

Jenna M. Norton, Lindsay Grunwald, Cara H. Olsen, Eric S. Marks, Tracey L. Koehlmoos. *Uniformed Services University of the Health Sciences, Bethesda, MD*.

Background: Despite the substantial human and financial costs associated with chronic kidney disease (CKD) and its high prevalence in the general population, little is known about rates of CKD in the nearly 9.5 million beneficiaries of the Military Health System (MHS). Diagnostic codes lack adequate sensitivity and validity for identifying CKD using health system data. Using laboratory-data may enable a more accurate assessment of the burden of CKD in the MHS.

Methods: We identified all MHS beneficiaries aged 18 to 64 who received care through the MHS from October 1, 2015 to September 30, 2018. CKD was identified by ICD-10 code and/or a validated laboratory value-based electronic phenotype for CKD. CKD was considered coded if an ICD-10 code was present and uncoded if no ICD-10 code was present. Characteristics of the coded and uncoded CKD populations were compared using two-tailed t tests (continuous variables) and Pearson's Chi Square test for independence (categorical variables).

Results: The total study population included 3,330,893 MHS beneficiaries. Of those, 105,504 (3.2%) were identified as having CKD. Of those with CKD, only 37% had an ICD-10 code for CKD. Compared to individuals with coded CKD, those with uncoded CKD were younger (average age 45 vs 52), more likely to be female, and more likely to be active duty, but less likely to be of Black race, to have diabetes or to have hypertension (p <.0001). Among those with test results recorded in the MHS, those with coded CKD had greater numbers of urine albumin, urine albumin-to-creatinine ratio, urine protein-to-creatinine ratio, serum creatine, and eGFR results (p <.0001).

Conclusions: Many MHS beneficiaries with laboratory values indicative of CKD were not coded for CKD, suggesting they may not be receiving appropriate management for this progressive and burdensome disease. Individuals with commonly recognized risk factors for CKD (e.g., older age, male sex, black race, diagnosed diabetes, diagnosed hypertension) were more likely to be coded for CKD, suggesting clinicians may be missing CKD in traditionally lower risk groups—despite available laboratory data to asses disease status.

Funding: Other U.S. Government Support

PO0509

Factors Associated with Screening and Recognition of CKD in the VA Healthcare System

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Background: The successful implementation of interventions to improve kidney disease outcomes requires early identification of CKD which involves screening at-risk population as well as recognizing CKD. We have reported suboptimal detection of proteinuria and documentation of CKD previously and now aim to identify factors associated with these rates.

Methods: We interrogated VISN-17 database for at-risk Veterans with hypertension (HTN) and diabetes seen regularly in primary clinics during 2012-19. The final cohort (N=270,170) charts were analysed for serum creatinine/eGFR, urine protein/albumin, ICD codes for CKD, and nephrology referral. CKD was defined as eGFR <60ml/min at least twice 90 days apart and/or urine albumin creatinine ratio (uACR) of >30 mg/g. Factors were examined which could be associated with screening and recognition.

Results: As shown in table, 94.3% patients had one or other screening procedures done. Urine protein/albumin was present in 56.4% charts, the least in patients with HTN only (40%). CKD by lab evidence was present in 42%; however, only 40% of these had documented ICD-codes for CKD or nephrology referral. There was no clinically significant difference between screened vs. unscreened or recognized vs. unrecognized groups in age, sex, and BMI. Hispanic race associated with decrease screening procedures but no difference in CKD recognition. Patients were more likely to have screening procedures as well documented CKD, if they had heart disease, stroke, cancer; higher frequency of specialty care visits, hospitalizations or ER visits; or elective procedures as vascular and cardiac catheterizations. There was no difference in BP control in screened vs. unscreened group but more patients with documented CKD had BP>140/90mmHg.

Conclusions: Protienuria was detected and CKD was recognized in half of the at-risk Veterans. Co-morbidities and health care visits other than primary care associated with increased screening and recognition suggest utility of initiatives at primary care level to educate the need for CKD detection and awareness.

Funding: Veterans Affairs Support

	CKD Screening			CKD Recognition		
Characteristics	Total N=276,179	eGFR or Urine Protein Present N=254,831 (94.3%)	eGFR or Urine Protein not Present N=15,339	Total N=107,131 (42%)	CKD documented N=42,832 (40%)	CKD not documented N=64,306
Age (Mean±sd)	62.1 (13.3)	62.1 (13.2)	61.7 (14.0)	66.6 (11.6)	68.0 (11.1)	65.7 (11.9)
Male, n (%)	253,094 (93.7%)	238,583 (93.6%)	14,511 (94.6%)	101,922	41,394 (96.6%)	60,528 (94.1%)
Race, n (%)						
Non-hispanic White	145,810 (53.9%)	140,989 (55.3%)	4,821 (30.1%)	61,565	24,007 (56.0%)	37,558 (58.4%)
Non-hispanic black	47,415 (17.6%)	46,014 (18.1%)	1,401 (9.1%)	19,088	7,800 (18.2%)	11,288 (17.5%)
Hispanics	**44,381 (16.4%)**	**39,136 (15.4%)**	**5,225 (34.1%)**	**14,321**	**6,095 (14.2%)**	**8,226 (12.8%)**
Asian	1,121 (0.4%)	1,032 (0.4%)	89 (0.6%)	291	109 (0.3%)	172 (0.3%)
BMI (Mean±sd)	30.7 (6.1)	30.7 (6.1)	30.4 (6.7)	30.7 (6.2)	30.6 (6.2)	30.7 (6.1)
Co-morbidities, n (%)						
Diabetes	129,904 (48.1%)	122,791 (48.2%)	7,113 (46.4%)	56554 (52.1%)	27,807 (64.8%)	38,747 (60.3%)
Hypertension	257,875 (95.4%)	243,502 (95.8%)	14,373 (93.7%)	104069 (97.1%)	42,149 (98.4%)	61,920 (96.3%)
Heart disease	**122,293 (45.3%)**	**116,361 (45.7%)**	**5,932 (38.7%)**	**52661 (58.4%)**	**28,257 (66.0%)**	**34,404 (53.5%)**
Peripheral arterial disease	26,791 (9.9%)	25,232 (9.9%)	1,469 (9.6%)	15568 (14.5%)	8,178 (19.1%)	7,390 (11.5%)
Stroke	**34,192 (12.7%)**	**32,739 (12.8%)**	**1,453 (9.5%)**	**19046 (17.7%)**	**9,105 (21.3%)**	**9,942 (15.5%)**
Cancer	**118,718 (43.9%)**	**113,267 (44.4%)**	**5,451 (35.5%)**	**54666 (51%)**	**23,232 (54.2%)**	**31434 (48.9%)**
Primary Care visits/yr (Mean±sd)	**4.09 (2.82)**	**4.09 (2.64)**	**3.97 (2.33)**	**4.45 (2.80)**	**4.80 (2.97)**	**4.23 (2.65)**
Specialty Care visits/yr (Mean±sd)	**0.57 (1.39)**	**0.56 (1.42)**	**0.33 (0.85)**	**0.78 (1.72)**	**0.98 (2.03)**	**0.64 (1.46)**
ER+inPatient visits/yr (Mean±sd)	**0.53 (1.40)**	**0.50 (1.43)**	**0.015 (0.20)**	**0.69 (1.58)**	**0.86 (1.82)**	**0.58 (1.38)**
Elective Procedures, n/yr						
Interven Radiological (Mean±sd)	0.58 (1.74)	0.61 (1.78)	0.16 (0.55)	0.72 (2.03)	0.59 (1.76)	0.81 (2.18)
Vascular (Mean±sd)	**0.051 (0.43)**	**0.054 (0.44)**	**0.0004 (0.02)**	**0.067 (0.57)**	**0.117 (0.70)**	**0.067 (0.46)**
Cardiac (Mean±sd)	**0.056 (0.36)**	**0.059 (0.37)**	**0.0006 (0.02)**	**0.093 (0.49)**	**0.121 (0.60)**	**0.075 (0.40)**
Median Blood Pressure Value						
<130/80 mmHg, n (%)	77947 (30.6%)	73528 (30.5%)	4419 (31.7%)	32922 (31.7%)	13316 (31.7%)	19606 (31.8%)
130-140/80-90 mmHg, n (%)	142746 (55.9%)	135050 (56%)	7696 (55.2%)	55579 (53.7%)	21809 (51.9%)	33770 (54.8%)
>140/90 mmHg, n (%)	34462 (13.5%)	32633 (13.5%)	1829 (13.1%)	15054 (14.6%)	6859 (16.4%)	8205 (13.4%)

PO0510

Spatial Distribution of Newly Detected CKD Among US Veterans, 2009-2018

Jennifer L. Bragg-Gresham,[1] Brenda W. Gillespie,[2] Yun Han,[1] Xiaosong Zhang,[1] Diane Steffick,[1] William Weitzel,[4] Susan T. Crowley,[3] Rajiv Saran.[1] *[1]University of Michigan Medical School, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Veterans Health Administration, West Haven, CT; [4]Veterans Health Administration, Ann Arbor, MI.*

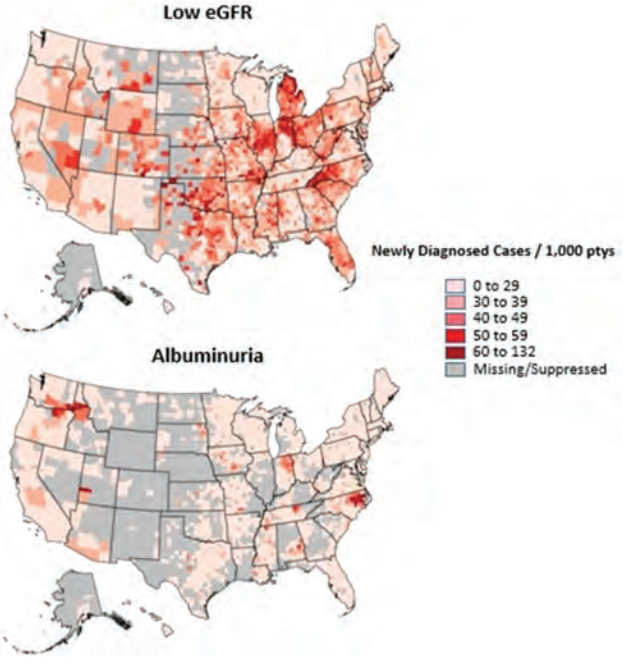
Background: While the rate of new end stage renal disease (ESRD) cases has slowed in recent years, less is known about trends in the incidence of pre-ESRD CKD. Using national data from the Veterans Health Administration (VHA) we examined the rates and spatial distribution of newly detected cases of CKD using laboratory measures.

Methods: Using data from 8.5+ million US Veterans over a decade (2009-18), in the VHA system during the previous 3 years with no indication of kidney disease, rates of newly detected kidney disease were calculated by year. Three measures of kidney disease were assessed by laboratory reports; 1) eGFR < 60 ml/min/1.73m^2, 2) albuminuria, and 3) either low eGFR or albuminuria. Spatial maps contain 3-year incidence rates (2016-18) by county, based on patient residence.

Results: Rates of newly detected low eGFR were steady from 2011 forward (~30/1,000 PY), after a drop from 55 to 31 cases between 2009 and 2011, a time when standardization of creatinine calibration to IDMS became mandatory and may explain the change in rates. Rates of newly detected albuminuria showed little variability (~10/1,000 PY). Areas of high incidence of low eGFR were present in northern Michigan, northern Indiana, central Illinois, and western North Carolina. Newly detected albuminuria was highest in coastal North Carolina, northern Idaho, northeastern Indiana, and on the border of Washington and Oregon.

Conclusions: Rates of newly detected disease reflect a combination of the true incidence rate as it presents to a health system, but is also influenced by the rate of testing for the disease in question. Despite this limitation, these findings are important for both individual and population health management, early detection, management and prevention.

Funding: Veterans Affairs Support



PO0511

Defining Criteria for CKD Stage 3 Patients Nephrology Referral: An Analysis Focused on CKD Progression and Mortality Risk

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Background: The high prevalence of CKD and its increasing awareness by primary care clinicians. While the referral of CKD stage 4 and 5 to a nephrology clinic is undisputable, the need for stage 3 patients referral is still subject to debate. Our objective was to investigate baseline characteristics of CKD stage 3 patients associated with subsequent CKD progression, in order to help determine which patients should be referred at this stage.

Methods: Retrospective analysis of all patients referred to a nephrology clinic over 6 years. We included CKD stage 3 patients with at least 36 months of follow-up or 24 of follow up with more than 3 serum creatinine determinations. CKD progression was defined by one of the following: 1) an eGFR decline superior to 5mL/min/year; 2) creatinine duplication; 3) The need for chronic RRT. Baseline covariates included demographics, comorbid conditions and laboratory values. Univariate and multivariate analysis were employed to determine independent predictors of CKD progression and mortality.

Results: Out of the 3008 patients 594 (19.8%) met the inclusion criteria (median age: 71.9 years; 63.8% male). Median follow-up was 4.9 years (IQR 2.2). 133 (22.4%) met the criteria for CKD progression and 110 (18.6%) died. CKD progression was associated with higher proteinuria (405.7 vs 65.5mg/gr, p<0.001), Diabetes (60.9 vs 45.3%, p=0.002), CHF (40.6 vs 28.7%, p=0.009), Anemia (68.0 vs 44.7%, p<0.001), higher diuretic use (48.9 vs 34.1%, p=0.002) and mortality (40.9 vs 12.2%, p<0.001) Albuminuria over 300 mg/gr [Odds ratio (OR) 3.57, 95% CI 2.20 - 5.80] and Anemia (OR 1.97, 95% CI 1.20 – 3.22) were associated with CKD progression. The independent predictors of mortality were: CKD progression (OR 4.49, 95% CI 2.69-7.50), Older age (OR per 1 year increase 1.03, 95% CI 1.01-1.05), presence of CHF (OR 1.75, 95% CI 1.03-2.98), presence of Hyperkalemia at first consultation (OR 2.12, 95% CI 1.00 – 4.52) and Anemia (OR 1.93, 95% CI 1.03 - 3.62).

Conclusions: Patients with macroalbuminuria and anemia at first consultation are at increased risk for rapid CKD stage 3 progression. In this group, patients with CHF, anemia and hyperkalemia (even at first consultation) have a higher risk of mortality. This study may be useful and help us in guiding which CKD stage 3 patients should be referred to a nephrology clinic.

PO0512

Laboratory-Based Potential Indications vs. Risk-Based Triage for Nephrology Referrals in the Veterans Affairs Health System

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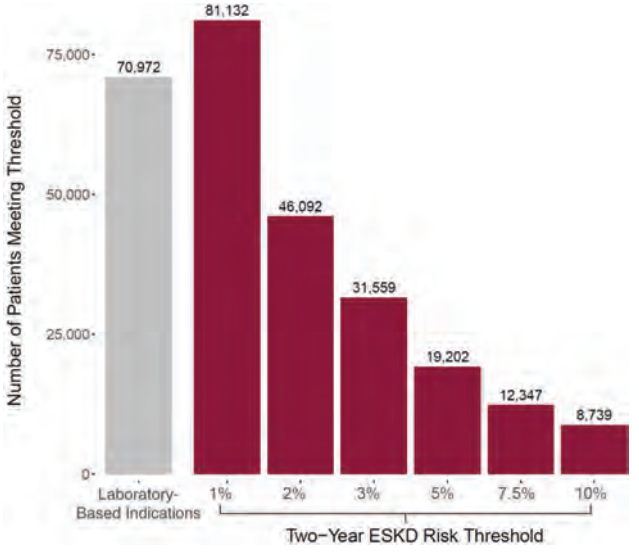
Background: Clinical decision support tools may facilitate identification of chronic kidney disease (CKD) and timely nephrology referral. Little is known about the potential effects they might have on the volume of nephrology referrals. We sought to estimate how the implementation of a CKD decision support tool could affect potential nephrology referral volume based on U.S. Veterans Affairs Health System (VA)/Department of Defense (DoD) guidelines, and the risk profile of referred patients.

Methods: In a retrospective cohort study of 434,735 patients with CKD, we determined the number of patients who met laboratory-based potential indications for nephrology referral based on VA/DoD guidelines. We used the Kidney Failure Risk Equation to estimate end-stage kidney disease (ESKD) risk and to determine how incorporating ESKD risk thresholds would modify referral volume.

Results: Among 70,972 patients meeting potential indications for referral who had not visited a nephrologist in 2013, 12,008 (16.9%) were referred in 2014. The two-year risk of ESKD was low in both groups, 2.9% [0.9-8.6%] in the referred group, compared to 1.3% [0.3-3.9%] in the unreferred group ($P < 0.001$). The number of patients meeting potential indications for referral was approximately equivalent to the number of patients with a two-year risk of ESKD exceeding 1%, or N=81,132. Among potential indications for referral, rapid eGFR decline accounted for 37.6% of eligible unreferred patients and was associated with the lowest two-year ESKD risk.

Conclusions: Laboratory-based potential indications for referral identify a large number of patients at low risk of ESKD. Further study is needed to determine the value of nephrology care for these populations.

Funding: Veterans Affairs Support



PO0513

Variation in Kidney Failure Risk Across Health Organizations Among Adults with CKD in Nephrology Ambulatory Care

Chi D. Chu,[1,2] Neil R. Powe,[1,4] Michael Shlipak,[1,3] Rebecca Scherzer,[1,3] Sri Lekha Tummalapalli,[1] Michelle M. Estrella,[1,3] Delphine S. Tuot.[1,4] *[1]University of California San Francisco, San Francisco, CA; [2]OptumLabs Visiting Scholar, Cambridge, MA; [3]San Francisco VA Medical Center, San Francisco, CA; [4]Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, CA.*

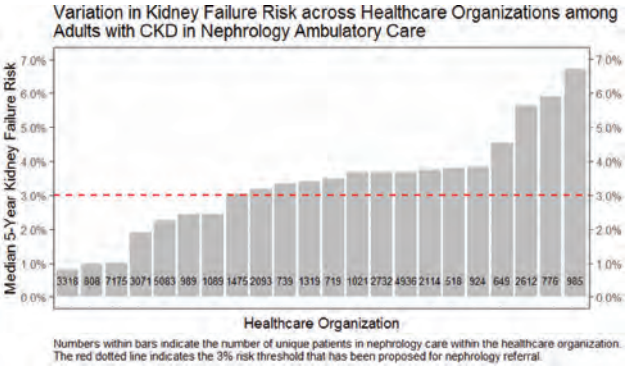
Background: Since most adults with chronic kidney disease (CKD) have low risk for end-stage kidney disease (ESKD) progression, subspecialty nephrology care should focus on patients at highest risk of progression. To optimize utilization of nephrology care, a threshold of 3% risk of ESKD at 5 years based on the Kidney Failure Risk Equation (KFRE) has been proposed for nephrology referral. To understand how application of this threshold in practice could impact CKD care delivery and subspecialty referral, we examined variation in 5-year ESKD risk distributions of patients in nephrology ambulatory care across U.S. healthcare organizations.

Methods: In 22 healthcare organizations, we identified patients age ≥18 years, with eGFR <60 ml/min/m² and concurrently measured urine albumin/creatinine ratio, who had an ambulatory encounter with a nephrologist from 1/1/2017-12/31/2018 using the OptumLabs® Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record data. We compared the distribution of patient-derived KFRE 5-year risk across healthcare organizations with ≥500 patients in nephrology care.

Results: Among 45,145 patients with CKD in nephrology care, the overall median 5-year ESKD risk was 2.4%. However, between organizations, the median 5-year ESKD risk varied widely, ranging from 0.8% to 6.7% (**Figure**). 54.5% of patients were below the 3% recommended referral threshold risk of ESKD.

Conclusions: There is substantial heterogeneity of ESKD risk across healthcare organizations in the population receiving ambulatory nephrology care. A greater understanding of the patient population and delivery system characteristics is needed to explain this heterogeneity, and associated health outcomes could inform recommended risk thresholds for referral and ongoing nephrology care.

Funding: NIDDK Support



PO0514

Prevalence of Comorbid Conditions at CKD Onset Among US Veterans

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Background: Comorbid conditions such as hypertension (HTN) and diabetes increase risk of adverse outcomes among patients with CKD. It is less clear whether such conditions develop prior to CKD onset or subsequently emerge as the disease progresses. Using a newly constructed national incident CKD cohort, we examined the prevalence of major comorbidities at the time of CKD onset by demographic groups.

Methods: The cohort included 1,074,238 subjects with new-onset CKD between 2002 and 2017 in the US Veterans Health Administration (VHA). CKD onset was defined as the first time when estimated GFR (eGFR; CKD-EPI equation) decreased to a value <60 mL/min/1.73 m² for >3 months. We excluded subjects in VHA for <2 years prior to first eGFR <60, or with CKD stage 4 or 5, or end-stage kidney disease (ESKD) when first identified. Thus, the first time identified was close to the onset of CKD stage 3. Comorbidities at CKD onset were ascertained from ICD-9/ICD-10 codes during any time before onset and through 6 months after onset.

Results: All subgroups (age, gender, race and ethnicity) had similar mean eGFRs at onset (51 ml/min/1.73m²). The percentage with age at onset ≤65 years was greater in males (74%) than females (43%), greater in Black (48%) than in American Indian or Alaska Native (39%), Asian or Pacific Islander (33%), and Hispanic (30%), which in turn were greater than Whites (23%). At CKD onset, HTN was highly prevalent, varying from 83% in females to 96% in Blacks; diabetes ranged from 36% in females to 61% in Hispanics; more than two-thirds had cardiovascular disease (CVD); and 19-28% had cancer across subgroups (Table).

Conclusions: This finding suggests that many veterans at the time of CKD onset had already developed some major comorbidities, which could make them particularly susceptible to death before ESKD.

Funding: NIDDK Support, Other U.S. Government Support

Percentages of patients with the individual comorbidity at CKD onset

Comorbidity	Age		Gender		Race and ethnicity				
	18-65 years	>65 years	Female	Male	American Indian or Alaska Native	Asian or Pacific Islander	Black	Hispanic	White
HTN	89.6	90.1	82.6	90.2	89.4	90.8	95.5	92.0	89.0
Diabetes	52.3	44.0	35.7	46.6	54.8	51.9	55.4	60.6	43.9
CVD	68.0	77.4	64.2	75.2	73.4	68.6	71.7	71.3	75.6
Chronic obstructive pulmonary disorder	31.1	29.5	34.7	29.8	31.4	24.9	27.6	24.2	30.5
Anemia	31.1	29.9	33.2	30.1	31.3	25.7	42.3	36.2	28.1
Cancer	18.5	27.9	20.8	25.5	21.3	20.7	26.5	24.0	25.4
Gastrointestinal bleeding disorders	19.3	15.9	16.7	16.8	18.5	15.9	22.0	20.5	15.7
Liver disease	9.9	3.4	6.1	5.1	6.7	5.2	7.7	9.2	4.5

PO0515

Classification of Cause of CKD Using ICD-9 and ICD-10 Codes

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Background: Current KDIGO guidelines classify CKD using three parameters: glomerular filtration rate (GFR), albuminuria, and cause of disease. While prognosis based on estimated GFR and albuminuria have been studied, less is known about the prevalence of disease etiology in CKD patients. We sought to classify various causes of CKD using billing codes for better assessment of the prevalence and risk implications of disease etiology in CKD staging.

Methods: We categorized cause of CKD with 18 potential etiologies and assigned relevant Internal Classification of Diseases (ICD) 9th and 10th revision Clinical Modification codes pertaining to each etiology. We applied the algorithm to two study populations, Johns Hopkins Medicine and Geisinger Health, to assess the prevalence of different etiologies of CKD in large health systems. To validate our CKD classification system, we determined CKD cause among 101 outpatients treated within Johns Hopkins Medicine through internal chart reviews and compared our findings to the classification algorithm generated CKD etiology.

Results: 43.3% and 26.4% of patients with eGFR <60 ml/min/1.73 m^2 in 2016 in the Geisinger and Johns Hopkins study population, respectively, had a billing code used in our classification algorithm. The most prevalent etiologies of CKD in patients with available billing codes at Geisinger were hypertensive nephrosclerosis (27%), diabetic nephropathy (13.6%), obstructive nephropathy (5.2%), and nephritic syndrome (4.9%). In contrast, the most common causes of CKD in the Johns Hopkins cohort were miscellaneous (12%), obstructive nephropathy (6.3%), and non-PKD hereditary disease (3.2%). Chart review revealed 56% concordance between cause of CKD determined by chart review and that by billing code, with higher agreement for polycystic kidney disease, kidney transplant, autoimmune disease, diabetic nephropathy, neoplasm, hypertensive nephrosclerosis, and solitary kidney.

Conclusions: We developed an algorithm for classifying CKD cause by ICD-9 and ICD-10 codes using electronic medical record data; however, validation suggests varying degrees of accuracy across different CKD etiologies.

PO0516

Epidemiology of Patients with High-Risk CKD: A Demographic Evaluation of Patients Who Had Indications for SGLT2 Inhibitors and GLP-1

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Background: The emerging evidence of the favorable effects of sodium-glucose co-transporter-2 inhibitors (SGLT2is) and glucagan-like peptide 1 receptor agonists (GLP-1) on renal function has brought hope and excitement to the nephrology communities in the US. However, many patients with high risk CKD and indications for SGLT2is and GLP-1 were not on the medication. We would like to identify the features of these patients and their primary care providers to offer targeted recommendations regarding concerns for initiating SGLT2is and GLP-1.

Methods: This is a preliminary analysis of data obtained from the Kidney Coordinated Health Management Partnership (K-CHAMP) study (NCT03832595), an ongoing, NIH funded pragmatic randomized control trial testing an electronic health record-based population health management approach to improve CKD care. The studied population included patients between ages 18 and 85 with either chronic kidney disease stage IV and above or features of high-risk progression based on CKD risk progression score calculated by the kidney failure risk equation. Patients were screened based on their risk score calculated by Epic EMR and arranged based on their upcoming PCP's appointments. Patients who were taking SGLT2is or GLP-1 were compared with patients who had the indications for either medication but were not on the medications.

Results: Baseline demographics such as median age, gender, race, and BMI were compared. Comorbidities, the presence of endocrinology referral, laboratory values and whether or not patients have been on angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were also compared. Clinicians' characteristics were compared as well. Patients who had the indications for SGLT2is but were not on them were more likely to be older in age, had low GFR (around low 30 ml/min) and low hemoglobin A1C. Patients who had the indications for GLP-1 but not on them were likely to have high A1C and likely to have already been on insulin.

Conclusions: Identification of features of high risk patients who had clinical indications for SGLT2i and GLP-1 but were not on the medication would be helpful in finding better ways to provide nephrology recommendations regarding SGLT2is and GLP-1.

Funding: NIDDK Support

PO0517

Disparities in CKD Progression by Medicare Advantage Enrollees

Clarissa J. Diamantidis,[1] Lindsay Zepel,[1,3] Virginia Wang,[1,2] Valerie A. Smith,[1,2] Sarah H. Scholle,[4] Loida A. Tamayo,[5] Matthew L. Maciejewski.[1,2] *[1]Duke University School of Medicine, Durham, NC; [2]HSRD, Durham VA HCS, Durham, NC; [3]OptumLabs Visiting Fellow, Minnetonka, MN; [4]National Committee for Quality Assurance, Washington, DC; [5]Centers for Medicare and Medicaid Services, Baltimore, MD.*

Background: The prevalence of chronic kidney disease (CKD) in Medicare beneficiaries has quadrupled in the past two decades, but little is known about risk factors affecting the progression of CKD. This abstract aims to understand the progression of CKD up to five years after study entry in a large cohort of Medicare Advantage (MA) enrollees and whether it differs by provider recognition of CKD, race and ethnicity, or geographic location.

Methods: In a cohort of 1,002,388 MA enrollees with CKD stages 1-4 based on 2013-2018 labs, progression was estimated using a mixed-effects model that adjusted for demographics, urbanicity, comorbidity, urine albumin-to-creatinine ratio, clinical recognition via diagnosed CKD, and time fixed effects. Race and ethnicity, geographic location, or clinical recognition of CKD were interacted with time in three separate regression models.

Results: Mean (median) follow-up was 3.1 (3.0) years. At study entry, Black and Hispanic MA enrollees had greater kidney function at study entry than other beneficiaries, but their kidney function declined faster compared to non-Hispanic Whites. At study entry, MA enrollees with clinically recognized CKD had estimated glomerular filtration rate levels that were 18.6 units (95% confidence interval (CI): 18.5-18.7) lower than levels of unrecognized patients, but kidney function declined more slowly in enrollees with clinical recognition of CKD. There were no differences in CKD progression by metropolitan or non-metropolitan areas.

Conclusions: These results suggest that patients with clinically recognized CKD and racial and ethnic minorities merit closer surveillance and management to reduce their risk of faster progression.

Funding: Other U.S. Government Support

PO0518

Impact of the Race Multiplier in the Estimated Glomerular Filtration Rate Equation on Care Delivery Among African-American CKD Patients

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Background: African-American patients with chronic kidney disease (CKD) have poorer outcomes, including in dialysis access placement and transplantation. Estimated glomerular filtration rate (eGFR) equations, which assign higher eGFR values to African-American patients, may be an inadvertent mechanism for inequitable outcomes. Electronic health record-based registries enable population-based examination of care across racial groups.

Methods: Cross-sectional study at two large academic medical centers and affiliated community primary care and specialty practices.

Results: Of 2225 African-American patients, 743 (33.4%) would hypothetically be reclassified to a more severe CKD stage if the race multiplier were removed from the CKD-EPI equation. Similarly, 167 of 687 (24.3%) would be reclassified from stage 3B to stage 4. Finally, 64 of 2069 patients (3.1%) would be reassigned from eGFR > 20 ml/min/1.73m^2 to eGFR ≤ 20 ml/min/1.73m^2, meeting the criterion for accumulating kidney transplant priority. Zero of 64 African-American patients with an eGFR ≤20 ml/min/1.73m^2 after the race multiplier was removed were referred, evaluated or waitlisted for kidney transplant, compared to 19.2% of African-American patients with eGFR≤20 ml/min/1.73m^2 with default CKD-EPI equation.

Conclusions: Our study reveals a meaningful impact of race-adjusted eGFR on the care provided to the African-American CKD patient population.

Funding: Private Foundation Support

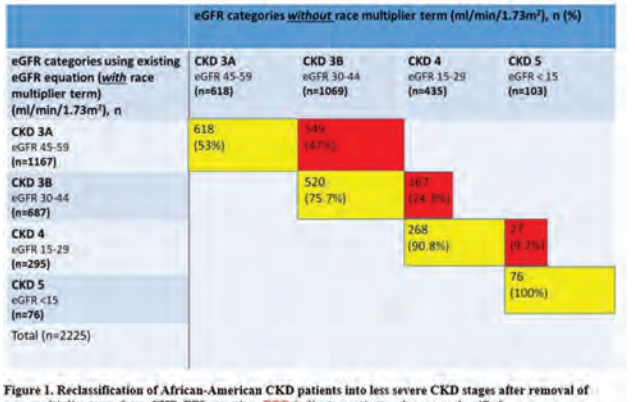

Figure 1. Reclassification of African-American CKD patients into less severe CKD stages after removal of race multiplier term from CKD-EPI equation. RED indicates patients who are reclassified.

Abbreviations: CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate

PO0519

Prevalence of Diabetes, Hypertension, Anemia, and Hyperkalemia as Frequent Comorbidities in Patients with CKD Regardless of their KDIGO Staging

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Background: Chronic kidney disease (CKD) is a worldwide public health problem. Currently in Mexico, the prevalence of CKD is only an estimate, based primarily on records of advanced stages of the disease. It is necessary to identify comorbidities and thus establish strategies to delay its progression and reduce morbimortality associated with CKD.**Objective:** To know the prevalence of comorbidities associated with CKD at different stages in an outpatient population who attended a 3rd level hospital.

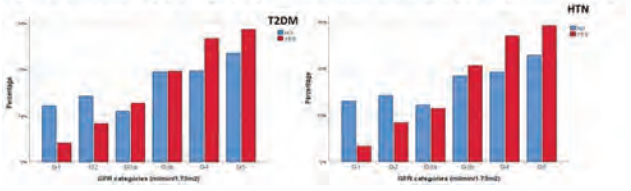
Methods: This is a cross-sectional retrolective study. Records of adult patients who attended an outpatient nephrology consultation in the period from February 2019 to February 2020 were included, with laboratory reports from 15 days prior to the inclusion date. Descriptive statistics were performed, with a 95% CI and a value of p≤0.05.

Results: 1772 patient records were included. 51% (907) were women, the mean age was 42 ± 24.2 years. 12% were on renal replacement therapy, 11% hemodialysis and 1% peritoneal dialysis. 87% (1546) lacked family history of CKD; 11% (192) were smokers. Regarding body mass index, 2% (32) presented low weight, 37% (562) normal weight, 53% (804) overweight and 8% (122) obesity. *Figure 1* shows the distribution by CKD stage and main comorbidities. The prevalence of proteinuria was 39% (693). 53% (826) had anemia. The prevalence of hyperkalemia (HK; $K^+ \geq 5$) was 29% (325). The prevalence of serum albumin <3.5 was 26%; 44% of the population had glucose> 100 mg/dl; 53% with triglyceride >150 mg/dl and 29% with total cholesterol ≥200 mg/dL.

Conclusions: A high prevalence of CKD comorbid risk factors such as diabetes, hypertension, anemia and HK were identified regardless of CKD staging, increasing in proportion in later stages.

Funding: Commercial Support - AstraZeneca

Figure 1. Distribution by CKD stage and presence of type 2 diabetes(left) and hypertension(right)



PO0520

Cystatin C Use in Clinical Practice

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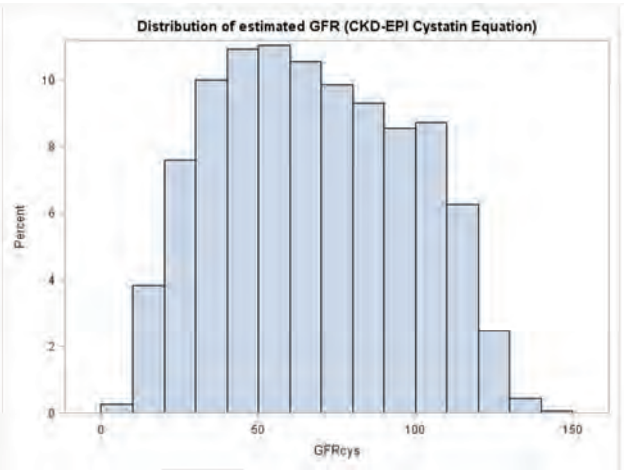
Background: Cystatin C is a filtration biomarker that can be used as an alternative for serum creatinine. The 2012 KDIGO guidelines advocate for the use of cystatin C to confirm the diagnosis of chronic kidney disease (CKD), but 9 years later it is not clear how this test is being used in clinical practice.

Methods: We examined 87,803 cystatin C levels obtained among 55,360 patients between 11/2011-6/2018 in the database of Laboratory Corporation of America Holdings (LabCorp®). The CKD-EPI cystatin equation was used to calculate the estimated GFR for each level. Descriptive analyses of patient age, sex, and ordering provider were constructed, and relationships between serum cystatin C and creatinine levels were examined with correlation analysis and linear regression.

Results: The mean age was 58±17;50.2% were women. Frequency of orders increased over time, from 6,323 tests in 2012, to 17,822 tests in 2017. Providers ordering cystatin C included: Internal/Family Medicine MDs (83%), radiologists (4%), mid-levels (4%), and 9% unknown. Cystatin C was ordered on patients with a wide range of estimated GFR values (Figure). Linear regression showed that 75% of the variation in cystatin C could be modeled if age, sex, BUN, and creatinine were known. Dispersion between actual and predicted cystatin was minimal at cystatin C levels ≤ 3.0 mg/L, representing estimated GFR values ≥ 15 mL/min/1.73m2.

Conclusions: Providers are ordering cystatin C with increasing frequency over time, for a variety of indications besides confirmation of borderline CKD. Cystatin can be modeled fairly reliably, using BUN, creatinine, sex, and age, for cystatin levels≤ 3.0 mg/L.



PO0521

Appropriate Interval Between Two eGFR Measurements for the Evaluation of the Association of eGFR Slope with Incidence of Renal Events

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Background: In recent years, growing evidence has shown the prognostic utility of eGFR slope for the risk of ESRD. Previous observational studies have assessed the association between renal events and eGFR slopes estimated by two measurements of eGFR but had great differences in the interval between two eGFR measurements. In this study, we thus aimed to determine the appropriate interval between two eGFR measurements to evaluate the association of eGFR slope with incidence of renal events.

Methods: This is a retrospective cohort study in 203 CKD patients who visited Nara Prefecture General Medical Center, Japan between 1 January 2013 and 31 December 2016 and in whom two or more than two measurements of eGFR levels were confirmed in medical records. eGFR slopes were estimated by using two measurements of eGFR at baseline and 0.5, 1, 1.5, 2, or 3 years. We excluded patients with acute kidney injury, urologic malignancies, nephrotic syndrome with steroid treatment or collagen diseases. Outcome was renal events defined as a composite of ESRD and eGFR decline of > 30%. C statistics were used to evaluate the association between eGFR slope and incidence of renal events.

Results: The median age of study participants was 67 (56-77) years and 71 (37%) were male. The median levels of baseline eGFR were 34 (21-48) mL/min/1.73m^2 and diabetes was present in 80 (39%) participants. During the median follow-up period of 38 months, renal events occurred in 52 participants. Medial levels of eGFR slopes$_{0.5,\ 1,\ 1.5,\ 2\ \text{and}\ 3yr}$ were -7.8, -3.6, -2.9, -0.9, -1.5 mL/min/1.73m^2, respectively. C-statistics of eGFR slopes$_{0.5,\ 1,\ 1.5,\ 2\ \text{and}\ 3yr}$ for renal events were 0.622, 0.691, 0.797, 0.858, 0.806, respectively, and that of eGFR slope$_{1.5yr}$ was significantly higher than that of eGFR slope$_{0.5yr}$ and eGFR slope$_{1yr}$ ($p<0.001$ and $p=0.001$, respectively). In stratified analysis, eGFR slope$_{1.5yr}$ had higher prognostic ability of renal events in patients with versus without diabetes, advanced CKD and proteinuria. C-statistics of renal events when considering baseline eGFR alone was 0.853 but combination use of baseline eGFR and eGFR slope$_{1.5y}$ significantly increased c-statistics, to 0.913 ($p=0.01$).

Conclusions: eGFR slope for high prognostic ability of renal events may be needed to be calculated by at least 1.5-year interval between two eGFR measurements.

PO0522

Rates of Clinical Events in Patients with CKD: A UK Population-Based Cohort Study

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Background: Epidemiology of clinical event rates in patients with chronic kidney disease (CKD) is limited and can impede the ability of dialysis organizations, government agencies, other institutions, and payers to counsel patients and assess quality of care.

Methods: The Clinical Practice Research Datalink (CPRD) is a large, longitudinal UK-based primary care database that covers 6% (~4 million people) of the population. CPRD is linked to Hospital Episode Statistics (HES), which contains information on all hospital admissions in England. We identified CKD patients with eGFR <60 ml/min/1.73m^2 in CPRD between 2004 and 2017. Adverse clinical events were identified using ICD-10 and READ codes. Non-dialysis dependent (NDD) patients were staged by eGFR. Dialysis dependent (DD) patients were identified using Classification of Interventions and Procedures (OPCS) and READ codes. Clinical events were identified by ICD10 and READ codes. Incidence rates per 100 person-years (PY) were calculated for selected adverse event stratified by dialysis status and CKD stage.

Results: We identified 310362 NDD and 5248 DD patients with a mean (standard deviation [SD]) age of 75.5 (10.2) years and a median (interquartile range [IQR]) follow-up of 87.5 (46.5-130.9) months. Among NDD patients 96%, 3%, and 1% of patient-years came from CKD 3, 4, and 5, respectively. Most event rates were consistently higher in DD CKD patients, compared to NDD CKD patients; and higher among CKD 4/5 compared to CKD 3 patients (Table 1).

Conclusions: Our results help establish baseline rates of specific clinical events and provide additional evidence of increased morbidity for DD vs. NDD patients, and for NDD patients with more severe vs. less severe kidney disease.

Funding: Commercial Support - AstraZeneca

Table 1: Incidence rates of adverse clinical events per 100 PY

Adverse events	NDD CKD 3 Rate	NDD CKD 4/5 Rate	DD Rate
Acidosis	0.5	1.2	2.3
Allergic anaphylaxis	0.1	0.1	0.1
Gastrointestinal hemorrhage	2.5	3.2	5.8
Hyperkalemia	0.7	2.2	4.9
Sepsis	1.3	2.2	7.4
Pancreatitis	0.1	0.2	0.4
Pneumonia	7.8	12.2	15.2
Pyelonephritis	0.1	0.2	0.7
Rhabdomyolysis	0.1	0.1	0.3
Seizure	0.4	0.5	1.0
UTI	7.1	12.6	9.8

PO0523

End Point Abstraction and Incident Events in a Cohort of >5000 CKD Patients After 6.5 Years of Follow-up in the German CKD (GCKD) Study

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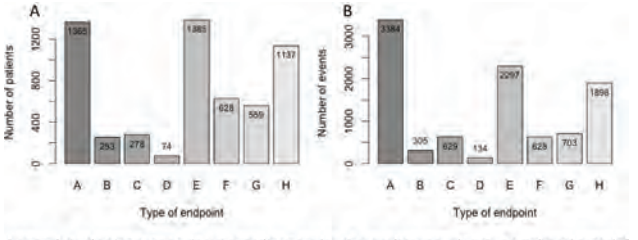
Background: Etiopathologies and progression of chronic kidney disease (CKD) differ among affected individuals with a differential risk to develop comorbid conditions like cardiovascular disease, adverse renal events like end-stage kidney disease (ESKD) or acute kidney injury (AKI), and early mortality. Evidence about CKD trajectories and a broad spectrum of adverse events in large cohorts of CKD patients under regular nephrological care is scarce, motivating the generation of such evidence from the ongoing GCKD study with 5217 enrolled patients.

Methods: In GCKD, endpoints are continuously abstracted from hospital discharge letters and death certificates based on a standardized endpoint catalogue (Fig. 1 legend). To reduce inter-observer variability, endpoints were abstracted by a trained physicians endpoint committee. Data from the first 6.5 years of follow-up was evaluated (data freeze 04/2020).

Results: Among all 5217 patients 2867 had at least one endpoint and 9978 endpoints occurred. At the end of the first 6.5 years, 628 patients were deceased. Cardiovascular endpoints occurred most frequently (Fig. 1) driven by arrhythmias (N_{events}=713) and decompensated heart failure (N_{events}=707), followed by renal events, which were driven mostly by 1176 non-dialysis dependent AKIs and 207 temporary dialysis events. 522 ESKD events occurred (457 dialysis, 65 kidney transplants). Hospitalizations due to infections were also frequent. Death occurred mainly due to cardiovascular disease (N=175) and due to infections (N=147). 26 patients died due to forgoing of dialysis.

Conclusions: Over an observation period of 6.5 years, 9979 incident endpoints occurred in a cohort of 5217 CKD patients. The highest number of endpoints occurred for cardiovascular and renal events. The high risk of recurrent events for patients in these categories underscores the need to focus on high-risk patient subgroups.

Funding: Government Support - Non-U.S.



Legend: Endpoint categories: A: cardiovascular, B: cerebrovascular, C: peripheral arterial disease, D: microangiopathy in diabetes, E: renal, F: mortality, G: malignomas, H: hospitalization due to infection

Figure 1: A) Number of patients with at least one endpoint and B) number of events

PO0524

Estimating the Future Burden of CKD Through Microsimulation Methods

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Background: Chronic kidney disease (CKD) is a debilitating and costly condition, impacting over 10% of people globally. Early diagnosis and proactive management could potentially mitigate the rates of progression to end stage renal disease. Understanding the future trajectory of CKD prevalence, progression, outcomes and the related economic burden are important considerations for public health and policy planning. This study estimates the epidemiological and cost burden of CKD with an emphasis on high-risk populations with macroalbuminuria, type 2 diabetes (T2D) and/or heart failure (HF), from 2020 to 2025.

Methods: A patient-level microsimulation was developed to estimate the epidemiological and economic burden of CKD in the UK. KDIGO 2012 recommendations were used to categorise patients according to eGFR and albuminuria using the Health Survey of England extrapolated to the UK population. The future prevalence and healthcare costs for the CKD population, as well as for subpopulations – macroalbuminura, T2D, HF – were estimated. Finally, "current practice" management scenario was compared to an early detection and proactive scenario.

Results: By 2025, CKD prevalence in the UK is expected to grow by 11% from ~9.1M to 10.2M corresponding to a £4B (18%) increase in annual cost from £18B, of which, £0.58B is incurred due to macroalbuminuria where prevalence is projected to reach 860,000 by 2025. Within the macroalbuminuria population, costs were comparable between patients with (390,000; £0.31B) and without (465,000; £0.27B) T2D. However, costs for patients with macroalbuminuria were 3-times higher than for CKD patients with HF (£0.11B, 140,000). Early identification and proactive management of patients with CKD and macroalbuminuria resulted in a cumulative £0.65B direct healthcare cost saving by 2025.

Conclusions: This model predicts that CKD poses a serious public health threat. The overall epidemiological burden for patients with macroalbuminuria was comparable between patients with and without T2D. Early detection along with proactive treatment may reduce CKD progression and more directly improve patients' quality of life while also reducing the long-term economic burden of CKD.

Funding: Commercial Support - AstraZeneca

PO0525

Identifying and Clustering CKD Progression Trajectories Using Machine Learning

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Background: There is evidence suggesting that estimated glomerular filtration rate (eGFR) slope can be used as a surrogate clinical endpoint in renal clinical trials. However, there are limited data on the characteristics of fast and slow progressors based on eGFR slope from large population-based studies.

Methods: We identified CKD patients (based on two consecutive eGFRs of <75ml/min/1.73m^2 recorded more than 90 days apart) aged ≥18 years from the UK Clinical Practice Research Datalink (CPRD) between 2004 and 2019. Estimated GFR measurements over a 3-year observation period post-index date (date of 2nd eGFR measurement) were extracted. Patients were clustered based on their eGFR trajectories using statistical (linear mixed effect models (LMM)) and machine learning techniques (unsupervised machine learning and Bayesian approaches). Association between trajectory clusters and all-cause mortality was assessed using Cox regression analysis.

Results: Preliminarily, 407,108 patients with 1.8 million eGFR measurement (median 4 (IQR: 2-6) eGFR measurements per patient) were identified. Using LMM, we found 5% of patients declined rapidly with an average rate of eGFR change per year -4.78 (95%CI: -9.40 to -3.28) whereas the majority (95%) remain stable or progressed slowly. A distinct fast progressing cluster was also detected using unsupervised machine learning and Bayesian methods which showed broadly linear patterns. Overall, there was an agreement between all three clustering approaches. These findings were replicated in the validation dataset showing consistent findings. Compared to stable/slow progressors, fast progressors were 3 times more likely (Hazard Ratio (HR)=2.82: 95%CI 2.75-2.90) to die following the 3-year observation period.

Conclusions: A clear fast progressing cluster was identified with an average eGFR decline of ≥5 ml/min/1.73m^2 per year with a higher risk of all-cause mortality compared to other clusters. Whilst Bayesian and unsupervised machine learning methods can detect non-linear patterns, we found broadly linear trajectories.

Funding: Commercial Support - AstraZeneca

PO0526

Using Autoencoders for Imputing Missing Data in eGFR Decline Trajectories of Patients with CKD

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Background: Using machine learning (ML) approaches to impute missing data has not been explored in CKD progression. We investigated the utility of a data-driven imputation to improve downstream classifier prediction of rapid eGFR decline in the CURE-CKD registry.

Methods: We analyzed CKD patients at UCLA (N=13,206) over a 2-year period. We used: 1) the dataset with missing data; and 2) a censored subset with no missing data. We introduced 33% and 66% missingness by removing values by removing values either missing completely at random (MCAR); missing at random (MAR); or missing not at random (MNAR). We included: eGFR, hemoglobin (HbA1c), systolic blood pressure (SBP), number of ambulatory and inpatient visits, age, sex, ethnicity, rurality status, diagnosis of hypertension, diabetes mellitus (DM), pre-DM, and use of renin angiotensin aldosterone system inhibitors. We introduced missingness on SBP and HbA1c to mirror the original dataset. We imputed missing values using an autoencoder ML model. To predict a 40% eGFR decline over 2 years, we developed random forest models using the full and resultant imputed datasets.

Results: On the full subset, the MNAR imputation method achieved a root mean squared error (RMSE) of 0. The MAR method achieved RMSE of 3.8 at 33% missingness and 5.4 at 66%. MCAR achieved RMSE of 38.5 at 33% missingness and 56.4 at 66%. Using the random forest model to predict rapid decline on the fully observed subset without removing and imputing data achieved a receiver operating characteristic (ROC) area under the curve (AUC) mean of 80.8%±1.1 and precision/recall (PR)-AUC mean of 23.9%±1.5; the same as our methodology on MNAR, which is explained by the RMSE of 0, shown in Table 1.

Conclusions: Our method accurately imputes clinical data values while accounting for uncertainty caused by missing values.

Funding: Other NIH Support - NIMHD

Method	Mean ROC-AUC Missingness 66% / 33%	Mean PR-AUC Missingness 66% / 33%
MNAR	80.8±1.1 / 80.8±1.1	23.9±1.5 / 23.9±1.5
MAR	69.1±1.5 / 74.2±0.9	22.8±1.5 / 23.3±1.8
MCAR	70.6±0.9 / 69.5±0.9	9.3±0.6 / 10.9±0.6

PO0527

Machine Learning Prediction of ESKD and Death in CKD Patients: Electronic Medical Record-Based Cohort Study

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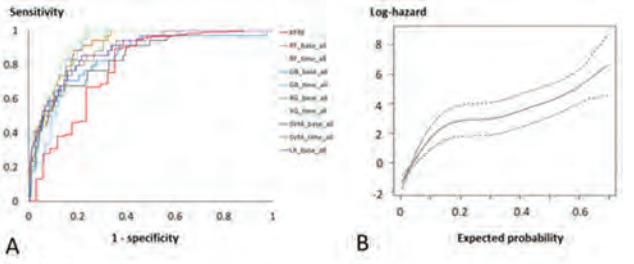
Background: Chronic kidney disease (CKD) is a risk factor for end-stage kidney disease (ESKD) and death. An accurate prediction of these risks is required to improve their prognosis. We developed the new machine learning models for the prediction of CKD progression and death using the electronic-medical-record-based CKD-patient big database in Japan (n=3,714, 66,981 claim data).

Methods: We developed 20 risk prediction models with 45 variables for the classification of the patients on the basis of their outcomes (ESKD and death) over 1 to 3 years using random forest (RF), Gradient Boosting Decision Tree (GB), eXtreme Gradient Boosting (XG), support vector machine, and multivariate logistic regression models using validation datasets including baseline or time-series datasets. The performance characteristics of the models were compared with those of the laboratory indices, and the kidney failure risk equation (KFRE) using the area under the prediction curves (AUCs) by bootstrapping 1000 times.

Results: 53.1% were male: age, 60.1±17.6 years; eGFR, 54.2±30.7 ml/min/1.73 m2; diabetes mellitus, 23.1%. In the validation dataset, 14 models showed statistically significantly higher AUCs for the prediction of outcomes than KFRE 0.782 (0.682, 0.881), and the RF, GB, and XG models based on time-series data showed the highest AUCs: 0.924 (95% CI 0.895, 0.953) (Fig. A). These three models also demonstrated the highest performance in the subgroup analysis that considers eGFR, DM, gender, and age. Moreover, the models' sensitivities were 0.971 (95% CI 0.914, 1.0). Cox proportional hazards models revealed that the probabilities predicted by these models represented the risk of the outcome ($p<0.0001$) (Fig. B).

Conclusions: The machine learning models exhibit better performance than pre-existing models in identifying patients at an increased risk of CKD progression and death. Thy will enable us to implement effective measures to improve patient's prognosis.

Funding: Government Support - Non-U.S.



A ROC curves of models
B Cox proportional hazards models show the relationship between the risk of the primary outcome over 1 year and the expected probability determined using a random forest model.

PO0528

Predicting Rapid eGFR Decline Using Electronic Health Record (EHR) Data Despite High Missingness in the CURE-CKD Registry

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Background: Patients with rapid eGFR decline tend to progress to kidney failure. Automated tools can identify individuals at risk of severe renal function decline and facilitate disease mitigation. We describe a deep neural network (DNN) for predicting the risk of rapid eGFR decline (>40% decrease in eGFR over 2 years) and identified populations at higher risk of rapid decline using the CURE-CKD Registry.

Methods: Variables include: age, sex, race/ethnicity, ACE inhibitor/ARB use, eGFR, systolic blood pressure (SBP), hemoglobin A1C, and the diagnosis of hypertension, type 2 diabetes (DM), pre-DM or chronic kidney disease (CKD) based on EHR coding from patients with CKD (N=93,567) and at-risk for CKD (N=913,289) with eGFR ≥15ml/min/1.73m^2 over 2 years. We trained and validated a 5-layer DNN, a logistic regression (LR) model, and a gradient boosted tree (GBT) model using a 60/20/20 train/test/validation split. We computed the risk distribution of all 25,475 subpopulations, based on all possible expert defined combinations of the above variables, and compared this risk distribution against the whole population's risk distribution using the Kolmogorov-Smirnov (KS) test. Subgroups with the highest risk of decline were identified using the KS test ($p<0.05$) on our highest performing model.

Results: The DNN achieved an area under the receiver operating curve (AUC-ROC) of 0.75 on the test set. The LR and GBT achieved an AUC-ROC of 0.72 and 0.73, respectively. The subpopulations with significantly highest average predicted risk across training, validation, and testing were 17,734. We identified the most frequent predictors of rapid eGFR decline across the highest risk populations. Of the top 100 significantly higher risk subpopulations the following variables were the most frequent: CKD (100%), SBP > 140 mmHg (72%), age 45-66 years (56%), DM (52%), and A1C > 8 (50%).

Conclusions: We developed a methodology that uses a risk model for rapid eGFR decline using big data and used its predictions, along with the KS test, to identify subpopulations with significantly high risk for rapid eGFR decline.

Funding: Other NIH Support - NIMHD

PO0529

A Machine Learning-Based Prediction Model for Trajectory of GFR in CKD Patients with Rapid Decline of GFR by Using a Big Database

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Background: There are various patterns of GFR trajectories in patients with chronic kidney disease (CKD), even among those with rapid declines in GFR. We sought to create a machine learning-based predictive model for extremely rapid decline of GFR in patients with CKD using a single hospital database.

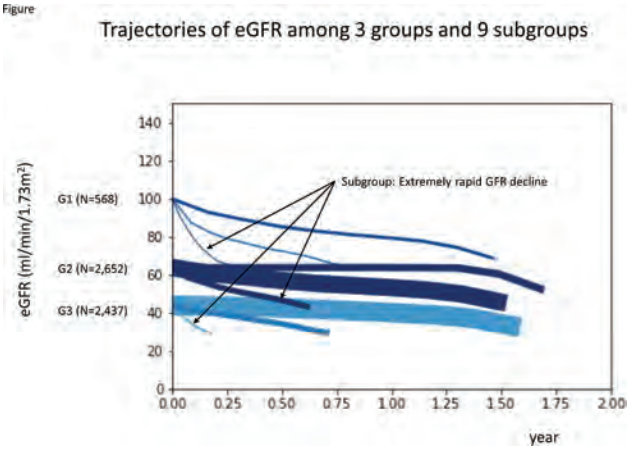
Methods: We used a database, which included the electronic medical records of 286,494 patients. We selected patients with CKD and rapid decline in kidney function, which was defined as an estimated GFR (eGFR) decline of 30% or more within two years. We used longitudinal statistics using data extracted from baseline, 90-, 180-, and 360-day windows prior to baseline and exponentially weighted averages (ESAs) where the weight was calculated as 0.9*(days/decay parameter). The random forest algorithm and python code with the scikit-learn library (https://scikit-learn.org/) were used for model creation.

Results: Patients were automatically classified, using machine learning, into three groups according to eGFR at baseline (G1; high GFR, G2; intermediate GFR, G3; low GFR) and nine subgroups according to the slope of eGFR decline. The subgroup with the

fastest GFR decline exhibited the steepest slope (Figure 1). The area under the curves for predicting the steepest (fastest) GFR decline by random forest model among the G1, G2, and G3 were 0.68, 0.72 and 0.81, respectively. Regarding feature importance, in the G1 group, hemoglobin of the 7-day ESAs and measures obtained 90 days prior to baseline ranked within the top five. Meanwhile, serum albumin and CRP at baseline ranked within the top seven in the G3 group.

Conclusions: The random forest model identified patients with extremely rapid GFR decline. Anemia in patients with higher eGFR, and nutritional status in patients with lower eGFR, emerged as strong risk factors.

Figure



PO0530

Automation of Renal Blood Flow Analysis from Dynamic Phase-Contrast MRI with Deep Learning

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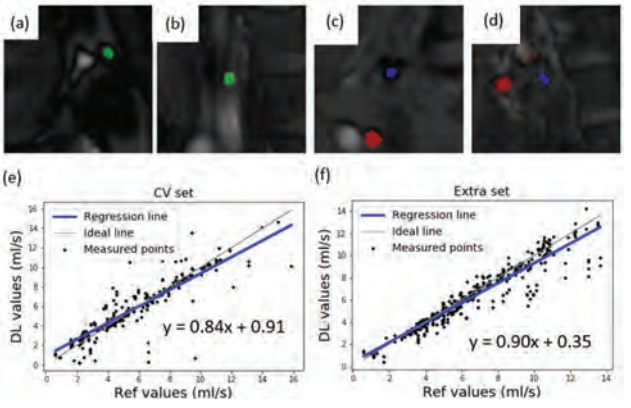
Background: Phase-contrast magnetic resonance imaging (PC-MRI) allows to assess renal blood flow (RBF), an important parameter in the development of chronic kidney disease (CKD). RBF assessments require time-consuming and observer-dependent delineations of the renal arteries. Thus, we have developed and evaluated a fully-automated deep learning model for renal artery segmentation.

Methods: PC-MRI data came from 131 subjects, four studies, three MRI vendors and a range of velocity encodings. The deep learning model (DL) was a deeply-supervised attention U-Net with residuals with the result re-introduced in a second iteration. Flow was estimated by integrating the flow values in the segmentations. Segmentation and flow results were compared for cross-validation (CV, 73 subjects) against manual delineations and reference flow measurements from external software. The remaining data (Extra) only had reference flow measurements, being only evaluated for flow.

Results: In 4-fold CV, a segmentation accuracy of Dice 0.71 ± 0.21 was obtained. Although most segmentations were relatively accurate, the model failed in ten out of 144 arteries. Flow measurements were relatively highly correlated in CV with no significant deviation from the reference: (r=0.84, DL: 5.8±3.0 ml/s vs Ref: 5.8±3.0 ml/s, p=0.98). The Extra set provided a high correlation and no significant deviation (r=0.94, DL: 6.4±2.8 ml/s vs Ref: 6.7±2.9 ml/s, p=0.11).

Conclusions: The method shows promise to support RBF measurements from PC-MRI. It may save analysis time and increase objectivity in the future. More high quality and representative training data are likely to improve accuracy and generalizability.

Funding: Government Support - Non-U.S.



Best segmentation results (a,b) and worst (c,d). Green shows true positives, blue false negatives, and red false positives. (e) and (f) show the linear regression plots comparing DL vs Ref for CV and Extra sets, respectively, with the fitting line in thick blue and the ideal line in thin gray

PO0531

Healthcare Engineering to Predict Time and Resource Impact of Integrating a CKD Education Intervention into Primary Care Practice

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Background: This study describes the novel use and application of healthcare engineering and Discrete Event Simulation (DES) to study the impact of adding a physician-led chronic kidney disease (CKD) education review for patients in two primary care settings.

Methods: We developed a computer model to simulate a General Internal Medicine and Family Medicine practice and used it to examine the impact of adding a physician-led CKD education review into routine primary care appointments. To create the computer models we gathered data using real-time process mapping and information from the electronic health record (EHR). The physician-led education review included physicians reviewing a one-page education information sheet, tailored to individual patients. Computer models of each clinic were developed to test the effect on patient flow and time through clinic appointments using different proportions of patients with CKD for which a physician would review the CKD education. We also tested varying amounts of time it would take for physicians to review CKD education within the model.

Results: Adding the physician-led review of CKD education into clinic visits did not significantly increase patient flow or time through clinic. Incrementally increasing potential times for the CKD education review, up to 10 minutes with 50% of all patients, did not reduce patient flow or significantly increase overall time of patients going through clinic from check-in to check-out. For General Internal Medicine, the 95% baseline Confidence Interval for patient time through clinic was between 53.4 min and 65.03 min whereas the 95% Confidence Interval when CKD education was reviewed with 50% of patients resulted in an estimated visit time between 57.54 min and 69.17 min. The estimated resource utilization of physicians increased by about 5%. Similar results were found for Family Medicine.

Conclusions: This research allowed us to perform a "what-if" analysis on the effect of introducing physician-led CKD patient education into routine primary care practice. Results show that it is possible to introduce patient education and support without major disruptions in clinic flow nor patient time through clinic.

Funding: NIDDK Support

PO0532

Kidney Outcomes Associated with Fibrosis and Inflammation on Kidney Wedge Sections

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Background: Interstitial fibrosis and tubular atrophy (IFTA) and inflammation are prognostically important but crudely assessed in biopsy reports. We used manual morphometry to characterize different patterns of IFTA and inflammation on large biopsy sections and their associations with CKD progression.

Methods: We studied 936 patients who had a radical nephrectomy due to renal cancer and no severe renal disease. A wedge section distal to tumor was used for morphometry. All areas of cortex, glomeruli, IFTA and inflammation were annotated. We calculated glomerular volume, % globally sclerotic glomeruli (GSG), overall %IFTA, mean area of each contiguous focus of IFTA (focus area), number of IFTA stripes (from capsule toward medulla) per cortex area, % subcapsular cortex with IFTA (%SC IFTA), % total inflammation (%TI), % inflammation outside (%I-non IFTA) and within foci of IFTA (%I-IFTA). We followed patients for progressive CKD censoring at cancer recurrence

or death. Progressive CKD was defined as kidney failure or 40% decline in eGFR from the baseline (4 months after surgery). Models were unadjusted, adjusted for %IFTA, and adjusted for %TI.

Results: At surgery mean age was 64 years, 64% male, 66% hypertensive, and 13% diabetic. Samples contained a mean of 349 glomeruli and mean baseline eGFR was 48 ml/min/1.73m^2. After a mean follow-up of 6.4 years there were 117 CKD progression events and 299 deaths. %IFTA and %TI predicted progressive CKD independent of each other (**Table**). %I-non IFTA (not %I-IFTA) contributed to this risk. After %IFTA adjustment, smaller mean IFTA focus area associated with a higher risk of CKD progression. These findings persisted with adjustment for clinical characteristics including eGFR and proteinuria.

Conclusions: Both total %IFTA and %TI (particularly %I-non IFTA) are important predictors of progressive CKD. At the same %IFTA, a greater number of small IFTA foci are more predictive of progressive CKD than fewer large foci of IFTA.

Table. Tubulointerstitial predictors of progressive CKD

	Mean (SD)	Unadjusted (p-value)	Adjusted for %IFTA (p-value)	Adjusted for % Total inflammation (p-value)	Adjusted for % GSG (p-value)
%IFTA	4.16 (8.17)	**1.32 (<.001)**	-	**1.17 (0.03)**	**1.16 (0.03)**
Mean IFTA Focus Area, mm^2	0.47 (0.49)	**1.18 (0.007)**	**0.84 (0.003)**	0.95 (0.36)	1.04 (0.57)
#Striped IFTA, mm^2 cortex area	0.17 (0.70)	**1.36 (<.001)**	1.15 (0.11)	**1.18 (0.04)**	**1.23 (<.001)**
%SC IFTA	12.63 (21.57)	**1.07 (<.001)**	0.98 (0.53)	1.01 (0.61)	1.01 (0.78)
%TI	0.53 (1.93)	**1.27 (<.001)**	**1.14 (0.04)**	-	**1.13 (0.03)**
%I-non IFTA	0.15 (0.32)	**1.15 (<.001)**	**1.08 (0.04)**	1.01 (0.84)	1.07 (0.08)
%I-IFTA	8.47 (11.58)	**1.11 (0.02)**	1.01 (0.79)	**0.88 (0.03)**	0.99 (0.83)

PO0533

Modification of the Association Between Dipstick Hematuria and Decline in Kidney Function by Proteinuria: Results from a Longitudinal Nationwide Survey

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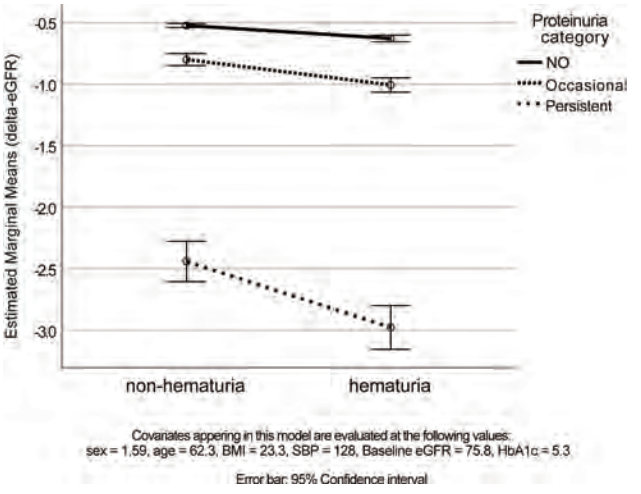
Background: We hypothesize that proteinuria has a modification effect on the association of hematuria with decline in kidney function.

Methods: Participants were recruited who have undergone multiple nationwide specific health checks between 2008 and 2014 and have been observed for ≥2 years. We divided the participants into two and three categories according to hematuria and proteinuria, respectively. Using analysis of covariance, changes in eGFR over time (delta-eGFR) adjusted for clinically relevant factors were examined among hematuria category stratified by proteinuria category.

Results: Among 253,679 participants, median delta-eGFR was -0.36 mL/min/1.73m^2 per year (IQR: -2.25-0.54) during a median observation period of 4.0 years (IQR: 3.1-5.0), with a median age of 65 years (IQR: 60-68) and median baseline eGFR of 75 mL/min/1.73m^2 (IQR: 65-87). Compared to non-hematuria group, hematuria group had a greater eGFR decline rate even after adjusting confounders including proteinuria category. When stratified by proteinuria category, hematuria-related eGFR decline rate gradually increased as the proteinuria category progressed (P for interaction <0.001).

Conclusions: Among general population, delta-eGFR levels with and without hematuria were comparable in the absence of proteinuria, but proteinuria levels had a synergistic effect on eGFR decline rate associated with hematuria.



PO0534

Mortality Following New Onset of CKD Among Veterans by Comorbid Conditions: Results from a US Large Incident CKD Population

Nilka Rios Burrows,[1] Devasmita Choudhury,[2,3] Wei Yu,[3] Meda E. Pavkov,[1] Robert Nee,[4] Alfred K. Cheung,[5,7] Keith C. Norris,[6] Guofen Yan.[3] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Salem VA Medical Center, Salem, VA; [3]University of Virginia, Charlottesville, VA; [4]Walter Reed National Military Medical Center, Bethesda, MD; [5]University of Utah Health, Salt Lake City, UT; [6]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [7]VA Salt Lake City Health Care System, Salt Lake City, UT.*

Background: Data on mortality rates after CKD onset are scarce. Using a recently constructed national incident CKD cohort, we examined mortality rates following new-onset CKD for various subgroups with or without comorbidities.

Methods: We identified 1,074,238 individuals with new-onset CKD between 2002 and 2017 in the US Veterans Health Administration (VHA). CKD onset was defined as the first time when estimated GFR (eGFR; CKD-EPI equation) decreased to <60 mL/min/1.73 m^2 for >3 months. Individuals excluded were those in the VHA for <2 years prior to first eGFR <60, or had CKD stage 4 or 5, or end-stage kidney disease when first identified. Thus, the first time identified was close to the onset of CKD stage 3. Comorbidities at CKD onset were ascertained from ICD-9/ICD-10 codes during any time before onset and through 6 months after onset. All individuals were followed for death status from onset through June 30, 2018.

Results: CKD patients with and without comorbidities had similar mean eGFRs at onset (51 ml/min/1.73m^2). Most (97%) were male and mean age at onset was 72 years. Hypertension (HTN) (90%), cardiovascular disease (CVD) (75%), and diabetes (46%) were the three most common comorbidities. For each comorbidity, mortality rate was substantially greater among those with compared to those without (Table). After adjustment for age, sex, race, ethnicity, and onset eGFR, mortality risks remained substantially greater among those with than those without the comorbidities, ranging from 12% greater with HTN to 100% greater with liver disease.

Conclusions: At time of CKD onset, mortality risk is greater in veterans with the presence of comorbidities. Intervention trials to examine the management and treatment of comorbidities on mortality in an incident CKD population might be warranted.

Funding: NIDDK Support, Other U.S. Government Support

Mortality by comorbid conditions

Comorbidity	Prevalence (%)	Death rate (per 1000 patient-years)		Adjusted hazard ratio (95% CI)	P value
		With the comorbidity	Without the comorbidity		
HTN	90	75.5	67.5	1.12 (1.11-1.13)	<0.001
CVD	75	86.4	46.0	1.75 (1.73-1.76)	<0.001
Diabetes	46	79.9	70.6	1.33 (1.32-1.34)	<0.001
Chronic obstructive pulmonary disorder	30	102.4	65.2	1.75 (1.74-1.76)	<0.001
Anemia	30	101.8	65.5	1.60 (1.59-1.61)	<0.001
Cancer	25	101.6	67.1	1.39 (1.38-1.40)	<0.001
Gastrointestinal bleeding disorders	17	89.0	72.2	1.35 (1.34-1.36)	<0.001
Liver disease	5	97.6	73.8	2.04 (2.01-2.06)	<0.001

PO0535

Impact of Variability in Estimated Glomerular Filtration Rate on Major Clinical Outcomes: A Nationwide Population-Based Study

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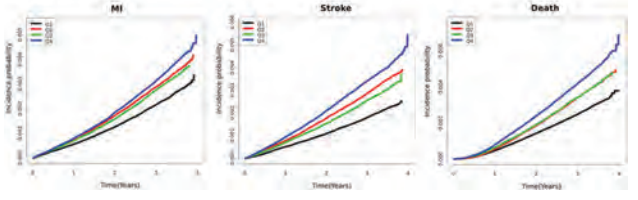
Background: The estimated glomerular filtration rate (eGFR), commonly estimated using the serum creatinine value, often fluctuates throughout the serial measurement. The clinical significance of GFR variation among the general population with normal renal function has not yet been demonstrated. Thus, we explored the impact of GFR variability on adverse clinical outcomes.

Methods: A nationwide retrospective cohort study using the Korean National Health Insurance System database was performed. National health screening examinees who underwent creatinine measurement ≥3 times between 2012 and 2016 were considered. Those with eGFR under 60 mL/min/m² were excluded. The fluctuation of eGFR was represented with variability independent of the mean (VIM) index; which was calculated by the standard deviation divided by the exponent of the regression coefficient of the mean. Then, the risks of myocardial infarction (MI), stroke and death were assessed according to the quartiles of the VIM.

Results: Of total 3,538,500 participants, 0.29% of myocardial infarction (MI), 0.14% of stroke, 0.36% of deaths were observed during the median follow up of 3.27 years. Participants with the highest VIM index, which represents the highest eGFR variability, were significantly associated with an increased risk of MI (hazard ratio [HR]; 1.10, 95% confidence interval [95% CI]; 1.04-1.16), stroke (HR: 1.16; 95% CI 1.09-1.23), and death (HR: 1.18; 95% CI 1.12-1.24). (Figure 1)

Conclusions: Increased eGFR variability exhibited an association with major clinical outcomes, indicating that monitoring eGFR variability might be a useful parameter for predicting the adverse outcomes.

Figure 1



PO0536

Development and Internal Validation of a Mortality Risk Prediction Model in Older Adults with Advanced Non-Dialysis-Dependent (NDD) CKD

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Background: Older adults with CKD expect practitioners to share prognostic estimates to inform decision-making regarding future care. The availability of useful mortality prediction models in NDD-CKD could reduce prognostic uncertainty and aid in identifying patients who would benefit from advance care planning (independent of dialysis initiation).

Methods: 699 patients with NDD-CKD stages 4-5 and age ≥60 were enrolled and followed between 2014 and 2019. Cox proportional hazards regression was used to model the risk of 1-year mortality. Candidate predictor variables included age, gender, race, Charlson Comorbidity Index (CCI), common labs and the provider's response to the Surprise Question ("Would you be surprised if this patient died in the next 12 months?", SQ, recorded using binary and 5-point Likert response scales). Optimism-corrected measures of model performance were calculated with bootstrap resampling. Model calibration was assessed visually.

Results: In the derivation cohort, age, CCI, hemoglobin values and the provider's Likert scale response to the SQ were predictive of 1-year mortality (Table 1). The C-statistic in the derivation sample was 0.76 and the optimism corrected C-statistic obtained by bootstrap resampling was 0.73. Visual examination of model calibration demonstrated good calibration.

Conclusions: A 1-year mortality risk prediction model in older adults with advanced NDD-CKD performed reasonably well and was well calibrated. Studies are needed to understand how to best leverage information on mortality risk to enhance patient-provider communication and ensure that future care delivered to patients is aligned with their priorities.

1-year Mortality Hazard Ratios

	Hazard Ratio (95% CI)
Age (per 12 yr increase)	1.57 (1.18 - 2.09)
CCI (per 2-point increase)	1.37 (1.12 - 1.67)
Hemoglobin (per 2.3 g/dl increase)	0.80 (0.65 - 0.99)
SQ - not at all surprised: neutral	2.06 (1.27 - 3.33)
Not surprised: neutral	1.12 (0.71 - 1.75)
Surprised: neutral	0.55 (0.33 - 0.92)
Very surprised: neutral	0.48 (0.28 - 0.82)

PO0537

Validation and Comparison of the Kidney Failure Risk Equation and a Novel Risk Calculator in Advanced CKD

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Background: The Kidney Failure Risk Equation (KFRE) is a widely used clinical tool for predicting risk of CKD G3-5 progressing to end-stage kidney disease (ESKD). A novel calculator (Grams) was developed for G4+ patients to predict ESKD, CVD events and death. The Grams model has not been externally validated. We aimed to assess this new tool in a cohort of advanced CKD patients for ESKD prediction and compare it to the KFRE.

Methods: This retrospective cohort study included 444 adult CKD G4+ patients (mean age 73 ± SD 12; mean eGFR 19.6 ± 6.1). The 2- and 5-year KFRE and 2 and 4-year Grams scores were compared in terms of discrimination and calibration (4 ESKD risk intervals <10%,10-20%, 20-40% and >40%). Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of KFRE-2 and Grams-2 were reported using 10% and 20% thresholds.

Results: Both models had similar discrimination for ESKD risk at the 2-(KFRE-2 AUC 0.82, 95% CI 0.80–0.87, Grams-2 AUC 0.80, 95% CI 0.75–0.86), 4-(Grams-4 AUC 0.81, 95% CI 0.77–0.86) and 5-year (KFRE-5 AUC 0.80, 95% CI 0.76–0.84) timepoints. Both were well calibrated with observed risk at predicted intervals of <10% and 10-20% at 2 years and <10%, 10-20% and 20-40% intervals at 4 and 5 years (Figure 1). Grams-2 under-predicted while KFRE-2 over-predicted risk at higher intervals (20-40% and >40%). KFRE-2 and Grams-2 had adequate sensitivity, performing similarly at ESKD risk thresholds of 10% (p=0.71) and 20% (p=0.48) (Table 1). Both had poor specificity and low PPVs at both thresholds.

Conclusions: The KFRE and Grams models perform similarly at lower ranges of risk in CKD G4+. The KFRE and Grams models however overestimate and underestimate risk respectively at higher risk intervals.

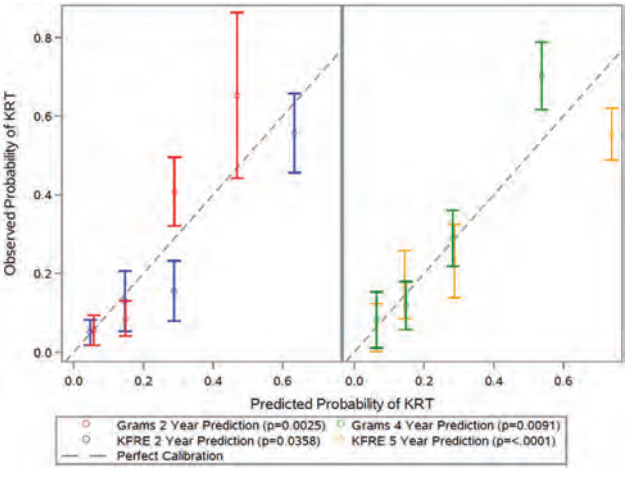

Figure 1

	10% ESKD Risk Threshold		20% ESKD Risk Threshold	
	KFRE-2	Grams-2	KFRE-2	Grams-2
Sensitivity	90	91	78	76
Specificity	48	38	67	77
PPV	30	26	36	45
NPV	95	94	93	93

Table 1

PO0538

Association of eGFR Index Category and Annual Slope with Adverse Clinical Outcomes in Japan

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Background: The relationship between the slope of eGFR with adverse clinical events has not been evaluated extensively. The objective of the study was to assess the association between eGFR and clinical outcomes.

Methods: The study population included persons with 3 or more eGFR values in the MDV database between January 1, 2014 and September 31, 2019. Patients were stratified into 5 index eGFR categories (TABLE). Least square regression model was used to examine the association between eGFR and its slope vs. study outcomes. Patients were stratified into 5 index eGFR categories (TABLE). Least square regression model was used to calculate the annual rate of eGFR change to stratify into 6 categories. Cox proportional hazard model was applied to examine the association between eGFR and its slope vs. study outcomes.

Results: 57,692 patients met the study criteria, and were grouped by index eGFR and its slope (TABLE). The mean age ranged from 56.69 to 74.21 in the index eGFR and from 65.3 to 67.2 in the slope categories. The risk of all-cause mortality or hospitalization, CV death, and any CV or renal outcomes were higher among the low and high index eGFR compared to the reference groups (grade 3 eGFR and -1~+1 slope), as well as those with rrapidly declining or increasing eGFR.

Conclusions: Our study showed that those with the highest or lowest categories in index eGFR and eGFR slope had a higher risk for adverse clinical outcomes. Further studies are needed to confirm the findings and explore potential reasons why high eGFR and rapid increase are associated with mortality, CV and renal events.

Funding: Private Foundation Support

Hazard Ratio of clinical events with eGFR and slope categories

	Hazard Ratio (95% CI)				
eGFR category with number (percentage)	All cause death	Cardiovascular Death	Any Hospitalization	CV Events**	Renal Events***
Index eGFR category (ml/min/1.73m2)* n=57,692					
G5:eGFR<15 N=552 (0.09%)	4.28 (2.87-6.4)	4.46 (2.7-7.34)	3.36 (2.83-4)	3.46 (2.8-4.26)	4.61 (1.86-11.4)
G4: eGFR:15-29 N=1,279 (2.21%)	2.88 (2.12-3.92)	2.95 (2.01-4.32)	1.89 (1.66-2.16)	1.77 (1.5-2.08)	2.01 (0.98-4.12)
G3: eGFR:30-59 N=14,442 (25.03%)	1.26 (1.08-1.47)	1.27 (1.04-1.56)	1.24 (1.17-1.32)	1.17 (1.08-1.27)	0.693 (0.445-1.08)
G2: eGFR:60-89 N=31,012 (53.75%) (reference)	1	1	1	1	1
G1: eGFR5:>90 N= 10,407 (18.03%)	1.47 (1.23-1.77)	1.46 (1.14-1.86)	1.17 (1.09-1.25)	1.29 (1.17-1.43)	5.07 (2.74-9.38)
Annual eGFR slope (ml/min/1.73m2/year) n=57,692					
<-5 N= 11083 (19.21%)	1.52 (1.33-1.74)	1.49 (1.26-1.77)	1.2 (1.14-1.26)	1.24 (1.16-1.32)	1.86 (1.43-2.42)
-3,-5 N= 6610 (11.45%)	1.15 (0.978-1.36)	1.1 (0.888-1.35)	1.04 (0.976-1.1)	1.08 (1-1.17)	1.62 (1.2-2.17)
-1,-3 N= 10612 (18.39%)	1.09 (0.939-1.27)	1.12 (0.928-1.35)	0.983 (0.932-1.04)	1.02 (0.954-1.09)	1.57 (1.2-2.07)
-1,+1 N=12028 (20.85%) (reference group)	1	1	1	1	1
+1,+3 N=7389 (12.81%)	1.06 (0.897-1.25)	1.1 (0.893-1.36)	0.994 (0.937-1.05)	1.03 (0.95-1.11)	1.74 (1.2-2.5)
>=+3 N=9970 (17.28%)	1.77 (1.54-2.04)	1.84 (1.54-2.2)	1.24 (1.18-1.31)	1.29 (1.2-1.38)	2.56 (1.74-3.77)

* eGFR = 194 x Cr-1.094x Age-0.287

**stroke, CHF, MI,

***ESRD, dialysis, acute kidney failure, renal transplant.

PO0539

Sex-Specific Differences in Clinical Outcomes Among Patients with CKD: Results from CKDopps

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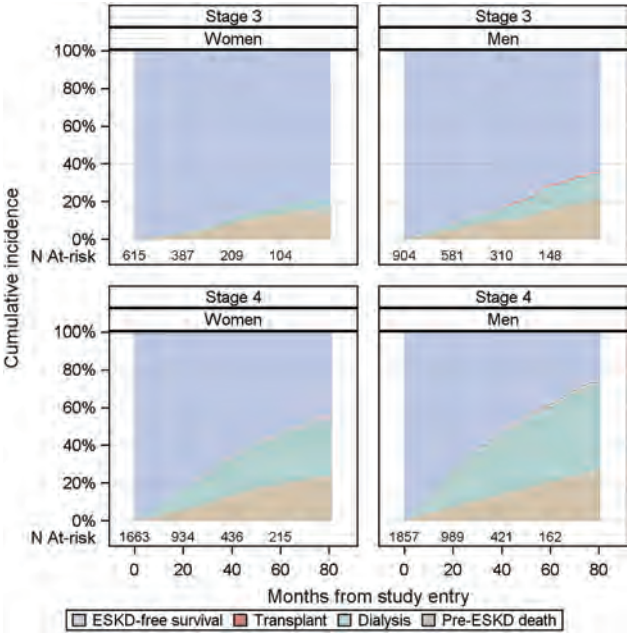
Background: Women have more chronic kidney disease (CKD) than men, but are under-represented in the dialysis population. We aimed to assess sex-specific differences in clinical outcomes among CKD Outcomes and Practice Patterns Study (CKDopps) participants.

Methods: Using data of 5682 CKDopps stage 3-5 patients from Brazil, Germany and the US, we reported cumulative incidence of pre-dialysis death, dialysis, and transplantation, by sex and CKD stage at CKDopps entry. We used Fine & Gray models to assess the effect of sex on the time to events, stratified by CKD stage. Models were adjusted for age and race, and then for eGFR slope in the first 6 months after enrolment, but not for case mix variables as men and women are biologically different.

Results: There were more men than women at baseline (54 vs 46%). Men were more likely on the transplant waitlist (13 vs 10%) and had higher median eGFR at dialysis initiation (11.2 vs 10.6 mL/min/1.73m^2). Over a median follow-up of 1.75 years, the crude cumulative incidence of dialysis was higher in men while that of death was similar (Figure). The age- and race-adjusted hazard ratio (HR) (95% CI) between men vs women was 1.59 (1.40-1.82) for dialysis, 1.24 (1.04-1.49) for death and 1.80 (0.85-3.80) for transplantation. After adjustment for eGFR slope, the HR for dialysis was 1.72 (1.46-2.01), but the HR for the other two outcomes remained similar.

Conclusions: Despite higher CKD prevalence in women, more men received treatment at nephrologist-run clinics in our study. Men had a higher chance of commencing dialysis before death, unexplained by CKD progression. This finding helps interpret the preponderance of men in the dialysis population.



PO0540

Predictive Value of Urine Osmolal Gap and Urine Anion Gap in CKD Progression

Hyung Duk Kim, Cheol Whee Park. *Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.*

Background: Metabolic acidosis is the major complication of chronic kidney disease (CKD) and associated with poor clinical outcome. Impaired renal ammonium excretion in CKD lead to metabolic acidosis. The urinary anion gap (UAG) and urinary osmolal gap (UOG) have been used to estimate urinary ammonium excretion because of the limitation of clinical application of direct ammonium measurement. We sought to determine whether UAG and UOG predict progression of CKD.

Methods: 185 patients with Stage II-V CKD were prospectively followed up at Catholic Medical College Multicenter Native Kidney Biopsy Cohort. 24-hour urine chemistry was measured at baseline. Routine laboratory test results were obtained at baseline and 1 year after enrollment. UAG and UOG were calculated using 24-hour urine chemistry results. Estimated GFR was calculated with CKD-EPI equation.

Results: Baseline characteristics are shown in Table 1. Positive association between UOG and decline of renal function was observed (Figure 1). The line indicates the regression line for the relation between decline of renal function and urine osmolal gap; $R = 0.035$, $\beta = 0.003$ ($P = 0.011$).

Conclusions: UAG and UOG predict decline in renal function in CKD patients. Further studies are required to determine the direct correlation between UAG and UOG and urinary ammonium excretion.

Figure1. Association between urinary osmolal gap and decline of renal function. The line indicates the regression line for the relation between decline of renal function and urine osmolal gap; $R = 0.035$, $\beta = 0.003$ ($P = 0.011$).

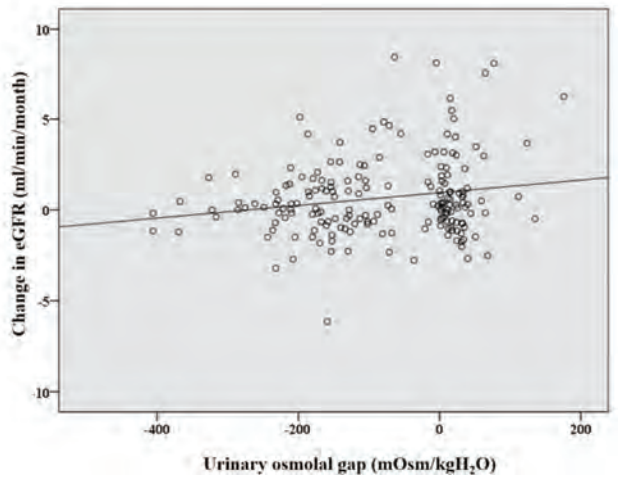


Figure1

Table1. Baseline characteristics

VARIABLE	URINE ANION GAP TERTILE 1 (N=62)	URINE ANION GAP TERTILE 2 (N=62)	URINE ANION GAP TERTILE 3 (N=61)	P VALUE
Age (years)	51.7 ± 17	52.4 ± 14	57.6 ± 13	0.06
Male (%)	34 (54.8)	36 (58.1)	37 (60.7)	0.80
Diabetes (%)	9 (14.5)	9 (14.5)	11 (18.0)	0.82
Hypertension (%)	29 (46.8)	29 (46.8)	32 (52.5)	0.76
BMI (kg/m²)	23.8 ± 4	23.7 ± 4	25.3 ± 3	0.06
Hemoglobin (g/dL)	12.0 ± 2	11.7 ± 2	12.2 ± 1	0.45
Creatinine (mg/dL)	2.0 ± 1	2.1 ± 1	1.8 ± 1	0.66
CKD-EPI eGFR (ml/min)	52.8 ± 23	49.4 ± 23	60.0 ± 22	0.03
Total CO2 (mEq/L)	22.1 ± 6	21.4 ± 5	22.5 ± 6	0.58
Spot urine protein-creatinine ratio (g/g)	3.7 ± 4	2.6 ± 4	3.3 ± 4	0.34
CKD-EPI eGFR at 1 year (ml/min)	57.4 ± 28	58.9 ± 26.1	69.7 ± 22.6	0.01

Table1.

PO0541

Risk Factors for Hemorrhage After Renal Biopsies: Analysis of Data from the National Inpatient Sample Database

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Background: Prior studies examining risk factors associated with bleeding from renal biopsy have demonstrated conflicting results. The purpose of this study is to utilize the large sample size of the National Inpatient Sample (NIS) Database to explore risk factors associated with post procedure hemorrhage.

Methods: Data were gathered from the NIS Database (2012-2013). Records with a closed percutaneous needle biopsy of the kidney (procedure code 5523) were selected, excluding patients under age 18. Bleeding was defined by a diagnosis of hemorrhage/hematoma complicating a procedure (ICD-9 codes 99811, 99812). Binary logistic regression was performed to explore associations between hemorrhage and age, sex, and comorbidities defined in the NIS severity elements.

Results: The data set included 13260 renal biopsies, with 626 instances of bleeding related to procedure. The overall model fit was excellent ($X^2 = 119.6$, $p < 0.000$). Seven comorbidities were significantly associated with bleeding. Obesity, age, hypertension were not significantly associated with bleeding.

Conclusions: Our results indicate that renal failure, female gender, coagulopathy, and anemia are risk factors for bleeding after renal biopsy, whereas obesity and hypertension are not. A strength of this study is the large sample size. It also suggests that peripheral vascular disease, collagen vascular disease, and weight loss increase bleeding risk. Limitations include lack of specific clinical details (e.g. creatinine levels) and risk for confounders. Also, though several individual risk factors were significant, the overall predictive value of the model was limited. In conclusion, this study supports previously thought of risk factors for hemorrhage after renal biopsy and introduces several factors that are of potential clinical significance.

Risk of Bleeding after Renal Biopsy By Comorbidity

	Relative Risk	Lower Limit CI	Upper Limit CI	p-value	Standard Error
Chronic Blood Loss Anemia	2.012	1.327	3.051	.0010	.212
Renal Failure	1.667	1.407	1.976	.0000	.087
Coagulopathy	1.600	1.289	1.986	.0000	.110
Peripheral Vascular Disorders	1.475	1.087	2.000	.0124	.155
Rheumatoid Arthritis/Collagen Vascular Diseases	1.415	1.063	1.883	.0172	.146
Female Gender	1.395	1.178	1.651	.0001	.086
Weight Loss	1.377	1.084	1.748	.0087	.122
Hypertension	1.086	0.920	1.282	.3295	.085
Age	0.998	0.993	1.003	.4607	.003
Obesity	0.844	0.664	1.072	.1649	.122

PO0542

Evaluation of Thromboelastometry and Multiple Electrode Aggregometry in ESRD

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Background: Bleeding and thrombosis rates are paradoxically increased in chronic kidney disease (CKD), but risk assessment for both is not possible with routine laboratory tests. We aimed to evaluate haemostatic changes in CKD stage 5 patients with modern techniques; using thromboelastometry (TEM), multiple electrode aggregometry (MEA), markers of thrombogenesis, fibrinolysis and endothelial activation.

Methods: TEM, MEA, thrombin antithrombin (TAT), alpha-2 antiplasmin, d-dimer and Intercellular Adhesion Molecule-1 (ICAM-1) were quantified in 50 CKD Stage 5 patients (including 20 haemodialysis patients) and 30 healthy controls. Patients taking antiplatelet agents were excluded from MEA analysis.

Results: TEM parameters showed hypercoagulability, with increased maximal clot firmness (MCF) & shorter clot formation time (CFT); and D-dimer, TAT and ICAM-concentrations were also increased in CKD Stage 5 patients compared to HC (Table 1). Platelet dysfunction was evident in CKD Stage 5 with lower aggregation in ADPtest and TRAPtest compared to HC.

Conclusions: Our study shows that the prothrombotic changes in CKD Stage 5 are due to increased coagulation and endothelial activation. Bleeding tendency may relate to platelet dysfunction and possibly increased fibrinolytic activation.

Table (1): Comparison of TEM, MEA, Alpha-2 Antiplasmin, D-dimer, Thrombin Antithrombin and ICAM-1 between Healthy Controls and CKD Stage 5 (Median and Interquartile Range (IQR))

	Healthy Controls n=30	CKD Stage 5 n=50	p-value
TEM			
EXTEM CT (42-74 sec)	56 (52,60)	58 (55,62)	p=0.056
EXTEM CFT (46-148 sec)	68 (62,81)	49 (40,66)	p<0.001
EXTEM MCF (49-71 mm)	67 (65,70)	72 (67,74)	p<0.001
FIBTEM MCF (9-25mm)	18 (15, 21)	25 (20, 32)	p=0.004
MEA			
ADPtest (57-113 U)	61 (41,78)	37 (20,61)	p=0.005
ASPItest (71-115 U)	75 (56,89)	64 (48,100)	p=0.904
TRAPtest (84-128 U)	112 (84,121)	78 (53,116)	p=0.012
Alpha-2 Antiplasmin ug/L	2173 (994,3641)	3075 (622,8000)	p=0.266
D-dimer µg/mL FEU	0.22 (0.14, 0.30)	0.76 (0.39, 1.52)	p<0.001
Thrombin Antithrombin ug/L	1.65 (1.01,2.49)	2.26 (1.58,3.82)	p=0.019
ICAM-1 ug/L	222 (191,248)	288 (249,326)	p<0.001

TEM: Thromboelastometry, CT: Clot Time, CFT: Clot Firmness Time, MCF: Maximum Clot Firmness, MEA: Multiple Electrode Aggregometry, ICAM-1: Intercellular Adhesion Molecule-1

PO0543

During $P2Y_{12}$ Antiplatelet Therapy, Treatment of Anemia Was More Frequent Among Peripheral Artery Disease Patients with Lower eGFR: The EUCLID Trial

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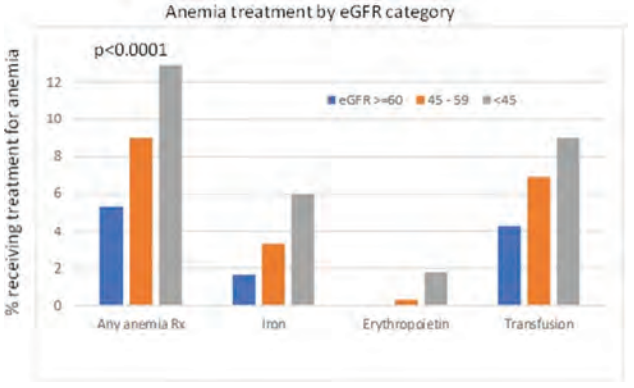
Background: Anemia independently predicts amputation and mortality among patients with peripheral artery disease (PAD). In the EUCLID trial, minor bleeding was more frequent among PAD patients with baseline eGFR<60 vs ≥60 ml/min/1.73m² (adjusted HR 1.51, 95% CI 1.07-2.15; p=0.02 for TIMI minor bleeding; HR 1.21, 95% CI 0.89-1.64; p=0.22 for TIMI major bleeding). We evaluated the impact of eGFR on hemoglobin (Hb) levels and anemia treatment.

Methods: EUCLID (NCT01732822) randomized symptomatic PAD patients to monotherapy with ticagrelor or clopidogrel for 30 months (median); treatment groups were combined for analysis. Independent predictors of Hb change from baseline were evaluated in a multivariable model including baseline Hb and eGFR, sex, age, and post-randomization revascularization procedures, myocardial infarction and anemia treatment.

Results: At baseline, 9025, 1870 and 1000 patients had eGFR ≥60, 45-59 and <45 ml/min/1.73m^2, respectively. Patients with lower eGFR were older, more often male and had higher prevalence of diabetes and hypertension. Mean Hb at baseline was 14.2, 13.5 and 12.7 g/dL for the 3 eGFR categories. Mean fall in Hb during the trial was 0.5±1.7 g/dL and did not differ by baseline eGFR category. On-study treatment with iron, erythropoietin and/or red blood cell transfusion was reported for 479 (5.3%), 165 (8.8%) and 129 (12.9%) patients, respectively (Figure, p<0.0001 across eGFR categories). In multivariable analysis, even after adjustment for baseline and post-randomization effects, baseline Hb was a significant independent predictor of Hb fall; anemia treatment was a significant independent predictor of Hb rise.

Conclusions: Among patients with PAD taking antiplatelet therapy in the EUCLID trial, those with lower eGFR were more often treated for anemia.

Funding: Commercial Support - AstraZeneca



PO0544

The Ratio and Difference of Urine Protein-to-Creatinine Ratio and Albumin-to-Creatinine Ratio Facilitate Risk Prediction of All-Cause Mortality: A Retrospective Cohort Study

David R. Chang,[1] Hung chieh Yeh,[1] Pei-Lun Chu,[2] Chin-Chi Kuo.[1] *[1]China Medical University Hospital, Taichung, Taiwan; [2]Fu Jen Catholic University Hospital, New Taipei City, Taiwan.*

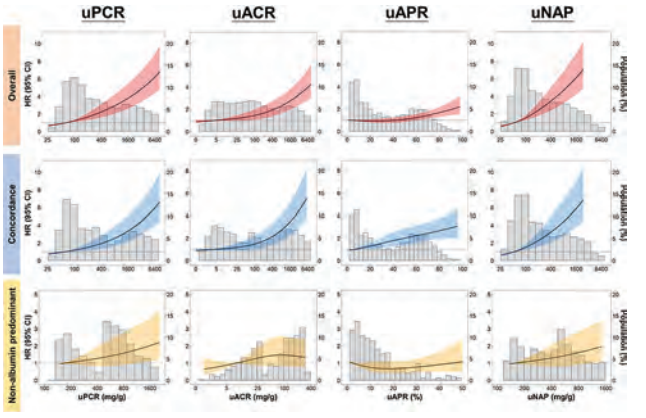
Background: The difference and ratio of albuminuria (defined by urine albumin-to-creatinine ratio, uACR) and proteinuria (defined by urine protein-to-creatinine ratio, uPCR) has not been systematically evaluated with relevant clinical outcomes. We aimed to assess the prognostic performance between the difference and ratio of uACR and uPCR with all-cause mortality.

Methods: This retrospective cohort study identified 2904 adult patients with concurrently measured uACR and uPCR from the same urine specimen in a tertiary medical center in Central Taiwan between January 2003 and June 2017. Urinary albumin-to-protein ratio (uAPR) was derived by dividing uACR by uPCR. Urinary non-albumin protein (uNAP) was calculated by subtracting uACR from uPCR. Conventional severity categories of uACR and uPCR were used to develop a risk matrix. We evaluated all-cause mortality based on uAPR and uNAP on a continuous scale using the multivariable Cox proportional hazards model.

Results: For each doubling increase in uPCR, uACR, and uNAP, the adjusted hazard ratios (aHRs) of all-cause mortality were 1.29 (95% confidence interval [CI]:1.24-1.35), 1.12 (1.09-1.16), and 1.41 (1.34-1.49), respectively. Linear dose-response association with all-cause mortality was only observed with uPCR and uNAP. The 3 × 3 risk matrices revealed that patients with severe proteinuria and minimal albuminuria had the highest risk of all-cause mortality (aHR 5.25, 95% CI: 1.88, 14.63). uNAP significantly improved the discriminative performance compared to that of uPCR (c-statistics: 0.834 vs. 0.828, *p*=0.03).

Conclusions: uNAP provides better mortality prognostic assessment than uPCR and uACR.

Funding: Private Foundation Support, Government Support - Non-U.S.



Hazard ratios for all-cause mortality based on uPCR, uACR, uAPR, and uNAP. Solid black lines represent aHRs based on restricted cubic splines for each urinary biomarker with knots at the 10th, 50th, and 90th percentiles.

PO0545

Metformin and the Risk of Lactic Acidosis in Patients with CKD Stage 3

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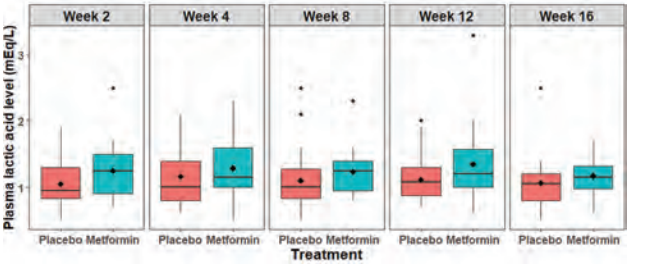
Background: Metformin has become the first-line therapy for the treatment of diabetes in patients with CKD stage 3. The use of metformin in CKD has been debated due to safety concerns related to lactic acidosis.

Methods: We assessed the safety of metformin in a double-blinded trial (NCT02252081). Fifty patients with CKD Stage 3 and metabolic syndrome and/or prediabetes were randomized to either metformin or placebo for 16 weeks. Metformin was started at 500 mg and titrated in 1-2 weeks up to 1500 mg/day in CKD 3a and 1000 mg/day in CKD 3b. Lactic acid (LA) levels were measured at weeks 2, 4, 8, 12, and 16. We compared the effect of metformin on LA between groups and over time using a mixed model and on plasma $HCO3^-$ and anion GAP (AG) using ANCOVA of change analysis.

Results: The mean age was 65±10 years old, 80% were male, BMI was 31.4±5.1 kg/m^2, 16% of patients were CKD Stage 3b. LA levels slightly increased with metformin, but in most patients remained within normal limits (≤2.5 mEq/L) [Figure 1 **;**p=0.054]. The association of metformin and LA remained non-significant in the multivariable-adjusted mixed model (β= 0.15, p=0.07) and remained steady over time (β= -0.003, p=0.54). Baseline eGFR had no effect on LA levels (β= 0.01, p=0.35), whereas higher BMI was associated with higher LA levels (β=0.02, p=0.03). Only 3 patients developed LA levels >3 mEq/L: 2 at week 2 which led to drug discontinuation and 1 at week 12 which was transient. The changes in $HCO3^-$ levels and AG were not statistically significant [($HCO3^-$: Metformin baseline 27±2.1 mEq/L, week 16 26.2 ± 2.8 mEq/L; placebo baseline 26.2±2.1 mEq/L, week 16 26.7±2.8 Eq/L; p=0.21) (AG: Metformin baseline 10.1±2.2 mEq/L, week 16 10.4±2.1 mEq/L; placebo baseline AG 10.4±2.2 mEq/L, week 16 9.9±2.3 mEq/L, p=0.42)].

Conclusions: Metformin use in patients with CKD stage 3 appears to be safe. LA levels mildly increased with metformin, but remained within normal limits and stable after week 2. Patients did not develop clinical or laboratory manifestations of acidosis based on $HCO3^-$ levels and AG.

Funding: Veterans Affairs Support



PO0546

Magnetic Resonance Imaging-Based Renal Function Estimation Using a Machine Learning Approach

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Background: In patients with deterioration of GFR with an unknown clinical course, it is quite difficult to determine whether the renal dysfunction is caused by a hemodynamic alteration or changes in the renal parenchyma, even when using kidney imaging. Therefore, to estimate renal function quantitatively based on the morphology of the renal parenchyma, we performed an advanced image analysis of renal magnetic resonance imaging (MRI) using machine learning (ML).

Methods: We used coronal DIXON water-dominant images obtained on a 3.0T MR device and a deep ML convolutional neural network (CNN) to evaluate renal function (eGFRcre). K-fold cross-validation (k = 5) was performed for the assessment of accuracy and generalization performance. The study protocol was approved by the IRB of our institute.

Results: A total of 196 patients (age, 57.9 ± 16.9 years; 128 males; CKD stage, G1 (n = 18), G2 (39), G3a (43), G3b (45), G4 (35), and G5 (16)) were included. After optimization of the CNN model, the accuracy, precision, recall, and f1-score of the confusion matrix, as well as the AUC of the ROC curve at thresholds of eGFRcre of 60, 45, and 30 were 0.80, 0.83, 0.90, 0.87, 0.86; 0.75, 0.71, 0.84, 0.77, 0.83; and 0.76, 0.80, 0.90. 0.85, 0.83, respectively. The output value of the CNN also showed a significant positive correlation with the normalized eGFRcre of the subjects (R^2 = 0.46, P < 0.01). When the difference in signal intensity between the renal cortex and medulla, as measured based on the region of interest method, was used as a diagnostic index, the accuracy was the same as that of ML if the threshold was eGFRcre 30 (AUC of the ROC curve, 0.84). Conversely, when the threshold was set at eGFRcre 45 or 60, the accuracy deteriorated gradually (AUC, 0.80 and 0.73, respectively).

Conclusions: Compared with the classical method, in which only the signal intensity is used, the ML approach was able to quantitatively evaluate differences in renal morphology regarding a wide range of renal functions. Our results may have clinical applications for assessing the cause of changes in kidney function in the conditions in which renal function and morphology diverge, e.g., in the early stages of acute kidney injury, renovascular hypertension, and therapeutic interventions that cause hemodynamic alterations.

Funding: Government Support - Non-U.S.

PO0547

Inflammation Mediates the Association of Depression Severity with Selective Serotonin Reuptake Inhibitor Treatment Response in Patients with CKD

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Background: Patients with chronic kidney disease (CKD) are at high risk for depression, which is associated with inflammation in patients with chronic diseases. We investigated whether depression severity is associated with response to treatment with sertraline and whether inflammation mediates this relationship in CKD patients with major depression (MDD).

Methods: We conducted the CKD Antidepressant Sertraline Trial (CAST), a randomized double-blind trial of 193 participants with stage 3-5 CKD and MDD randomized to sertraline or placebo for 12 weeks. Depressive symptoms were assessed using the Quick Inventory of Depressive Symptomatology (QIDS). High sensitivity C-reactive protein (hsCRP) was measured at baseline. Logistic regression determined associations of QIDS and hsCRP with treatment response (≥50% decrease) or improvement (≥3-point decrease) in QIDS. Interaction P<0.10 was considered significant.

Results: Fifty-five (28.5%) participants achieved treatment response. Baseline depression severity by QIDS correlated positively with hsCRP, rho=0.162, P<0.05. Median (IQR) hsCRP was 5.0 (2.0, 14.6) mg/L in sertraline responders and 2.7 (0.8, 6.0) mg/L in non-responders, P=0.03. Higher baseline QIDS was associated with increased odds of response in the sertraline group, OR (95% CI) per 1-point increase 1.26 (1.04-1.53), but lower odds in the placebo group, 0.77 (0.61-0.97), interaction P=0.002 **(Figure)**. Higher baseline hsCRP was associated with higher odds of response, OR per log-unit increase 1.52 (1.06-2.19), and improvement, 1.66 (1.11-2.48), in the sertraline group, but not in the placebo group, interaction P=0.08 for response and 0.03 for improvement, even after controlling for baseline depression severity by QIDS score **(Figure)**.

Conclusions: Higher depression severity was associated with improvement in depressive symptoms and response to treatment with sertraline in CKD patients. This may be explained by elevated baseline inflammation. Future studies should test whether sertraline is more effective than placebo in CKD individuals with higher plasma hsCRP.

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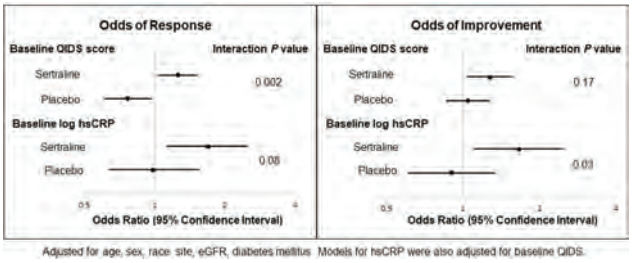

PO0548

Prospective Study of Patient-Reported Outcomes After Endovascular Renal Ablation in Individuals with Chronic Kidney Pain and Opiate Use

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Background: Endovascular renal ablation (ERA) may be useful for palliating and in some instances relieving refractory kidney pain (RKP) but is not widely available. We report our experience of ERA in 20 patients with RKP.

Methods: We conducted a prospective study of patient-reported outcomes pre and post ERA for RKP. Baseline & subsequent pain questionnaires (McGill Pain (MPQ), Brief Pain Inventory (BPI), Opioid oral morphine milligrams equivalent (MME)) & QOL (LASA-6, PHQ-9 & SF-8) were obtained. The Wilcoxon test was used. ERA using an open irrigated ablation catheter was performed in a spiral manner distal to proximal upto the renal artery ostium. Power was titrated between 5-30 watts guided by change in impedance.

Results: We performed 24 ERA (3 bilateral, 21 unilateral; 4 redos) in 20 patients, female:male; 14:6; median age 40yr. 12 patients (60%) had Loin Pain Hematuria Syndrome(LPHS), 4 (20%) ADPKD, and others 4 (20%). 17 of 20 have completed the baseline questionnaires & 9 of 17 patients have 6mo data. All nine experienced variable or complete reductions in pain & QOL from baseline to 6mo (**Table1**). A median of 8mo pain relief was reported. After their first ERA, responders (pain relief >6mo) median 8.5mo (n=12/20;60%) while 4 (20%) reported pain relief <6mo (non-responders) median 2mo. 3 (15%) had no relief, and 1 was lost to FU. In the redo ERA, there was no relief in 2; in 1 pain relief lasted 4mo (non-responder), and in the other, relief was 8mo (responder). Following the first ERA, MME decreased by ≥30% in 6, increased in 7 (≥30% in 6;15% in 1), was unchanged in 3, and no data was available in 4. **There were** 3 access site hematomas, one acute renal artery dissection (procedure related) requiring stents & one renal artery stenosis (5mo later) treated by percutaneous transluminal angioplasty but subsequent reduced kidney function.

Conclusions: Among patients with RKP undergoing ERA, half achieved objective improvement in pain & QOL at 6 mo. Prospective randomized studies with careful patient selection are required to assess the role of ERA for palliation of pain.

Assessments of Pain & QOL

	Improved-outcome	Baseline N=17	6 months N=9	p value
Tool	Pain perception	5.7	3.1	0.02
BPI (Pain)	General Interference	6.2	3.1	0.03
	Mood Interference	6.1	3.6	0.01
	Walking interference	4.3	3.7	0.01
	Activity interference	6.6	2.8	0.02
	Relations interference	5.3	2.8	0.01
	Enjoyment interference	7.1	4.4	0.02
	Overall Interference	6.1	3.2	0.01
SF-8 LASA-6	Physical Function	34.4	12.8	0.01
	Role Physical	32.1	12.4	0.01
	Social Function	33.8	12.6	0.02
	Role Emotional	37.7	9.4	0.03
	Physical Composite	29.6	13.4	0.01
	Physical Well-Being	4.1	3.3	0.002

PO0549

Clinical Impact of Body Muscle Mass for Kidney Function Evaluation: New eGFR Formula Based on Serum Creatinine and Body Muscle Mass

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Background: Kidney function is globally evaluated by estimated glomerular filtration ratio (eGFR) based on serum creatinine (Cre). Since Cre is influenced by body muscle mass, there is serious concern of overestimation of eGFR among elderly people with less muscle volume due to frailty. In this study, eGFR based on Cre (eGFRcreat) and CysC (eGFRcys) were analyzed in association with psoas muscle mass index (PMI) by CT image among CKD patients whose kidney function was accurately evaluated by measured GFR (mGFR) computed from inulin clearance (Cin).

Methods: Study design was single-center cross-sectional retrospective study. Study subjects were consecutive 184 CKD patients (123 males) at Nagoya university hospital whose Cin and abdominal CT were examined within 1 year between 2009 and 2013. New eGFR formula based on Cre and PMI (eGFRcreat-PMI) were developed in 122 patients and validated in 62 patients, which were randomly determined to each cohort. 20%

accuracy for Cin was analyzed by eGFRcreat and eGFRcys calculated by eGFR formulae for Japanese. The performance of eGFRcreat-PMI was assessed by means of bias (eGFR-mGFR), accuracy (percentage of estimates within 20% of mGFR), root mean squared error, and correlation coefficient. In PMI tertile subgroups and GFR(Cin) subgroups (<30, 30-60, 60<), the performance of each formulae was assessed.

Results: Patients' characteristics (n=184, mean(SD) or median[IQR]) were age: 62 [50, 70], eGFRcreat: 58.5 (25.5), eGFRcys: 59.4 (25.9), Cin: 55.0 (25.0) and PMI: 7.29 [6.18, 9.11]. Log-PMI was significantly associated with age, gender, log-BMI, log-Cre and uCre in univariate analyses, and with age, gender and log-BMI in multivariate analysis. New GFR formula (eGFRcreat-PMI) was well correlated with Cin. 20% accuracies for Cin was the highest in eGFRcreat-PMI (74.5%), compared to eGFRcys (67.9%) and eGFRcreat (68.5%), which was more prominent among low PMI tertile group (77.4% in eGFRcreat-PMI, 67.7% in eGFRcys, and 71.0% in eGFRcreat) and high PMI tertile group (73.8% in eGFRcreat-PMI, 59.0% in eGFRcys, and 60.7% in eGFRcreat).

Conclusions: Body muscle mass seriously influences accuracy of kidney function evaluation, and new GFR formula based on PMI and Cre would be useful for accurate evaluation of kidney function, especially among patients with low and high body muscle mass.

PO0550

Incidence and Predictors of Non-Alcoholic Fatty Liver Disease in CKD

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Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing due to the global epidemics of obesity and diabetes mellitus, which are commonly seen in CKD. We studied the incidence and predictors of NAFLD in those with CKD.

Methods: We conducted a retrospective cohort study of patients with incident CKD (eGFR <60 mL/min/1.73 m2 for ≥90 days) in the Veterans Health Administration from 2005-2016. Patients with no NAFLD at the time of CKD diagnosis were followed for a primary outcome of NAFLD, defined as development of sustained elevated alanine aminotransferase levels in the absence of hepatitis B or C virus infection or alcoholic liver disease, identified by laboratory values and diagnosis codes. We calculated incidence rates for NAFLD for the entire study population and by CKD stage. Predictors of NAFLD were evaluated using Cox proportional hazards regression, considering death and ESKD as competing risks.

Results: Of 1,155,901 veterans with CKD but no NAFLD, 51,584 (4.4%) developed NAFLD at a rate of 0.86 (0.85-0.87) per 100 person-years during 4.74 years follow-up. A total of 3.9% developed ESKD at a rate of 0.76 (0.75-0.77) per 100 person-years, and 33% died at a rate of 6.5 (6.5-6.5) per 100 person-years during the same time period. In a multivariable model, age >50 (vs. 40-49 years) (HR 0.72, 95% CI 0.67, 0.77), women, blacks and veterans with advanced CKD were less likely to develop NAFLD; however, presence of diabetes, higher BMI, anemia, CHF, and hypertension were associated with higher risk of developing NAFLD (Table).

Conclusions: Patients with CKD have a high incidence of NAFLD, which was associated with diabetes, BMI, and CHF. Future studies should determine if interventions targeting these factors may reduce NAFLD risk.

Factors associated with incident NAFLD in CKD

Variable	Level	HR (95% CI)
Sex	Female	0.88 (0.83, 0.92)
Race	Blacks (vs. Whites)	0.66 (0.64, 0.68)
CKD Stage (Ref: Stage 3A)	Stage 3B	0.89 (0.87, 0.91)
	Stage 4	0.77 (0.74, 0.81)
	Stage 5	0.60 (0.50, 0.74)
Comorbid condition	Diabetes	1.18 (1.15, 1.20)
	BMI >25	1.24 (1.20, 1.28)
	BMI >30	1.43 (1.39, 1.48)
	CHF	1.03 (1.00, 1.07)
	Coronary heart disease	1.18 (1.13, 1.24)
	Hypertension	1.04 (1.02, 1.07)

PO0551

Alterations of Gray Matter Volumes and Connectivity in Patients with CKD

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Background: Our previous study demonstrated that patients in End stage renal disease had decreased structural and functional brain connectivity, and there was significant association between brain connectivity and cognitive function. The aim of this study was to evaluate the alterations of structural and functional connectivity using graph theoretical analysis in the neurologically asymptomatic patients with relatively early stage chronic kidney disease (CKD).

Methods: We prospectively enrolled neurologically asymptomatic 20 patients with CKD stage 3 and 20 healthy controls, and all of the subjects underwent diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI). Using data from the structural and functional connectivity matrix based on DTI and rs-fMRI, we calculated network measures, including global efficiency, local efficiency, mean clustering coefficient, characteristic path length, and small-worldness index, and investigated the differences between the patients with CKD and healthy controls.

Results: The patients with CKD had altered global structural connectivity and preserved functional connectivity compared to healthy controls. The all of the measures of global structural connectivity were significantly different between the patients with CKD and healthy controls. However, all of the measures of global functional connectivity in the CKD patients were not different from those in healthy participants. In the CKD patients, the functional betweenness centrality of the right insular cortex, right occipital pole, and right thalamus was significantly different from that in healthy subjects. The structural betweenness centrality of the left calcarine, right posterior cingulum was significantly different from that in healthy subjects.

Conclusions: There were significant alterations of global structural connectivity between patients with CKD and control. However, functional connectivity of brain network was preserved in contrast to ESRD patients.

PO0552

CKD and Metabolic Risk Factors: A Cross-Sectional Study Based on 398,120 Adults in China

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Background: Chronic kidney disease (CKD) has become a worldwide health problem. The prevalence of CKD varied within countries by different socio-demographic characteristics and economic status. Olderly people are particularly susceptible to kidney damage from age-related decline in glomerular filtration and chronic disease states, such as diabetes mellitus (DM) and hypertension (HTN). It is necessary to understand the epidemiological features and the association risk factors of CKD in adults, especially in these elderly population.

Methods: We did a cross-sectional survey based on the records of universal health examinations of the residents in Binhai county of China in 2018. A total of 398,120 participants aged ≥ 18 years in this study had underwent blood test, body measurements and general demographic characteristics registration. Then 31.6% of subjects who aged ≥ 65 years (n=37,533) were randomly selected to complete the routine urinalysis. Chronic renal insufficient (CRI) was defined by eGFR < 60 mL/min.1.73 m^2(CKD-EPI), while CKD was defined by CRI or presence of proteinuria. We analyzed the epidemiological features and the association between CKD and relevant covariates by logistic regression models in the general and elderly population.

Results: The age- and gender- standardized prevalence of CRI was estimated to be 1.10% (95% CI, 1.07%-1.13%) in Chinese adult population. It was 0.86% among men (95% CI, 0.82%-0.90%) and 1.34% among women (95% CI, 1.29%-1.39%). Female, aging, central obesity, elevated triglycerides, systolic blood pressure, fasting blood glucose (FBG) and heart rate were independent risk factors for CRI in the general adults. Rates of CRI increased significantly by age, especially when people aged ≥ 60 years. Furthermore, the prevalence of CKD was 17.7% (95% CI, 17.3%-18.1%) in the elderly. Aging, HTN, elevated triglyceride and FBG were still found to be independent risk factors for CKD in this subgroup. Elevated FBG had the strongest correlation with CKD, gender was no longer association with CKD in the elderly.

Conclusions: Aging, HTN, elevated triglyceride and FBG were all independent metabolic-related risk factors associated with CKD in Chinese adults. More attention should be paid to metabolic diseases such as DM, HTN and hyperlipidemia to prevent CKD in adults, especially in the elderly.

Funding: Government Support - Non-U.S.

PO0553

Are There Any Further Modalities for Prediction of Subclinical Volume Overload in Advanced Stages of CKD?

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Background: Subclinical volume overload is commonly seen in our daily practice which represents a debatable issue. These patients respond favorably to diuretics despite lacking clinical signs of volume overload. Therefore a proper assessment of the volume status in Chronic Kidney Disease (CKD) patients leads to a better control of their medical condition and prevents further deterioration of their clinical situation into the well-known sequelae. Although many tools were used to detect volume overload in such patients as biomarkers, ultrasonography, bio-impedance, echo, and blood viscosity, many non-specific results were due to presence of concomitant comorbidities. The use of Bio Impedance Spectroscopy (BIS) is a recent tool increasingly used due to its appealing features as being non-invasive. BIS is an objective fluid status assessment method, which is shown superior to classical methods such as BP monitoring and weight control in many studies. Combining some of these tools may improve their accuracy and specificity. Inferior vena cava collapsibility index (IVCCI) with Brain Natriuretic Peptide (BNP) can be combined for more specific volume status assessment.

Methods: To assess the usage of combined IVCCI and BNP level in CKD patients to predict subclinical volume overload, 110 patients with CKD (stage 4&5) & not on dialysis and having normal LV systolic function were included with exclusion of the following: 1) Patients with other causes of raised BNP than volume overload (i.e. anemia and heart failure). 2) Patients on diuretics. Complete history, clinical examination and basic laboratory were done for all included patients. IVCCI, BNP serum level were evaluated. By using BIS, we estimated Fluid overload (FO) and extracellular water (ECW). The patients who exhibited a FO/ECW ratio >15% were considered to have volume overload.

Results: Among the 110 cases, we found that 26 patients (23.6%) had subclinical hypervolemia as diagnosed by FO/ECW ratio >15. IVCCI ≤ 38% had higher diagnostic

performance than BNP ≥24 pg/ml. Combining both IVCCI ≤38% and BNP ≥24pg/ml increased the specificity and negative predictive value for detection of subclinical hypervolemia.

Conclusions: Combined elevated BNP level and decreased IVCCI could be more precise tools for subclinical volume overload detection in CKD patients.

PO0554

Sensitivity of Urinary N-Terminal Osteopontin-to-Creatinine Ratio in Predicting Renal Function Loss

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Background: Osteopontin (OPN) is a multifunctional protein that gets cleaved to create N- terminal OPN (ntOPN). ntOPN has been reported in urine in kidney diseases but little is known about the sensitivity of ntOPN to creatinine ratio (ntOCR) as a urinary biomarker compared to the urinary albumin-to-creatinine ratio (UACR). This study is aimed to explore the prognostic value of ntOCR regarding renal function loss in a subset of the metabolic syndrome in men (METSIM) study with a high incidence of diabetes mellitus.

Methods: The METSIM study recruited 10,197 Finnish men between 2005 and 2010 and reexamined participants at two 5-year follow-ups. We performed a prospective observational study of a METSIM cohort of 137 participants, 45-72 years old at entry, with available urine at baseline and the first follow-up period, after 3.8±1.4 years. Serum and urinary levels of the ntOPN were quantified by ELISA. Using estimated glomerular filtration rate (eGFR), UACR and urine albumin excretion (UAE) of progressors and non-progressors, data were analyzed by paired t-test and Wilcoxon matched-pairs signed-rank test. The area under the receiver-operating characteristics (ROC) curve (AUC) was used to assess the sensitivity/specificity of variables in predicting the progression of CKD. Pearson correlation coefficient was performed to detect the relationships between the values of variables.

Results: Compared to the CKD non-progressors, the progressors had significantly higher eGFR at baseline (96.95 vs. 87.75 mL/min/1.73 m^2, p<0.00) and lower eGFR at follow-up (86.11 vs. 91.40 mL/min/1.73 m^2, p=0.01). The baseline urine levels of ntOCR were higher in progressors than non-progressors (6.83 vs 3.68 pmol/mg, p=0.05). There were no differences in the UAE, UACR, or serum ntOPN between the two groups. However, baseline urinary ntOCR predicted renal function loss with an AUC of 0.60 (p=0.05), and the change between baseline and follow-up had a higher AUC value of 0.63 (p=0.01).

Conclusions: Our study suggests that urinary ntOCR might be a promising predictive biomarker for renal function loss in a population with high rates of metabolic syndrome and diabetes. Measurements at the second METSIM follow-up may confirm this observation. Further studies are needed in females, larger size populations, and long-term follow up.

Funding: Other NIH Support - NCATS

PO0555

Effect of Renin-Angiotensin System Blockade in Immunoglobulin A Nephropathy Only with Persistent Hematuria

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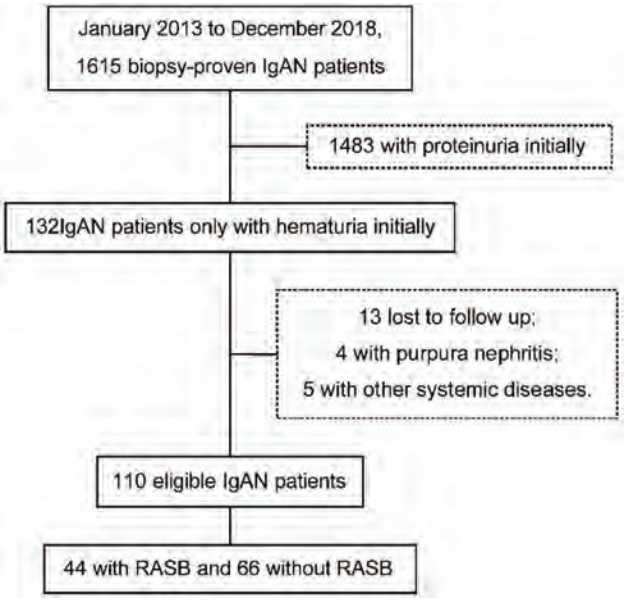
Background: Recent guideline recommended that long-term renin–angiotensin system blockade (RASB) should be used in immunoglobulin A nephropathy (IgAN) when proteinuria > 1g/d. If proteinuria is 0.5–1g/d, RASB is also suggested. We tried to investigate whether IgAN patients only with persistent hematuria and without proteinuria can benefit from RASB.

Methods: IgAN patients only with persistent hematuria initially from January 2013 to December 2018 from four centers were included. We divided patients into treatment and untreated group according to the use of RASB. The primary outcome was the appearance of proteinuria, the secondary outcome was the decreased percentage of hematuria and the rate of estimated glomerular filtration rate (eGFR) decline. Effect of RASB on the outcomes was assessed by multivariate Cox regression models and a propensity score matching.

Results: 110 eligible patients were included and 44 (41.0%) received RASB. Patients in the treatment groups had higher diastolic pressure. The unadjusted primary outcome of RASB treated patients was better than the untreated individuals. The multivariate Cox regression revealed that RASB lowered the risk of primary outcome, besides, RASB decreased more percentage of hematuria. No obvious difference was found in the rate of eGFR decline between two groups.

Conclusions: RASB decreased the risk of proteinuria appearance and increased the remission of hematuria in IgAN only with persistent hematuria initially, but it did not obviously impact the blood pressure of patients without hypertension and the rate of eGFR decline.



PO0556

Fibrates and CKD Patients: A Controversial Issue

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Background: Fenofibrates were not previously known to affect renal function tests until some reports indicated that these drugs may lead to a decrease in renal function. Likewise, the nephrotoxic effect of fibrates remains to be vague and unclear.Fenofibrate's safety in patients with renal insufficiency is an issue because it may increase plasma creatinine. Furthermore, guidelines regarding fenofibrate dosing in renal impairment vary internationally. We investigated fenofibrates' effects on cardiovascular and on advanced CKD, according to eGFR. The multiple incidents of elevated kidney function tests for patients on fibrates have led us to make this study to review our experience as well as literature on this matter.

Methods: A prospective cohort study over 6 months with a total of 80 patients on fibrates divided into 2 groups, 40 of which received statins and the other 40 continued on fibrates. All our patients were subjected to full history, clinical examination and complete baseline labs. The kidney function tests including serum creatinine and eGFR were measured at 0,1, 2 and 6 months' intervals and lipid profile at 0,3,6 months serially in both groups.

Results: Out of the baseline values of the kidney function tests that were recorded on previous fibrate therapy, the statin group (n=40) showed a significant decrease in all kidney function values including serum creatinine by (0.9mg/dL P=0.001) and an increase in eGFR (8.9 mL/min/1.73 m2, P<0.001). Whilst in the other 40 patients who continued to receive fibrates the kidney function tests continued to rise as serum creatinine showed a significant increase in their mean serum Cr levels (by 0.9 mg/dL or 20%, P=0.001), and a significant decrease in their mean eGFR values (by 8.2 mL/min/1.73 m2 or 20.55%, P<0.001). On the other hand total and LDL Cholesterol were significantly lower in Statin group at all follow up intervals. Also triglycerides were significantly higher in Statin group at the end of month-6 from baseline.

Conclusions: In our study fibrates administration showed a short term state of renal insufficiency. The long term effects of fibrates versus variable renal derangement are yet to be identified. As to lipid profile, shifting from fibrates to statins led to a stastically significant rise in triglycerides but it's clinical impact is yet to be investigated, so established guidelines might need a revision regarding clinical benefits of fibrates versus it's renal injury.

PO0557

Calciphylaxis: An Uncommon Skin Manifestation in Non-Dialysis CKD Patients

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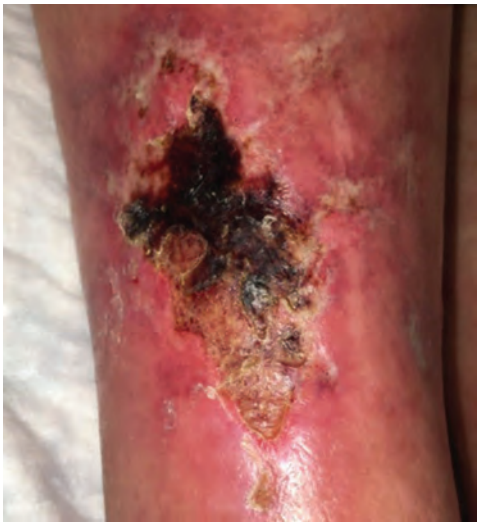
Introduction: Calciphylaxis is a rare but fatal skin disorder seen in 1-4% of dialysis patients. It is characterized by ischemia and necrosis of the skin tissue due to the deposition of calcium in the arterioles and subcutaneous tissues. The risk of infection is increased, and once ulceration develops, the mortality rate can be above 80%. Risk factors include diabetes, warfarin, vitamin D, obesity, female, white race and mineral-bone disorder. The skin findings ranging from livedo reticularis to nodules, plaques, or deep ulcerations. The treatment is focused on supportive care. To date, there is no strong studies to suggest that sodium thiosulfate (STS), bisphosphonates, or calcimimetics are curative. However, STS is commonly used despite the lack of strong supporting data.

Case Description: We report a case of a 76-year-old Caucasian woman with a history of stage G4/A3 chronic kidney disease, insulin-dependent diabetes, hypertension, secondary hyperparathyroidism, and obesity, who presented with severe pain and redness on both legs. The skin lesions had progressed to the painful ulcerations and eschars on both shins one month after the initial visit. A skin biopsy was performed and histopathology was consistent with calciphylaxis. She was started on STS 25 mg intravenously (IV) twice a week and cinacalcet 30 mg by oral route (PO) thrice a week. The patient showed improvement within one month of the treatment.

Discussion: Calciphylaxis in non-dialysis patients is uncommon; however, it should be considered in those with predilection factors. The skin biopsy is crucial for the diagnosis, which can lead to proper management of such a rare yet lethal disease. STS is the most common drug used to treat calciphylaxis. It acts as a calcium chelator with some antioxidative and vasodilation properties leading to recovery.



PO0558

Calciphylaxis: Clinical Features, Therapeutic Options, and Outcomes

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Background: Calciphylaxis is characterized by microvascular disease with calcification of the middle layer of the arterioles, intimal hyperplasia and thrombotic occlusion, conditioning areas of ischemia and skin necrosis. Given the rarity of this pathology, there is a lack in literature regarding clinical presentation, diagnostic approach and therapeutic management. We performed a descriptive analysis of clinical, epidemiologic, laboratory characteristics, treatment options and outcomes in a population of patients with calciphylaxis.

Methods: Retrospective analysis of all calciphylaxis diagnosed in a single-center between January 2003 and December 2019.

Results: The diagnosis of calciphylaxis was made in 9 patients, 7 of whom were female, with a mean age of 63.4±10.9 years. Eight patients were on renal replacement therapy (all hemodialysis) at the time of diagnosis, with a dialysis vintage of 66.4±82.4 months and one patient had no chronic kidney disease. Six patients were taking warfarin, with an average of 46 months on anticoagulation. The mean pre-diagnostic serum calcium value was 9.4 mg/dL, with an average phosphorus level of 4.5 mg/dL, phosphocalcic product was 42 mg^2/dL^2 and the average PTH was 1078 pg/mL. The onset or increase in calcium-containing phosphorus binders was recorded in 6 patients, with cinacalcet being used in only 4 patients. Five patients underwent bisphosphonate therapy, 1 undewent sodium thiosulfate, 3 were submitted to hyperbaric chamber sessions, 2 underwent dialysis intensification and 3 patients were submitted parathyroidectomy. Three patients died within 12 months of diagnosis. Mean follow-up time was 28.8±24.5 months.

Conclusions: More than 60% of patients were under warfarin, reinforcing the role of vitamin K antagonists in the pathogenesis. Mean time on dialysis was highly variable, from the 1st to the 216th month since the beginning of the technique. The standard of treatment varied according to the drugs available and the clinical evidence that supported its use at the time of diagnosis. The registered deaths corresponded to patients diagnosed later in the course of the disease, reinforcing the importance of a high clinical suspicion regarding the appearance of trophic skin lesions in this population as a form of early diagnosis to prevent mortality.

PO0559

Role of Adipose Tissue-Derived Mesenchymal Stem Cells in CKD: A Phase 1 Study Assessing Safety and Clinical Feasibility

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Background: Chronic kidney disease (CKD) is a most common progressive disorder associated with high mortality and huge socio-economic burden globally. We hypothesize that allogeneic adipose tissue mesenchymal stromal cells (hASCs) are renotropic and may retard CKD progression through anti-apoptotic, anti-fibrotic, and anti-inflammatory effects. In this study, we will assess the safety and tolerability of a hASCs infusion in CKD patients with various underlying etiologies.

Methods: We performed a single-arm phase I clinical trial with a 6-month follow-up. This study enrolled 12 eligible CKD patients with an estimated glomerular filtration rate (eGFR) of 15-44 mL/min/1.73m^2 (mL/min). Patients were allocated to receive low, moderate, or high dose of allogeneic cultured hASCs infusion. We investigated the safety issues and kidney function during the follow-up visits.

Results: There was no patient lost to follow-up. We observed two treatment related adverse events (AE) in high dose group. One subject experienced grade 1 slow speech immediately after hASCs infusion, which was resolved on the next day and completely normal afterwards. The AE was considered possibly related to study treatment and met dose-limiting toxicity (DLT). Another subject experienced grade 1 bradyphrenia after the infusion, and the situation was resolved during the following 9 days, however, this AE was not considered as DLT. One SAE was reported in moderate dose group, who was hospitalized for persistent heavy proteinuria, and later proved as diabetic nephropathy stage 4 by renal biopsy. No significant reduction in eGFR was noted among all treated patients, and specifically an improvement in eGFR was noted among those with baseline eGFR>30mL/min. No significant reduction in proteinuria was noted.

Conclusions: This trial demonstrated the safety and tolerability of allogenic hASCs infusion in stages 3b and 4 CKD patients. Patients with reserved renal function (e.g. eGFR>30mL/min) could be more beneficial from hASCs compared to those without. hASCs efficacy and dosing interval in various CKD stages should be investigated in future randomized placebo-controlled trial among various CKD population.

PO0560

Pegunigalsidase Alfa, Novel Pegylated Enzyme Replacement Therapy, Evaluated in Fabry Patients with Progressing Kidney Disease: A Randomized Clinical Trial Study Design

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Background: Fabry disease (FD) is an X-linked multisystem lysosomal storage disorder, affecting males and females caused by the deficient of α-galactosidase-A (α-Gal-A) activity. Long-term disease manifestations include progressive renal failure, hypertrophic cardiomyopathy, cardiac rhythm disturbances, stroke, and death. Two enzyme replacement therapies (ERT) and oral chaperon therapy are commercially available. The clinical benefit of available treatments may not be as robust as anticipated, especially in the subset of males with 'classic' Fabry disease. In the context of ERT, a combination of factors including dose, dosing interval, presence of anti-drug antibodies, estimated glomerular filtration rate (eGFR), and age at the time of ERT initiation, and proteinuria could explain the less than optimal responses achieved by the currently available ERT. Pegunigalsidase alfa is a novel PEGylated homo-dimer ERT which is more stable, has a favorable safety profile, potentially less development of anti-drug antibodies, and enhanced pharmacokinetic profile (~80 hours half-life and higher AUC) compared to other available ERT.

Methods: Adult FD patients (males and females) deteriorating in kidney function with annualized eGFR ≤ -2 mL/min/1.73 m^2/year while on agalsidase beta have been enrolled into BALANCE, a phase-III double-blind active control study (NCT02795676), and were randomized (2:1 ratio) to pegunigalsidase alfa or continue agalsidase beta for 2 years at 1 mg/kg every other week. The primary outcome is the difference in the mean annualized slope of eGFR during the study between the two groups.

Results: Description of the baseline characteristics for approximately 75 patients enrolled at 29 US and European study sites by: age, sex, enzymatic activity, genetic mutations, FD symptoms, previous FD treatment length, kidney function (eGFR, eGFR slope and UPCR), Lyso-Gb3, and anti-drug antibodies pre-treatment status.

Conclusions: The current work describes the design and methods of the study protocol and the baseline characteristics for approximately 75 enrolled patients in the study.

Funding: Commercial Support - Chiesi USA, Protalix Biotherapeutics

PO0561

Pegunigalsidase Alfa, PEGylated α-Galactosidase-A Enzyme in Development for the Treatment of Fabry Disease, Shows a Correlation Between Renal Gb3 Inclusion Clearance and Reduction of Plasma Lyso-Gb3

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Background: Fabry disease (FD) is caused by the loss of function of the lysosomal enzyme α-Galactosidase-A leading to the accumulation of globotriaosylceramide (Gb3). Reduction in histological Gb3 burden in renal peritubular capillaries (PTC) is considered an appropriate and objective surrogate endpoint, likely to predict the clinical benefit of treatment in FD. Pegunigalsidase-alfa is a novel PEGylated enzyme in development for the treatment of FD with enhanced pharmacokinetics.

Methods: The phase I/II (NCT01678898) dose-ranging studies (0.2mg/kg; 1 mg/kg; 2mg/kg) were designed to evaluate the safety (primary objective), pharmacokinetics and efficacy (secondary objective) of pegunigalsidase-alfa administered IV every 2 weeks in adult symptomatic FD treatment naïve male and female patients. The Barisoni Lipid Inclusion Scoring System (BLISS) was adopted to quantitively assess patients' renal biopsies taken at baseline and at 6 months of treatment. BLISS methodology consists of counting the number of Gb3 inclusions per peritubular capillary; a decrease in the score is indicative of clinical improvement.

Results: Renal biopsies were available and evaluated in 13 out of 16 patients allocated in the three dose groups. Mean BLISS score at baseline was 4.23, proving an important renal involvement, and was reduced to a mean of 0.83 after 6 months (-67.8% ± 3.3 %) with an 86.5% reduction in the 1 mg/kg dose cohort. From the totality of the available biopsies (14, including one subject with an FD cardiac variant), 78.6% of patients reached ≥50% reduction in BLISS score.

Conclusions: These results show a profound reduction in Gb3 inclusion in PTC after 6 months of pegunigalsidase-alfa treatment. A high correlation (r=0.800) between the reduction in plasma Lyso Gb3 and the reduction of kidney Gb3 inclusions in the kidney biopsies was observed, giving additional support to the potential effectiveness of pegunigalsidase alfa in treating FD.

Funding: Commercial Support - Chiesi USA, Protalix Biotherapeutics

PO0562

Switching from Agalsidase Alfa to Pegunigalsidase Alfa for Treating Fabry Disease: One Year of Treatment Data from Bridge, a Phase 3 Open-Label Study

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Background: Pegunigalsidase-alfa is a novel, PEGylated α-Galactosidase-A enzyme in development for the treatment of Fabry disease (FD).

Methods: Bridge (PB-102-F30, NCT03018730) is a phase III, open-label, switch-over study, designed to assess the safety and efficacy of pegunigalsidase-alfa (1 mg/Kg EOW) in adult FD patients previously treated with agalsidase alfa for at least 2 years.

Results: This is an interim report of 12-months on-treatment data generated from the first 16 patients (9 males and 7 females) out of the 22 adult patients enrolled. Baseline characteristics: age 24-60 years, the mean estimated Glomerular Filtration Rate (eGFR) 75.45 in males and 85.78 mL/min/1.73m² in females, annualized eGFR slope was -5.04 and -5.18 mL/min/1.73m²/year, respectively, mean residual leucocytes enzymatic activity 5.9% of lab normal mean in males and 27.9% in females, and plasma lyso-Gb3 53.6 and 13.8 nM, respectively. After one year the mean annualized eGFR slope improved from -5.10 mL/min/1.73m²/year while on agalsidase alfa, to -0.23 mL/min/1.73m²/year on pegunigalsidase-alfa. According to Wanner et al. 2018, FD patients with eGFR slope between ≥ -5 and < -3 mL/min/1.73 m²/year are defined as kidney disease progressing and with eGFR slope < -5 mL/min/1.73 m²/year are defined fast progressing. The therapeutic goal is to reach eGFR slope ≥ -3 mL/min/1.73 m²/year for the progressing, and ≥ -5 mL/min/1.73m²/year or more than 50% decrease in progression for the fast progressing. In this interim analysis, 100% of the progressing patients and 66.7% in the fast progressing group achieved the proposed therapeutic goals after switching to pegunigalsidase-alfa. The switch to pegunigalsidase-alfa was safe and well-tolerated. The majority of the patients who completed the study rolled over to a long-term extension study, continuing receiving pegunigalsidase-alfa.

Conclusions: These results suggest a potential benefit of pegunigalsidase-alfa on renal function for FD patients currently treated with agalsidase alfa, to be confirmed by long-term data.

Funding: Commercial Support - Chiesi USA, Protalix Biotherapeutics

PO0563

Tolerance for Potassium Supplementation in Patients with CKD

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Background: Recent studies have shown an association between higher potassium (K^+) intake and better kidney outcomes in patients with chronic kidney disease (CKD). However, K^+ supplementation in CKD may be limited by the risk of hyperkalemia (>5.5 mEq/L). In this study in patients with CKD our aims were to (1) analyze the effect of K^+ supplementation on whole-blood K^+ (WBK^+), (2) identify factors associated with a rise in WBK^+, and (3) identify risk factors for hyperkalemia.

Methods: To do so, we analyzed the results of the 2-week open-label run-in phase of a randomized clinical trial studying the renoprotective effect of long-term K^+ supplementation in patients with progressive CKD and hypertension.

Results: In 151 patients (67±11 years, 74% males, eGFR 32±9 ml/min/1.73 m², 83% on renin-angiotensin inhibitors), K^+ supplementation (40 mEq/day) increased urinary K^+ excretion from 73±24 to 106±28 mEq/day, WBK^+ from 4.3±0.5 to 4.7±0.5 mEq/L, and plasma aldosterone from 294 (210-447) to 366 (271-504) pg/mL (P<0.001 for all). The majority of patients (n=138, 91%) remained normokalemic. K^+ supplementation had no significant effect on urinary sodium excretion (158±62 to 155±68 mEq/day), systolic blood pressure (132±15 to 132±15 mmHg), or eGFR (32±9 to 32±8 mL/min/1.73 m²). Multivariable linear regression identified that age (β 0.008, 95%CI 0.001 to 0.02), female sex (β 0.2, 95%CI 0.001 to 0.3), renin-angiotensin inhibitor use (β 0.2, 95%CI 0.05 to 0.4), diuretic use (β -0.1, 95%CI -0.3 to 0.0), baseline WBK^+ (β -0.3, 95%CI -0.5 to -0.2), and baseline bicarbonate (β -0.03, 95%CI -0.06 to -0.01) are independently associated with a change in WBK^+ after K^+ supplementation. The 13 patients who developed hyperkalemia (WBK^+ 5.8±0.2 mEq/L) were older (74±7 vs. 66±11 years), more often had diabetes (69 vs. 36%), had lower eGFR (26±8 vs. 33±8 ml/min/1.73 m²), lower baseline bicarbonate (22.5±3.8 vs. 24.8±3.4 mEq/L), and higher baseline WBK^+ (4.8±0.4 vs. 4.2±0.4 mEq/L, P<0.05 for all).

Conclusions: In conclusion, the majority of patients with advanced CKD remains normokalemic upon K^+ supplementation, despite the use of renin-angiotensin inhibitors. This short-term study illustrates the feasibility of investigating the renoprotective potential of K^+ supplementation in patients with CKD and provides the characteristics of patients in whom this is safe.

Funding: Private Foundation Support

PO0564

The Effect of Amiloride and Triamterene on Proteinuria in Patients with Proteinuric Kidney Diseases

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Background: Proteinuric kidney diseases are associated with a significant risk of developing end-stage renal disease. Treatment options after maximizing the renin-angiotensin-aldosterone system (RAAS) inhibition are limited. Amiloride, a diuretic inhibiting epithelial sodium channel (ENaC), has been reported to have antiproteinuric effects in animal studies independent of its action on ENaC. This study was designed to specifically examine the effect of Amiloride and triamterene in patients with significant proteinuria.

Methods: It is a cross-over pilot trial where each patient acted as his/her own control. Patients with proteinuria more than 1.0g/day, eGFR >30ml/min/1.73m2, and on the highest tolerable dose of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for at least 8 weeks were recruited. They received amiloride 5 mg twice daily or triamterene 50 mg twice daily for 8 weeks. All the patients then entered a washout phase for 4 weeks, followed by a crossover to the other trial drug for 8 weeks. Weight, blood pressure, metabolic panel, urine studies, and 24-hour urine protein excretion were frequently monitored. Patients with serum potassium >5.5 or an increase in serum Cr >30% one week after the treatment were withdrawn.

Results: A total of 12 patients were enrolled and completed the study. Amiloride reduced 24-hour urine protein by 25.4% (P=0.0435), UPCR by 31.6% (P=0.0104), UACR

by 39.4% (P=0.0049). Triamterene reduced 24-hour urine protein by 33.7% (P=0.0153), UPCR by 29.4% (P=0.0130), UACR by 28.6% (P=0.0294). The effect on the 24-hour urine protein is not significantly different between the two drugs. The average change on the eGFR is -2 and -9 ml/min/1.73m2 in the amiloride and triamterene groups, respectively. Average systolic blood pressure reduction is 11 and 3 in amiloride and triamterene groups, respectively. The average change in the weight is -0.5 and -0.7 kg in amiloride and triamterene groups, respectively. Three patients exited the study due to hyperkalemia.

Conclusions: Both amiloride and triamterene showed the effect of proteinuria reduction regardless of the underlying pathology. This effect appears to be independent of the RAAS, given that patients were all on RAAS blockade. Large scale trials are needed to evaluate the antiproteinuric and renoprotection effects of ENaC inhibitors.

PO0565

Comparison of Extended-Release Calcifediol (ERC), Immediate-Release Calcifediol, Cholecalciferol, and Paricalcitol for Treating Secondary Hyperparathyroidism (SHPT) in CKD

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Background: Serum total 25-hydroxyvitamin D (25D) levels above 50.8 ng/mL are required to produce meaningful and progressive reductions in plasma intact parathyroid hormone (iPTH) in patients with stages 3 or 4 CKD [Strugnell et al 2019]. The current study compared the abilities of four treatment regimens to increase serum 25D to this level and to reduce iPTH in this population.

Methods: Subjects with stage 3 or 4 CKD, SHPT (iPTH ≥85 and <500 pg/mL) and vitamin D insufficiency (25D <30 ng/mL) underwent an 8-week washout from previous vitamin D therapies and were randomized to 60 days of open-label treatment with: 1) ERC 60 mcg/day; 2) immediate-release calcifediol (IRC) 266 mcg/month; 3) high-dose cholecalciferol (HDC) 300,000 IU/month; or 4) paricalcitol plus low-dose cholecalciferol (PLDC) 1 mcg and 800 IU/day. Paricalcitol was increased to 2 mcg/day after 30 days if iPTH was not reduced by 30% and safety parameters allowed. Subjects were monitored for changes in serum 25D, calcium (Ca) and phosphorus (P), and plasma iPTH.

Results: Mean (SD) post-washout/pre-treatment baseline levels for 25D and iPTH in the per-protocol population were 20.6 (6.6) ng/mL and 145 (90) pg/mL, respectively. No differences were observed at baseline between treatment groups (14-17 subjects each). At the end of treatment, mean 25D (ng/mL) increased to 82.9 (17.0) with ERC (P<0.05), 30.8 (11.6) with HDC (P<0.05), 26.3 (6.8) with IRC and 24.2 (7.3) with PLDC. All subjects treated with ERC attained 25D levels ≥30 ng/mL vs. only 44% with HDC (P<0.001), 20% with IRC and 14% with PLDC. Most ERC subjects (94%) attained 25D levels >50.8 ng/mL. The proportion of subjects who achieved at least a 20% reduction in iPTH were 71% with ERC, 38% with HDC, 20% with IRC and 79% with PLDC. No changes from baseline were observed in mean Ca or P in any treatment group, but one instance of hypercalcemia (>10.3 mg/dL) was observed with PLDC treatment.

Conclusions: ERC was safe and more effective at increasing serum 25D and decreasing plasma iPTH than IRC, HDC or PLDC in patients with SHPT, vitamin D insufficiency, and stage 3 or 4 CKD.

Funding: Commercial Support - OPKO Health, Inc; Vifor Pharma

PO0566

Renoprotective Effects of Febuxostat and Allopurinol in Patients with Hyperuricemia and CKD: A Meta-Analysis

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Background: Hyperuricemia is associated with rapid deterioration of renal function in patients with chronic kidney disease (CKD). The two most common urate-lowering drugs available are allopurinol and febuxostat. Randomized controlled trials and observational studies have shown that the individual drugs have potential to slow down deterioration of renal function in CKD patients. However, it is unclear which drug is more effective because of insufficient direct comparison between the two. Hence our study aims to perform a meta-analysis to assess the renoprotective and urate-lowering effects between the two drugs in patients with CKD and hyperuricemia.

Methods: A comprehensive literature search using PubMed was performed with the following search terms: febuxostat, allopurinol, chronic kidney disease, renoprotection. Five relevant studies were selected and analyzed using Cochrane Revman v5.3. Outcomes assessed were changes in estimated glomerular filtration rate, serum creatinine, level of proteinuria and/or albuminuria and change in serum uric acid levels.

Results: Five studies comprising 606 patients were selected – 304 treated with febuxostat and 302 with allopurinol. No significant differences were found in the changes in serum creatinine (mean difference (MD) -0.02; CI -0.07, 0.03; P = 0.39) and eGFR (MD 2.09; CI -0.67, 4.84; P = 0.14) from baseline to 3 months between the two group. Significant difference in the change in eGFR, favoring Febuxostat, was observed after 6 months (MD 4.94; CI 2.25, 7.64, P = 0.003). Significant decrease in proteinuria (MD -0.24; CI -0.42, -0.07, P = 0.007) and albuminuria (MD -80.47, CI -149.29, -11.64, P = 0.02) were observed more in the febuxostat group after 3 months; however these changes were not significant after 6 months. Serum uric acid levels were significantly more reduced in the febuxostat group both after 3 (MD -0.90; CI -1.14, -0.67, P < 0.00001) and 6-months (MD -1.50; CI -1.70, -1.30, P < 0.00001).

Conclusions: Our study showed that febuxostat might be more renoprotective (as measured by eGFR change in 6 months) and offers a better anti-proteinuric and urate-lowering effect. However, more studies are needed to assess its efficacy across the spectrum of CKD, including those requiring hemodialysis and post-transplant patients.

PO0567

CKD Is Associated with Attenuated Plasma Metabolome Response to Oral Glucose Tolerance Testing

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Background: Chronic kidney disease (CKD) is associated with decreased anabolic response to insulin contributing to protein-energy wasting. Targeted metabolic profiling of the response to oral glucose tolerance testing (OGTT) may help identify metabolic pathways contributing to disruption in incretin response.

Methods: Using targeted metabolic profiling, we examined the plasma metabolome in 58 moderate to severe non-diabetic CKD patients with estimated glomerular filtration rate (eGFR)<60ml/min per 1.73m^2 and 37 healthy controls with normal eGFR before and after 2h of 75g oral glucose challenge. We used linear mixed effect models adjusting for potential confounders of age, sex, race, and body weight to determine the interaction of eGFR and change in metabolites in response to OGTT by CKD status. Pathway analyses were performed using Metaboanalyst.

Results: CKD patients had lower eGFR compared to healthy control (37.3 ± 12.5 Vs. 89.3 ± 17.1 ml/min per 1.73m^2). Oral glucose challenge was associated with a marked reduction in a wide array of metabolites, predominantly amino acids, TCA cycle intermediates, and bile acids. CKD status was associated with attenuated OGTT induced prominent changes in pathways of taurine metabolism, phenylalanine, tyrosine and tryptophan biosynthesis, nicotinamide metabolism, and TCA cycle (Figure 1).

Conclusions: Targeted plasma metabolic profiling in response to OGTT suggests a broad disruption of amino acid and mitochondrial energy metabolism in CKD patients. These findings motivate further investigation into the incretin response in patients with CKD and the impact of incretin mimetics such as GLP-1 receptor agonist.

Funding: NIDDK Support

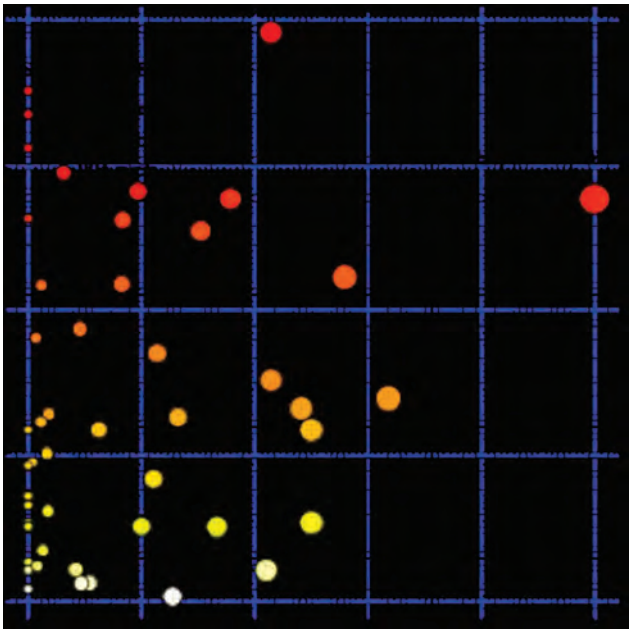

Figure 1: Pathway analysis of OGTT challenege in CKD vs control subjects.

PO0568

The Effects of Allopurinol on the Progression of CKD According to Baseline Serum Urate Level: Results from Post Hoc Analyses of the CKD-FIX Trial

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Background: Allopurinol did not slow decline in estimated glomerular filtration rate (eGFR) over 2 years in patients with chronic kidney disease (CKD) at risk of progression in the CKD-FIX trial. We assessed the effect of allopurinol on eGFR slope by baseline serum urate level.

Methods: In this trial, 369 adults with stage 3 or 4 CKD, without history of gout, and either urinary albumin-to-creatinine ratio ≥265 mg/g or eGFR decrease ≥3.0 mL/min/1.73 m^2 in the preceding year, were randomized to allopurinol or placebo. The primary outcome was change in eGFR up to 104 weeks using the CKD-EPI creatinine equation. This post hoc subgroup analysis describes outcomes in 352 participants according to baseline serum urate level (normouricemic and hyperuricemic [serum urate >6 mg/dL in women and >7 mg/dL in men], and tertiles of baseline serum urate level).

Results: At baseline, 65 (18.5%) and 287 (81.5%) participants had normouricemia and hyperuricemia, respectively. The mean serum urate level in the normouricemic group was 5.9 mg/dL (4.8 mg/dL for women, 6.1 mg/dL for men), and mean serum urate in the hyperuricaemic group was 8.7 mg/dL (8.3 mg/dL for women and 8.9 mg/dL for men). There were no significant differences in change in eGFR between allopurinol and placebo in normouricemic (mean difference [MD] 0.35, 95%CI -2.72 to 3.42 mL/min/1.73 m^2/year) and hyperuricemic (MD -0.06, 95%CI -1.20 to 1.08 mL/min/1.73 m^2/year) participants (interaction P value = 0.84). The mean serum urate levels in the lowest, middle and highest tertiles were 6.3 mg/dL, 8.0 mg/dL and 10.0 mg/dL, respectively. The result for the primary outcome was consistent across all tertiles of baseline serum urate level (interaction P value for subgroup analysis = 0.49).

Conclusions: In CKD patients at risk of progression, the effect of allopurinol on eGFR decline was not modified by baseline serum urate.

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PO0569

CKD Progression End Points as Potential Surrogates for Kidney Failure: Findings from the CKDopps

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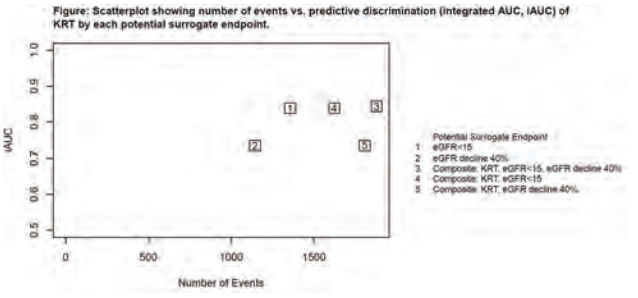
Background: Many potential surrogate endpoints for kidney failure (KF) have been used in clinical trials and observational studies of chronic kidney disease (CKD). Individual and composite surrogate endpoints must be compared to ensure accurate research that maximizes power and facilitates harmonization across studies, particularly among an international sample of advanced CKD patients.

Methods: Using data from CKD stage 3-5 patients from Brazil, France, Germany, and the US enrolled in the CKD Outcomes and Practice Patterns Study (CKDopps), we defined potential individual surrogate KF endpoints based on reaching (1) eGFR<15 mL/min/1.73m^2 and (2) eGFR decline of ≥40%, and composite surrogate endpoints that combine (1) and (2) with and without kidney replacement therapy (KRT, dialysis or transplant). We used each individual and composite endpoint as a time-varying indicator in an unadjusted Cox model to predict time from study entry to the hard outcome of KRT. Potential surrogate endpoints were compared by number of events and prediction accuracy (integrated area under the time-varying receiver operating curve [iAUC]).

Results: N=5242 patients had median (IQR) baseline eGFR of 26.8 (20.7-35.5) and 1448 KRT events over a median (IQR) follow-up time of 2.7 (1.2-3.0) years. Potential surrogate endpoints that included eGFR<15 had higher prediction discrimination compared with those that only included 40% eGFR decline (Figure, iAUCs of 0.83-0.84 vs. 0.73-0.73). Composite endpoints had higher event counts than non-composite endpoints (Ns of 1622-1878 vs. 1144-1356, see Figure x-axis).

Conclusions: A composite KF endpoint defined by the earliest occurrence of either KRT, eGFR<15, or eGFR decline of 40% had the highest prediction discrimination for KRT and the highest number of events among a cohort enrolled at low eGFR. This endpoint should be further evaluated and considered for clinical research studies to optimize power while sufficiently capturing KF.



PO0570

Treatment for CKD: A Systematic Literature Review and Population Comparison

Juan Jose Garcia Sanchez,[1] Juliette C. Thompson,[2] David A. Scott,[2] Naveen Rao,[1] Elisabeth SOrstadius,[3] Glen James,[1] Stephen Nolan,[1] Eric T. Wittbrodt,[4] Alyshah Abdul Sultan,[1] Bergur V. Stefansson,[3] Dan Jackson,[1] Neil S. Hawkins,[2] Keith R. Abrams.[2] *[1]BioPharmaceuticals Medical, AstraZeneca, Cambridge, United Kingdom; [2]Visible Analytics, Oxford, United Kingdom; [3]BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [4]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD.*

Background: DAPA-CKD is the first renal outcomes trial assessing the efficacy and safety of a sodium–glucose cotransporter-2 inhibitor, dapagliflozin, vs placebo, added to standard of care in patients with chronic kidney disease (CKD) with/without type 2 diabetes (T2D). Several other agents have been or are currently under investigation for their effect on renal and cardiovascular outcomes in CKD; however, comparisons of efficacy are challenging, due to differences in study design, duration, patients and endpoint definitions. We conducted a systematic literature review of randomized controlled trials (RCTs) in CKD, with the aim of assessing inter-study comparability.

Methods: Searches of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and grey literature sources were conducted to identify phase 3–4 RCTs of adults (≥18 years) with albuminuric CKD with/without T2D, published in English between 1990 and March 25, 2020. Studies of ≥12 weeks duration that reported clinical outcomes, adverse events, quality of life or patient-reported outcomes for pharmacologic CKD treatments were eligible for inclusion.

Results: Preliminarily, 13,451 unique citations were identified, and 204 full-text manuscripts were included after abstract screening **(Figure)**. Data from 81 RCTs were included: 24, 39 and 18 in patients with CKD with/without T2D, CKD with T2D and CKD without T2D, respectively.

Conclusions: As anticipated, differences in the inclusion of patients with/without T2D between studies make comparisons difficult. Future work will compare additional relevant study characteristics, with further insights available in October 2020.

Funding: Commercial Support - AstraZeneca

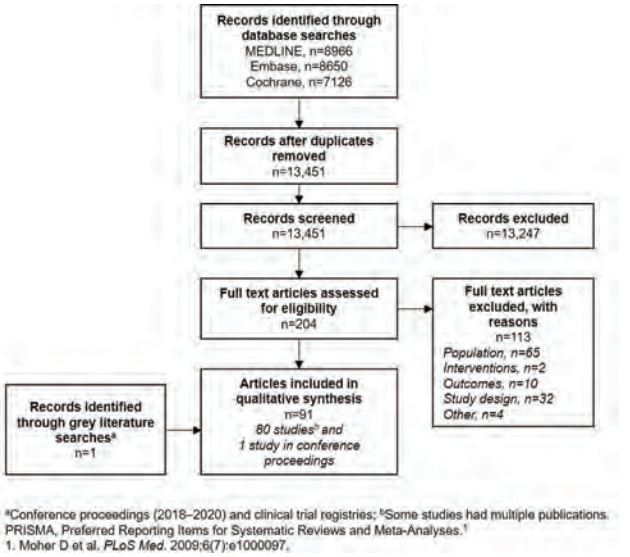


Figure: PRISMA diagram

PO0571

A New Vision for Nephrology Trials in Canada

Alicia Murdoch,[2] Francois Madore,[1] Dwight Sparkes,[2] Karthik K. Tennankore,[3] Arris H. Vorster,[2] Rita Suri.[4] *[1]Universite de Montreal, Montreal, QC, Canada; [2]Can-SOLVE CKD Network, Vancouver, BC, Canada; [3]Dalhousie University, Halifax, NS, Canada; [4]McGill University, Montreal, QC, Canada.*

Background: The Canadian Nephrology Trials Network (CNTN) was established in 2014 to improve the quantity and quality of clinical trials in nephrology in Canada. With inception of the Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) Network in 2016, CNTN received additional funding to expand its mandate. We surveyed and assembled a broad cross-section of Canadian kidney patients, nephrology researchers, and other relevant stakeholders in order to establish an expanded new vision for CNTN.

Methods: In July-August 2018, we administered two separate surveys – one to patient members of Can-SOLVE CKD and the second to members of CNTN and other Canadian nephrology investigators. We then conducted a two-day visioning workshop in September 2018 to discuss how best to support nephrology research in Canada. Over 40 stakeholders participated, including 10 patients, 22 researchers, and members of the Can-SOLVE CKD Operations Team.

Results: Through the survey, we identified two issues that were at least moderately challenging: inability to facilitate multi-site trials (81%) and lack of engagement with community sites (74%). Three key themes emerged from the visioning exercise: peer review, training, and engagement. A summary report captured workshop discussions and was used to inform revisions to CNTN's structure and governance. Three new working committees were created: Capacity Building, Communication and Engagement, and Scientific Operations; as well as a governing Executive Committee. Each committee is co-chaired by a nephrologist and patient, who take turns leading the Executive Committee.

Conclusions: With its new vision and committee structure, CNTN aims to promote a culture of collaboration within the Canadian kidney community and integrate patients into research. The network offers resources to enhance nephrology researchers' ability to conduct clinical trials, directly involve patients in designing studies, and motivate change in patient care based on patient priorities through increased peer review, engagement, and training.

Funding: Government Support - Non-U.S.

PO0572

Implementation of Surprise Question Assessments Using the Electronic Health Record in Older Adults with Advanced CKD

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Background: The Surprise Question (SQ; "Would you be surprised if this patient died in the next 12 months?") is a validated prognostication tool for mortality and hospitalization among patients with advanced CKD. Yet, barriers in clinical workflow have slowed SQ implementation into practice. We sought (1) To evaluate implementation outcomes following use of electronic health record (EHR) decision support to automate collection of the SQ, and (2) To assess the prognostic utility of the SQ for mortality and hospitalization/emergency room (ER) visit.

Methods: We developed and implemented a synchronous decision support [best practice alert (BPA)] algorithm in the electronic health record (EHR) to identify patients attending an outpatient nephrology follow-up visit who were ≥ 60 years of age with an eGFR<30. At the time of the visit, a 'pop-up' BPA was triggered, prompting the physician to answer the SQ (dichotomized). To evaluate implementation, we assessed provider response rate, and efficiency of responses. We assessed the SQ's prognostic utility in survival and time-to-hospital encounter (hospitalization/ER visit) analyses. We abstracted EHR data on patient sociodemographics and clinical characteristics. Physicians provided their demographic and clinical practice characteristics.

Results: Among 510 unique patients for whom the BPA triggered, 95 had the SQ completed (18.6%) by 16 unique providers. Among those patients with completed SQ, nearly all providers (97.9%) completed the SQ on the clinic appointment day, and 61 (64.2%) the first time the BPA fired. Providers answered "No" for 27 (28.4%) and "Yes" for 68 (71.6%) patients. By 12 months, 6 (6.3%) "No" patients died; 3 (3.2%) "Yes" patients died (age-adjusted hazards ratio [HR] 0.35, CI[0.13, 0.94]). About 40% of "No" patients and 25% of "Yes" patients had a hospital encounter by 12 months (HR 1.85, CI[0.927, 3.689]).

Conclusions: We successfully integrated the SQ into the EHR for routine collection to aid in clinical practice. Our response rate indicates additional implementation efforts are needed to encourage further integration of the SQ in clinical practice. Consistent with prior research, the SQ has reasonable prognostic utility for mortality and future hospital encounters.

Funding: Private Foundation Support

PO0573

Telehealth for Adults with CKD: A Systematic Review and Meta-Analysis

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Background: Evidence has supported improved quality of CKD care when assisted with telehealth, while these results were predominantly based on cohort observation or small-scale randomized controlled trials(RCTs). Moreover, robust findings regarding its effects on endpoints were still limited. This study thus aimed to evaluate impacts of telehealth on non-dialysis CKD patients.

Methods: This study was conducted and reported according to PRISMA statement. We searched databases including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedicine Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Wanfang Database and VIP Database until 2019 April. Relevant studies regarding telehealth for non-dialysis CKD population were screened, reviewed, selected and assessed of quality for systematic review and meta-analysis. The protocol was registered at PROSPERO(CRD42017073665).

Results: Eighteen trials involving 4749 patients were included for systematic review and 4 for further meta-analysis. The qualitative study summarized different study population, telehealth intervention type(consultation, education, monitoring) and variable results of outcomes measured(endpoints, surrogate values, patient-centered outcomes). The quantitative analysis comparing the telehealth and control group detected no significant difference in systolic blood pressure(SBP), diastolic blood pressure(DBP) and serum creatinine(SCr) at 12 months, but found significantly lower SCr level at 6 months, preserved estimated glomerular filtration rate(eGFR) at 6 months and at 12 months in telehealth group.

Conclusions: This study detected advantages of telehealth on delaying CKD progression but uncertain impacts on decreasing endpoint incidence.

Funding: Government Support - Non-U.S.

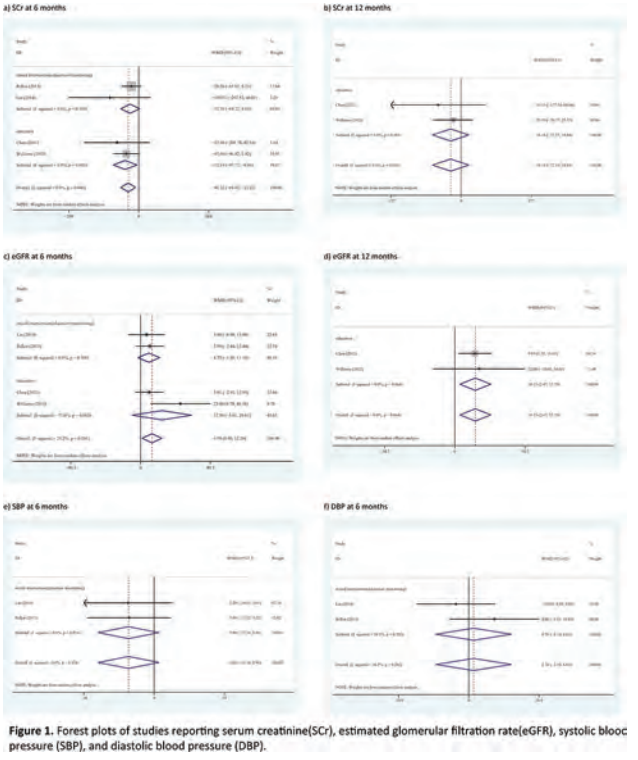

Figure 1. Forest plots of studies reporting serum creatinine(SCr), estimated glomerular filtration rate(eGFR), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

PO0574

Telenephrology Care for Veterans in the COVID-19 Pandemic

Juan D. Salcedo Betancourt,[1] Carlos A. Torres,[1] Yanetsy Olivera Arencibia,[1] Vasuki N. Venkat,[1,2] Daniel J. Soberon,[1,2] Marco A. LadinoAvellaneda.[1,2] *[1]University of Miami School of Medicine, Miami, FL; [2]Miami VA Healthcare System, Miami, FL.*

Background: Chronic kidney disease (CKD) affects 37 million adults in the United States. Since 2013 our Nephrology section has carried out a telenephrology clinic and implemented electronic consults (E-consults). During the COVID-19 pandemic, we implemented changes to evaluate patients with kidney disease. The aim of this study is to report our experience.

Methods: This is a single-center, retrospective chart review study, which evaluated the effect of our telenephrology clinic (video-on-demand and telemedicine clinic visits), as well as E-consults. Between January 2013 and 2020, 410 patients were seen at telemedicine clinic visits, and 1020 E-consults were evaluated. During the COVID-19 pandemic, between March 2020 and May 2020, 40 patients were assessed through video-on-demand.

Results: For telemedicine, a total of 169 patients were included, 99.4% were males, and 87% were white. The mean age was 66 ± 10 years, 92% had hypertension, and 41% diabetes mellitus. The baseline eGFR was 45 ± 14 ml/min/1.73m2. A one-way analysis of variance was conducted showing a statistically significant reduction on the systolic (SBP) and diastolic (DBP) blood pressure (p-value = 0.000), and improvement in potassium and bicarbonate levels (p-value = 0.000). Phosphorus levels did not show a significant difference (p-value 0.37). There was a significant association between attendance to >3 telenephrology visits and SBP control (p-value=0.027), DBP control (p-value=0.002) and potassium improvement (p-value=0.013). The overall decrease in GFR was 1.2 ± 11.1 ml/min/1.73 m2 (95% CI -0.41 to 2.95), lower than the reported natural progression of CKD (1.03 ml/min/1.73 m2/year). A survey for the video-on-demand patients showed 100% satisfaction, reflecting that patients felt their renal care needs were fulfilled. E-consults were answered in less than 24 hours, with 100% satisfaction from primary care physicians.

Conclusions: This is the first study evaluating the use of telenephrology in patients with kidney disease during the COVID-19 pandemic. In our cohort, telenephrology interventions improved SBP, DBP, bicarbonate, and potassium control. All three options improved health outcomes and guaranteed safety during the COVID-19 pandemic, at a reduced cost for the patient and the institution.

PO0575

Telenephrology: A Feasible Option for Inmates

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Background: Socioeconomic and racial disparities are factors that contribute to the disproportionately high burden of chronic disease amongst the incarcerated population in the United States. Access to care can be compromised because of the burden of cost to a facility, lack of staff to transport patients and physical distance from specialists. Telenephrology has been shown to be a feasible option in the correctional setting for specialties such as mental health, infectious disease, cardiology, and primary care, but has not been studied in nephrology. In this quality improvement study, we showed telenephrology is a feasible option that can be implemented for CKD and hypertension management.

Methods: Using quality improvement methodology, data was collected from the electronic medical record for all telenephrology appointments from January 2015 to June 2019. Demographic data, comorbidities, appointment compliance, and clinical data including eGFR and blood pressure were tracked for analysis. Data for patients seen over a period of at least 3 years were included in the CKD progression portion and those seen at least 4 times for the blood pressure management.

Results: There were 871 appointments schedule over the 4.5 year period with 86% completed. Technology limited 3.5% of the cancelled appointments. The population was predominantly men (96%) of black race (51.9%) with hypertension (78%) and CKD (75.2%) being the most common comorbidities. There were 214 patients included in the analysis for management of CKD that showed an average annual change in eGFR of -1.57 mL/min/1.73 m^2 (95% CI: -2.87 to -0.27). There were 79 included in the hypertension analysis with 19.0% achieving a goal BP of ≤130/80 mm Hg and 63.3% achieving a BP of ≤140/90 mm Hg.

Conclusions: Telenephrology can be successfully carried out in the correctional facility population with a low number of cancellations due to technology. The study sample showed mild-to-moderate CKD progression consistent with previously reported population rates of eGFR decline suggesting comparable management. The smaller subset in hypertension showed control that was less than the rates achieved in a nationally representative sample of CKD patients (52% and 75%). This marks an area that requires improvement. Continued rising referrals to telenephrology suggest provider acceptance but it is important to study and adjust management to provide at least equal care as in person visits.

PO0576

Nephrology eConsultation: The "Curb Side" Consult for the 21st Century

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Background: The Nephrology Division at the University of Rochester receives on average 120 new outpatient referrals per month. While every effort is made to see new referrals promptly, this demand exceeds the capacity to evaluate these patients in a timely manner. To decrease waiting time and increase efficiency, we developed a Nephrology eConsultation program. Here we report our experience with time and value-based metrics as well as primary care provider (PCP) satisfaction.

Methods: After a year-long pilot phase, in September 2019 we expanded the eConsult program to provide electronic nephrology consultation to PCPs across the University health system for renal-related issues such as mild to moderate acute kidney injury, CKD, electrolyte disturbances, and proteinuria.

Results: Within the first 8 months of the expanded program, 110 eConsult requests were received. Of these, 62 were deemed medically appropriate and completed, with 46 (74.2%) related to acute kidney injury, CKD, or azotemia, 6 (9.7%) related to electrolyte imbalances, and 4 (6.5%) related to proteinuria. The mean time for a nephrologist to complete an eConsult was 18.3 minutes (Table 1). Of the 48 deemed inappropriate for eConsults, 36 (75%) were converted to in-person visits due to complexity (Table 2). All eConsults were completed within 67 hours (mean time 15.5 hours). Survey of PCP satisfaction showed that 68% of PCPs were very satisfied and 32% were satisfied with the nephrology eConsult program.

Conclusions: eConsultation in Nephrology has the potential to provide timely, cost effective, and remote guidance to PCPs for more straightforward questions, while prioritizing the limited resource of face-to-face nephrology consultation for patients with more complex diseases. This also offers financial advantages, as the work relative value units (wRVUs) for eConsult is 0.7, or up to 2.8 wRVUs per hour in our model. eConsultation in Nephrology could also be integrated with the rapidly evolving field of telemedicine to improve delivery of care remotely and increase provider and potentially patient satisfaction.

Funding: Clinical Revenue Support

Table 1: Accepted eConsults

eConsult Diagnosis	Number of eConsults	Percentage of total completed eConsults (%)	Mean time to complete eConsult (minutes)
CKD, AKI and Azotemia	46	74.2	18.2
CKD Stage 1-4	36	58.1	18.0
CKD Stage 1-3	34	54.8	17.6
CKD Stage 4	2	3.2	25.0
Acute Kidney Injury	2	3.2	25.0
Proteinuria	4	6.5	17.8
Electrolyte imbalance	6	9.7	18.5
Azotemia (not CKD or AKI)	8	12.9	18.2
Other	6	9.7	18.0
Total	62	100.0	18.3

Table 2: Rejected eConsults

eConsult Diagnosis	Number of eConsults	Percentage of total rejected eConsults (%)	Reason for rejection
Acute Kidney Injury	2	4.2	Case complexity - face-to-face visit required
CKD Stage 3	6	12.5	Patient following with another nephrologist
CKD Stage 3	5	10.4	Case complexity - face-to-face visit required
CKD Stage 4	8	16.7	Patient following with another nephrologist
CKD Stage 4	3	6.3	Case complexity - face-to-face visit required
CKD Stage 5	1	2.1	
Hyperkalemia	3	6.3	
Hyponatremia	3	6.3	
Proteinuria	5	10.4	
Other	8	16.7	Condition not managed by nephrology
Other	3	6.3	PCP asking general question, not formal eConsult
Other	1	2.1	
Total	48	100.0	

Data

PO0577

Development of a Global CKD Personal Impact Index (CKD-PII) Assessing the Reality of Living with CKD

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Background: CKD affects >700M people globally, but its full burden and personal impact attributes (PIA)—impact on instrumental activities of daily living—are under-recognized. Quality of life (QoL) measures fail to show the full patient experience. A Global CKD-PII uncovering the direct and indirect daily impact of CKD on patients may improve understanding of disease burden and secondary complications. The development of the CKD-PII using a geographically diverse cohort of CKD patient-reported aggregate data is described.

Methods: A multiphase approach was used to develop CKD-PII. In Phase 1, social media landscape audit and qualitative interviews determined PIA to understand disease burden. Patient conversations within online communities gauged the social, economic and physical impact of CKD. Each attribute was assigned as high, medium or low impact based on the lexicon, overall sentiment and self-reported effect on patient's QoL. Qualitative, moderated phone interviews followed an engagement model, whereby key PIA and language and characterization of attributes were further explored. Findings of Phase 1 informed Phase 2, a quantitative survey. Data from both phases will culminate in the development of CKD-PII.

Results: Phase 1: Social media landscape analysis leveraged 12 months of relevant patient dialogues (n=156) and shortlisted 11 key PIA from >200M internet sources. Among the key PIAs identified, dietary impacts (19%), time lost to appointments/dialysis (45%) and mental health implications (44%) were rated as high impact. Qualitative interviews (n=15) uncovered key PIA identified consistently. Phase 2: An online survey questionnaire was administered to quantify the extent of patients' experience of PIA. The CKD-PII synthesizes data from all research phases into an insights and perspectives report evaluating global perspectives.

Conclusions: Uniquely, CKD-PII will use metrics to showcase the real-life impact of CKD, beyond QoL, providing insights into the patient experience that other studies do not typically address. The social media data facilitates understanding of critical issues and patient needs in an organic environment. This cohort of global patient-reported data will raise awareness of the deeper impact of CKD and develop tangible and realistic solutions for both patients and doctors to solve the challenges uncovered.

Funding: Commercial Support - AstraZeneca

PO0578

Lowering Mortality in CKD Stage 3B and CKD Stage 4 with Increased Outpatient Nephrology Visits

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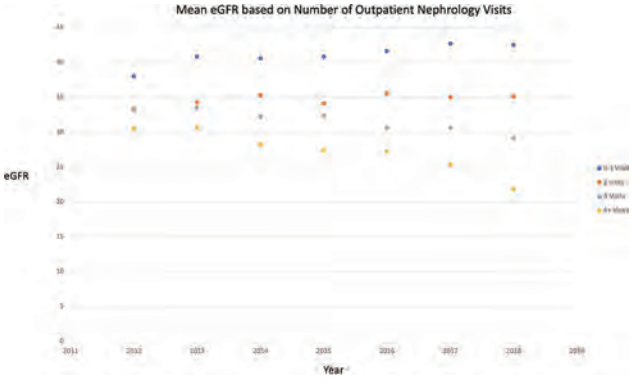
Background: Management of Chronic Kidney Disease(CKD) is complex requiring comprehensive evaluation of multiple organ systems. We hypothesized that more frequent outpatient nephrology visits is associated with lower mortality in advanced CKD patients.

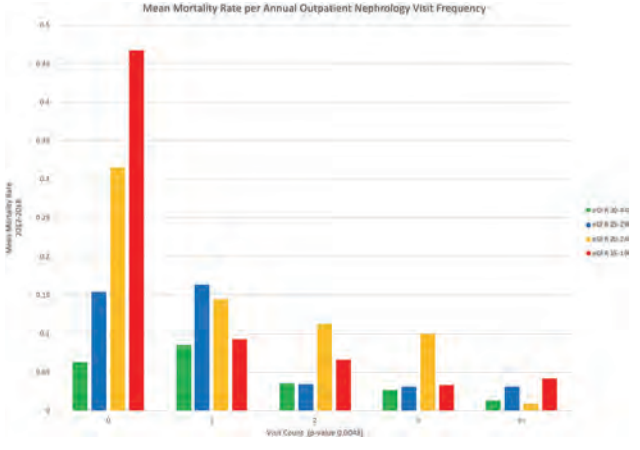
Methods: CKD3B & CKD4 patients at Kaiser Permanente Southern California Orange County were followed from 2012 to 2018. Patients were divided into 4 groups based on initial eGFR per MDRD equation; eGFR 30-44, 25-29, 20-24, and 15-19. Each eGFR group was further divided by the number of annual nephrology visits(0, 1, 2, 3, and 4+). Patients who transitioned to dialysis, kidney transplant, or lost to follow up during the 7 years were excluded. Annual all-cause mortality was analyzed based on the number of nephrology visit in each eGFR category using ANOVA.

Results: The cohort consisted of 2943 individuals, 59% female, 41% male, mean age 77.4. 42% of patients were diabetic and 89% had hypertension. Lower starting eGFR had increased mortality over time while renal function stayed fairly stable. Increased outpatient visit was seen with lower eGFR during the follow up period, Figure 1. All CKD3B and CKD4 patients gained a statistically significant reduction in mortality when seen at least twice in nephrology clinic annually, $p<0.04$, in Figure 2. For eGFR ≤24, the mortality benefit was observed with 1 or more nephrology visit, $p<0.005$.

Conclusions: CKD stage 3B and 4 patients seen in nephrology clinic at least twice a year had improved survival. More frequent follow up was associated with lower eGFR. The relationship between the lower eGFR and the improved survival warrants further investigation.

Funding: Clinical Revenue Support





PO0579

Uptake of Evidence-Based Recommendations to Improve Care for CKD Patients in the Kidney Coordinated Health Management Partnership (Kidney CHAMP) Study

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Background: Medication therapy in patients with chronic kidney disease (CKD) is focused on slowing CKD progression, managing causes of CKD, and preventing cardiovascular morbidity and mortality. The aim of this project was to assess the uptake of evidence-based medication recommendations (recs) provided to primary care providers (PCP) of patients with high-risk CKD by an interdisciplinary nephrology team.

Methods: This project is part of Kidney CHAMP, an ongoing NIH funded, pragmatic randomized controlled trial testing an electronic health record (EHR)-based population health management (PHM) approach to improve CKD care. Eligible patients are 18-85 years with CKD who have a high risk of progression to ESKD and are not being followed by a nephrologist. Patients in the intervention arm receive a nephrologist-led electronic consult and pharmacist-led telephonic medication therapy management (MTM). Recs are provided in the EHR for the PCP to review and order at the upcoming office visit. We focused on medication recs related to the progression of CKD and prevention of cardiovascular disease, which included use of RAAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and HMG-CoA reductase inhibitors (statins).

Results: From July 1, 2019 to January 31, 2020, 125 patients received an e-consult and 121 patients received MTM. A total of 83 recs were provided to PCPs. Uptake of recs for initiation or dose escalation of RAAS inhibitors was the highest, with 19 of 46 recs (41%) being implemented. Two of eight recs regarding GLP-1 receptor agonists were implemented (25%) and two of 24 recs for SGLT-2 inhibitor initiation were implemented (8%). Five recs for statin initiation were made and none were implemented; however, baseline statin use was high at >75%.

Conclusions: Many patients with high risk CKD receive suboptimal care, which can be effectively identified by interdisciplinary nephrology teams using an EHR-based PHM platform. Uptake of RAAS inhibitor recs was highest. However, initiation of medications with recent FDA approved indications for CKD management remained poor. Future research is needed to identify barriers and strategies to increase uptake of evidence-based CKD recs and thereby improve patient care.

Funding: NIDDK Support

PO0580

Interdisciplinary Care Improves Patient Preparedness for ESRD in a High-Risk Patient Population with CKD

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Background: The Kidney Care Choice initiative has made improving the quality of care for patients with late-stage CKD a national priority. Interdisciplinary care (IDC), including nurse practitioner (NP) driven care coordination, is an intervention that may improve health outcomes in patients with CKD. Few studies have evaluated this model of healthcare delivery in racial-ethnic minorities.

Methods: We compared incident ESRD patients who received NP care coordination as part of our IDC clinic (n=84) to a contemporaneous cohort of incident ESRD patients (n=245) who received usual nephrology care alone at Montefiore Medical Center from 10/1/2013—10/31/2017. Clinical data were extracted using Clinical Looking Glass®, and chart reviews were done for validation. Patients included in our study had established care for CKD stage 4/5 and had at least one nephrology clinic visit within 3 months preceding their progression to ESRD. All patients were eligible for IDC, but receipt of IDC was limited by resource availability.

Results: Of the 329 incident ESRD patients included in our study, the mean age was 59.6 years (SD 13.8), 47% were female, and 86% were African American or Hispanic. The baseline characteristics were similar between the groups, except the IDC group had a lower prevalence of hypertension (60% vs 77%). The mean eGFR was 8 ml/min/1.73m^2 at dialysis initiation. Fifty percent of patients had an arteriovenous (AV) access prior to developing ESRD. However, compared to the usual care group, patients in IDC group were more likely to have a mature AV access at HD initiation (41% vs 33%); start HD as an outpatient (30% vs 19%); receive a preemptive transplant (4% vs 2%); do peritoneal dialysis (7% vs 4%); and be listed for kidney transplant (44% vs 15%) prior to developing ESRD. Receipt of IDC was associated with a higher odds (OR 3.9 [95% CI 2.0 - 7.8]; $P< 0.001$) of kidney transplant listing compared to usual care alone after adjusting for sociodemographic and clinical factors. Other outcomes also favored IDC but were not statistically significant.

Conclusions: Interdisciplinary care is associated with better ESRD preparedness compared to usual nephrology care alone in racial-ethnic minorities. Larger multicenter randomized studies are needed to determine the effectiveness of IDC among patients with advanced CKD.

Funding: Other NIH Support - KL2TR001071

PO0581

Patient Outcomes Following Discharge from a CKD Clinic

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Background: In Ontario, Canada multidisciplinary care for patients with advanced chronic kidney disease (CKD) is delivered in Multi-Care-Kidney-Clinic (MCKC) operated by Regional Programs funded through a provincial network based on the number of eligible patients. These eligibility criteria were progressively revised between 2016 and 2018 from an absolute estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2 to less than 15 ml/min/1.73m^2 or a two-year risk of end-stage kidney disease, calculated by the Kidney Failure Risk Equation (KFRE), greater than 10%. The objective of this study was to ascertain the outcomes of existing MCKC patients who were discharged as these criteria were implemented.

Methods: This is a retrospective cohort study of prevalent CKD patients in MCKC in 2013 in the region of South Eastern Ontario, followed to January 2020. The outcomes were discharge from MCKC, re-referral, initiation of kidney replacement therapy (KRT), and death. Data were extracted from electronic medical record. Death was ascertained through Ontario's Office of the Registrar General. Patients' 2 and 5-year KFRE scores were calculated using the 4-variable KFRE.

Results: Of the 643 MCKC patients in 2013 with available data, 470 (73%) continued follow-up in MCKC, while 142 (22%) and 31 (5%) were discharged to primary care and general nephrology respectively. Of those discharged to primary care, 52 (37%) died, while 15 (11%) were re-referred to nephrology, and 8 (6%) initiated KRT within median (IQR) times of 982 (560) and 850 (1411) days from discharge respectively. Five (63%) of the 8 discharged patients who required KRT did so for unforeseen acute illness rather than progressive CKD.

Conclusions: The results of this study suggest that gradually moving MCKC funding eligibility criteria from absolute eGFR level to one based on both eGFR and the KFRE prediction model resulted in the discharge of a significant number of patients. Notably, few of the discharged patients ultimately required KRT that could have been prevented. This study offers a regional perspective with low loss to follow-up as there is only one Renal Program in the region. The results may not be generalizable to different populations, health care systems, or predictive models. Further research is needed to establish the optimal KFRE criterion upon which MCKC funding eligibility can be based.

PO0582

Association of CKD with Early Heart Failure Readmissions in Adults

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Background: Heart failure is a complex chronic disease with multiple comorbidities that contribute to frequent hospitalization. We aimed to examine the impact of chronic kidney disease on the 30-day readmission rate among patients hospitalized with heart failure.

Methods: We performed a retrospective analysis of the National Readmission Database (NRD) 2016- 2017. We identified adult patients with a primary hospital diagnosis of heart failure. We compared baseline demographics and calculated all-cause 30-day readmission rates. Multivariate survey logistic regression was used to identify predictors of readmission.

Results: We identified a total of 865,328 patients admitted with heart failure. 839,625 patients were discharged alive. Among which 181,130 (21.5%) had at least one readmission within 30 days. The in-hospital mortality of index admissions and readmissions was 2.9% and 6.5%, respectively. The 30-day inpatient mortality was 4.0%. The mean length of stay of index admission and readmissions were 5.3 days and 6.4 days, respectively. The most common reasons for all-cause readmissions were acute on chronic heart failure (systolic, diastolic, combined), hypertensive heart and chronic kidney disease with heart failure, sepsis, acute kidney failure. After adjusting for multiple covariates, 30-day readmission was independently associated with chronic kidney disease [adjusted odds ratio (aOR) 1.2, 95% confidence interval (CI) 1.17- 1.23, p<0.001], coronary artery disease (aOR 1.01, 95% CI 1.07- 1.11), chronic obstructive pulmonary disease (COPD) (aOR 1.20, 95% CI 1.18- 1.22). Younger age, lower-income, discharge from larger hospitals were also predictive.

Conclusions: Further prospective studies with focus on multilevel interventions are needed to help reduce early readmission associated significant morbidity and resource utilization for this high-risk population.

Table 1. Independent predictors of heart failure readmission

Factor	Univariate Odds ratio (95% confidence interval)	p-value	Multivariate Odds ratio (95% confidence interval)	p-value
Chronic kidney disease	1.409 (1.384- 1.435)	<0.001	1.201 (1.172- 1.231)	<0.001
Coronary artery disease	1.154 (1.135- 1.173)	<0.001	1.087 (1.068- 1.107)	<0.001
Diabetes Mellitus	1.203 (1.182- 1.224)	<0.001	0.990 (0.971- 1.010)	0.336
COPD	1.302 (1.280- 1.324)	<0.001	1.200 (1.180- 1.222)	<0.001
Female sex	0.948 (0.933- 0.963)	<0.001	1.009 (0.992- 1.026)	0.308
Age	0.993 (0.992- 0.994)		0.990 (0.989- 0.991)	<0.001
Median Income in the patient's zip code				
0-25th percentile	Reference		Reference	
26th to 50th percentile	0.905 (0.884- 0.927)	<0.001	0.938 (0.915- 0.961)	<0.001
51st to 75th percentile	0.865 (0.845- 0.885)	<0.001	0.911 (0.890- 0.938)	<0.001
76th to 100th percentile	0.858 (0.835- 0.881)	<0.001	0.928 (0.903- 0.954)	<0.001
Insurance				
Medicare	Reference		Reference	
Medicaid	1.275 (1.240- 1.311)	<0.001	1.089 (1.055- 1.125)	<0.001
Private	0.779 (0.752- 0.806)	<0.001	0.726 (0.700- 0.752)	<0.001
Other	0.672 (0.629- 0.720)	<0.001	0.617 (0.576- 0.662)	<0.001
Charlson comorbidity score	1.120 (1.115- 1.125)	<0.001	1.070 (1.063- 1.077)	<0.001
Teaching hospital	1.044 (1.018- 1.070)	0.001	1.020 (0.9960 1.044)	0.099
Hospital bed size				
Small	Reference		Reference	
Median	1.077 (1.043- 1.113)	<0.001	1.058 (1.026- 1.091)	<0.001
Large	1.095 (1.062- 1.130)	<0.001	1.053 (1.023- 1.085)	<0.001

PO0583

Machine Learning (ML) Driven CKD Care Navigation Confers Robust Value Through Adoption of Home Dialysis and Transplantation

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Background: The ESRD patient journey is an abyss of lost opportunity for home dialysis or transplantation (Tx). Despite known value of home dialysis (Home hemodialysis (HHD), Peritoneal Dialysis (PD)) and Tx, CKD patients default to in center hemodialysis (IC-HD) after crashing into ESRD. This picture exists absent upstream navigation with management of comorbidity and misaligned fee for service economic forces incenting IC-HD. We report early results of ML directed care navigation upstream of CKD and multidisciplinary co management (Primary care (PCPs) and Nephrology) driving greater adoption of Tx and HHD/PD in a large integrated health system in the intermountain West.

Methods: A custom-built ML algorithm identified chronic kidney disease (CKD) patients using synthetic data from multiple Electronic Health Record sources. Features used to identify CKD included but were not limited to eGFR, other laboratory values, ICD-10 codes, comorbidity clusters, CKD risk factors (DM, HTN etc.), scheduling data, DRG data, biopsy and imaging data. ML output triggered workflows of Kidney Care Navigators (KCNS) who, using a customer relationship management utility (CRM) co-managed comorbidity of CKD with PCPs and navigated patients to nephrology consultation aiming improved HHD/PD/Tx adoption rates

Results: Over 6 mo, among 12000 CKD records, the ML algorithm identified 1898 patients not seen by a nephrologist. KCNs interfaced with PCPs co-managing ESRD and CKD patients using CRM;1169 unique patients generated 1873 workflows (Fig, A); 58 PC of ESRD pts. adopted HHD/PD and pre emptive Tx vs. historic averages of 12 percent. Fig, B.; 7 year Net Present Value, $ 28,000,000 vs. Capital outlay of $2,00,000 (Fig., C).

Conclusions: 1) ML-Driven CKD Care Navigation conferred robust value through five-fold increased home dialysis/transplant adoption in a large integrated health system. 2) Our approach is generalizable across EHRs and with synthetic data ML, allows multi-institutional collaboration or consortia to deliver value in CKD at scale.

Funding: Clinical Revenue Support

Figure:

C

Financial Summary	Total
Operating Income	$ 53,277,258.36
Depreciation Expense	$ (1,469,250.00)
Operating Cash Flow	**$ 54,746,508.36**
Capital Expense	$ 2,026,250.00
Cumulative Cash Flow	
Discount Rate	
Cumulative 7 year NPV	**$ 28,131,269.63**

Figure

PO0584

A Medication Use Evaluation of Patiromer in a Clinical Practice Setting at a Veteran's Affairs Medical Center

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Background: Patiromer is cation exchange polymer approved for treatment of hyperkalemia. There is limited data regarding the utility, adverse effects, frequency of laboratory monitoring and discontinuation rate of Patiromer in a clinical practice setting.

Methods: We performed a retrospective, observational review of veterans prescribed one or more doses of patiromer between 10/2015 and 11/2019 at the Veterans Affairs Northeast Ohio Hospital System (VANEOHS), to evaluate changes to RAAS inhibitor therapy, adverse effects resulting in patiromer discontinuation, and monitoring of serum potassium level. Patiromer prescription characteristics, concomitant medications, laboratory characteristics and adverse effects were collected for each veteran over the study time period. Baseline characteristics are reported as means; relative frequency of outcomes are reported as percentages.

Results: 69 Veterans with hyperkalemia were included for analysis. Mean age was 70 years, African-American race 29%, diabetes 90%, chronic kidney disease 91%, 17% ESRD on dialysis, and heart failure 36%. The most common patiromer dose was 8.4 g daily (78%), prescribed for a mean 274 (SD 3-1250) days. 21% of patients had repeat labs within 2 weeks and 54% within 4 weeks of patiromer initiation. 77% of patients achieved normokalemia (K< 5.0 meq/L) by the first follow up lab draw. Amongst 52 veterans with chronic, continuous patiromer use, 22 (41%) were taking RAAS inhibitors at baseline; 15 (29%) veterans either maintained or increased RAAS inhibitor dose over the study period. 28 (54%) discontinued patiromer with 7 (25%) veterans doing so due to GI complaints.

Conclusions: In a clinical setting at a Veteran's Affairs hospital, patiromer therapy preserved RAAS inhibitor use and improved serum potassium levels, but was discontinued at a high rate due to adverse effects

PO0585

The Practical Patterns of Medication and the Association Between CKD Stage and Polypharmacy: The Fukuoka Kidney Disease Registry Study

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Background: Polypharmacy has emerged as one of the important medical and socioeconomic problems in an aging society. Chronic kidney disease (CKD) is also one of the important medical problems for older people. However, the extent to which CKD is involved in polypharmacy still has not been fully explored yet.

Methods: We examined 3,968 Japanese CKD patients using baseline data from a multicenter prospective cohort study in a cross-sectional manner. We used the baseline data of prescribed medicines on medical records. We evaluated the association between CKD stage and polypharmacy (defined as ≥6 medicines/day; Kojima T, et al. Geriatr Gerontol Int, 2012) using logistic regression analyses with adjustment for potential confounding factors.

Results: At baseline, the prescribed medicines varied between 0 and 17, and the median (interquartile range) was 5 (3–7). Among 3,968 CKD patients, 1,540 (38.8 %) patients showed polypharmacy. The multivariable-adjusted odds ratios for polypharmacy were 1.42 [95% confidence interval, 0.77–2.61] for G2, 1.44 [0.78–2.65] for G3a, 2.44 [1.34–4.49] for G3b, 4.00 [2.17–7.37] for G4 and 8.64 [4.53–16.5] for G5, respectively, compared with patients in the lowest category (G1) as the reference value. In the higher glomerular filtration rate (GFR) category (>G3b), many drugs, including angiotensin-2 receptor blockers, calcium channel blockers, uric acid synthesis inhibitors, proton pump inhibitors, aspirins, loop diuretics, and cation exchange resins were prescribed more frequently than the lower GFR category (≦G3a). In addition, aldosterone blockers, biguanides, fibrates, non-steroidal anti-inflammatory drugs, and sulfonylureas were continuously prescribed despite decreased GFR.

Conclusions: The higher GFR categories were independently associated with higher odds of polypharmacy. This might reflect the increasing prescription for managing to control symptoms caused by decreased GFR. We also have to pay more attention to prescribe medicines according to renal function.

PO0586

A Pilot and Feasibility Randomized Clinical Trial Targeting Sedentary Behavior in CKD: Sit Less, Interact and Move More (SLIMM) Study

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Background: Sedentary behavior (engaging in activities in the seated/ lying position) is highly prevalent and associated with mortality in CKD.

Methods: In a 24-week pilot and feasibility RCT, we tested the feasibility of a 'Sit Less, Interact, Move More (SLIMM)' intervention to replace sedentary activities with casual stepping activities in CKD. Participants wore an accelerometer for 7 days before randomization to measure baseline sedentary and stepping durations. In the SLIMM group (N=54), these data were used to develop individualized plans targeting sedentary behavior; accelerometry was repeated every 4 weeks to monitor adherence and to provide personalized feedback. The standard of care (SOC) group (N=52) were provided physical activity guidelines and underwent followup accelerometry at weeks 8, 16 and 24.

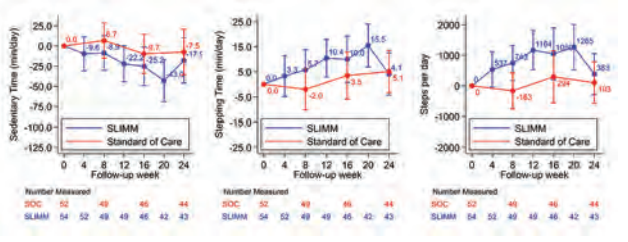
Results: Mean age was 69 ±13 yrs, 42% were women. 5%, 38%, 43% and 14% had CKD stages 2, 3A, 3B/4 and ESKD, respectively. Sedentary and stepping durations did not change in the SOC group. In the SLIMM group, the maximum decrease in sedentary duration, increase in stepping duration, and the number of steps/day, were seen at week 20 but attenuated at week 24 (Fig1). In separate linear mixed effects models (Table 1), overall treatment effects of the intervention on sedentary duration, stepping duration and the number of steps were not significant. The SLIMM intervention significantly reduced BMI and body fat%.

Conclusions: It is feasible to reduce sedentary duration and increase stepping duration in CKD but additional measures along with SLIMM intervention may be needed to sustain its effect on sedentary behavior.

Funding: NIDDK Support

Mixed effects models of treatment effects in SLIMM vs. Stand of Care groups

	Mean change (95% CI)	p-value
Sedentary duration, min/d	-15.6 (-41.0, 9.6)	0.22
Stepping duration, min/d	6.5 (-2.7, 15.6)	0.16
Number of steps/d	631 (-166, 1429)	0.12
Body mass index, kg/m2	-1.09 (-1.92, -0.26)	0.010
Body fat, %	-2.29 (-4.44, -0.14)	0.038



Least square means estimates of sedentary and stepping durations and the number of steps/day by intervention group

PO0587

The Effects of Allopurinol on the Progression of CKD According to Baseline Kidney Function: Prespecified Analyses of the CKD-FIX Trial

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Background: The CKD-FIX trial showed that allopurinol did not slow the decline of estimated glomerular filtration rate (eGFR) over 104 weeks in patients with chronic kidney disease (CKD) and risk of progression. In this study, we assessed the effect of allopurinol on change in eGFR according to CKD stage at baseline.

Methods: Three hundred and sixty nine adults with CKD stage 3 or 4, no history of gout, and who were at risk of progression (identified by either urinary albumin-to-creatinine ratio ≥265 mg/g or eGFR decrease ≥3.0 mL/min/1.73 m^2 in the preceding year) were randomized to receive allopurinol or placebo. Primary outcome was rate of change in eGFR up to 104 weeks using the CKD-EPI creatinine equation. This pre-specified subgroup analysis describes outcomes in patients with CKD stage 3 and stage 4.

Results: At baseline, 178 (49%) patients had CKD stage 3 (mean eGFR 41 mL/min/1.73 m^2, mean serum urate 7.9 mg/dL) and 185 (51%) patients had CKD stage 4 (mean eGFR 23.1 mL/min/1.73 m^2, mean serum urate 8.4 mg/dL). In patients with CKD stage 3, change in eGFR did not differ between the allopurinol (-3.67 mL/min/1.73 m^2/year, 95% CI -4.97 to -2.38) and placebo (-3.34 mL/min/1.73 m^2/year, 95% CI -4.59 to -2.09) groups (mean difference [MD], -0.33 mL/min/1.73 m^2/year, 95% CI -2.13 to 1.47). In patients with CKD stage 4, there was no difference in change in eGFR between the allopurinol (-2.89 mL/min/1.73 m^2/year, 95% CI -3.74 to -2.03) and placebo (-2.89 mL/min/1.73 m^2/year, 95% CI -3.73 to -2.04) groups (MD, 0.00 mL/min/1.73 m^2/year, 95% CI -1.18 to 1.17). The interaction P value for subgroup analysis was 0.87.

Conclusions: In CKD patients at risk of progression, the effect of allopurinol on eGFR decline was not modified by baseline kidney function.

Funding: Government Support - Non-U.S.

PO0588

Effects of the SGLT2 Inhibitor Dapagliflozin on Proteinuria in Non-Diabetic Patients with CKD (DIAMOND): A Randomized Double-Blind Cross-Over Trial

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These benefits are unlikely mediated by improvements in glycemic control alone. We therefore examined the renal effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes.

Methods: A multicenter double-blind placebo controlled 6-week crossover study was performed in six hospitals in the Netherlands, Canada, and Malaysia. Patients (18-75 years old), without diagnosis of diabetes, 24-h urinary protein excretion >500 and ≤3500 mg/24h and estimated glomerular filtration rate (eGFR) ≥25 ml/min/1.73m^2 on stable renin angiotensin system blockade were included. Participants were randomly assigned to one of the two consecutive treatment periods of first placebo and then dapagliflozin 10 mg/day or vice versa. The primary outcome was percentage change from baseline in 24-h proteinuria. The main secondary outcome was change in iohexol measured GFR (mGFR).

Results: Fifty-eight patients were screened of whom 53 patients were randomized. Median baseline proteinuria was 1110 mg/24h (IQR 730, 1560) mg/24h; mean mGFR was 58.3 ml/min/1.73m^2 (SD 23). The difference in mean proteinuria change from baseline between dapagliflozin and placebo was 0.9% (95% CI: -16.6, 22.1; p=0.93). Compared to placebo, mGFR changed with dapagliflozin treatment by -6.6 ml/min/1.73m^2 (95% CI: -9.0, -4.2; p<0.0001) at week 6, which was completely reversible within 6 weeks after dapagliflozin discontinuation. Differences between dapagliflozin and placebo in body weight, systolic blood pressure and hematocrit were -1.5 kg (95% CI: -3.0, -0.03; p=0.0455), -3.6 mmHg (95% CI: -7.6, 0.4; p=0.0775) and 0.02 L/L (95% CI: 0.01, 0.03; p<0.0001). HbA1c did not change. The number of patients with adverse events during dapagliflozin treatment (n=17; 32.1%) and during placebo treatment (n=13; 25.0%) was similar. No hypoglycemic events were reported.

Conclusions: Six week treatment with dapagliflozin does not affect proteinuria in patients with chronic kidney disease without diabetes, but did induce acute and reversible decline in mGFR, body weight reduction, and increased hemoconcentration.

Funding: Commercial Support - AstraZeneca

PO0589

The Impact of Decline in Renal Function on the Clinical and Economic Burden of CKD: An Application of the DAPA-CKD Cost-Effectiveness Model

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Background: The efficacy of dapagliflozin for the treatment of chronic kidney disease (CKD) was assessed in DAPA-CKD, which was stopped early for overwhelming efficacy. Cost-effectiveness analysis of new treatments plays an important role in the effective allocation of healthcare resources. The objective of this study was to develop a model for evaluating the cost-effectiveness of dapagliflozin based on the pending results of DAPA-CKD, and to demonstrate its functionality by characterizing the health economic burden of CKD progression from a UK payer perspective.

Methods: A lifetime microsimulation model was developed to estimate health economic outcomes in patients with CKD. Disease progression was modelled based on a linear decline in estimated glomerular filtration (eGFR) rate. Patients were eligible for renal replacement therapy (RRT) at end-stage renal disease. Life expectancy was estimated using a published risk equation of 10-year mortality in CKD patients. Incidence of cardiovascular (CV) events was linked to CKD stage based on published data. Outcomes were evaluated in two hypothetical patient cohorts with stage 3a CKD; one with standard eGFR decline (-0.65mL/min/1.73m^2 annually) and one with rapid eGFR decline (-4.20). Published cost and utility estimates were applied and discounted at 3.5%.

Results: CKD patients with rapid eGFR decline had a reduced life expectancy of 9.1 years compared with 6.4 years in those with standard rates of eGFR decline. Patients with rapid eGFR decline experienced an additional 326 CV events per 1,000 patients and spent an additional 0.4 years receiving RRT. Reduced life expectancy, increased rates of CKD progression and CV event incidence translated to 2.4 fewer quality adjusted life years gained in patients with rapid eGFR decline (5.5 versus 7.9) and an additional £937 of direct healthcare expenditure.

Conclusions: The DAPA-CKD cost-effectiveness model is capable of estimating health economic outcomes in patients with CKD, projecting health benefits and costs consistent with previously published estimates. This study shows that improved diagnosis and management of CKD may reduce the burden imposed by CKD on both patients and healthcare systems.

Funding: Commercial Support - AstraZeneca

PO0590

Development of a CKD Model in Cynomolgus Monkeys and Its Application to Test Zampilimab, a Monoclonal Antibody (mAb) Specific for Human Transglutaminase 2 (TG2)

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Background: TG2, a crosslinking enzyme involved in wound healing, is linked to the development of renal fibrosis. TG2 irreversibly crosslinks proteins via ε(γ-glutamyl) lysine dipeptide bonds, including extracellular matrix (ECM) proteins. TG2 accelerates ECM deposition and renders the matrix resistant to ECM proteases, forcing ECM homeostasis towards accumulation. TG2 also crosslinks large latent TGFβ1 into the ECM, releasing the active pro-fibrotic TGFβ1 dimer. Zampilimab (IC50 0.2nM, K_d 120pm), a humanized mAb specific for human TG2, is under investigation for the treatment of fibrosis. Application of zampilimab in a primary human cell model of renal fibrosis had positive results; however due to human specificity, zampilimab efficacy cannot be tested in rodent *in vivo* models.

Methods: A unilateral ureteric obstruction model of CKD was developed in aged cynomolgus monkeys. Zampilimab was applied prophylactically immediately following model induction. TG2 activity was measured using an *in-situ* activity assay, and zampilimab target occupancy determined by competitive immunofluorescence. Renal fibrosis was measured by computerized image analysis and histopathological scoring of Masson's trichrome, Picosirius red and H&E stained slides with hydroxyproline measured by amino acid analysis.

Results: Ligation of the left ureter led to development of severe tubulointerstitial fibrosis with elevated TG2 antigen levels and activity, leading to end-stage histology by 6 weeks. This primate model has a greater expansion of the tubular basement membrane than similar rodent models, with histology more closely resembling obstructive disease in man. Following zampilimab intervention in a 4-week study, 7 days post final dose, TG2 activity remained completely inhibited at a high dose, whereas 70% of activity returned at a low dose. However, both zampilimab doses ameliorated the level of renal fibrosis by pathology score, computerized determination of fibrotic index and hydroxyproline.

Conclusions: Our primate model of CKD demonstrated that zampilimab can effectively block TG2 activity and prevent renal fibrosis. A Phase 1/2 study of zampilimab for the treatment of post-renal transplant fibrosis is ongoing (NCT04335578).

Funding: Commercial Support - UCB Pharma

PO0591

Conditional Deletion of Myeloid-Specific Mitofusin 2 Promotes Kidney Fibrosis

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Background: Mitochondrial dysfunction is implicated in the pathogenesis of CKD. Mitochondrial dynamics regulate macrophage mitochondrial stress responses; we hypothesize that their impairment leads to kidney fibrosis. We determined the role of myeloid-specific mitochondrial fusion proteins (MFN)1 and MFN2 in PINK1-mediated mitophagy in experimental and human kidney fibrosis.

Methods: *Pink1*$^{-/-}$, myeloid-specific *Mfn1* (*LysM-Cre*$^{+/-}$*Mfn1fl/fl*), *Mfn2* (*LysM-Cre*$^{+/-}$*Mfn2fl/fl*) null mice and corresponding controls were subjected to unilateral ureteral obstruction (UUO,7-days) or adenine diet (AD,28-days). Kidneys, renal macrophages (RMs), bone marrow-derived macrophages (BMDMs), PBMCs, and plasma were analyzed by western blot, qPCR, Mito stress test, ELISA, immunohistochemistry, flow cytometry, confocal and electron microscopy. Patients with renal biopsy-proven interstitial fibrosis & tubular atrophy (IFTA,*n*=6) and severe-CKD (GFR<30 ml/min,*n*=15) were compared to controls (no IFTA,*n*=9) and mild/moderate-CKD (GFR≥30 ml/min,*n*=8).

Results: MFN1 and MFN2 expression decreased in kidneys after UUO or AD, and BMDMs after TGF-β1 treatment. AD-fed *LysM-Cre*$^{+/-}$*Mfn2fl/fl* but not *LysM-Cre*$^{+/-}$*Mfn1fl/fl* mice displayed increased renal expression of CD11b+F4/80+ macrophages than AD-fed controls. Increases in fibronectin, CD206, galectin-3, and TGF-β1 expression in the kidneys and RMs were higher in AD-fed *LysM-Cre*$^{+/-}$*Mfn2fl/fl* mice than AD-fed controls. TGF-β1-induced inhibition of mitophagy and increases in mitochondrial mass, size, and superoxide levels were greater in *LysM-Cre*$^{+/-}$*Mfn2fl/fl* RMs and BMDMs than *LysM-Cre*$^{+/-}$*Mfn1fl/fl* and controls. The reduction in colocalization of MFN2 but not MFN1 with renal mitochondria after UUO was higher in *Pink1*$^{-/-}$ mice. PBMCs from patients with severe-CKD showed higher superoxide levels and lower MFN2 expression than mild/moderate-CKD. IFTA was associated with lower renal expression of MFN1 and MFN2 and higher circulating CCL2 levels than controls. Decreased MFN2 and PINK1 expression in TGF-β1-treated human RMs was associated with increased fibrotic response.

Conclusions: This study is the first to suggest that myeloid-specific MFN2 but not MFN1 by regulating renal macrophage mitochondrial biogenesis and mitophagy prevents fibrosis. Mitophagy inducers may attenuate macrophage superoxide production and progression of kidney fibrosis.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO0592

EZH2 Mediates Renal Fibrosis and Links Activation of Notch Signaling and Suppression of Klotho and BMP-7 Expression

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Background: Our previous studies have shown that pharmacological blocking EZH2 (Enhancer of Zeste Homolog 2), a histone H3 lysine 27 methyltranferse, attenuates renal fibrosis in a murine model of renal fibrosis, but the underlying mechanism in this process remain undefined.

Methods: In this study, we used two highly selective EZH2 inhibitors and conditional knockout mice to evaluate the effect of EZH2 inhibition on renal fibrosis and activation of profibrotic signaling pathways and expression of renoprotective proteins in two murine models of chronic kidney disease (CKD) induced by UUO and 5/6 nephrectomy (SNx).

Results: Global inhibition of EZH2 by administration of gambogic acid or GSK-126 and conditional depletion of EZH2 in pericytes suppressed renal fibroblast activation and fibrogenesis in the kidney with UUO and SNx. Treatment with these inhibitors or EZH2 siRNA also inhibited serum- and TGF-β1-induced activation of renal fibroblasts in culture. Moreover, pharmacological and genetic inhibition of EZH2 suppressed expression of Notch-1, Notch-3, Jagged-1 and HES-1 and HEY-2 in vivo and in vitro. Similarly, inhibition of EZH2 was effective in inhibiting phosphorylation of extracellular signal-regulated kinase 1/2, AKT and NF-kB as well as expression of multiple profibrogenic cytokines/chemokines and renal macrophage infiltration. In contrast, EZH2 inhibitors prevented injury-induced downregulation of Klotho and BMP-7, two anti-fibrotic proteins in the kidney.

Conclusions: These results revealed that EZH2 may promote renal fibrosis and activation of renal fibroblasts by activation of Notch signaling, downregulation of Klotho and BMP-7 and induction of inflammation in the injured kidney. Targeting EZH2 may be a novel therapeutic strategy to treat CKD.

Funding: NIDDK Support, Other NIH Support - National Natural Science Foundation of China

PO0593

Kidney Targeted Renalase Agonist Peptide Rescues Severe Model of Cisplatin-Induced AKI and CKD

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Background: Cisplatin (CP) causes Chronic Kidney Disease (CKD) upon repeated doses and limits its chemotherapeutic use. Renalase (RNLS) is a protein that activates kinases linked to survival and attenuates acute ischemic and CP-induced kidney injury. We now seek to target delivery of RNLS specifically to kidney to prevent CP-induced CKD.

Methods: CKD was induced in RNLS knockout (KO) (severe) and wild type (WT) mice by 2 doses of CP 15 mg/kg 2 weeks apart. The RNLS agonist peptide RP81 was synthesized and encapsulated in mesoscale nanoparticles (MNP) that target the kidney. Its cytoprotective activity was tested *in vitro* using TKPTS proximal tubule cells and *in vivo* using RNLS KO mice. RP81MNP or empty MNP was administered weekly for 4 weeks. Renal injury and function was evaluated by immunohistochemistry and plasma creatinine (Cr). The mechanism of action of RP81MNP was investigated using single cell RNA sequencing (scRNAseq) of whole kidney cells.

Results: MNP were retained intracellularly by TKPTS cells and were localized to proximal tubules *in vivo*. RP81MNP protected TKPTS cells from CP-induced cytotoxicity: cell viability was enhanced 3.5-fold, n=6, p<.05, compared to empty MNP. Naked RP81 increased cell viability 1.72-fold, n=6, p<.05 over BSA control. Compared to WT, CP in KO caused more severe AKI (Cr: 0.61 mg/dL ± 0.05 vs. 0.13±0.03 in WT, n=3, $p<0.05$), higher mortality (45% death at 4 weeks n=20, p<0.005), and more severe CKD (Cr 0.16 ± 0.02 mg/dl, vs 0.12 ± 0.01, n=5, p<0.05;). In KO given CP, RP81MNP ameliorated AKI (Cr 0.30 ± 0.05 mg/dL vs 0.64 ± 0.14 in control, n=5, p<0.05;) and CKD (increased kidney weight: 176mg ± 7.0, vs 145.4± 4.5, decreased plasma Cr: 0.10± 0.01 vs 0.16± 0.02, and KIM-1: 124.3±15.1 pg/ml vs 227±28.4). RP81MMP significantly reduced plasma cytokines IL-1β, IL-2, IL-6, KC, and TNFα and inhibited regulated necrosis. ScRNAseq revealed that RP81MNP preserved tubule and vasculature cell mass and decreased infiltrated immune cells caused by CP.

Conclusions: We conclude that RP81MNP attenuates CP-induced CKD by diminishing cell death pathways and inflammation activated by CP. These data suggest that RP81MNP may be an effective therapeutic agent to prevent CKD in patients treated with repeated doses of cisplatin.

Funding: NIDDK Support

PO0594

Pyruvate Kinase M2 in Renal Tubular Cells Is a Key Regulator of Kidney Repair After Ischemic Injury

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Background: Tissue injury and repair is associated with changes of metabolism. In kidneys, metabolic changes including mitochondrial dysfunction and induction of glycolysis have been reported in renal fibrosis and chronic kidney disease. It remains unclear whether and how the metabolic changes contribute to kidney injury and repair. We have examined the effects of glycolysis inhibitors and the ablation of pyruvate kinase M2 (PKM2, an enzyme in glycolysis) in kidney tubules. Glycolysis inhibitors (including PKM2 inhibitor shikonin) suppressed renal fibrosis in the mouse model of unilateral ureter obstruction (UUO). Interestingly, in vitro the inhibitors suppressed fibrotic gene expression (e.g. fibronectin and a-SMA) in fibroblasts, but not in cultured renal tubular cells.

Methods: To further understand the role of glycolysis in renal tubular cells in vivo, we established a mouse model in which PKM2 ablation in renal tubule cells can be induced by doxycycline. To this end, PKM2-floxed mice were bred with Pax8-rtTA/LC1 CRE recombinase mice to create an inducible renal tubule-specific PKM2 knockout (iRT-PKM2-KO) mouse model. Exposure to doxycycline for 5-7 days induced PKM2 ablation in all renal tubules in iRT-PKM2-KO mice, but not in wild-type littermates. These mice were subjected to 30 minutes of unilateral renal ischemia-reperfusion one day after initial doxycycline treatment, and kidneys were collected at 2 weeks later for histology, immunoblot analysis, and fibrosis staining.

Results: Wild-type mice showed increased expression of collagen I, collagen IV, vimentin and a-SMA in kidney tissues. The increase of collagen I was significantly attenuated in iRT-PKM2-KO mice, while collagen IV and vimentin induction was marginally inhibited and no inhibition for fibronectin and a-SMA in these mice. Wild-type and iRT-PKM2-KO kidney tissues had similar levels of Sirius red staining of collagen fibrils. We further examined Lotus Tetragonolobus lectin (LTL) staining of proximal tubules, which detected obviously more intact proximal tubules in iRT-PKM2-KO mice than in wild-type littermates.

Conclusions: Together, these results indicate a pathogenic role of glycolysis in maladaptive kidney repair. Importantly, PKM2 and associated metabolism contribute to the degeneration of renal tubules after acute kidney injury.

Funding: NIDDK Support, Veterans Affairs Support

PO0595

Proximal Tubule-Specific DPP4 Deletion Slows Kidney Disease Progression in Obese Mice

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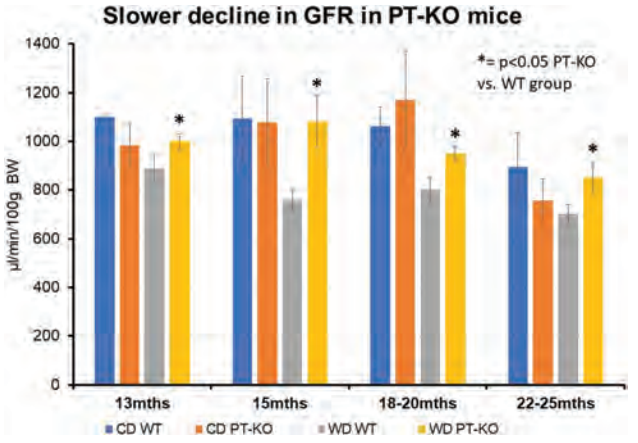
Background: Obesity is a major risk factor for Chronic Kidney Disease progression to End Stage Renal Disease and/or Dialysis. Increased absorption of fats and/or sugars from Western Diet (WD) likely leads to kidney tubular injury in obesity. We observed that whole body dipeptidyl peptidase 4 (DPP4) deletion as well as inhibition in WD-fed mice results in decreased kidney injury which, in turn was associated with a decrease in proximal tubule DPP4. Therefore, we **hypothesized** that proximal tubule (PT) DPP4 activation leads to injury and progression of kidney disease.

Methods: PT-KO and WT littermates were fed a WD starting 4-6 wks of age and continued for 2 years. GFR and albuminuria were monitored periodically. Tissue histology was performed at select intervals. GeLC-MS was used to separate kidney peptides and Scaffold 4/iPathwayguide used to analyze the Proteomics data.

Results: WD-fed WT mice gained 150-200% weight of chow-fed [CD] mice and had a greater decline in GFR than CD-fed animals over 2 years (50% vs. 20%, p<0.05). WD-fed PT-KO mice had a lesser decline (~35%) when compared to WT mice. This was true for both male and female mice. Concomitantly, there was an increase in albuminuria in WD-fed WT mice that was mitigated in PT-KO mice. PAS/PSR stained sections showed worsening fibrosis, tubular dilatation and glomerulomegaly, tubular vacuolization in WD-fed WT mice that was mitigated in PT-KO mice. Oil Red O staining showed increased fat accumulation in glomeruli and tubules of WD-fed WT mice that was mitigated in KO mice. Proteomics analysis followed by immunoblots showed that WD-feeding led to an increase in cell adhesion proteins and ribosomal machinery that was significantly suppressed by KO. In addition, there was a shift towards reduction in gluconeogenesis and improved fatty acid oxidation in KO mice.

Conclusions: Obesity without diabetes can lead to rapid decline in GFR in both male and female mice. DPP4 inhibition may slow decline if started early in the course of developing obesity and/or insulin resistance.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Inc.



PO0596

The PAR-1 Antagonist Vorapaxar Protects Against AKI to CKD Transition

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Background: Protease-activated receptor-1 (PAR-1) has been reported as a coagulation regulator in the pathophysiology of AKI. Beyond its normal function in haemostasis, aberrant PAR-1 signaling may lead to the development of tubulointersitial fibrosis, and subsequently CKD.

Methods: We investigated whether the administration of PAR-1 antagonist vorapaxar, an FDA-approved drug for reducing thrombotic cardiovascular events, has any renoprotective effect in a robust kidney fibrosis murine CKD model following unilateral ischemia reperfusion injury (UIRI), as well as in hypoxia-induced cultured rat proximal tubular epithelial cells (NRK-52E).

Results: Vorapaxar reduced morphological abnormalities and the expression of tubular injury marker KIM-1 in UIRI kidneys. Mice treated with vorapaxar showed less intrarenal accumulation of ECM proteins including fibronectin, α-smooth muscle actin and collagen 1 via TGF-β/Smad signaling after UIRI. IR-induced endothelial dysfunction and macrophage infiltration were also decreased by vorapaxar treatment. In NRK-52E cells, PAR-1 expression was activated under a hypoxic milieu associated with upregulation of TGF-β-induced ECM protein accumulation.

Conclusions: Vorapaxar diminishes renal fibrosis through TGF-β/Smad signaling in UIRI model, and protects against tubular injury during AKI to CKD transition. A PAR-1 targeted strategy by vorapaxar as a therapeutic approach in human CKD warrants further. **Funding:** Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2018.

PO0597

Sphingosine Kinase 2 in Kidney Perivascular Cells Promotes Inflammation and Fibrosis Through S1PR1 Signaling

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Background: Sphingosine 1-phosphate (S1P) is a sphingolipid, which is produced by two different kinases, sphingosine kinase (SphK) 1 and 2. S1P is exported through Spns2 or Mfsd2b, and then reacts with S1P receptors (S1PR1-5) to affect myriad cell functions. We recently showed that *Sphk2*$^{-/-}$ mice were protected from renal fibrosis when compared to wild type or *Sphk1*$^{-/-}$ mice (PMID: 27799486). We hypothesized that *Sphk2* deletion in renal perivascular cells confers the protection from progressive kidney fibrosis.

Methods: Male *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$ and *Foxd1Cre*$^{-}$ *Sphk2*$^{fl/fl}$ (control) mice were used. For unilateral ischemia-reperfusion injury (IRI), left kidney was clamped for 30 min; right nephrectomy was performed at day 13. For bilateral IRI, both kidneys were clamped for 30 min. Mice were euthanized at day 14 to evaluate kidney fibrosis (unilateral IRI) and at day 1 to evaluate the extent of acute kidney injury (bilateral IRI). Primary kidney perivascular cells were isolated from kidneys of *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$ and control mice.

Results: In the unilateral IRI model, *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$ mice demonstrated better kidney function (plasma creatinine), less kidney fibrosis (histology) with less macrophage infiltration, and suppressed expression of fibrosis-related genes (*Acta2, Col1a1, Col3a1*) in the kidneys compared with control mice but there was no difference in plasma S1P between the groups. In contrast, in the bilateral IRI model, there was no difference between the groups in kidney function, kidney *Havcr1/Lcn2* expression, and histology at day 1. In *in vitro* studies, *Sphk2*-deficient perivascular cells expressed less inflammatory cytokines, such as *Ccl2, Il6, Cxcl1*, after LPS stimulation compared with control perivascular cells. *Sphk2*-deficient and control perivascular cells robustly expressed *Spns2*, but not *Mfsd2b*, and *S1pr1-3* among the five S1P receptor subtypes. Among *S1pr1-3*, only knockdown of *S1pr1* resulted in suppressed expression of inflammatory cytokines after LPS stimulation.

Conclusions: *Sphk2* deletion in renal perivascular cells was protective against kidney fibrosis. *In vitro* studies suggested that S1P produced by Sphk2 is exported through Spns2 and reacts with S1PR1 to enhance the inflammatory signal in these cells, leading to immune cell infiltration and subsequent fibrosis in the kidneys.

Funding: NIDDK Support

PO0598

Histone Demethylase JMJD3 Protects Against Renal Fibrosis by Suppressing TGF-β and Notch Signaling

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Background: The Jumonji domain containing-3 (JMJD3), a specific histone demethylase for trimethylation on histone H3 lysine 27 (H3K27me3), is associated with the pathogenesis of many diseases, but its role in renal fibrosis remains unexplored. Here, we examined the role of JMJD3 and mechanisms involved in the activation of renal fibroblasts and development of renal fibrosis.

Methods: Murine models of 5/6 nephrectomy (SNx) and ureteral unilateral obstruction (UUO) were used to assess the effect of a specific JMJD3 inhibitor, GSKJ4, and genetic deletion of JMJD3 from FOXD1 stroma-derived renal interstitial cells on the development of renal fibrosis and activation of renal interstitial fibroblasts. Cultured rat renal interstitial fibroblasts (NRK-49F) and mouse renal epithelial (mTECs) cells were also used to examine JMJD3-mediated activation of profibrotic signaling.

Results: JMJD3 and H3K27me3 expression levels were upregulated in the kidney of mice subjected to SNx 5/6 and UUO. Pharmacological inhibition of JMJD3 with GSK J4 or genetic deletion of JMJD3 led to worsening of renal dysfunction as well as increased deposition of extracellular matrix proteins and activation of renal interstitial fibroblasts in the injured kidney. This was coincident with decreased expression of Smad7 and enhanced expression of H3K27me3, transforming growth factor β1 (TGFβ1), Smad3, Notch1, Notch3 and Jagged1. Inhibition of JMJD3 by GSK J4 or its specific siRNA also resulted in the similar responses in cultured NRK-49F and mTECs exposed to serum or TGFβ1. Moreover, JMJD3 inhibition augmented phosphorylation of AKT and ERK1/2 in vivo and in vitro.

Conclusions: These results indicate that JMJD3 confers anti-fibrotic effects by limiting activation of multiple profibrotic signaling pathways and suggest that JMJD3 modulation may have therapeutic effects for chronic kidney disease.

Funding: NIDDK Support

PO0599

Induction of CKD by Gene Deletion of Canonical Transient Receptor Potential 1 (TRPC1) Channels Independent of Hypertension and Nephromegaly Despite Diabetes and Metabolic Syndrome

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Background: TRPC1 gene on chromosome 3q22-24 is in the linkage region for diabetic nephropathy. Despite reduced expression in diabetes, no causal relationship has been shown. Since null mice are obese, hypertriglyceridemic and diabetic with fatty liver, we evaluated potential renal phenotypes, testing the hypothesis of impaired Ca signaling, as we found reduced cell free Ca in bone, renal, and parathyroid cells.

Methods: From 3rd to 22nd mon, metabolic, cardiac & abdominal ultrasound (US) & clearance (Cl) studies were done in age- & sex-matched littermates of TRPC1 +/+, +/-, & -/- mice. Creatinine (Cr) was analyzed by creatininase or HPLC; glomerular filtration rate (GFR) by inulin Cl. Systolic (S) & diastolic (D) BP was measured by arterial (A) cannulation.

Results: Null mice were hyperglycemic from the 3rd mon & developed diabetes from 6 to 22 mon by standard IP glucose tolerance test. Nephromegaly was absent in null mice since kidney volume by US (0.38 vs. 0.46 at 7 mon & 0.4 vs 0.5 cc at 11-20 mon) was 16% smaller & kidney (K) to body (B) weight (W) (1.2 vs.1.5 % at 7 mon & 1.1 vs.1.5 % at 11-20 mon) was lighter by 17-28 %. Chronic injury & scarring were suggested by 37% increase in echogenicity at 20 mon, though normal at 7 or 11 mon. Urine albumin/Cr ratio in null mice rose barely (64-71%). But at 17 mon, CrCl fell by 30% ($p<0.01$) in null ♀ & by 46% ($p<0.01$) in null ♂. GFR at 22 mon corroborated stage III CKD as inulin Cl fell by 45-48%, whether expressed per mouse, per g KW, or per 100 g BW. Haploid TRPC1 deletion reduced CrCl by in 40% ($p<0.05$) at 16 mon vs 44% by diploid deletion ($p<0.02$). TRPC1 deletion significantly reduced, not raised, mean SBP (113 vs 131 torr), DBP (77 vs 86 torr), & MABP (89 vs 98 torr). Since TRPC1 was implicated in cardiac hypertrophic signaling, smooth muscle proliferation & mesangial cell contraction, we did cardiac US & found 33% reduced cardiac output in -/- mice (14 vs 21 ml/min) & 14% smaller heart mass, corroborated by 20% lower weights measured at 22 mon.

Conclusions: 1. TRPC1 deficiency impairs Ca signaling, retards renal & heart development, compromizes hemodynamics and produces hypoplastic nephropathy. 2. Null mice provide an excellent model to study progressive CKD independent of hypertension and heavy proteinuria.

Funding: NIDDK Support, Veterans Affairs Support, Clinical Revenue Support

PO0600

The Novel Soluble Guanylyl Cyclase (sGC) Activator Runcaciguat Induced Renal Vasodilation and Reduced Kidney Damage in a Rat CKD Model

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Background: CKD progression is associated with impaired NO/sGC/cGMP-signaling, low cGMP production and increased oxidative stress. Oxidative stress modifies the native sGC to oxidized, heme-free apo-sGC which cannot be activated by NO anymore. Runcaciguat is a novel potent and selective sGC activator that binds and activates heme-free sGC independently of NO and restores NO/sGC/cGMP signaling. We investigated the effects of Runcaciguat on intrarenal hemodynamics and in a rat model of T2D-associated CKD.

Methods: Hemodynamic effects were analyzed *ex vivo* in isolated renal afferent/efferent arterioles and in perfused kidneys. Effect of Runcaciguat on kidney protection was evaluated in diabetic and proteinuric rats. ZSF1 rats (12w, male, n=6/gp) were implanted with telemetry systems and treated daily orally for up to 12 weeks with Runcaciguat, Enalapril or placebo. Key parameters included proteinuria, kidney structural changes, biomarkers, kidney gene expression, systemic hemodynamics, and substance plasma exposures.

Results: Runcaciguat dilated renal afferent/efferent arterioles under NO depletion and increased blood flow, GFR and cGMP production in NO-depleted, isolated perfused kidneys. In ZSF1 rats, Runcaciguat dose-dependently reduced proteinuria (-17%, -50%, -85% @ 1, 3, 10 mg/kg/bid) without changing mean arterial pressure at steady-state. The reduction of proteinuria was significantly higher than with Enalapril (-39%, -63% @ 20, 60 mg/kg/d) at doses significantly reducing systemic blood pressure. Runcaciguat reduced kidney structural damages and kidney and liver weight. Runcaciguat reduced glycosylated hemoglobin and plasma triglycerides while Enalapril did not. Metabolic improvement was accompanied by gene expression changes suggesting improvement of vascular and endothelial functions independently of interaction with the Renin-Angiotensin-Aldosterone system. Runcaciguat plasma concentration was dose-proportional after acute and chronic dosing.

Conclusions: Runcaciguat prevented further decline in kidney function and structure independent of blood pressure in CKD rats. Our data suggest that the novel sGC activator Runcaciguat represents a promising treatment option for CKD patients.

Funding: Private Foundation Support

PO0601

Inhibition of KIM-1-Mediated Fatty Acid Uptake by a Novel Inhibitor Attenuates Pro-Fibrotic Responses in Multiple Models of Human Primary Kidney Epithelial Cells Including Kidney Tubuloids

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Background: Tubulointerstitial damage is strongly associated with many forms of kidney injury including diabetic kidney disease. Kidney Injury Molecule-1 (KIM-1), a scavenger receptor, is the most upregulated proximal tubule protein with kidney injury. We hypothesized that KIM-1-mediated uptake of fatty acids (FAs) contributes to tubulointerstitial damage.

Methods: Human DKD renal biopsy samples were analyzed. Human primary epithelial cell cultures were established from the non-tumor kidney tissue removed from patients with a renal mass. To grow human renal tubuloids, primary cells were cultured on ultra-low attachment plates for several days. Cells were transferred into media containing multiple growth factors and 5% fetal bovine serum. Cells and tubuloids were treated with palmitate acid with certain groups having siRNA knockdown of KIM-1. Conditioned media from FA-treated human primary cells and tubuloids were applied to mouse primary kidney fibroblasts. An inhibitor for KIM-1-mediated FA-uptake was identified from >14,400 compounds and tested for its anti-fibrotic ability.

Results: KIM-1 expression in DKD patients was positively correlated with tubulointerstitial inflammation and fibrosis. FA-BSA uptake was markedly reduced in cells depleted of KIM-1 indicating the relative importance of KIM-1 to proximal tubule FA uptake. High-dose FA treatment increased cell death. FA treatment increasedγH2AX expression, a marker for DNA damage response. FA also increased the number of cells in the G2/M phase without an increase of those in S phase by cell cycle analysis, indicating that cells are likely arrested in G2/M phase. Our newly identified inhibitor for KIM-1, JB1, prevented FA uptake at least in part by inhibiting the direct binding of FA to KIM-1. JB1 reduced the pro-fibrotic effect of conditioned media from FA-treated human primary cells and tubuloids.

Conclusions: KIM-1 enhances the proximal tubular uptake of FA, leading to proximal tubule damage, pro-fibrotic responses and increase in cell death. Our findings support the role of KIM-1 as a target for chronic kidney disease including DKD and our work introduces a new candidate therapeutic agent.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim

PO0602

Histone Deacetylase 6 Inhibition Mitigates Renal Fibrosis by Suppressing TGF-β/SMAD3 and eGFR Signaling Pathways

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Background: We have recently shown that histone deacetylase 6 (HDAC6) is critically involved in the pathogenesis of acute kidney injury, however, its role in renal fibrosis remains unclear.

Methods: In this study, we examined the effect of ricolinostat (ACY-1215), a selective inhibitor of HDAC6, on the development of renal fibrosis in a murine model induced by unilateral ureteral obstruction (UUO).

Results: HDAC6 was highly expressed in the kidney following UUO injury, which was coincident with deposition of collagen fibrils and expression of α–smooth muscle actin, fibronectin, and collagen III. Administration of ACY-1215 reduced these fibrotic changes and inhibited UUO-induced expression of transforming growth factor β1 and phosphorylation of Smad3, but increased expression of Smad7. ACY-1215 treatment also suppressed phosphorylation of epidermal growth factor receptor and several signaling molecules associated with renal fibrogenesis, including AKT, signal transducer and activator of transcription 3 and NF-κB in the injured kidney. Furthermore, ACY-1215 was effective in inhibiting dedifferentiation of renal fibroblasts to myofibroblasts in cultured renal interstitial fibroblasts.

Conclusions: Collectively, these results indicate that HDAC6 inhibition can attenuate renal fibrosis development by suppression of TGFβ1 and EGFR signaling.

Funding: NIDDK Support, Other NIH Support - National Natural Science Foundation of China

PO0603

Crucial Role of STAT6 Signaling in Renal Fibrosis

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Background: Kidney fibrosis is a pathologic characteristic of chronic kidney disease, resulting in progressive loss of kidney function to end-stage kidney failure. We have recently demonstrated that bone marrow-derived fibroblasts contribute to the pathogenesis of kidney fibrosis. In this study, we investigated the role of STAT6 in activation of bone marrow-derived fibroblasts and development of renal fibrosis in folic acid nephropathy.

Methods: To investigate the role of STAT6 in myeloid fibroblast activation and kidney fibrosis, we used STAT6 knockout mice or treated wild-type mice with AS1517499, a STAT6 inhibitor. Wild-type mice treated with vehicle were used as controls. Folic acid was administered at 250 mg/kg intraperitoneally to induce kidney fibrosis. Kidneys were harvested 2 weeks after folic acid injection.

Results: Folic acid injury led to activation of STAT6 in the interstitial cells of the kidney, which was abolished by treatment with AS1517499. Wild-type mice treated with AS1517499 accumulated fewer bone marrow-derived fibroblasts in the kidneys following folic acid injury compared with vehicle-treated mice. AS1517499 treatment significantly inhibited myofibroblast activation, reduced total collagen deposition, and suppressed expression of extracellular matrix proteins after folic acid injury. Compared with wild-type mice, mice with STAT6 deficiency exhibited fewer myeloid fibroblasts and myofibroblasts and expressed less α-SMA protein in the kidneys following folic acid injury. Furthermore, genetic deletion of STAT6 significantly reduced total collagen deposition and ECM protein production in the kidneys with folic acid nephropathy.

Conclusions: Our results demonstrate that STAT6 signaling plays an important role in the activation of bone marrow-derived fibroblasts during the development of renal fibrosis in folic acid nephropathy. AS1517499 may serve as a novel therapeutic agent for the treatment of chronic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

PO0604

The Role of HNF4α in CKD Progression

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Background: Acquired kidney mitochondrial dysfunction is a prominent feature of Chronic Kidney Disease (CKD), and is associated with onset and progression of CKD. HNF4α is a transcription factor highly expressed in proximal tubules which controls the expression of genes involved in critical metabolic pathways. As a result, mutations in *Hnf4α* are associated with mitochondrial defects. We previously found that *Hnf4α* is reduced in the kidneys of Col4a3^{KO} mice with progressive CKD and it correlates with hyperphosphatemia. Here we tested the hypothesis that kidney *Hnf4α* is reduced in response to hyperphosphatemia and that *Hnf4α* decline in CKD contributes to mitochondrial dysfunction and CKD progression.

Methods: We fed WT mice a control (Ctr) and a high phosphate diet (HPi) for 6 weeks. We confirmed that *Hnf4α* expression was reduced in the kidneys Col4a3^{KO} mice by RT-PCR and next performed RNA sequencing (RNAseq) to identify genes and molecular pathways affected by HNF4α reduction in CKD. Finally, to further evaluate the causal role of *Hnf4α* reduction in CKD progression, we treated Col4a3^{KO} mice with a daily dose of 30μg/g of HNF4α antagonist (BI-6015) for 5 days.

Results: WT mice fed a HPi diet showed a significant 70% reduction in kidney HNF4α mRNA and protein expression, suggesting that hyperphosphatemia, a hallmark of progressive CKD, contributes to HNF4α downregulation in the kidney. Kidney molecular profiling by RNAseq of Col4a3^{KO} mice showed increased acquired mitochondrial dysfunction and reduced oxidative phosphorylation, suggesting that impaired mitochondrial function strongly contributes to CKD progression. Downstream pathway analyzes showed that the vast majority of these genes (~80 %) are regulated by HNF4α. Pharmacological inhibition or HNF4α in Col4a3^{KO} mice led to an accelerated decline in kidney function (200% increase in BUN), demonstrating the crucial role of HNF4α in CKD progression.

Conclusions: These results suggest that HNF4α is a master regulator of mitochondrial function in kidney and might represent a novel therapeutic target to improve outcomes in CKD.

Funding: NIDDK Support

PO0605

An In Vitro Model to Elucidate the Synthesis of Extracellular Matrix Proteins Involved in Renal Interstitial Fibrosis

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Background: Accumulation of extracellular matrix (ECM) proteins is a hallmark of renal fibrosis, which can lead to altered tissue homeostasis, kidney failure, and ultimately death. Many different cell types are involved in this process, but fibroblasts are the main source of ECM proteins such as fibronectin, collagen type I (COL I), III (COL III), and VI (COL VI). Recently it was suggested that a fragment of COL VI released during collagen maturation is, in fact, a bioactive molecule (endotrophin; ETP) with signaling potential, indicating that collagens are not just passive structural proteins. In this study, we investigated the effect of transforming growth factor (TGF)-β and ETP on the synthesis of different ECM proteins by human renal fibroblasts in the scar-in-a-jar (SiaJ) cell model.

Methods: Cells were seeded in 48-well plates at 30.000 cells/well and incubated for 24h in DMEM + 10% FBS for adherence. Cells were starved by incubating them for further 24h in DMEM + 0.4% FBS. Fresh medium was added at day 0 with 225/150 mg/mL Ficoll 70/400 and 1% ascorbic acid, containing 0.02 nM TGF-β or either 12 or 30 nM ETP. Medium was changed and collected on days 3, 6, 10, and 13. Biomarkers of COL I (PRO-C1), III (PRO-C3), VI (PRO-C6), and fibronectin (FBN-C) formation were assessed in the medium by enzyme-linked immunosorbent assays developed at Nordic Bioscience.

Results: Stimulating renal fibroblasts with 0.02 nM TGF-β significantly increased the formation of COL I ($P<0.0001$), III ($P<0.0001$), and fibronectin ($P<0.0001$) compared to unstimulated cells. Interestingly, TGF-β treatment suppressed the formation of COL VI compared to untreated cells. Stimulating with 30 nM ETP significantly increased the formation of COL I ($P<0.0001$) and III ($P<0.0001$) compared to unstimulated cells. 12 nM ETP significantly increased the synthesis of fibronectin compared to unstimulated cells ($P<0.0001$).

Conclusions: Different growth factors induce different protein expression profiles in fibroblasts. Interestingly, ETP, which originates from the ECM, drives renal fibrosis through increasing COL I and III as well as fibronectin. This SiaJ model, combined with the investigated biomarkers of ECM formation, could be used to elucidate the mechanisms behind acute and sustained matrix production profiles.

PO0606

FoxM1 Inhibition Ameliorates Renal Interstitial Fibrosis (RIF) by Decreasing Extracellular Matrix and Epithelial-to-Mesenchymal Transition

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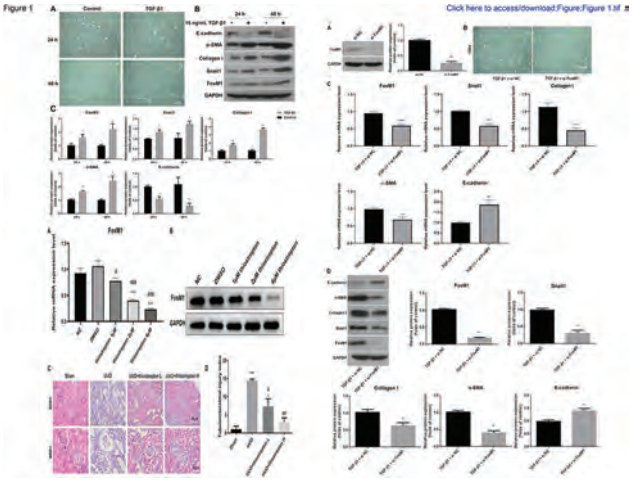
Background: FoxM1 is a transcriptional regulator involved in tumor development, pulmonary fibrosis, and cardiac fibrosis. However, its role in RIF has yet to be elucidated.

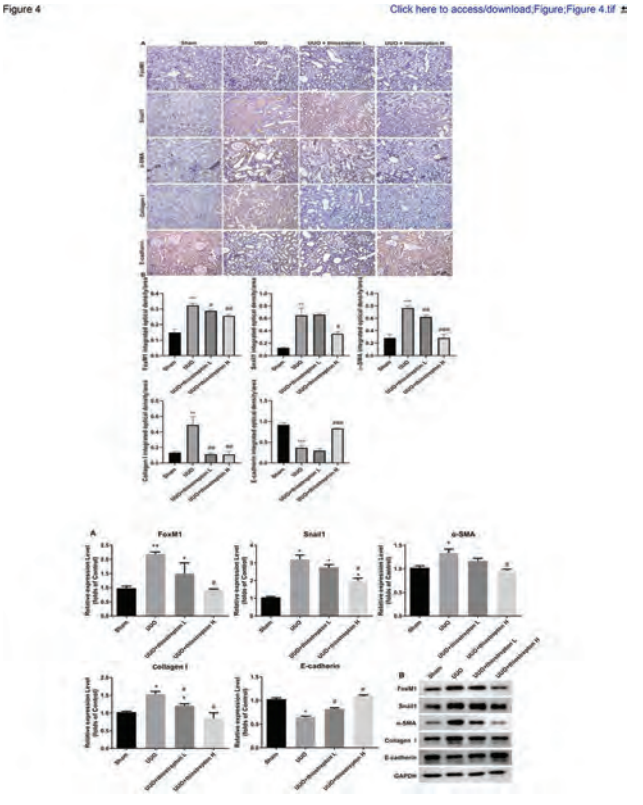
Methods: We established a TGF-β1-stimulated human proximal tubular epithelial cell (HK-2) model *in vitro* and a unilateral ureteral obstruction (UUO)-induced rat RIF model *in vivo*. FoxM1 inhibition was achieved by siRNA interference *in vitro* and by injecting thiostrepton into UUO-induced RIF rats *in vivo*. The degree of renal damage and fibrosis were determined by histological assessment via hematoxylin and eosin staining. Immunohistochemistry, western blots, and qPCR were used to determine the expression levels of FoxM1, Collagen I, E-cadherin, α-SMA, and Snail1

Results: FoxM1 inhibition could ameliorate RIF and reduce the deposition of Collagen I. H&E staining revealed that renal structural damage, inflammatory cell infiltration, and ECM deposition were significantly attenuated by thiostrepton treatment in the UUO rats. FoxM1 downregulation significantly suppressed EMT, as evidenced by decreased protein and mRNA expression levels of α-SMA and Snail1 and a significant increase in protein and mRNA expression levels of E-cadherin.

Conclusions: FoxM1 inhibition could be a novel therapeutic strategy for the treatment of RIF.



Protein levels in TGF-β1-induced HK-2 cells.FoxM1 downregulation inhibited TGF-β1-induced EMT



PO0607

The Macrophage Recruitment in the Unilateral Ureteral Obstruction Is Associated with the Raise of MCP-1 and Is Dependent of Lipocalin 2 Expression

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Background: The persistent renal inflammation has been proposed as a crucial mechanism at the early stages of renal disease. The macrophages recruitment, as part of the pathogenic events, depends of the monocyte chemoattractant protein-1 (MCP-1) raise. In addition, studies in patients have demonstrated that neutrophil gelatinase-associated lipocalin (NGAL, also called Lipocalin-2), it is overexpressed during early stages of renal lesion. However, whether NGAL is relevant for macrophages recruitment at renal level, and if this is related to the increase of MCP-1, remains unknown. Our objective was to determine whether NGAL promotes the pro-inflammatory status during the unilateral ureteral obstruction (UUO), characterized by the macrophage recruitment and the increase of MCP-1.

Methods: Male C57BL/6 Wild type (WT) y NGAL-KO mice (8-12 weeks) were underwent to UUO and to Sham surgery (control group) during 3 and 7 days (n=8), in order to determine the associated damage at kidney level and the raise of MCP-1 in peripheral blood mononuclear cells (PBMC).

Results: In WT mice, the UUO induced luminal tubular dilation starting at 3 days (P<0.001 vs. Sham), and an induction of plasma urea (76.36 ± 5.37 mg/dL. P<0.01 vs. Sham). In addition, UUO increased NGAL levels in PBMC, plasma and urine (24.1 μg/L in Sham vs. 103.8 μg/L and 134.5 μg/L in UUO, at 3 and 7 days, respectively). This was in accordance with the renal induction of NGAL (mRNA and protein, P<0.001 vs. Sham), and with the increase of mRNA for the following pro-inflammatory mediators: TGF-β1, CCL5 (RANTES) and MCP-1, with a *peak* at 7-days. The genetic abalation of NGAL prevented tubular dilation (34.24 ± 6.55 μm. P<0.01 vs. UUO WT) and the rise of MCP-1 induced by UUO in kidney and PBMC (P<0.001 vs. WT). This was accompanied with a low grade of macrophage infiltration in kidney of NGAL-KO mice underwent to UUO (15.2% in WT vs. 7.3% in NGAL-KO).

Conclusions: The renal overexpression of MCP-1 and the macrophage recruitment induced by UUO is dependent of NGAL presence. Our results suggest that NGAL, by a regulation on MCP-1, may be crucial for macrophage chemoattraction during the early stages of renal disease. **Acknowledgments.** Fondecyt #1201251 and Fondecyt #3201016

PO0608

Enabled ICOS$^+$-RTE-Tresp Proliferation Is Involved in the Pathogenesis of Active Systemic Lupus Erythematosus (SLE)

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Background: Dysfunction of CD4$^+$-regulatory-T-cells (Tregs) and CD4$^+$-responder-T-cells (Tresps) is an important trigger in the development of active systemic lupus erythematosus. By now, underlying mechanisms are not fully understood.

Methods: To determine differences in the differentiation of inducible costimulatory molecule (ICOS)$^+$- and ICOS$^-$-Tregs/Tresps, their percentages of CD45RA$^+$CD31$^+$-recent thymic emigrant (RTE)-Treg/Tresps and CD45RA$^+$CD31$^-$ mature naïve (MN)-Treg/Tresps as well as CD45RA$^-$CD31$^+$ and CD45RA$^-$CD31$^-$-memory-Treg/Tresps (CD31$^+$- and CD31$^-$-memory Treg/Tresps) within total Tregs/Tresps were calculated. Additionally, subsets were stained for the proliferation marker Ki67. 124 healthy control patients and 117 with a preexisting lupus erythematosus (102 patients in remission, 15 patients with a flare) were measured.

Results: SLE patients in remission show an increased differentiation of ICOS$^+$-RTE-Tregs and ICOS$^-$-RTE-Tregs via resting MN-Tregs into CD31$^-$-memory-Tregs compared to healthy control patients. In contrast, proliferation of ICOS$^+$-RTE-Tresps into ICOS$^+$CD31$^-$-memory-Tresps is inhibited. Similarly, active SLE patients show an increased differentiation of ICOS$^+$-RTE-Tregs and ICOS$^-$-RTE-Tregs via resting MN-Tregs. Moreover, proliferation ability of ICOS$^+$-RTE-Tresps is not inhibited but enabled in these patients. Both SLE patients in remission and active SLE patients show an impaired ICOS$^-$-RTE-Tresp differentiation compared to healthy control patients. Hence, the ratio of ICOS$^-$-Tregs/ICOS$^-$-Tresps within CD4$^+$-T-cells is significantly increased in both SLE remission and active SLE patients compared to healthy control patients. In contrast, the ratio of ICOS$^+$-Tregs/ICOS$^+$-Tresps is significantly increased in SLE remission patients, but decreased in active SLE patients compared to healthy control patients.

Conclusions: Proliferation of ICOS$^+$-RTE-Tresps is medically inhibited in SLE remission patients. In active SLE patients, proliferation is enabled decreasing the ICOS$^+$-Treg/ICOS$^+$-Tresp ratio.

PO0609

Involvement of Calcium-Sensing Receptor in the Development of Interstitial Fibrosis

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Background: Physiological and pathophysiological role of renal Ca sensing receptor (CaSR) have not been well understood. We have reported the down regulation of CaSR in the process of renal interstitial fibrogenesis along with the down regulation of Mg transporting molecules, suggesting that CaSR plays an important role in the development of renal damage associated with Mg deficiency. We report here an analysis of the effects of calcimimetics administration on renal fibrosis models.

Methods: The left ureters of 8-week-old SD rat were ligated to create unilateral ureter obstruction (UUO) models and studied after 7 days. Cinacalcet 1.0 mg/day, a calcimimetics, was administered to a part of UUO animals. Experiments were performed in three groups of sham group, UUO group and UUO+Cinacalcet group (n=5). Fibrosis was evaluated by Azan staining and analysis of mRNAs of fibrosis-related molecules. We also studied on mRNA expression of Mg-transporting molecules.

Results: It was confirmed from immunohistochemistry and gene expression that CaSR expression was remarkably decreased by UUO (RT-PCR: sham 1.01±0.09 vs UUO 0.04±0.00, n=5). Cinacalcet treatment partially restored the expression by approximately 50% compared to UUO group. In Azan staining, an increase in the fibrosis area and a recrease in the non-damaged tubules were apparent in UUO, however, Cinacalcet treatment partially rescued. mRNA expression of TGF-beta and MCP-1 was not significantly decreased by Cinacalcet treatment as compared to UUO group. mRNA expression of claudin-14, 16 and 19, Mg transpirting molecules, seemed to be increased by Cinacalcet treatment, however, it was not statistically significant. However, Cinacalcet partially, but significantly increased the mRNA expression of TRPM6 comparing to UUO group (sham: 1.01±0.07, UUO: 0.35±0.01, Cinacalcet: 0.41±0.02).

Conclusions: The expression of claudin-16 and TRPM6 was significantly decreased with the development of fibrosis in UUO. The effect of CaSR activation and upregulation by Cinacalcet was limited, however, it restored the progression of fibrosis and impairment of Mg reabsorption. CaSR may play a key role for the Mg loss-relating renal fibrogenesis.

PO0610

Fibroblast-Specific LRP-1 Promotes Renal Fibrosis

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Background: LRP-1, a scavenger receptor up-regulated during obstructive nephropathy, has been shown to mediate the actions of multiple profibrotic factors including tPA, TGF-β1, and CTGF. However, the in vivo role of LRP-1 in kidney fibrosis remains largely unknown.

Methods: We generated a novel fibroblast-specific LRP-1 knockout mouse (LRP-1-/-) and induced the unilateral ureteral obstruction (UUO), a classic model of chronic kidney disease (CKD), in these mice to investigate the in vivo role of LRP-1 in kidney fibrosis.

Results: It was found that LRP-1-/- mice had similar phenotype as their littermate controls (LRP-1+/+). However, after UUO injury, LRP-1-/- mice displayed significantly decreased fibrosis, as demonstrated by reduced renal collagen content and FSP-1 abundance, in comparison with their littermates. We further found that obstruction-induced epithelial damage was alleviated in LRP-1-/- mice. After UUO, LRP-1+/+ mice displayed decreased E-cadherin and increased vimentin expression, suggesting that epithelial-to-mesenchymal transition (EMT) was induced in the obstructed kidneys. Intriguingly, LRP-1-/- mice showed significantly reduced EMT as demonstrated by restoration of E-cadherin and elimination of vimentin induction.

Conclusions: Thus, it is clear that fibroblast LRP-1 promotes kidney fibrosis through EMT.

Funding: NIDDK Support, Private Foundation Support

PO0611

Essential Renal Tubular Proteins Are Lost by Excretion Within Novel Large Extracellular Vesicles During Chronic Renal Insufficiency

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Background: Within weeks of surgery, the 5/6 nephrectomy (5/6Nx) rat spontaneously develops renal disease including tubular damage, brush border loss, and the production of very large extracellular vesicles present in the tubule lumen. These large renal tubule extracellular vesicles (LRT-EVs) are too large to be microsomes or exosomes, and lack markers of apoptotic bodies, and thus may represent an undescribed vesicle. We hypothesized that formation and excretion of these vesicles represents a pathological mechanism by which important tubule proteins are lost in chronic renal insufficiency.

Methods: We performed a longitudinal, histologic examination for the presence of LRT-EVs in renal tubules of 5/6Nx and sham-operated rats, and a proteomic analysis of LRT-EVs isolated from 5/6Nx rat urine 10 weeks following surgery.

Results: Histologic examination revealed virtually no LRT-EVs in sham-operated rat tubules at any time point. LRT-EVs were present in 5/6Nx rat tubules at all measured time points including 2, 4, 5, 7, and 10 weeks post-surgery, and exhibited a marked increase in percentage of tubule presence between week 5 (7.0 ± 2.7%) and week 7 (51.1 ± 6.5%). This increase temporally corresponds to a time of rapid progression of renal disease. Median LRT-EV diameter upon microscopic image analysis was 2.5 μm. Proteomic analysis of isolated LRT-EVs revealed them to contain a wide array of functionally essential tubule proteins including but not limited to basolateral Na^+/K^+ ATPase subunits, sodium-glucose co-transporters, aquaporin 1, megalin, cubilin, and mitochondrial VDAC.

Conclusions: Loss of important tubule proteins through production and urine-excretion of previously unreported LRT-EVs may represent a hitherto unappreciated aspect of chronic renal insufficiency.

Funding: Other NIH Support - NHLBI

PO0612

Indoleamine-2, 3-Dioxygenase Activates Wnt/β-Catenin to Induce Kidney Fibrosis

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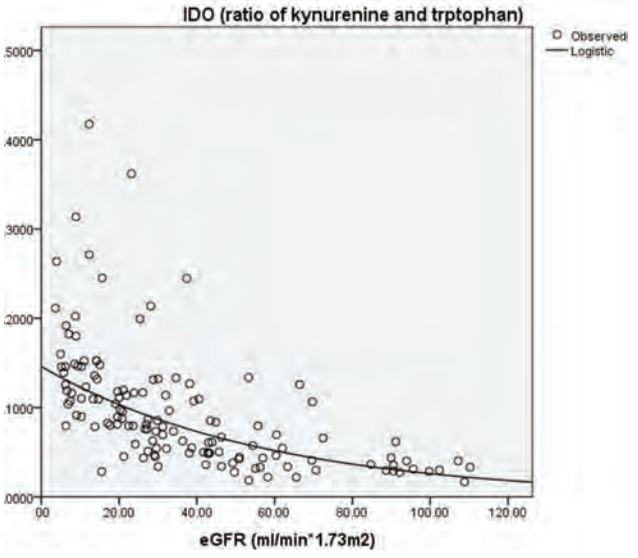
Background: Dysorder of tryptophan metabolism catalyzed by indoleamine-2, 3-dioxygenase (IDO) is common in chronic kidney disease which manifests as increased kidney fibrosis. IDO is also reported to be involved in fibrosis of other organs while little is known about correlations of IDO and fibrosis in kidney disease.

Methods: Wild type (WT) mice and IDO$^{-/-}$ mice were employed. Mice in Sham group underwent exposure of renal artery while mice in AKI group received unique renal artery ischemia-reperfusion injury (IRI) and the contralateral kidney was removed at day 13 after IRI. Samples were collected at day 14. Kidney function, morphology and fibrosis markers were analyzed. Prostaglandin E2 (PGE2) was administrated to WT AKI mice. Clinically, a total of 115 CKD patients and 30 non-CKD patients were recruited. IDO was

calculated by the ratio of kynurenine and tryptophan. Correlations between indicators were analyzed. The ROC curve was also performed.

Results: WT AKI mice revealed elevated expression of IDO and worse kidney function. PAS staining exhibited less loss of tubular epithelial cells and atrophy tubules in $IDO^{-/-}$ AKI mice. Additionally, fibrosis markers, including α-SMA, fibronectin and vimentin, were more severer in WT AKI mice. GSK-3β and β-catenin were significantly decline in $IDO^{-/-}$ AKI mice. On top of that, PGE2 administration revealed reduced IDO expression and decreased levels of GSK-3β and β-catenin resulting in lower expressions of α-SMA, fibronectin and vimentin in WT AKI mice. In patients, IDO had negative correlations with eGFR (r=-0.742, p<0.001). Further, the linear regression showed IDO was an independent influence factor of eGFR. ROC curve showed the area under the ROC curve was 0.825 for IDO.

Conclusions: IDO could activate Wnt/β-catenin pathway to induce kidney fibrosis. PGE2 could ameliorate kidney fibrosis via inhibiting IDO expression.



Scatter plot of IDO associated with eGFR

PO0613

Human Induced Pluripotent Stem Cell-Derived Kidney Micro-Organoids for High Throughput Disease Modeling in Drug Discovery

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Background: Human kidney contains around 1 million nephrons, more than 2 dozen different cell types. Reproducing physiological kidney cell types in-vitro is limited. Recent advancements in human iPSCs differentiation provide an opportunity to culture and utilize multicellular kidney structures "kidney-organoids". We have employed a kidney micro-organoid in suspension culture this method eventually accelerates kidney organoids to the industrial scale and differentiates from traditional low throughput transwell organoids. This method involves differentiation of iPSCs to intermediate mesoderm using CHIR and FGF9 and spontaneous aggregation in the swirler culture leads to mature to kidney organoids, this can be used to study kidney disease in a high-throughput manner.

Methods: We aimed to model human kidney inflammatory and genetic disease in-vitro using kidney micro-organoids, treatment with different insults to reproduce CKD microenvironment eg. IL-1b, TGFb, Angiotensin-II and protamine sulphate.

Results: After 24h of stimulation, we noted significant upregulation of kidney injury biomarkers including KIM1 and inflammatory cytokines. Reproducing genetic diseases like PKD is very challenging in-vitro, we show treatment of cultured micro-organoids with forskolin (to elevate intracellular cAMP) altered the transportation of ciliary proteins and promoted cyst formation, resembling human PKD. These observations clearly demonstrate the use of micro-kidney organoids to study renal diseases in-vitro for drug discovery applications with human translatable functional biomarkers.

Conclusions: Impact statement: Kidney micro-organoids provide a platform for high throughput modeling of human kidney diseases related fibrosis, inflammation and genetic disease like polycystic kidney disease with human translatable biomarkers in drug discovery.

PO0614

CKD of Unknown Origin (CKDuo): Is the Problem Dehydration, Water Contamination, or Both?

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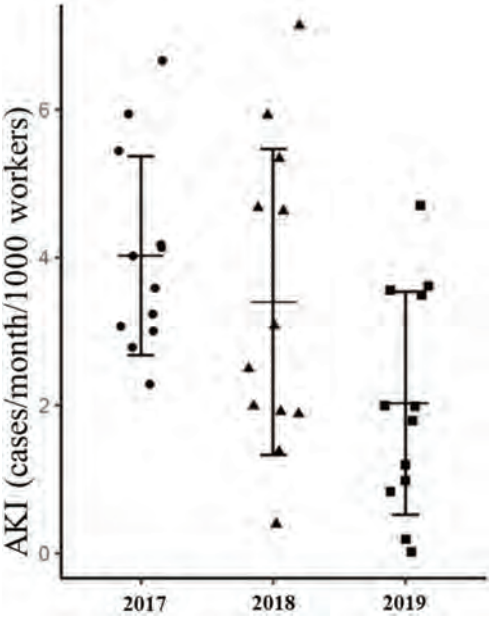
Background: An increasing number of people of Central America develop CKDuo. The disease is characterized by chronic tubulo-interstitial nephritis. Occasionally, it presents as an acute kidney injury (AKIuo). The cause(s) remain unknown. Some sustain that dehydration is responsible. Others believe the disease is caused by water contaminated with heavy minerals or agrochemicals. To prevent dehydration, workers in these regions ingest 8-12L of water/day. Hence, even if concentrations of toxins are in "acceptable range", the cumulative intake may reach toxic levels. If this hypothesis is correct, purified water should reduce the incidence of the disease. In 2017 a Nicaraguan sugarcane factory (SER) adhered to the Adelante initiative, consisting of reducing working hours, exposure to heat and dehydration. In 2017-18, these measures had no impact on the incidence of AKIuo.

Methods: During the 2019 season, SER adopted the policy of providing highly purified drinking water to > 6000 workers (1L/hour during working hours). The effects on AKIuo were monitored. Comparisons were made of the monthly incidence of AKIuo during years 2017, 2018 and 2019, by One-way ANOVA.

Results: With the introduction of purified water, the incidence of AKI decreased from 4.0±1.3 cases in 2017 and 3.4±2.1 in 2018 to 2.0±1.5 cases/1000 workers/month in 2019 (P< 0.02).(Fig.1)

Conclusions: Although preliminary, these data support the hypothesis that contaminated water may play a major role in AKIuo. This raises enormous public health issues. If dehydration is responsible, the remedies are hydration and less heat exposure. If toxins and agrochemical are responsible, the remedy is providing highly purified water to those at risk. The potential impact of these measures on CKDuo remains to be determined.



PO0615

Effects of Chronic Intermittent Hypoxia on umod-/- Rats' Model Link to Alterations of Gut Microbiota

Na Wang, Yuqing Chen. *Renal division, Peking University First Hospital, Beijing, China.*

Background: Previous studies showed that both obstructive sleep apnea and uromodulin (UMOD) were associated with gut microbiota regulation. Here we explored the interaction effects of chronic intermittent hypoxia (CIH) and UOMD expression on variation of gut microbiota and association with phenotype.

Methods: umod-/- and wild type (WT) Sprague Dawley rats were attributed into 4 groups (N=10 in each group), umod-/- and WT under CIH, umod-/- and WT under normal air. All four groups were fed with same chaw for 10 weeks. All rats were anesthetized to collect fecal samples from large intestine directly and blood at the end of 10 weeks feeding. The bacterial composition was analyzed based on 16S ribosomal DNA pyrosequencing. Bioinformatics tools, including sequence alignment, abundance, and taxonomic diversity, were used in microbiome data analyses. Correlation analysis between differential genera and changed biochemical indicators were measured.

Results: Under normoxia, the serum phosphorus(P*) tend to be lower in umod$^{-/-}$ group compared with WT group (1.9±0.2 vs 2.1±0.2mmol/L, P=0.064). Under normoxia environment, the α-diversity of gut microbiota decreased in umod$^{-/-}$ group compared with WT group (Chao1 index, 301.8±30.2 vs 374.3±55.3,P=0.005), and the composition of microbiota was clearly separated between two groups (PCoA, P<0.001). The abundance of g-Lactobacillus (P=0.002) and g-Phascolarctobacterium (P=0.026) increased and g-Ruminococcus (P=0.023) decreased in umod$^{-/-}$ group compared with WT group. g-Ruminococcus showed positive relationship with serum phosphorus (R=0.511, P=0.043). When CIH was added as an environment condition, the serum phosphorus(P*) increased in umod$^{-/-}$ group obviously (2.3±0.3 vs 1.8±0.2 mmol/L,P=0.002). Gut composition in umod$^{-/-}$ were still clearly separated from WT (PCoA, P<0.001). The abundance of g-Lactobacillus, g-Phascolarctobacterium and g-Ruminococcus showed no difference. The abundance of g-Blautia (P=0.008), g-Sutterella (P=0.008), g-Anaerostipes (P=0.008) increased and g-Flavonifractor (P=0.008) and g-Anaerotruncus (P=0.008) decreased in umod$^{-/-}$ CIH group compared with wild type CIH group. G-Sutterella showed positive relationship with Phosphorus (R=0.831, P<0.001).

Conclusions: Chronic intermittent hypoxia can interact with uromodulin to affect serum phosphorous in umod$^{-/-}$ rats. These changes were strongly linked to the alterations in gut microbiota.

PO0616

Influence of Colonic Dialysis on the Distribution of Gut Microbiome in CKD Stage 3-5 Patients

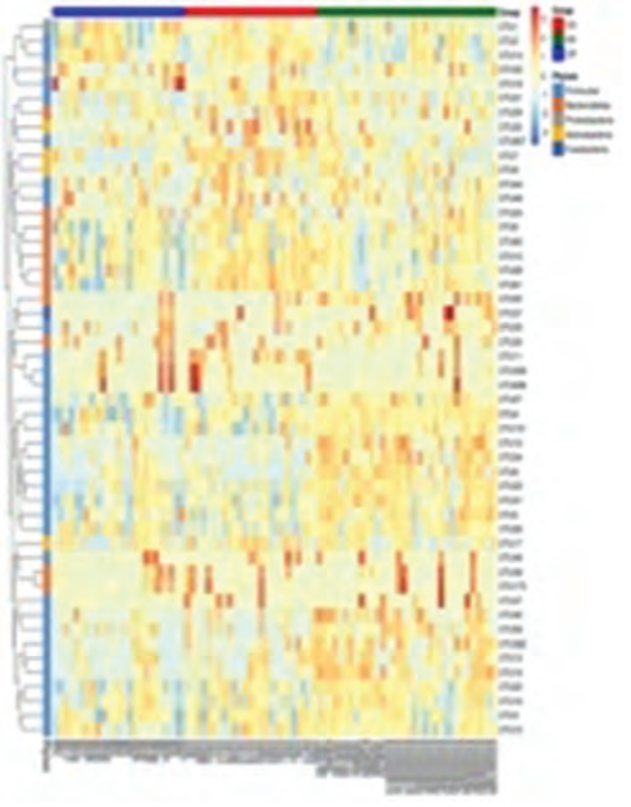
Hui Xu. *Department of Nephrology, Xiangya Hospital, Central South University, Changsha, China.*

Background: Chronic kidney disease (CKD) becomes a major public health challenge given high incidence rates in the world. colonic dialysis (CD) has been used in pre-dialysis CKD patients (CKD3-5) in many hospitals of China because of its advantages of simple operation, low price and few complications. The gut microbiome is a potential cause of CKD progression and serve as a promising therapeutic target. We raise the question that whether CD improve renal function by affecting intestinal microbiome in CKD3-5 patients. Improving the imbalance of intestinal microbiome is considered a potential therapeutic target to decline chronic kidney disease(CKD) progression. We amied to investigate the influence of colonic dialysis(CD) on the distribution of gut microbiome in CKD3-5 patients.

Methods: We studied gut microbiota in 50 patients with CKD, 25 CD patients, 25 outpatients(OP), and compared to 34 healthy subjects(HS). The gut microbiome composition was analyzed by a 16S ribosomalRNA(16S rRNA) gene-based sequencing protocol.

Results: we found that there was no significant difference in the richness of intestinal microbiota between CD and HS, but the richness of bacterial in OP decreased significally (HS VS. OP p = 0.002). CD can increase the abundance of some short chain fatty acid(SCFA) producing bacteria and decrease the abundance of some uremic toxin producing bacteria. CD also can increase the abundance of some anaerobic bacteria in intestine. Compared with OP, the profile of intestinal microbiota in CD group and HS group was more similarity.

Conclusions: Our study reveals CD treatment alterings microbiome profile and increases microbiome richnessll in CKD3-5.



PO0617

Asymptomatic Hyperuricemia, a Regulator of Innate Immunity in CKD

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Background: Asymptomatic hyperuricemia (HU) is common in patients with chronic kidney disease (CKD) but the causative role of HU on CKD progression remains controversial. Two large multi-center randomized controlled trials, CKD-FIX and PERL study, have now disproven a causal relation. On the other hand, a causative role of HU exists with gout but a rapid correction of HU with urate lowering therapy can also elicit acute gout attacks. This suggests a more complex role of HU in this context. Hence, we hypothesized that soluble uric acid (sUA) has immunomodulatory effects on neutrophil function during the immune response to monosodium urate (MSU) crystals.

Methods: Alb-creERT2;*Glut9*$^{lox/lox}$ and *Glut9*$^{lox/lox}$ control mice were injected with tamoxifen and placed either on a chow or acidogenic diet with inosine to induce HU with or without CKD. After 3 weeks, MSU crystals or vehicle were injected into air pouches or postcapillary venules in the cremaster muscle of transgenic mice. Leukocyte infiltration and the extent of inflammation were assessed by flow cytometry, intravital microscopy, and ELISA. Blood neutrophils were isolated from CKD stage G2-4 and G5D patients or healthy individuals and neutrophil transwell migration assays performed.

Results: We found that HU impaired leukocyte recruitment into MSU crystal-injected air pouches of mice with or without CKD. Intravital microscopy revealed that HU specifically reduced leukocyte adhesion, extravasation, and tissue inflammation. The CKD-mediated attenuation of MSU crystal-induced inflammation was fully reversible by treating HU with urate lowering therapy. In neutrophils isolated from healthy individuals, sUA diminished β2 integrin activation and expression, and hence impaired neutrophil migration *ex vivo*. This process was dependent on the intracellular uptake of sUA via the urate transporter SLC2A9/GLUT9. An impaired migratory capability was also observed in neutrophils from CKD patients.

Conclusions: We identify sUA as an endogenous modulator of innate immunity. HU modulates neutrophil migration by altering efficient β2 integrin activation via SLC2A9 in gouty arthritis related or unrelated to CKD. This process provides a molecular explanation for several previously unexplained clinical phenomena in the context of gout and renal failure.

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PO0618

Serum Lysyl Oxidase Is a Potential Diagnostic Biomarker for Kidney Fibrosis

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Background: Kidney fibrosis is the ultimate consequence of advanced stages of chronic kidney disease (CKD); however, there are currently no reliable biomarkers or noninvasive diagnostic tests available for the detection of kidney fibrosis. Lysyl oxidase (LOX) promotes collagen crosslinking, and serum LOX levels have been shown to be elevated in patients with fibrosis of the heart, lungs and liver. However, serum LOX levels have not been reported in patients with kidney fibrosis. We explored whether serum LOX levels are associated with kidney fibrosis.

Methods: Overall, 202 patients with kidney disease underwent renal biopsy, scoring of kidney fibrosis and determination of the area of kidney fibrosis. LOX levels were measured in serum and in kidney tissues. We analyzed the association of circulating LOX and tissue LOX levels with the scores and areas of kidney fibrosis. LOX expression was also investigated with *in vitro* and *in vivo* kidney fibrosis models.

Results: Serum LOX levels were higher in patients with kidney fibrosis than in those without kidney fibrosis ($p<0.001$) and higher in patients with moderate-severe kidney fibrosis than in patients with mild kidney fibrosis ($p<0.001$). Both serum LOX and renal tissue LOX levels correlated with the area of kidney fibrosis ($r=0.748$, $p<0.001$; $r=0.899$, $p<0.001$, respectively). ROC curve analysis of serum LOX levels showed an AUC of 0.80 (95% CI: 0.74 to 0.86). The optimal serum LOX level cutoff point was 253.34 ρg/ml for the prediction of kidney fibrosis and 306.56 ρg/ml for the prediction of moderate-severe renal fibrosis. LOX expression levels were significantly upregulated (2.3-2.6-fold and 6-fold, respectively) in *in vitro* and *in vivo* interstitial fibrosis models.

Conclusions: Both serum LOX and tissue LOX levels correlated with the presence and degree of kidney fibrosis in patients with CKD. These results suggest that serum LOX levels could potentially serve as a noninvasive diagnostic biomarker for kidney fibrosis and may further potentially serve as a stratified biomarker for the identification of mild and moderate-severe kidney fibrosis.

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PO0619

Tubulointerstitial Fibrosis and Markers of Kidney Tubule Secretion

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Background: Tubular secretion plays an important role in the efficient elimination of endogenous solutes and medications, and lower secretory clearance is associated with risk of kidney function decline. We evaluated whether the biopsy measurement of tubular damage atrophy and interstitial fibrosis was associated with lower tubular secretory clearance in persons undergoing kidney biopsy.

Methods: The Boston Kidney Biopsy Cohort is a prospective cohort study of persons undergoing native kidney biopsies for clinical indications. Trained pathologists scored interstitial fibrosis and tubular atrophy (IFTA) on a semi-quantitative scale. We measured plasma and urine concentrations of nine endogenous secretory solutes using a targeted liquid chromatography mass-spectroscopy assay. We used linear regression to test associations of urine to plasma ratios (UPR) of these solutes with IFTA score after controlling for estimated GFR (eGFR) and albuminuria.

Results: Among 418 persons, the mean age was 53 years, 51% were women, 64% were White and 18% were African American. The mean eGFR was 50 ml/min/1.73m^2 and median albumin/creatinine ratio was 890 mg/g. Compared to individuals with no IFTA, those with >50% IFTA had 27 to 76% lower UPR for the all 9 secretory markers. After adjusting for age, sex and race, these associations remained essentially unchanged. After further adjusting for eGFR and albuminuria this association were attenuated [Image] but the trend across groups remained statistically significant (p for trend <0.05) for all 9 solutes. For example, persons with >50% IFTA had, on average, 44% lower (95% CI 12% - 65% lower) UPR of p-cresol sulfate, a highly protein bound secretory solute, compared to persons with no IFTA. A composite secretory index incorporating UPR for all 9 secretory solutes using the min-max method showed similar results.

Conclusions: Greater IFTA severity is associated with lower tubular clearance of endogenous solutes clearance even after adjusting for eGFR and albuminuria.

Funding: NIDDK Support

UPR ratio of secretory solutes among persons with IFTA relative to persons with no IFTA

	IFTA severity					p for trend
N=418	0%	1 - 10%	11 - 25%	26 - 50%	> 50%	
Cinnamoylglycine	ref	12% (-17, 51)	4% (-26, 45)	-31% (-52, -2)	-27% (-53, 13)	0.025
Hippurate	ref	33% (3, 73)	-15% (-36, 14)	-26% (-46, -1)	-30% (-52, 2)	0.002
Indoxyl sulfate	ref	13% (-13, 48)	-7% (-31, 24)	-23% (-43, 5)	-35% (-56, -5)	0.004
Isovalerylglycine	ref	10% (-13, 40)	6% (-19, 39)	-10% (-32, 19)	-27% (-49, 4)	0.038
Kynurenic acid	ref	18% (-10, 56)	-3% (-28, 32)	-30% (-49, -4)	-31% (-54, 2)	0.005
P-cresol sulfate	ref	2% (-26, 39)	-3% (-31, 37)	-36% (-56, -8)	-44% (-65, -12)	0.002
Pyridoxic acid	ref	6% (-17, 36)	6% (-20, 39)	-24% (-43, 2)	-37% (-56, -10)	0.002
Tiglylglycine	ref	24% (-4, 61)	17% (-12, 56)	-8% (-32, 25)	-22% (-47, 13)	0.06
Xanthosine	ref	-1% (-21, 24)	-1% (-23, 27)	-16% (-35, 9)	-30% (-50, -3)	0.018
Composite Secretory Index	ref	13% (-10, 42)	1% (-22, 31)	-23% (-41, 1)	-34% (-53, -7)	0.002

Adjusted for age, sex, race, eGFR and ACR

PO0620

Proximal Tubule Albumin Uptake: Potential Role for Endothelin System in Sickle Cell Disease Mice

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Background: Elevated plasma endothelin-1 (ET-1) reported in sickle cell disease (SCD) patients correlate with microalbuminuria, a major mortality risk factor in SCD. ET-1 contributes to glomerular and tubular injury in SCD, as evidenced by increased glomerular permeability to albumin and urinary excretion of tubular injury markers. Although selective ET_A receptor antagonism reduces albuminuria in humanized sickle cell (HbSS) mice, the mechanism of this action remains unclear. The aim of the study was to determine whether selective ET_A receptor antagonism prevents albuminuria by preserving the expression of tubular albumin-associated transporters in proximal tubule (PT) cells.

Methods: Male C57BL/6 or HbSS and genetic control (HbAA) mice were used to determine the effect of ET-1 on the expression of proximal tubule albumin trafficking mediators, such as megalin and NHE-3.

Results: Exposure of primary mouse PT cells to ET-1 (50nM) for 8h decreased megalin (53% reduction) and doubled NHE-3 expression. Pre-treatment with the ET_A antagonist, BQ123 (1 μM), preserved megalin expression and had no effect on NHE-3. Moreover, selective ET_B receptor blockade (BQ788, 1 μM) prevented ET-1-mediated increase in NHE-3 expression. Primary PT cells isolated from HbSS mice showed decreased megalin mRNA expression as well as protein abundance relative to HbAA PT controls. Ten-week treatment with selective ET_A receptor antagonist (10mg/kg/day) preserved expression of megalin at control levels. There were no differences in NHE-3 mRNA expression in HbSS PT cells regardless the treatment. Interestingly, PT cells from HbSS cultured with HbSS plasma and ET-1 (10nM) had decreased NHE-3 protein abundance compared to non-treated cells.

Conclusions: These results potentially uncover a novel role for ET-1 in PT albumin handling and suggest that PT ET-1 receptor signaling contributes to albuminuria in SCD.

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PO0621

Phosphate and Fibroblast Growth Factor 23 Are Mediators of Lung Injury in CKD

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Background: Although well-documented in chronic kidney disease (CKD), the role of phosphate in pulmonary pathology is not widely known. Phosphorus, or phosphate in its oxidized circulating form, is normally removed from the body by healthy kidneys. CKD disrupts this process, leading to hyperphosphatemia in later stages. We have shown that fibroblast growth factor 23 (FGF23), a key regulator of phosphate metabolism, is elevated in inflammatory lung diseases; that increase in FGF23 contributes to unfavorable clinical outcomes. To improve outcomes for patients with concomitant CKD and pulmonary disease, we wanted to examine direct actions of phosphate and FGF23 and their potential underlying mechanisms.

Methods: For *in vitro* experiments, human lung fibroblasts were treated with 0 to 5 mM sodium phosphate. Expression levels of interleukin (IL)-8 and collagen (COL)1A1 were analyzed by qPCR. Cell counts and viability were quantified with trypan blue staining. *In vivo*, we placed C57Bl/6 mice on a high phosphate (3%) diet to elevate serum phosphate levels in absence of kidney injury and administered bleomycin via oropharyngeal aspiration to generate an acute pulmonary inflammatory response. Serum FGF23 levels were measured by ELISA and serum analysis for phosphate and renal function were obtained. Expression of FGF23 pathway and inflammatory markers were analyzed in murine lung and kidney tissue using qPCR and western blotting.

Results: Augmented phosphate concentrations increased IL-8 and COL1A1 expression from human lung fibroblasts with a concomitant reduction in overall cell number. Serum FGF23 levels were significantly upregulated in mice on a high phosphate diet and further increased in these mice when exposed to bleomycin. Serum phosphate and creatinine levels were significantly elevated. High phosphate and bleomycin increased local FGF23 expression in murine lung tissue.

Conclusions: Upregulation of FGF23 in response to bleomycin during a high phosphate diet suggests that inflammation induced by primary lung injury is worsened by systemic elevation of serum phosphate levels. Our data suggest that in CKD, high serum phosphate levels may increase susceptibility and progression of lung injury. Our results indicate that the existence of a pulmo-renal crosstalk is exaggerating pulmonary injury.

PO0622

APOL1 Risk Variants Mediate Increased Oxidative Phosphorylation Complexes Biogenesis and Mitochondrial Dysfunction

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Background: Susceptibility to focal segmental glomerulosclerosis (FSGS) in African Americans is associated with genetic variants of the Apolipoprotein L1 gene (*APOL1*) named G1 and G2. APOL1 risk variants (RV) are a major driver of mitochondrial dysfunction. The mitochondrial specific lipid cardiolipin (CL) interacts with oxidative phosphorylation (OXPHOS) complexes and plays an important role in the biogenesis of OXPHOS complexes. While APOL1 function was assessed in tagged and overexpressed systems, studies evaluating the functions of endogenous APOL1 protein are missing.

Methods: We studied mitochondrial function using human urinary podocyte-like epithelial cells (HUPECs) established from patients with FSGS carrying different APOL1 alleles. Protein and mRNA levels were measured by WB and quantitative PCR respectively. TEM was performed to study mitochondrial morphology. OXPHOS complexes were studied by BN-PAGE analysis followed by WB. To study how APOL1 RV contributes to mitochondrial dysfunction, we purified APOL1-6xHis protein using HeLa cells infected with lentivirus carrying the APOL1 G0, G1 under the CMV promoter, followed by protein-lipid overlay assay.

Results: The expression of endogenous APOL1 was decreased in HUPECs carrying RVs (G1/G2 HUPECs) when compared to G0/G0 carrying HUPECs. We observed reduced mitochondrial function in the presence of increased OXPHOS complexes in G1/G2 HUPECs. Using TEM, reduced mitochondrial matrix density and increased mitochondrial area were detected in G1/G2 HUPECs. Hyperbranched mitochondria in G1/G2 HUPECs were accompanied by a significant increase in the mRNA levels of mitochondrial fission and fusion proteins FIS1 and MFN1. The affinity of APOL1 G1 to CL was significantly higher than the affinity of APOL1 G0 to CL, when normalized to 6xHis tagged APOL1 expression. We found the mRNA level of cardiolipin synthase (CRLS1) was significantly increased in G1/G2 HUPECs, which is consistent with the overexpression of OXPHOS complexes in G1/G2 HUPECs.

Conclusions: Our findings indicate that endogenous APOL1 RV expression in human podocytes is associated with mitochondrial dysfunction in the presence of increased OXPHOS complexes, and that APOL1 RVs interact with CL thus interfering with CL function in mitochondria.

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PO0623

Uncovering Genomic Alterations in DOCA-Salt Nephropathy Rats Treated with Finerenone

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Background: The aldosterone antagonist spironolactone has antifibrotic effects but its clinical use is limited due hyperkalemia, especially in patients with kidney disease. The novel nonsteroidal and selective mineralocorticoid antagonist finerenone has recently been developed with pronounced antifibrotic activity at doses which have only limited effect on the potassium homeostasis. The exact molecular transcriptional targets of spironolactone and finerenone, however, remain unknown. Since there are more than 20 different cell types in the kidney, single cell RNA and single cell epigenome (ATAC) analysis can help to define transcriptional targets.

Methods: We treated uninephrectomized, Sprague-Dawley rats injected with DOCA and salt with a high dose of finerenone (10mg/kg/d), spironolactone (50mg/kg/d), or vehicle. Outcome parameters included blood pressure, serum and urine electrolytes, albuminuria, renal and cardiac histology. Single nuclei suspension was prepared from kidneys and hearts for single nuclear RNA and single nuclear open chromatin (ATAC) profiling using the 10X Genomics Chromium platform as well as bulk RNA sequencing.

Results: Finerenone and spironolactone resulted the same degree of blood pressure reduction. DOCA treated rats developed severe myocardial hypertrophy and focal vasculopathy, glomerulosclerosis and tubulointerstitial fibrosis. Finerenone significantly attenuated cardiac and renal histological damage. DOCA-salt rats developed marked albuminuria which was significantly attenuated by spironolactone and finerenone. Serum potassium was elevated in the spironolactone group at weeks 6, but it was unchanged compared to controls in the finerenone group. Bulk RNA-seq results revealed the reduced enrichment of immune response related transcripts in finerenone group compared with DOCA and spironolactone group. Single-nuclei open chromatin and gene expression profiling uncovered genomic alterations in different cell types in finerenone-treated kidneys.

Conclusions: Taken together, these findings demonstrated that treatment with finerenone protected from DOCA salt induced cardiac hypertrophy, glomerulosclerosis and kidney fibrosis without a significant increase in serum potassium. Single cell epigenome analysis highlighted transcriptional targets of aldosterone, spironolactone and finerenone.

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PO0624

Cell Type-Specific Chromatin Architecture Reveals Target Genes for Kidney Disease Risk Variants

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Background: Although GWAS studies have identified hundreds of genetic variants associated with kidney diseases, the identification of causal variants and their target genes are rather limited. Most of disease-associated variants locate in non-coding elements. The roles of these elements are cell type-specific. Additionally, due to the non-linear regulation of the elements, the identification of causal variants as well as their target genes is even more challenging.

Methods: In order to understand the genetic risk of kidney diseases, we generated a cell type-specific set of epigenetic landscape including transcription-centered 3D chromatin organization, histone modifications distribution and transcriptome with HiChIP, ChIP-seq and RNA-seq respectively, in kidney tubule cells. We integrated the epigenetic annotation to identify causal variants and target genes which were further tested by CRISP techniques in zebrafish.

Results: We identified genome-wide functional elements and thousands of interactions between the distal elements and target genes. The results revealed that risk variants for renal tumor and chronic kidney disease were enriched in kidney tubule cells. We further pinpointed the target genes for the variants and validated two target genes by CRISP techniques in zebrafish, demonstrating that SLC24A1 and MTX1 were indispensable genes to maintain kidney function.

Conclusions: Our results produce valuable multi-omic resource and establish a bioinformatic pipeline in dissecting functions of kidney diseases-associated variants based on cell type-specific epigenetic landscape.

PO0625

A Comprehensive Transcriptome Profiling of Adipocyte Na-K-ATPase Signaling in Uremic Cardiomyopathy by RNA Sequencing Analysis

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Background: Oxidant stress plays a key role in the development and progression of uremic cardiomyopathy. We have recently demonstrated that adipocyte dysfunction and uremic cardiomyopathy developed in partial nephrectomy mice model, were significantly ameliorated by adipocyte-specific expression of NaKtide, an antagonist of Na/K-ATPase signaling. Hence, to better characterize the cellular transcriptome that are involved in various biological pathways associated with adipocyte function, we aim to explore the genomic approach in the present study, through RNAseq analysis.

Methods: For invitro studies, mouse adipocytes were subjected to oxidized LDL (oxLDL) or indoxyl sulfate (IS) with or without pNaKtide treatments. Partial nephrectomy was performed in C57Bl6 mice in order to produce experimental uremic cardiomyopathy. Specific expression of NaKtide in adipocytes was achieved using a lentivirus construct driven by an adiponectin promoter. A complete RNAseq analysis was performed using DESeq2 R package in combination with packages to perform over-representation analysis (ORA) and gene set enrichment analysis (GSEA).

Results: Several gene subsets corresponding to various biological processes and molecular phenotype were differentially expressed in adipocytes with in vitro oxLDL/IS treatments and in vivo PNx model. These genes, compared using GSEA analysis, showed that more than 75% of the Kegg pathways were similar among the in vitro treatments and in vivo model. The pathways that were common between in vitro and in vivo treatments, including adipogenesis, ROS signaling, inflammatory response and oxidative phosphorylation pathways, have profound impact on the pathogenesis of uremic cardiomyopathy. The overall analysis showed a widespread normalization of gene expression by pNaKtide/adipose specific NaKtide treatments that were altered in uremic cardiomyopathy.

Conclusions: The study provides a detailed genome-wide molecular information about adipocyte function in relation to uremic cardiomyopathy pathogenesis. These data provide deeper insight into the activation of pathways associated with adipocyte Na/K-ATPase signaling, which may be a viable clinical target for the prevention and treatment of uremic cardiomyopathy.

Funding: Private Foundation Support

PO0626

Transcriptomic Profiling Identifies Potential Mediators of Tubular Injury Sensitization of Glomeruli to Subsequent Second Hits

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Background: Previous studies have shown that even isolated mild tubular injury leads to more severe glomerular damage in response to subsequent injury. The responsible mediators for this sensitization are unknown.

Methods: Double transgenic male mice, Nep25/DTR^{+} (expressing human CD25 receptor on podocytes and Diphtheria toxin receptor on proximal tubular cells) and Nep25/DTR^{-} (n=5 per group) were used. Tubular injury was induced by injecting diphtheria toxin, followed by uninephrectomy (Nx) 4 weeks later and induction of glomerular injury

by LMB2 toxin (CD25 ligand) one week after Nx. Mice were sacrificed 4 weeks after LMB2. Glomeruli and tubules from Nx were separated by sieving technique, RNA was isolated from tubules and next generation RNA sequencing was performed.

Results: Histopathological analysis and urinary Kim-1 at Nx and sacrifice confirmed mild tubulointerstitial fibrosis at Nx in Nep25/DTR+ but not Nep25/DTR- mice, and more severe glomerulosclerosis and albuminuria at sacrifice after LMB2 in Nep25/DTR$^+$ vs Nep25/DTR$^-$ mice. RNA sequencing revealed 283 differentially expressed genes between the groups, with 93 over-represented and 190 under-represented in Nep25/DTR$^+$ vs Nep25/DTR$^-$. GO of biological processes showed involvement in 13 processes, with the highest amount of genes involved in cellular processes, biological regulation and metabolic processes. STRING analysis of protein-protein interactions (PPI) based on cellular processes detected interactions between the Serpin family members: plasminogen activator inhibitor PAI-1 (*Serpine1)*, alpha-1-antitrypsin 1-2 (*Serpina1b)*, protein Z-dependent protease inhibitor (*Serpina10*) and complement C4b (*C4b*). In addition, members of the non-canonical Wnt signalling pathway Wnt-9a (*Wnt9a)* and Wnt-10a *(Wnt10a)* and their interactors latent transforming growth factor beta binding protein 2 (*Ltbp2*) and VANGL planar cell polarity protein 2 (*Vangl2*) were over-represented and PPI of these genes was found. Quantitative real-time PCR confirmed numerically higher expression of all above-mentioned genes in Nep25/DTR$^+$.

Conclusions: High-throughput RNA sequencing of isolated tubules with mild injury revealed potential novel mediators of glomerular sensitization to a subsequent injury. Further experimental validation of the effects of the identified molecules on glomerular injury are warranted.

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PO0627

A Novel Short ACE2 Variant Causes ACE Suppression and Fosters Ang 1-7 Formation in a Murine Model of CKD

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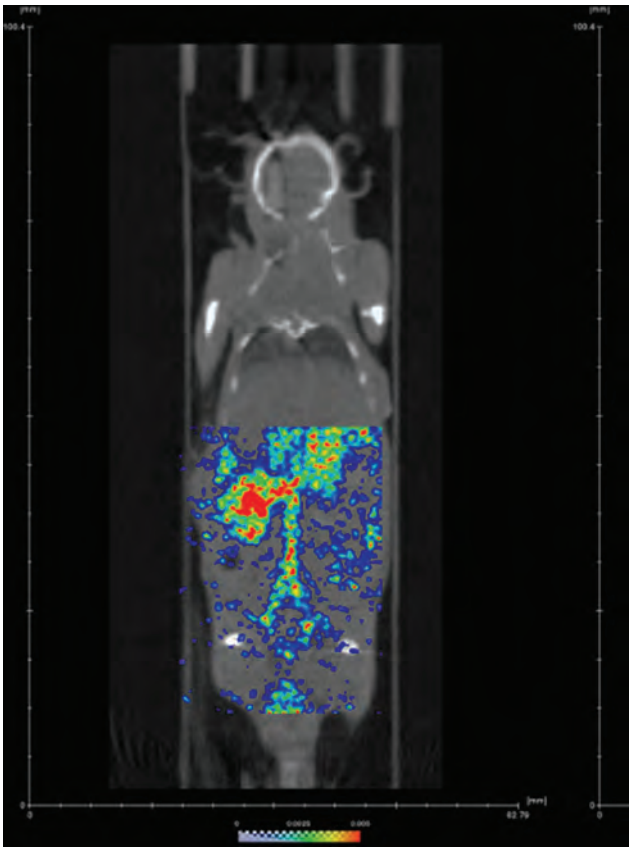
Background: ACE2 is a monocarboxypeptidase that cleaves Ang II to form Ang-(1-7). It is a large molecule the administration of which leads to increased enzyme activity in plasma, but not in the urine or kidney tissue. We have developed a truncated form of ACE2 that has a longer half-life by fusing it with an Albumin-binding domain (ABD) and is still short enough to be filtered by the kidney. In this study we examined the impact of this novel variant of ACE2 on kidney RAS in a model of CKD.

Methods: We used a 5/6 Nephrectomy model in CD-1 mice. The ACE2-ABD was given 3 days post-ablation surgery and thereafter every 3-4 days (3 ug/g BW) for 5 weeks. Afterwards, mice were euthanized and kidneys collected for analyses of RAS components.

Results: Administration of ACE2-ABD resulted in increased plasma ACE2 activity (768 vs. 12 RFU/ul/hr, p<0.0001). In kidney lysates there was also an increase in ACE2 activity (32 vs. 22 RFU/ug protein/hr, p=0.03) and a decrease in ACE activity (7187 vs. 4006 RFU/ug protein/hr, p=0.0001). These changes in enzymatic activities were accompanied by a significant increase in kidney Ang-(1-7) (90 vs. 37 fmol/mg protein, p=0.0014) without a significant change in Ang II levels (272 vs. 299 fmol/mg protein). To verify the kidney uptake of our ACE2 variant SPECT/Micro-CT imaging was performed. After the injection of radiolabeled ACE2-ABD kidney uptake was clearly seen (red) (Figure).

Conclusions: A long-acting form of a short ACE2 variant fused with ABD given every 3-4 days resulted in sustained plasma ACE2 activity and an increase in kidney ACE2 activity associated with suppressed kidney ACE activity. These enzymatic changes provide a favorable kidney RAS profile with increased Ang-(1-7), which overall should be renoprotective.

Funding: NIDDK Support



PO0628

Disruption of the H3K4 Methyltransferase MLL-1/Menin Complex Attenuates Renal Fibrosis Development by Inhibiting Epithelial-Mesenchymal Transition and Fibroblast Activation

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Background: The MLL-1/menin was disrupted by MI-503 and/or siRNA in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO), cultured mouse proximal tubular cells and fibroblasts exposed to serum and transforming growth factor β1 (TGFβ1). Protein expression or activation was determined by immunofluorescent microscopy and immunoblot analysis.

Methods: The MLL-1/menin was disrupted by MI-503 and/or siRNA in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO), cultured mouse proximal tubular cells and fibroblasts exposed to serum and transforming growth factor β1 (TGFβ1). Protein expression or activation was determined by immunofluorescent microscopy and immunoblot analysis.

Results: Injury to the kidney increased MLL1 and menin expression and H3K4 monomethylation (H3K4me1) in renal tubular epithelial cells and fibroblasts. Administration of MI-503, a highly selective inhibitor of the MLL1/menin complex, attenuated renal fibrosis and expression of α-smooth muscle actin, fibronectin and collagen I. Treatment with MI-503, MLL1 siRNA or menin siRNA also inhibited TGFβ1 and serum-induced activation of epithelial-mesenchymal transition (EMT) in vitro. Moreover, UUO injury induced epithelial expression of phospho-histone 3 at Serine 10 and expression of profibrotic factors, TGFβ1 and connective tissue growth factor; and blocking the MLL1/menin complex with MI-503 inhibited these responses. Finally, MLL1 inhibition reduced expression of snail and twist, two transcription factors involved in the development of EMT and renal fibrosis and the expression of *proliferating cell nuclear antigen,* cyclin D1 and p27 in fibroblasts.

Conclusions: Our data suggest that targeting disruption of the MLL1/menin complex can attenuate renal fibrosis through inhibition of EMT and fibroblast activation/proliferation.

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PO0629

Transcriptomic Profiling of Thick Ascending Limb Cells In Vivo Reveals the Complex Network of Genes Regulated by Uromodulin

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Background: Tamm-Horsfall Protein (THP or Uromodulin, gene: *Umod*) is a protein uniquely made in the kidney by cells of the thick ascending limbs (TAL) of the loop of Henle. We previously established that THP has protective biological functions. Furthermore, THP production is decreased with chronic kidney disease (CKD). It was suggested that the promoter region of the *Umod* can regulate other genes. THP deficiency itself could alter the expression of other genes. Here, we used an unbiased approach to study the effect of a deletion in the *Umod* promoter/gene and the resultant THP deficiency on the transcriptomic profile of TAL cells in vivo.

Methods: THP$^{-/-}$ mice resultant from deletion of exons 1-4 and part of the *Umod* promoter were used, along with THP$^{+/+}$ controls. Immuno-fluorescence guided laser microdissection was performed to isolate TAL cells from the medulla of kidneys of THP$^{-/-}$ and THP$^{+/+}$ mice. After RNA extraction, next generation RNA sequencing and transcriptomic analysis was performed.

Results: The transcriptomic profile of medullary TAL cells was comprehensively defined *in vivo*. 85% of the top 250 expressed genes were common between THP$^{+/+}$ and THP$^{-/-}$ TAL cells. Overall, 33 protein-coding genes, including *Umod*, were differentially expressed (FDR<0.05). These encompassed genes with a variety of functions such as immunomodulation (*Erdr1*, *Gp2*), cytoskeletal/extracellular matrix fibers (*Lama1*, *Cttnbp2*) and signal transduction (*Camk2b*, *Ptprn2*). One down-regulated gene was a direct neighbor to the Umod locus (*Gp2*) on chromosome 7. However, many other affected genes were on different chromosomes. Bioinformatic analysis revealed that THP deficiency is associated with significant clustering of genes involved in connective tissue formation and activation or dysfunction of molecular mechanisms that could lead to fibrosis.

Conclusions: We delineated a comprehensive transcriptomic profile of TAL cells *in vivo* from mouse kidneys. Although highly expressed genes in TAL may not be altered by THP deficiency, many close and distant genes are regulated by the *Umod* locus or altered by the absence of THP. The absence of THP may also prime the TALs cells towards a fibrosis program. These findings may contribute to understanding the pathogenesis of CKD progression.

Funding: NIDDK Support, Veterans Affairs Support

PO0630

Lipid Metabolic Profiling of Ex Vivo Isolated Glomeruli as a Screening Platform for Modelling Glomerular Metabolic Dysfunction During Renal Disease

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Background: Dysregulated renal metabolism is a hallmark of loss of function in CKD. It is established that changes in tubular metabolism impact tubular functionality during progression of CKD. However, lipid metabolism in the glomerulus during CKD remain poorly described. Here, we use Isolated Glomeruli (IRG) to study lipid metabolism for metabolic drug discovery in kidney diseases.

Methods: Sprague Dawley rat glomeruli were isolated by differential sieving. We used disease inducers: Adriamycin 1uM (ADR) and AngiotensinII 100nM (AngII) for 24h. To probe metabolic activity, we used an LC-MS approach to quantify uptake and excretion rates of relevant metabolites in culture media, and to measure intracellular metabolites and lipids.

Results: We developed a new cultivation protocol for IRG, using organoids media and shaking platform to maximizing the biological activity. Metabolic and lipidomic profiles of IRG were monitored up to 150h. We saw significant metabolic activity for a wide range of metabolites: Uptake and excretion rates rapidly changed during the first 24h of culture, after which they declined. Metabolic rates for glutamine, glutamate and alanine were comparatively stable. Following treatment with AngII or ADR glomeruli exhibited metabolic changes after 24h: AngII reduced asparagine uptake, and induced trends towards lower substrate uptake consistent with reduced metabolic activity. Both ADR and AngII perturbated intracellular metabolite levels: nucleosides adenosine (-159%) and inosine (-171%), increases in 1,3-BPG (+194%), and changes in NAD (+209%), which suggest alterations in pentose phosphate pathway. Multivariate analysis revealed differentially responding lipid clusters: specifically, significant abundance and saturation ratio increases of intracellular FFA, including stearate (+34%), oleate (+102%) and arachidonate (+107%), as well as the depletion of several phosphatidylcholine and phosphoethanolamine species following AngII, which have been implicated as renal injury markers and/or relevant to renal injury protection.

Conclusions: Our results show alterations in lipid metabolism after IRG stimulation with AngII and ADR after 24h. We propose IRG/lipid metabolome as a novel platform/tool for understanding lipid signalling and improving CKD drug discovery.

Funding: Commercial Support - AstraZeneca

PO0631

Study on the Mechanism of Microinflammation with Uremia Caused by Lactobacillus Activation of Intestinal Macrophages by Mincle

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Background: My previous studies have found that Intestinal macrophages in the uremic rats are polarized towards a proinflammatory phenotype and assist bacterial translocation resulting in microinflammation. However, it is still unclear what kind of mechanism activates intestinal macrophages in uremia.

Methods: Male Sprague-Dawley rats were randomly divided into two groups: sham, uremia. Immunochemistry was used to analyze the expression of macrophage-inducible C-type lectin (Mincle). RT-PCR and western blot were employed to assess the mRNA and protein expression of toll-like receptor 4 (TLR4).

Results: Our RCT study found that the number of Lactobacilli in the intestines of patients with end-stage diabetic nephropathy was significantly higher than that in non-diabetic patients. The plasma levels of endotoxin, CRP, IL-6, and TNF-a in the uremia group were greater than those in the sham group (p>0.05)(Table 1). Compared with the sham group, the uremia group exhibited macrophages with higher staining intensities for Mincle and higher mRNA and protein expression of TLR4(Figure1-2).

Conclusions: The solution to this scientific problem will not only clarify the molecular mechanism of intestinal bacteria in controlling the activation of intestinal macrophages, but also to clarify the micro-inflammation state of uremia.

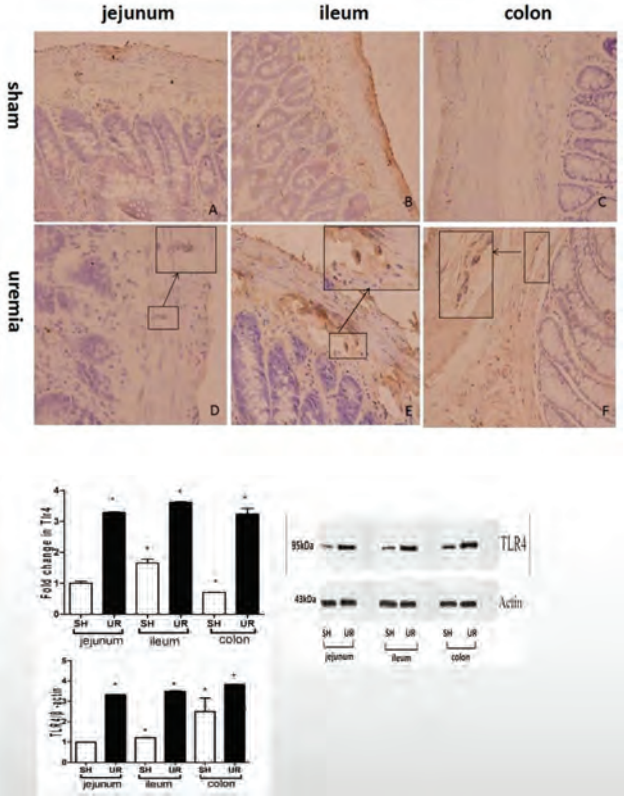
Funding: Government Support - Non-U.S.

Table 1. Body weight, hematocrit, and blood chemistry results

Group (n = 10)	Body weight (g)	Creatinine (μmol/L)	Urea (mmol/L)	Endotoxin (Eu/mL)	CRP(mg/mL)	IL-6(pg/mL)	TNF-α (pg/mL)
Sham	560.4 ±16.6	31.5 ±6.7	6.05 ±0.85	0.016±0.005	2.48 ±0.28	18.26 ±3.72	20.9 ±0.28
Uremia	516.6 ±14.5	95.7 ±35.6*	18.10 ±8.50*	0.033 ±0.009*	5.2 ±0.77*	31.07 ±10.06*	30.4 ± 7.73*

Data are presented as the mean ±SD.

*p < 0.05 vs. the sham group



PO0632

Angiotensin II Type 1a Receptor Loss Ameliorates Chronic Tubulointerstitial Damage After Renal Ischemia Reperfusion

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Background: Although angiotensin II (Ang II) type 1 receptor blocker was reported to attenuate chronic tubulointerstitial damage (TID) after renal ischemia reperfusion (IR), its effect is limited. The aim of this study is to reveal whether suppressed activation of angiotensin II type 1a receptor (AT1a) ameliorates severe chronic tubulointerstitial damage (TID) after renal ischemia reperfusion (IR).

Methods: To induce severe chronic TID after renal IR, unilateral renal ischemia for 45 min was performed via clamping of right renal pedicle using cerebral aneurysm clip in AT1a knockout homo ($AT1a^{-/-}$) male mice and wild type ($AT1a^{+/+}$) male mice. Right and left kidneys were removed at 3, 28 and 70 days postischemia. Left kidneys were used as control. Furthermore, another $AT1a^{+/+}$ mice were administered hydralazine to maintain the same levels of systolic blood pressure (SBP) as the $AT1a^{-/-}$ mice because the SBP levels of the $AT1a^{-/-}$ mice were significantly lower compared to the $AT1a^{+/+}$ mice.

Results: Acute tubular necrosis in IR-kidneys of both $AT1a^{-/-}$ mice and $AT1a^{+/+}$ mice was observed at 3 days postischemia, and the degree was significantly more severe in the IR-kidneys of $AT1a^{-/-}$ mice than in the IR-kidneys of $AT1a^{+/+}$ mice. Conversely, the degrees of both interstitial fibrosis at 28 and 70 days postischemia and proximal tubular loss at 70 days postischemia were significantly attenuated in the IR-kidneys of $AT1a^{-/-}$ mice compared to the $AT1a^{+/+}$ mice. While marked renal atrophy at 70 days postischemia was induced in the $AT1a^{+/+}$ mice, such a development was not provoked in the$AT1a^{-/-}$ mice. Although the administration of hydralazine in the $AT1a^{+/+}$ mice mildly attenuated the degree of TID at 70 days postischemia, the degree of the $AT1a^{+/+}$ mice was significantly greater compared to the $AT1a^{-/-}$ mice. Because renal expression levels of angiotensin-(1-7) protein at 28 days postischemia was significantly higher in the $AT1a^{-/-}$ mice compared to the$AT1a^{+/+}$ mice, renala ngiotensin-(1-7) may contribute to amelioration of chronic TID after IR in the $AT1a^{-/-}$ mice.

Conclusions: Early administration of Ang II type 1 receptor blocker in recovery phase after AKI may be useful for prevention of AKI-to-CKD transition.

Funding: Private Foundation Support

PO0633

Anti-Interleukin 22 Antibody Relieves Angiotensin II-Induced Renal Injury in Mice Through Inhibiting NLRP3 Inflammasome Activation

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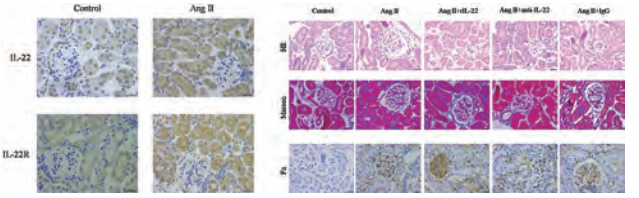
Background: Interleukin-22 (IL-22) is considered as a proinflammatory cytokine and participates in the pathogenesis of inflammatory and autoimmune diseases. Previously, we found that serum IL-22 increased significantly in hypertensive renal damage patients, and IL-22 were positively correlated with renal damage. The aim of this study was to investigate whether anti-IL-22 antibody exerts renoprotective effect via inhibiting NLRP3 inflammasome activation in angiotensin II (Ang II) induced hypertensive renal damage in mice.

Methods: Ang II was infused subcutaneously at a rate of 1.5 mg/kg/d to C57BL/6 mice for 28 days to establish the hypertensive model. One day after modeling, mice were injected intraperitoneally every other day with saline, recombinant mouse IL-22 (rIL-22; 20 ug/kg), mouse anti-IL-22 monoclonal antibody (anti-IL-22 mAb; 1.25 ug/mouse) or isotype IgG. So mice were divided into 5 groups: control, Ang II, Ang II+rIL-22, Ang II+anti-IL-22, Ang II+IgG. 28 d after Ang II infusion, all mice were euthanized. Blood pressure, urinary albumin/creatinine ratio, serum creatinine (Scr) and renal histopathology were measured. NLRP3, cleaved caspase-1 and IL-1β in kidney were detected by western blot. Renal inflammatory factors were detected by ELISA, IL-22 and IL-22R1 in kidney were detected by immunohistochemistry, fibrotic related factors expression in kidney were evaluated by western blot.

Results: IL-22 and IL-22R1 Levels were elevated in kidney of Ang II-induced mice. Anti-IL-22 mAb therapy ameliorated proteinuria excretion, Scr and renal pathological damage in mice with established hypertensive renal injury. Blood pressure in Ang II-infused mice was also decreased after the treatment of anti-IL-22 mAb. In addition, anti-IL-22 mAb reduced NLRP3, cleaved caspase-1, IL-1β, TNF-α and IL-6 expression in kidney, along with inhibition of renal fibrotic related factors expression.

Conclusions: Anti-IL-22 antibody can reduce renal inflammation and fibrosis in Ang II-induced hypertensive mice, which may be through suppression of NLRP3/caspase-1/IL-1β pathway, suggesting it might exert therapeutic potential for the treatment of hypertensive renal injury.

Funding: Government Support - Non-U.S.



IL-22, IL-22R expression and renal pathology

PO0634

PD-1 Regulates Group 3 Innate Lymphoid Cells in Renal Fibrosis

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Background: Group 3 Innate Lymphoid Cells (ILC3) belong to a new family of innate effectors, participating in lots of inflammatory and fibrotic diseases. However, limited information exists on the molecular mechanisms regulating these cells. Here, we investigated the expression and function of the immune checkpoint programmed cell death-1(PD-1) in ILC3 during renal fibrosis.

Methods: Unilateral ureteral obstruction (UUO)-induced renal injury tested subsets of ILC3 activities in immune responses and tissue fibrosis. Kidney and intestine were collected to define the frequency, localization and characterization of $PD\text{-}1^{+}$ILC3. Loss/gain-of-ILC3s in UUO mice were designed to investigate their roles in renal fibrosis progression. And the fibrogenic effects of ILC3s and the regulatory activity of PD-1 were determined by *in vitro* co-culture experiments.

Results: ILC3 were accumulated rapidly in fibrotic kidneys, with surrounding by increasing number of active myofibroblasts, and more interestingly, coincided with a robust depletion from the intestines of mouse models, suggesting a functional recruitment of ILC3 after kidney injury. Moreover, fibrosis was associated with an increase of PD-1 expression in ILCs, and up-expression of PD-1 ligand, PD-L1 was also detected in fibrotic kidney, suggesting a possible involvement of PD-1/PD-L1 pathway. Adoptive transfer of purified intestinal ILC3 into UUO mice significantly enhanced renal fibrosis than those with PBS, whereas PD-1-deficent ILC3 protects kidney from fibrosis. Notably, mice that lacked ILC3s exhibited reduced inflammatory infiltration and decreased fibroblast activation. *In vitro* studies, direct co-culture of WT-ILC3 with primary renal fibroblasts exacerbates inflammatory response and extracellular matrix production (ECM), which could be blocked by the treatment with neutralizing anti-IL-17A and anti-IL-22 antibodies. Yet co-cultured with PD-1-deficent ILC3 displayed reduced fibrotic activity.

Conclusions: Our findings provided the first evidence that during renal fibrosis, PD-1/PD-L1 axis might play a regulatory role in ILC3 migration and fibrogenesis via producing pro-fibrotic cytokines IL-17A and IL-22.

PO0635

Interaction Between the Na-K-ATPase and CD40 Signaling in Proximal Tubule Epithelial Cells (PTECs) Contributes to Renal Inflammation and Fibrosis

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Background: We have demonstrated that signaling through the Na/K-ATPase-α1 subunit/c-Src kinase (NKA-α1/c-Src) complex and activation of the pro-inflammatory receptor, CD40 induce renal inflammation and fibrosis in both clinical and experimental models of ischemic and chronic kidney disease (CKD). Circulating cardiotonic steroids (specific ligands of Na/K-ATPase) are significantly elevated in CKD that not only stimulate NKA-α1/c-Src signaling, but also regulate CD40 signaling by upregulation of CD40 expression in PTECs. Furthermore, soluble CD40 ligand (sCD40L)-stimulated CD40 signaling in PTECs is dependent on NKA-α1/c-Src signaling. However, the interplay between Na/K-ATPase and CD40 signaling-induced renal inflammation and fibrosis has not been thoroughly investigated.

Methods: RNA sequencing was performed on pig PTECs with and without a functional NKA-α1/c-Src signaling complex (Ly-α2 cells and Lx-α2 cells, respectively) following treatment with sCD40L (100ng/mL) for 24hrs. In pig PTECs LLC-PK1 cells treated with the cardiotonic steroid telocinobufagin (TCB), immunoprecipitation was performed to detect protein-protein interaction.

Results: Treatment with sCD40L in Ly-α2 cells demonstrated a significant increase in gene expression of pro-inflammatory and pro-fibrotic mediators [CXCL9, CXCL10, IL1R1, complement C3, and COL1A2 (all > 5-fold increase)] compared to Lx-α2 cells. In LLC-PK1 cells, short-term TCB treatments (up to 1 hr) stimulates interaction between NKA-α1 and CD40 that presents under resting conditions. Long-term TCB treatment (24 hr) still shows the NKA-α1 and CD40 interaction, but reduced NKA-α1 and CD40 interaction was also observed in comparison to control, suggesting a possible endocytosis of NKA-α1 (by the cardiotonic steroid) and CD40.

Conclusions: In renal proximal tubular cells, CD40-induced pro-inflammatory and pro-fibrotic signaling is dependent on the NKA-α1/c-Src complex, and there is an

interaction between NKA-α1 and CD40 that was enhanced by activation of the NKA-α1/c-Src signaling. A regulation through expression level and/or endocytosis of NKA-α1 and CD40 might be involved to control signaling strength.

Funding: NIDDK Support

PO0636

Soluble Uric Acid, a Negative Regulator of Monocyte Activation in Innate Immunity

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Background: While monosodium urate (MSU) crystals are known to trigger acute inflammation in gouty arthritis, published data on soluble uric acid (sUA) in this context are discrepant. We hypothesized that diverse sUA preparation methods account for this discrepancy and that a novel animal model with clinically relevant levels of asymptomatic hyperuricemia (HU) and gouty arthritis can ultimately clarify this issue.

Methods: Soluble UA was prepared either by pre-warming or solubilized with NaOH. THP-1 cells or CD14+ monocytes from patients with HU and healthy individuals were pre-incubated with sUA prior to stimulation with MSU crystals or LPS. Intracellular sUA uptake via urate transporters was quantified using siRNA technology. *In vivo*, Alb-creERT2;*Glut9*$^{lox/lox}$ and *Glut9*$^{lox/lox}$ control mice were injected with tamoxifen and placed on a chow diet with inosine to induce HU. After 3 weeks, MSU crystals or vehicle were injected into air pouches, and leukocyte infiltration and the extent of inflammation were assessed by flow cytometry, RT-PCR, ELISA.

Results: We found that pre-warmed UA created erroneous results because of microcrystal contaminants triggering IL-1β release. Solubilizing UA with NaOH avoided such artifact. This microcrystal-free preparation suppressed LPS- or MSU crystal-induced monocyte activation, a process dependent on the intracellular uptake of sUA via the urate transporter SLC2A9/GLUT9. CD14+ monocytes isolated from HU patients were less responsive to inflammatory stimuli compared to monocytes from healthy individuals. Treatment with plasma from HU patients impaired the inflammatory function of CD14+ monocytes, an effect fully reversible by removing sUA from HU plasma with rasburicase. Moreover, Alb-creERT2;*Glut9*$^{lox/lox}$ mice with HU (serum UA of 9-11mg/dL) showed a suppressed inflammatory response to MSU crystals compared to *Glut9*$^{lox/lox}$ controls without HU.

Conclusions: We unravel a technical explanation for discrepancies in the published literature on immune effects of sUA and identify HU as an intrinsic suppressor of innate immunity, where sUA modulates the capacity of monocytes to respond to danger signals. Thus, sUA is not only a substrate for the formation of MSU crystals but also an inhibitor of sterile inflammation and may explain several clinical observations in the context of gout and CKD.

Funding: Government Support - Non-U.S.

PO0637

PP2Acα Promotes Macrophage Accumulation and Activation to Accelerate Tubular Cell Death and Kidney Fibrosis Through Regulating Rap1 and TNFα Production

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Background: Macrophage accumulation and activation play an essential role for kidney fibrosis, the underlying mechanisms remain to be explored.

Methods: Analyzing the kidneys of patients and animal models with kidney fibrosis. Generating the mice with macrophage PP2Acα ablation.

Results: We observed a significantly increased induction of PP2Acα in macrophages. We then generated mice with macrophage-specific deletion of PP2Acα. These mice developed less renal fibrosis as indicated by less macrophage accumulation, tubular atrophy or extracellular matrix deposition. In cultured cells, the deficiency of PP2Acα in macrophages resulted in decreased cell motility by inhibiting the activity of Rap1. Furthermore, TNFa production was downregulated in macrophages with PP2Acα-deficiency and co-culture of PP2Acα-deficient macrophages and renal tubular cells resulted in less tubular cell death, which was due to decreased TNFα production via phosphorylation of STAT6 in macrophages.

Conclusions: This study shows that PP2A promotes macrophage accumulation and activation, hence accelerating tubular cell death and kidney fibrosis through regulating Rap1 and TNFa production.

PO0638

Investigating LOX and Its Role in AT1R/β-Arrestin Biased Signaling Pathway-Induced Renal Interstitial Fibrosis

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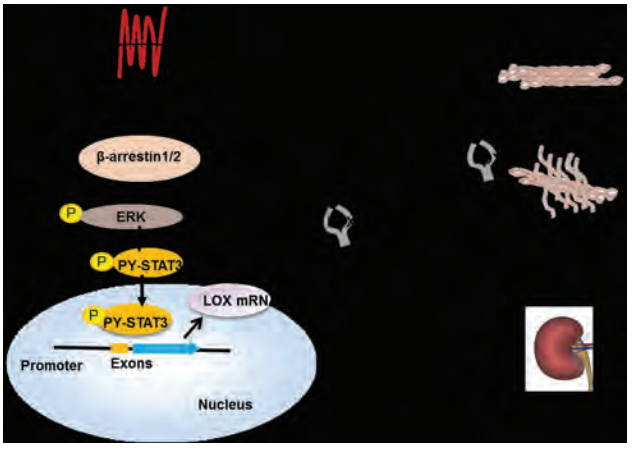
Background: We studied the downstream and mechanism of β-arrestins signaling in renal fibrosis process and the role of lysyl oxidase (LOX) in the AT1R-β-arrestin pathway

Methods: The mechanism of β-arrestins signaling was studied in normal rat kidney tubule epithelial cells (NRK-52E) treated with SII in vitro. BAPN or placebo was administered during ischemia reperfusion (IR)-induced fibrosis progression. Collagen crosslinking and fibrosis progression were assessed histologically and biochemically.

Results: The mRNA and protein levels of β-arrestin-1 and β-arrestin-2 were significantly upregulated in renal fibrosis model both in vitro and in vivo. SII activated the ERK-STAT3 PY705 but not STAT3-Try727 in nucleus of NRK-52E cells, which effects were abolished when transfection of siRNA targeting β-arrestin-1 and β-arrestin-2 or pretreated with PD98059 (MEK inhibitor). LOX was strongly induced in fibrotic kidney and NRK-52E cells treated with SII. Active LOX significantly increased collagen crosslinking. In established IR-28d renal fibrosis, LOX inhibition promoted fibrosis reversal and with a 25% decrease insoluble collagen. Gene silencing of β-arrestin-1+2 or STAT3 apparently inhibited SII-induced LOX expression in vitro. Besides, chromatin immunoprecipitation (ChIP) assay clearly demonstrating the interaction between STAT3 and the LOX promoter, which indicated LOX is a direct target gene of SII-β-arrestins-STAT3 signaling.

Conclusions: The ERK/STAT3 was downstream of AT1R-β-arrestins, ERK entered the nucleus and activated STAT3-PY705. LOX mediates collagen crosslinking and fibrotic matrix stabilization during renal fibrosis via the AT1R-β-arrestins-ERK-STAT3-PY705 signaling. By blocking this profibrotic pathway, therapeutic LOX inhibition attenuates the fibrosis and suggesting target the LOX has significant potency for the treatment of patients with fibrotic kidney disorders.

Funding: Government Support - Non-U.S.



PO0639

Downregulated Endothelial JMJD3 Accelerates Neointimal Hyperplasia of Arteriovenous Fistula in CKD

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Background: Epigenetic changes are involved in vascular remodeling. The histone demethylase, Jmjd3, is a transcriptional co-activator that promotes endothelial regeneration. Despite the importance of Jmjd3 in maintaining endothelial function, its role in neointima formation in AVF remains unknown.

Methods: Mice with JMJD3 specific knockout (KO) in ECs was generated. CKD and AVF models were created in Wild type and Jmjd3 EC-specific KO mice. Evans blue, immunostaining assays were used to characterize JMJD3 expression and vascular pathology. Mouse primary ECs and VSMCs were isolated to study the signaling pathways that regulate Jmjd3 expression and endothelial mesenchymal transition (EndMT). The changes found in mouse AVFs were assessed in AVFs from ESRD patients.

Results: JMJD3 expression was downregulated in endothelium of CKD mice. Specific KO of JMJD3 in EC stimulated endothelial barrier dysfunction, EndMT, and inflammatory cells infiltration in AVFs. There were more VSMC proliferation and collagen deposition in AVFs created in Jjmd3 KO mice vs. that of in WT mice. Specific KO of JMJD3 in EC accelerated neointimal hyperplasia of AVF in CKD mice. *In vitro*, inhibition of JMJD3 activity reduced EC proliferation and migration. Suppression of Jmjd3 enhanced the level of histone H3K27me3 promoting its binding to the promoter of EC markers (VE-cadherin and eNOS). These responses resulted in EnMT and VSMC proliferation. Moreover, the expression of JMJD3 is reduced through TGFβ1/Hes1 signaling pathway. In AVFs from ESRD patients, the decreased expression of JMJD3 in ECs was associated with endothelial dysfunction, EndMT, and ECM deposition plus neointimal hyperplasia. Remarkably, endothelial expression of Hes1 in AVFs from ESRD patients was correlated with the decreased JMJD3 level.

Conclusions: These findings demonstrate that TGFβ1-Hes1-JMJD3 signaling exist in ECs which epigenetically regulates EC differentiation and barrier function leading to neointimal hyperplasia of AVF in CKD.

Funding: NIDDK Support

PO0640

Renal Macrophage Infiltration Precedes Macrophage to Myofibroblast Transition and T-Cell Recruitment Following Repeated Low-Dose Cisplatin Treatment

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Background: Cisplatin is a commonly used chemotherapeutic agent with dose-limiting nephrotoxicity. 30% of patients who receive cisplatin develop acute kidney injury (AKI), which significantly increases the risk of developing renal fibrosis and chronic kidney disease (CKD). There are currently no therapies approved to prevent or treat cisplatin-induced kidney injury (CDDP-KI) and fibrosis. Other models of renal fibrosis have demonstrated that macrophages can play a pro-fibrogenic role by differentiating into myofibroblasts, the main effector of fibrotic development. Macrophage to myofibroblast transition (MMT) is proposed to occur when bone marrow derived M2 macrophages undergo chronic TGFβ stimulation. We hypothesize that cisplatin promotes fibrosis and CKD development through stimulating chronic macrophage activity and MMT in the kidney.

Methods: We used a clinically relevant, repeated low dose model of CDDP-KI to characterize the immune response and MMT in the kidney following cisplatin treatment.

Results: Flow cytometric analysis revealed significantly increased numbers of renal infiltration of Ly6C hi inflammatory monocytes and F4/80 lo infiltrating macrophages after four doses of cisplatin. These populations remained elevated above vehicle treated controls after a 6-month age out. At the four dose timepoint, we observed an increase in CD206+ F4/80+ cells and *Arg-1* mRNA, indicating M2 polarization. We also identified a population of F4/80+ CD206+ αSMA+ cells present in the kidney, suggesting MMT is occurring. Interestingly, at the 6-month timepoint renal CD4+ and CD8+ T cell populations remained significantly elevated in cisplatin-treated mice compared to vehicle treated controls.

Conclusions: These studies provide insight on how the immune response to CDDP-KI can promote CKD via infiltration of bone marrow derived macrophages and subsequent M2 polarization and MMT. These early events orchestrate an immune response that continues up to 6-months after cisplatin treatment. Therefore, targeting macrophages could be a potential strategy for preventing the AKI to CKD transition triggered by cisplatin.

Funding: NIDDK Support

PO0641

Microvascular Loss and Remodeling in Human Kidneys Distal to Severe Atherosclerotic Renovascular Disease

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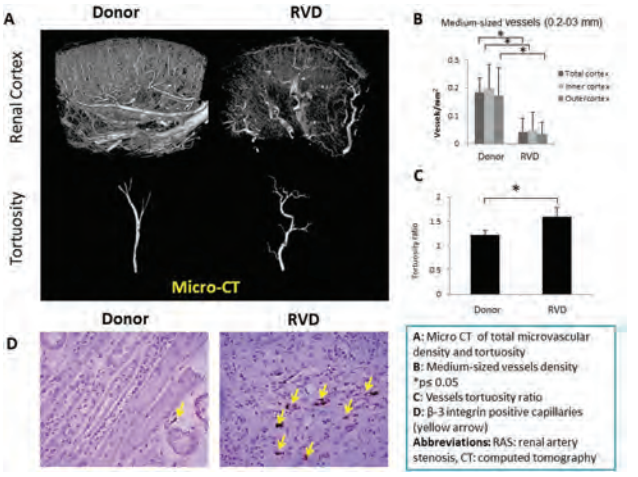
Background: Renovascular disease (RVD) may induce hypertension and kidney injury, but its effect on the microcirculation of the post-stenotic human kidney remains unclear.

Methods: Kidneys were collected from patients with RVD undergoing unilateral nephrectomy due to refractory hypertension (n=5) and deceased donor kidneys (DK) discarded due to incompatibility (n=7). Renal microvasculature (MV) was studied *in vitro* using micro CT after infusing contrast agent into the renal artery. Kidneys were also compared for angiogenic gene and protein expression.

Results: Age and sex were comparable between RVD and DK. RVD had reduced density of medium-sized (0.2-0.3mm) MV vs. donor kidneys (Fig. A-B, p=0.04), whereas density of small (0.02-0.2mm) and large (0.3-0.5 mm) MV was similar. Vascular tortuosity ratio was higher in RVD vs DK (Fig. C, p=0.05). The number/tubule of peritubular capillaries (PTC) was significantly lower in RVD, as was CD31+ area, whereas numbers of new angiogenic vessels (β3 integrin+, Fig. D) and pericytes were higher. Renal fibrosis and MV remodeling (media/lumen) were greater in RVD, as were oxidative stress and angiopoietin-1 expression, whereas VEGF (p=0.9) and FLK-1 (p=0.2) protein or gene expression were unchanged.

Conclusions: Human RVD kidneys develop marked MV remodeling and loss, particularly of PTC and medium-size MV. Angiopoietin-1 upregulation may promote new PTC formation, but fails to offset overwhelming MV loss distal to severe RVD. These findings underscore the major component of microvascular injury in the development of ischemic kidney disease.

Funding: NIDDK Support



PO0642

Combined Efficacy of the Novel Nonsteroidal and Selective Mineralocorticoid Receptor Antagonist Finerenone and the SGLT2 Inhibitor Empagliflozin in a Non-Diabetic Cardiorenal Rat Model

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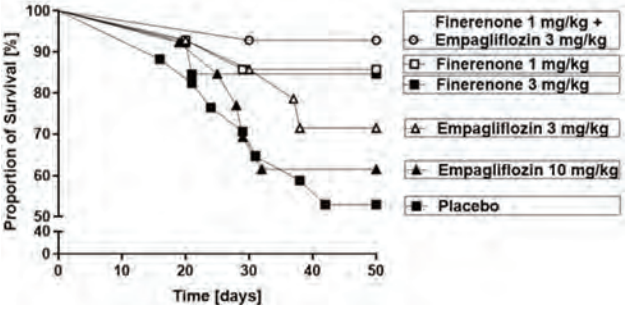
Background: Finerenone and SGLT2 inhibitors have demonstrated clinical benefits in CKD patients with T2D. Efficacy of finerenone and SGLT2i, especially in combination, is unknown in non-diabetic kidney disease.

Methods: Cardiorenal morbidity and mortality was studied in hypertensive and proteinuric L-NAME (20 mg/L) treated renin-transgenic (mRen2)27 rats. Rats (10-11 weeks old female, n=13-17/group) were treated once daily orally for up to 7 weeks with placebo, finerenone (1 and 3 mg/kg), empagliflozin (3 and 10 mg/kg), or a combination of the respective low doses. Key outcome parameters included mortality, blood pressure, proteinuria, kidney histology and gene expression.

Results: Placebo-treated rats demonstrated a 50% mortality rate over the course of 7 weeks (figure). Drug treatment resulted in variable degrees of survival benefit, most prominent and statistically significant in the low dose combination group (figure). Low dose combination revealed an early, sustained and efficacious proteinuria reduction (-86%, p<0.05) and was highly efficient on renal histology parameters. Monotherapies of finerenone (-27% @ 1 mg/kg, p = n.s.; -87% @ 3 mg/kg, p<0.05) and empagliflozin (-38% @ 3 mg/kg, p = n.s.; -64% @ 10 mg/kg, p = n.s.) dose-dependently reduced proteinuria with a comparable protection from renal lesions at higher dosages. Treatment with finerenone and the combination significantly decreased systolic blood pressure while empagliflozin alone and in combination acted strongly glucosoric.

Conclusions: Both, MRA by finerenone and SGLT2i by empagliflozin confer renal protection in preclinical non-diabetic, hypertensive kidney disease. Combination of these two modes of action at low dosages revealed efficacious reduction in proteinuria and mortality indicating a strong potential for combined clinical use in respective cardiorenal patient populations.

Funding: Commercial Support - BAYER AG



PO0643

Novel Small Molecule Inducers of ABCA1-Dependent Cholesterol Efflux Preserve Renal Function in Mouse Models of FSGS and Alport Syndrome

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Background: Pathological accumulation of cholesterol in podocytes is associated with the progression of kidney disease. Depletion of podocyte cholesterol by non-specific means, with agents such as cyclodextrin, or by specific upregulation of ABCA1- mediated cholesterol efflux, have shown promise in renal disease models, but have not progressed in clinical development.

Methods: The effects of novel compounds (Cpds A and G) that induce ABCA1-mediated cholesterol efflux were evaluated in comparison to LXR agonists in differentiated human podocytes *in vitro*. *In vivo* efficacy studies of Cpds A & G were conducted in mouse models of proteinuric kidney disease (Adriamycin-induced nephropathy and Alport Syndrome).

Results: ABCA1-mediated cholesterol efflux was significantly increased in podocytes by all agents. While an LXR agonist resulted in accumulation of ABCA1 at the plasma membrane, it also induced significant accumulation in microsomal fractions. In contrast, Cpds A & G induced the redistribution of ABCA1 from intracellular sites to the plasma membrane. In ADR challenged mice, Cpd A and Cpd G reduced ACR by 8 and 30-fold, respectively, compared to controls. In Col4A3 knockout mice, Cpd G significantly reduced ACR, serum creatinine and blood urea nitrogen, as well as prevented weight loss and mortality vs. control mice. We found that increased accumulation of cholesterol esters in the kidney cortex of ADR challenged mice strongly correlated with albuminuria. In both the FSGS and Alport models, Cpd G significantly reduced lipid droplet formation and cholesterol ester content in kidney cortex.

Conclusions: In summary, our studies describe the effects of novel small molecule drugs in renal disease models that induce ABCA1-mediated cholesterol efflux independently of LXR. This may represent a promising new therapeutic strategy for the treatment of kidney diseases and disorders of cellular cholesterol homeostasis.

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PO0644

Metformin Therapy Is Able to Halt the Progression of Established CKD in Rats

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Background: Metformin, first-line drug for type-2 diabetes, exerts benign pleiotropic actions beyond its prescribed use and emerging data show protective effects against the development/progression of renal impairment. Current treatment strategies for chronic kidney disease (CKD) mainly focus on controlling important risk factors, while effective treatment directly targeting the kidney is lacking. However, in 2019, the FDA approved the use of the sodium-glucose co-transporter-2 (SGLT2) inhibitor, canagliflozin, to treat diabetic nephropathy. Here, the ability of metformin to attenuate the progression of established, non-diabetic CKD was investigated and compared to canagliflozin.

Methods: Adenine-induced CKD rats (n=86) were assigned to different treatment groups to receive 200 mg/kg metformin, 4 or 5 weeks after the start of the adenine diet (0.25%), *i.e.* after CKD had developed, or 25 mg/kg canagliflozin 4 weeks after the start of the diet, by daily oral gavage, during 4 weeks. Each treatment group was compared to a vehicle (1% carboxymethylcellulose) group.

Results: Serum creatinine levels dramatically rose in vehicle-treated CKD rats: from 0.7 ± 0.1 mg/dL (week 0) to 1.5 ± 0.1 mg/dL (week 4), 2.6 ± 1.2 mg/dL (week 5) and further to 6.2 ± 0.3 mg/dL (week 8) and 4.8 ± 1.1 mg/dL (week 9). Canagliflozin treatment did not alter the increase in serum creatinine as indicated by serum creatinine levels at week 8 (5.8 ± 0.4 mg/dL). In contrast, metformin treatment almost completely prevented the increase from week 4 or 5 on, as indicated by the serum creatinine levels after 8 (2.0 ± 0.5 mg/dL) and 9 (2.9 ± 0.5 mg/dL) weeks ($p<0.05$ vs. vehicle). Canagliflozin treatment did not alter the tubulointerstitial area percentage, while this parameter was 33% lower at week 8 and 23% lower at week 9 in metformin-treated CKD rats compared to vehicle treatment ($p<0.05$ vs. vehicle). Further histological examination revealed more tubular proliferation (PCNA positive cells) and less interstitial inflammation (CD45 positive cells) in metformin-treated rats compared to vehicle-treated animals.

Conclusions: In conclusion, metformin is able to attenuate the progression of pre-existing adenine-induced CKD in rats. Our data do not present evidence for a beneficial effect of canagliflozin on progression of non-diabetic CKD.

PO0645

The Novel Soluble Guanylyl Cyclase (sGC) Activator Runcaciguat Attenuates Hypertensive Cardiorenal Rat Diseases

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Background: Chronic kidney disease (CKD) is often associated with arterial hypertension, leading to the development of hypertensive nephropathy and ultimately kidney failure that is poorly prevented by current treatment options. Hypertension and nephropathy are associated with impaired NO/sGC/cGMP signaling, low cGMP production and increased oxidative stress. Runcaciguat is a novel potent and selective, NO- and heme-independent sGC activator. Here we investigated the therapeutic potential of Runcaciguat in rat models of hypertension associated chronic kidney disease.

Methods: Hypertensive rats (Sprague Dawley, 12-13 weeks old male, n=13/ group, angiotensin II (ANG) minipumps, 450ng/kg/min) were treated orally twice daily for 2 weeks with Runcaciguat (0.3, 1 or 3 mg/kg), losartan (30 mg/kg) or placebo. In a second study, male Renin-transgenic rats (mRen2/27, 8 weeks old, L-NAME 30-50 mg/L, n=18-24/group) were treated twice daily orally for up to 8 weeks with Runcaciguat (1, 3 or 10 mg/kg) or placebo. Key outcome parameters included mortality, blood pressure (BP), proteinuria, kidney histology, kidney and heart biomarkers and kidney gene expression.

Results: In the 2-week-treated ANG-rats, Runcaciguat dose-dependently and significantly reduced proteinuria without changing BP. Losartan significantly decreased BP and proteinuria. Runcaciguat reduced kidney LCN2 (NGAL) expression. In the 8-week-treated Renin-transgenic rats, Runcaciguat significantly and dose-dependently improved mortality from 58% (placebo) to 56%, 39% and 28% (@ 1, 3, 10 mg/kg). At all tested doses, Runcaciguat significantly reduced kidney and heart hypertrophy and increased creatinine clearance. At the highest dose, Runcaciguat also significantly reduced BP and proteinuria.

Conclusions: The novel oral sGC activator Runcaciguat exhibits cardiorenal protection and improved survival in hypertensive rat models. Our data strongly suggest that Runcaciguat represents a promising treatment option for hypertensive kidney disease patients.

Funding: Private Foundation Support

PO0646

The Novel Nonsteroidal and Selective Mineralocorticoid Receptor Antagonist Finerenone Differentiates from SGLT2 Inhibitor Empagliflozin by Anti-Fibrotic Effects in a Progressive Mouse Kidney Fibrosis Model

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Background: Finerenone and SGLT2 inhibitors have demonstrated clinical benefits in CKD patients with T2D. Cellular and molecular mechanisms responsible for these benefits are incompletely understood. MR-signaling has been linked to fibrosis *in vitro* via plasminogen activator inhibitor-1 (PAI-1) modulation. Here we investigated potential effects and mechanisms in a relevant preclinical mouse kidney fibrosis model.

Methods: Kidney fibrosis was induced in mice via unilateral ureteral obstruction. In a series of experiments, mice (C57/Bl6J, 8 weeks old male, n=10-12/group) were treated orally for 10 days with the MR antagonist finerenone (3 and 10 mg/kg), the SGLT2 inhibitor empagliflozin (10 and 30 mg/kg), or in a direct comparison of both drugs. Interstitial myofibroblast accumulation was quantified via alpha-smooth muscle actin (αSMA) and interstitial collagen deposition via Sirius red fast green staining. Secondary analyses included kidney mRNA expression of inflammatory and fibrotic markers and pathways.

Results: Myofibroblast accumulation was dose-dependently reduced in finerenone-treated mice (-22% @ 3 mg/kg, p=0.1; -41% @ 10 mg/kg, p=0.002) as well as collagen deposition (-22% @ 3 mg/kg, p=0.1; -44% @ 10 mg/kg, p=0.001). These antifibrotic effects of finerenone on protein level were matched on mRNA expression level (including collagens type III and IV). In contrast, treatment with SGLT2 inhibitor strongly increased urinary glucose excretion but had neither significant effects on kidney myofibroblasts (0% @ 10 mg/kg, p=0.7; -10% @ 30 mg/kg, p>0.99) nor on collagen deposition (-6% @ 10 mg/kg, p=0.9; -9% @ 30 mg/kg, p=0.8). In finerenone-treated mice reduced kidney fibrosis was paralleled by reduced kidney PAI-1 expression (-19% @ 3mg/kg, p=0.3; -41% @ 10 mg/kg, p=0.002).

Conclusions: Finerenone has direct anti-fibrotic properties resulting in reduced myofibroblast and collagen deposition in a mouse model of progressive kidney fibrosis.

Funding: Commercial Support - Bayer AG

PO0647

The Novel Potent and Selective Vasopressin V1a Antagonist BAY2327949 Blocks Arginine Vasopressin-Mediated Decline of Renal Blood Flow and Tissue Oxygenation

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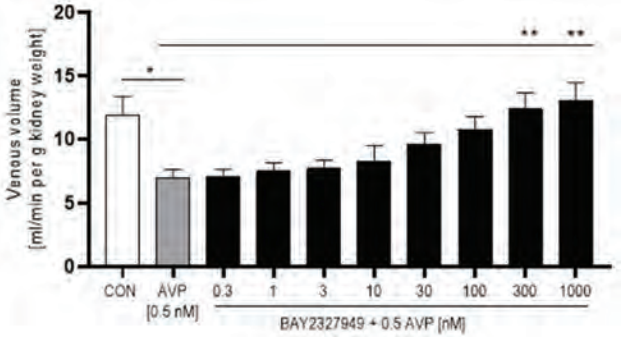
Background: Hypoxia is a major contributor to kidney disease progression. Arginine vasopressin (AVP) potently induces renal medullary vasoconstriction via vascular V1 receptors resulting in reduced renal blood flow (RBF). Here we characterized the kidney-protective properties of a recently identified, potent and selective V1a receptor antagonist.

Methods: BAY 2327949 was characterized in Chinese hamster ovary cells expressing recombinant human and rat V1a and V2 receptors. Vasodilatory effects were investigated on isolated *A. renalis* rings from male Wistar rats (n=10). RBF and intrarenal tissue oxygenation were studied in isolated perfused rat kidneys and in anesthetized rats (n= 5-8 per group) via Laser Doppler Flowmetry.

Results: *In vitro* receptor profiling showed high potency and selectivity of BAY 2327949 for human V1a receptor (IC50 hV1a: 1.2 nM, IC50 hV2: 170 nM). BAY 2327949 mediated dose-dependent relaxation (IC_{50}= 3.1 nM) of isolated rat *A. renalis* vessel rings precontracted by AVP. BAY 2327949 improved the AVP-mediated reduction of perfusate and venous flow (figure) without affecting urinary volume. *In vivo*, infusion of AVP significantly increased mean arterial pressure (CON: 97±1, AVP: 135±12; mean±SD) which was normalized by BAY 2327949 in a dose-dependent manner (90±5; p<0.0001). Infusion of AVP reduced both renal perfusion (CON: 1060±8, AVP: 758±107) and tissue oxygenation (CON: 27±1, AVP: 17±4). BAY 2327949 dose-dependently restored RBF (960±30; p<0.0001) and increased pO_2 (25±0.4; p<0.0001).

Conclusions: BAY 2327949 is a novel potent and selective vasopressin V1a receptor antagonist blocking the detrimental effects of elevated vasopressin levels on renal perfusion and oxygenation in rats, suggesting potential benefit for patients with cardiorenal diseases.

Funding: Commercial Support - Bayer AG



PO0648

Apabetalone, an Inhibitor of BET Proteins, Downregulates Alkaline Phosphatase and Improves Cardiovascular Risk

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Background: Elevated serum alkaline phosphatase (ALP) predicts major adverse cardiac events (MACE). ALP is associated with vascular calcification (VC), inflammation & endothelial dysfunction in patients with cardiovascular disease (CVD) &/or chronic kidney disease (CKD). Apabetalone is an inhibitor of BET proteins - epigenetic readers modulating gene expression in pathological VC & inflammation. We studied apabetalone's impact on tissue non-specific ALP (TNALP) expression in cell culture, then analyzed serum ALP in phase 2 trials.

Methods: Expression of TNALP (gene symbol *ALPL*) was measured in primary hepatocytes, HepaRG, HepG2, primary mesangial cells (MC), vascular smooth muscle cells (VSMC) & vascular endothelial cells by q-PCR. TNALP was assessed by immunoblot & flow cytometry, ALP activity by enzymatic assays. Serum ALP was measured in CVD patients in phase 2 trials (ASSERT, SUSTAIN & ASSURE). Subpopulations had CKD (eGFR<60).

Results: Apabetalone downregulated *ALPL* expression in liver cells by 60-80%. HepG2s had lower TNALP protein >55%, enzyme activity >40% & TNALP positive cells 15-30%; renal MCs had >90% decreases in *ALPL* expression & TNALP enzyme activity (p<0.001). *ALPL* was suppressed 50-70% in 3 vascular endothelial cell types with apabetalone. In VSMCs, apabetalone lowered *ALPL* expression, TNALP protein, enzyme activity & extracellular calcium deposition. In ASSERT, apabetalone dose dependently reduced serum ALP (p<0.001). In combined phase 2 analysis, apabetalone lowered ALP (p<0.001), including patients in the CKD subgroup (p=0.008). Notably, the apabetalone-mediated decreases in serum ALP in phase 2 correlated with reduced MACE at 12-14 weeks (HR 0.64 per 1-SD in ALP, 95% CI 0.46–0.90 p=0.009 1-SD=13U/L); similar associations were observed at 24–26 weeks (HR 0.66 per 1-SD ALP 95% CI 0.43–0.99 p=0.045; 1-SD=14U/L).

Conclusions: Apabetalone lowers serum ALP, consistent with reduced hepatic, renal & vascular TNALP production. Modulation of ALP by apabetalone may affect pathogenetic processes to lower cardiovascular risk. This study provides insight to MACE reductions in phase 2 clinical trials.

Funding: Commercial Support - Resverlogix

PO0649

Renal Expression of L-Type Fatty Acid Binding Protein in Addition to Angiotensin II Type 1a Receptor Loss Ameliorates Chronic Tubulointerstitial Damage After Renal Ischemia Reperfusion

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Background: Although angiotensin II (Ang II) type 1 receptor blocker was reported to attenuate chronic tubulointerstitial damage (TID) after renal ischemia reperfusion (IR), its effect is limited. We had revealed the importance of renal L-type fatty acid binding protein (L-FABP) with antioxidative effect in various renal disease models. Therefore, the aim of this study is to elucidate the renoprotective effect of renal L-FABP and Ang II type 1a receptor (AT1a) loss against chronic TID after renal IR.

Methods: To induce severe chronic TID after renal IR, unilateral renal ischemia for 60 min was performed via clamping of right renal pedicle using four types of male mice; wild type mice (hL-FABP$^{-/-}$AT1a$^{+/+}$), human L-FABP chromosomal transgenic mice (hL-FABP$^{+/-}$AT1a$^{+/+}$), AT1a knockdown homo mice (hL-FABP$^{-/-}$AT1a$^{-/-}$), and generated hL-FABP$^{+/-}$AT1a$^{-/-}$ mice. Right and left kidneys were removed at 10 weeks after IR.

Results: While marked renal atrophy and progressive TID were found in each IR-kidney of hL-FABP$^{-/-}$AT1a$^{+/+}$, hL-FABP$^{+/-}$AT1a$^{+/+}$ and hL-FABP$^{-/-}$AT1a$^{-/-}$ mice, the degrees of both atrophy and TID were significantly ameliorated in the IR-kidneys of the hL-FABP$^{+/-}$AT1a$^{-/-}$ mice. Systolic blood pressure levels in the hL-FABP$^{+/-}$AT1a$^{-/-}$ mice were similar to the hL-FABP$^{-/-}$AT1a$^{-/-}$ mice. These results suggested that antioxidative effect of L-FABP in addition to AT1a loss may be related to suppression of chronic TID after IR.

Conclusions: Increased expression of renal L-FABP in addition to suppressed activity of AT1a may be a useful strategy for prevention of AKI-to-CKD transition.

Funding: Private Foundation Support

PO0650

Development of a Synthetic Biotic, SYNB8802, for the Treatment of Enteric Hyperoxaluria

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Background: Enteric hyperoxaluria (EH) is a metabolic disease that results from excessive absorption of oxalate from dietary sources. Increased oxalate levels can lead to the formation of kidney stones and, ultimately, to kidney failure. EH occurs most frequently in patients with underlying gastrointestinal disorders, including inflammatory bowel disease, short bowel syndrome, or individuals who have undergone bariatric surgery. There is a high unmet need for new EH therapies, as a low oxalate diet is the only option currently available to patients. Synlogic is developing a novel Synthetic Biotic™ medicine for the treatment of EH, designated as SYNB8802.

Methods: SYNB8802 is an engineered bacterium derived from *Escherichia coli* Nissle 1917 (*EcN*) that has been engineered to metabolize oxalate to formate and CO_2 in the gastrointestinal tract.

Results: Inoculation of SYNB8802 into minimal media showed significant consumption of oxalate and production of formate as compared to un-engineered (EcN) bacterial strain. When administered concomitantly with ^{13}C-oxalate to healthy mice, SYNB8802 decreased the urinary recovery of ^{13}C-oxalate, indicative of its ability to consume oxalate *in vivo*. In healthy non-human primates (NHP) administered approximately 400 mg of dietary oxalate, SYNB8802 lowered the urinary recovery of oxalate and ^{13}C-oxalate in a dose dependent manner by up to 75% as compared to vehicle. In addition, Synlogic has developed a mathematical model that predicts clinically meaningful reductions in urinary oxalate in EH patients.

Conclusions: Overall, SYNB8802 represents a promising new approach for the treatment of enteric hyperoxaluria.

PO0651

A Novel Small Molecule Modulating the Mitochondrial NEET Proteins Improves Inflammation and Fibrosis in Kidneys of Nonalcoholic Steatohepatitis Mice

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Background: Non-alcoholic steatohepatitis (NASH) is a disease characterized by excessive fat accumulation, inflammation, and ballooning degeneration of hepatocytes, with or without fibrosis in the liver. It is now reported that NASH not only affects the liver but is also associated with chronic kidney disease (CKD). However, the morphological appearance of NASH kidneys has been poorly characterized. These observations highlight the need for a treatment that targets both conditions. Here, we assessed the effect of a novel chemistry that regulates the function of 3 mitochondrial proteins called the NEET proteins, previously reported to be important in metabolic diseases, on a diet-induced NASH model in mice.

Methods: Mice were fed with a high fat diet for 30 weeks prior treatment with ENYO's molecule for 8 weeks. The kidneys and livers were collected at sacrifice and sections were stained with H&E, PAS and picrosirius red staining to analyze their morphology. Specific immunostainings and qRT-PCR were performed to quantify the extent of inflammation (CD3, MAC1 and F4/80) and fibrosis (Col1a1, Col3a1, fibronectin).

Results: NASH mice displayed severe renal lesions such as glomerulosclerosis, tubular casts, tubular lipid accumulation and interstitial fibrosis. Mononuclear cell infiltration was also massively increased, in particular in the perivascular areas. Quantitative RT-PCR revealed a significant increase of the expression of several fibrosis and inflammation markers. Therapeutic administration of ENYO's molecule was shown to resolve these lesions with a return back to normal regarding fibrosis, and a 50% and 35% decrease in lymphocyte and macrophage accumulation, respectively. In the liver, inflammation and fibrosis were also attenuated, specifically in the periportal zone that has been shown to be correlated with the severity of the disease. Interestingly, the most significant responders in the liver were also the best responders in the kidneys.

Conclusions: We have shown that NASH mice developed CKD, recapitulating the phenotypes observed in humans. Moreover, we have identified a new treatment, that by targeting NEET proteins, protects mice from the development of both liver and renal lesions.

PO0652

SIRT3 Deacetylates PDHE1α to Regulated Mitochondria Metabolism in Tubular Epithelial Cells During Renal Fibrosis

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Background: Abnormal energy metabolism is considered to be related to renal interstitial fibrosis. Pyruvate dehydrogenase α (PDHE1α) is the main catalytic enzyme of pyruvate dehydrogenase complex (PDHC) linking glycolysis to the TCA cycle. N-lysine acetylation is an important post-translational modification involves in energy metabolism. SIRT3 is a mitochondrial deacetylase that mediates the activity many metabolic enzymes.

Methods: Unilateral ureteral obstruction (UUO) or ischemia-reperfusion (I/R) were used to induce renal fibrosis in C57BL/6J mice or SIRT3 knockout mice. Primary tubular epithelial cells (PTCs) were stimulated by TGF-β1. Protein array and the acetylation array by LC-MS/MS were performed on tubules separated from sham or UUO-operated mice. K149R, K267R, K385R mutations in PDHE1a were transfected into PTCs.

Results: Acetylome showed that the majority of proteins were hyper-acetylation after UUO. GO enrichment analysis revealed that PDH was the most obviously enriched GO term. Immunoprecipitation analysis confirmed that PDHE1α acetylation was enhanced after UUO or I/R operation. Activation of SIRT3 by HKL could block the hyper-acetylation of PDHE1α, restored PDH enzyme activity, and inhibited the phosphorylation of PDHE1α in mice with UUO or I/R. On the contrary, Sirt3 KO mice had more acetylated PDHE1α, more phosphorylated PDHE1α and defective PDH enzyme activity. In vitro, increased PDHE1 acetylation was accompanied by reduced PDH enzyme activity and increased PDHE1α phosphorylation in PTCs after TGF-β1 stimulation. Activation of SIRT3 by HKL repressed the effect of TGF-β1. Inhibition SIRT3 activity by 3-TYP or SIRT3 siRNA transfection have the same effect as TGF-β1. K149, K267, K385 were identified as the main potentially lysine acetylated sites in PDHE1α. Acetylation of PDHE1α, the activity of PDH and PDHE1α phosphorylation remained unchanged in PTCs with the K385R mutation stimulated with TGF-β1 or SIRT3 siRNA transfection.

Conclusions: In summary, our data showed that mitochondrial proteins involved in regulating energy metabolism were acetylated and targeted by SIRT3 in PTCs. The deacetylation of PDHE1α at lysine 385 by SIRT3 plays a key role in metabolic reprogramming in renal fibrosis.

Funding: Government Support - Non-U.S.

PO0653

Empagliflozin Restores CKD-Induced Impairment of Endothelial Regulation of Cardiomyocyte Relaxation and Contraction

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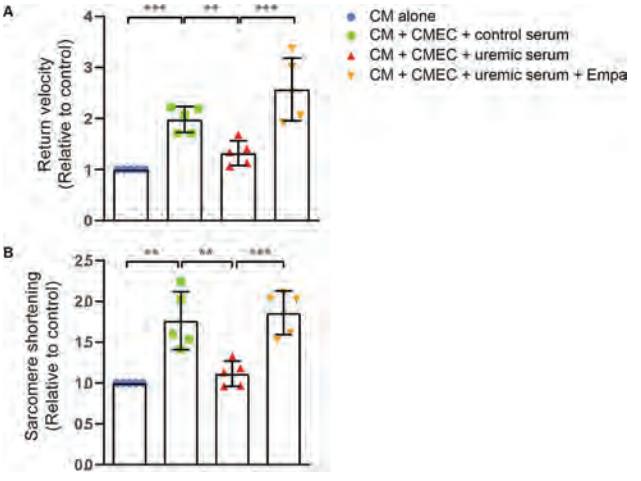
Background: Chronic kidney disease (CKD) promotes development of cardiac abnormalities and is highly prevalent in patients with heart failure (HF), particularly HF with preserved ejection fraction (HFpEF). CKD and HF are associated with endothelial dysfunction and have been shown to benefit from a sodium-glucose co-transporter 2 inhibitor, empagliflozin. We hypothesized that uremic serum from CKD patients impairs cardiomyocyte (CM) relaxation and contraction by inducing endothelial cell dysfunction and that empagliflozin protects against this effect.

Methods: Co-culture system of human cardiac microvascular endothelial cells (CMECs) with adult rat ventricular cardiomyocytes (CMs).

Results: We showed that CMECs promote CM relaxation (return velocity, Fig. A) and contraction (sarcomere shortening, Fig. B). Serum from CKD patients impaired endothelial enhancement of CM function which was rescued by empagliflozin (Fig. A-B). Exposure to uremic serum reduced nitric oxide (NO) bioavailability in CMECs and increased mitochondrial reactive oxygen species (ROS) and 3-nitrotyrosine level, indicating NO scavenging by ROS. Empagliflozin restored endothelial enhancement of NO level in CMs by restoring endothelial NO bioavailability and reducing endothelial mitochondrial ROS, an effect that was largely independent of sodium-hydrogen exchanger-1.

Conclusions: Serum from CKD patients impairs CM relaxation and contraction through induction of endothelial dysfunction driven by an increase in mitochondrial ROS production. Empagliflozin restores the enhancement effect of CMECs on CM function by reducing mitochondrial oxidative damage, leading to reduced ROS accumulation and increased endothelial NO bioavailability.



PO0654

Genetic Ablation of CD148 Increases Renal Macrophage Inflammation and Fibrosis in Ureteral Obstructed Kidney

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Background: CD148 is a transmembrane protein tyrosine phosphatase expressed in several cell types including epithelial, endothelial, and hematopoietic cells. Macrophages express high level of CD148, and its expression is up-regulated by lipopolysaccharide (LPS) which activates innate immune response through toll-like receptor 4. Recently the innate immune system has been recognized as an important modulator of the inflammatory response during infection and tissue injury/repair. However relatively little is known about CD148 function in this cell type and kidney disease model. Here we showed influences of CD148 depletion on unilateral ureteral obstruction (UUO) model and macrophage polarization.

Methods: UUO surgeries were performed in CD148 KO and wild-type (WT) mice on DBA2/J background. Histological and gene expression analysis were performed 3 days and 10 days after UUO to investigate inflammation and fibrosis. Flowcytometry was used to analyze macrophage polarization using CD38/Egr2 method. Primary culture of peritoneal macrophages isolated from these mice were used for *in vitro* study. After LPS stimulation, inflammatory response (TNFα, IL-1b, IL-6) was quantified by qPCR and ELISA.

Results: CD148KO mice developed more severe renal fibrosis than WT mice at day10. They showed more severe tubular damage compared to WT mice at day3. F4/80 staining revealed increased infiltrated macrophages in outer medulla lesion and flowcytometry showed increased population of inflammatory subtype (M1; CD11b+F4/80+CD38+Egr2-) in CD148KO mice. Although there were no significant

differences in whole kidney analysis of inflammatory cytokine qPCR between them, renal macrophages isolated from CD148KO mice showed higher expression of inflammatory cytokine expression (TNFα, IL-1b, IL-6). Peritoneal macrophages derived from CD148KO mice showed higher inflammatory cytokine expression (TNFα, IL-1b, IL-6) to LPS, accompanied by higher phosphorylation of Erk. In addition, Erk inhibitor, U0126 diminished the difference between WT and CD148KO macrophages.

Conclusions: Our data suggests that CD148 negatively regulates macrophage M1 polarization through Erk and its deficiency accelerates macrophage inflammation in UUO kidneys, leading to advanced tubular injury and renal fibrosis.

Funding: Commercial Support - Bayer AG

PO0655

LRG1 Promotes Renal Fibrosis by Enhancing TGF-β-Induced Smad3 Pathway

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Background: Renal fibrosis is a final convergent pathway for CKD progression, but effective fibrosis therapy is lacking. We recently showed that leucine-rich alpha-2 glycoprotein-1 (LRG1), a secreted glycoprotein, is highly upregulated in diabetic kidneys and potentiated the endothelial TGF-β signaling, mediated by ALK1 receptor and Smad1/5 activation, to increase angiogenesis and worsen DKD progression. However, increased LRG1 expression was not limited to the endothelial cells in the diabetic kidneys, but also found in the renal tubular epithelial cells (RTECs). Therefore, we examined whether LRG1 contributes to the TGF-β signaling in RTECs leading to renal fibrosis progression.

Methods: We examined the expression of LRG1 in the tubulointerstitium RNAseq datasets of human CKD. We explored the potential mechanism in LRG1 upregulation in cultured RTECs and examined the specific TGF-β/Smad signaling pathway mediated by LRG1 using shRNA-knockdown. We examined the effects of global *Lrg1* ablation in unilateral ureteral obstruction (UUO) and aristolochic acid nephropathy (AAN) models of renal fibrosis. We also examined the effects of RTEC-specific overexpression of LRG1 in renal fibrosis in vivo. We further compared the activation of Smad proteins in the RTECs of control, $Lrg1^{-/-}$, and Pax8-$LRG1^{OE}$ mice with UUO.

Results: We found that the *LRG1* mRNA transcript was markedly increased in the microdissected tubulointerstitium of human CKD. In cultured RTECs, LRG1 expression was upregulated by a pro-inflammatory cytokine TNF-α, and chromatin IP assay confirmed the binding of p65 subunit NF-κB to the LRG1 promoter region. Importantly, LRG1 enhanced the TGF-β-induced Smad3 activation, but not of Smad1/5, and the expression of pro-fibrotic genes in RTECs. The global knockout of *Lrg1* attenuated renal fibrosis in mice with UUO or AAN. In AAN mice, *Lrg1* ablation also improved renal function. In contrast, the RTEC-specific overexpression of LRG1 markedly heightened the renal fibrosis in vivo. The level of Smad3 phosphorylation in RTECs in the obstructed kidneys was directly associated with the loss or gain of LRG1 expression.

Conclusions: Our current study attributes a previously undescribed role of LRG1 as a key modulator of the canonical TGF-β/Smad3 signal transduction in RTECs and suggests that the targeting of LRG1 may be an effective approach against renal fibrosis.

Funding: NIDDK Support

PO0656

Single-Nucleus RNA Sequencing Identifies New Classes of Renal Proximal Tubular Epithelial Cell in Kidney Fibrosis

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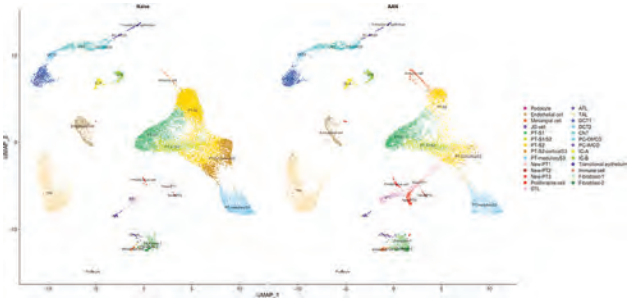
Background: Proximal tubular cells (PTC) play a central role in nephron recovery versus fibrosis following renal injury. PTC heterogeneity is well-documented but poorly-characterized in extant single-cell sequencing data. Here we have determined PTC phenotype in renal fibrosis by single-nucleus RNA sequencing (snRNA-seq).

Methods: Kidneys were harvested from naïve mice and mice with renal fibrosis induced by chronic aristolochic acid administration. Nuclei were isolated using Nuclei EZ Lysis buffer. Libraries were prepared on the 10X platform and snRNA-seq completed using Illumina NextSeq 550. Downstream bioinformatics analyses used Seurat.

Results: A total of 23,885 nuclei were analyzed. PTC's were found in five abundant clusters, mapping to S1, S1-2, S2-cortical S3, and medullary S3 segments. Additional cell clusters were present ("new PTC clusters") at low abundance in normal kidney and in increased number in kidneys undergoing regeneration/fibrosis following injury. These clusters exhibited clear molecular phenotypes, permitting labeling as, proliferating, dedifferentiated-intermediate, dedifferentiated-regenerating, and (present only following injury) dedifferentiated-senescence. Each of these clusters exhibited a unique gene expression signature, including multiple genes associated with renal injury response and fibrosis progression. Comprehensive pathway analyses revealed metabolic reprogramming, enrichment of cellular communication and cell motility, and various immune activations in new PTC clusters. In ligand-receptor analysis, new PTC clusters promoted fibrotic signaling to fibroblasts and inflammatory activation to macrophages.

Conclusions: SnRNA-seq permits the dissection of cell-type and cell-subtype-specific responses. We identified previously unknown, injury-associated PTC clusters. These exhibit highly specific and restricted gene signatures, including canonical PTC injury genes previously assumed to be expressed at low level throughout injured PTC, on the basis of bulk expression analyses.

Funding: Government Support - Non-U.S.



PO0657

Artificial Intelligence-Driven Target Identification in CKD

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Background: Involvement of multiple pathways and complex pathophysiology are few of the hallmarks of Chronic Kidney Disease (CKD). These reasons contribute to the challenge for drug discovery in CKD, which is a major contributor to global disease burden. Availability of a wealth of CKD omics data has opened avenues for novel insight generation through unbiased integrative analysis. In a pioneering effort AstraZeneca and BenevolentAI initiated a collaboration to leverage the potential of artificial intelligence (AI) to generate novel hypotheses for drug targets in CKD.

Methods: We have created a CKD knowledge graph (CKD-KG) - a knowledge base of biological and chemical entities (genes, small molecules, etc) and their relationships (gene-disease associations, therapeutic drugs, biological processes, etc) and augmented with CKD specific information derived from both public and AstraZeneca proprietary data sets. The CKD-KG was constructed by aggregating information from structured biomedical databases, machine learning (ML)-based extraction from unstructured sources, and patient-centric omics datasets (i)unstructured: 140M documents, 1B relationships, (ii) structured: 30M relationships, 3B omics data points, (iii) 35 licensed data sources, and (iv) 53 CKD omics datasets. The CKD-KG was used as input to BenevolentAI's relational inference and causal reasoning ML models to produce target hypotheses for CKD.

Results: The fleet of models identified 295 potential targets that were triaged down to 69 targets. These 69 targets have been further prioritized based on an in-house human target validation pipeline, and additional criteria such as safety and druggability, in line with AstraZeneca's 5R framework. We are undertaking *in vitro* studies via genetic modification in selected cell types to generate target-specific CKD-linked readouts. Subsequently, we will employ *in vivo* studies to confirm the mechanism of action for targets that had shown successful *in vitro* readouts. Eventually, we will progress targets with compelling novel biology within our renal portfolio.

Conclusions: CKD-KG enables a transformative approach to generating novel target hypotheses with the potential of improving health outcomes for CKD patients.

Funding: Commercial Support - AstraZeneca AB

PO0658

Twist1 in T Lymphocytes Exaggerates Kidney Fibrosis After Ureteral Obstruction

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Background: T cells play a critical role in directing kidney fibrogenesis. The transcription factor Twist1 limits pro-inflammatory cytokine production in T cells, but the role of T cell-derived cytokine mediators regulated by Twist1 in kidney damage has not been fully elucidated. To explore the role of T cell Twist1 in kidney scar formation, we subjected mice with T lymphocyte-specific deletion ("TKO") of Twist1 and controls to the UUO.

Methods: 129/SvEv mice with a floxed allele for the gene encoding Twist1 or TNFα were bred with CD4-Cre mice to yield Twist1 TKO or TNFα TKO mice with robust but selective deletion of Twist1 mRNA [>90% vs. WTs in $CD4^+$ T cells, and >85% vs. WTs in $CD8^+$ T cells; p<0.0001] or TNFα mRNA in T cells (published), respectively. Twist1 TKO, TNFα TKO, and WT controls underwent UUO with assessment of kidney fibrosis and T cell phenotype at 14 days.

Results: 2 weeks after UUO, Twist1 TKO mice developed less kidney fibrosis compared to WTs as quantitated by western blot for Col1 (0.75±0.06 vs 1.0±0.05 au; p=0.02) and αSMA (0.65±0.01 vs 1.0±0.08 au; p=0.001) and by RT-PCR for Col1 (0.69±0.08 vs 1.0±0.10 au; p=0.048), fibronectin (0.76±0.07 vs 1.0±0.06 au; p=0.03), TGFβ1 (0.73±0.08 vs 1.0±0.04 au; p=0.004) and PAI-1 (0.47±0.05 vs 1.0±0.09 au; p=0.001). Twist1 TKO mice also showed attenuated kidney injury as indicated by NGAL mRNA expression (0.53±0.06 vs 1.0±0.16 au; p=0.04). Twist1 can suppress proinflammatory mediators such as TNFα and IL17A in T cells. At 14d, flow cytometry revealed similar T cell and macrophage numbers in the obstructed WT and Twist1 TKO kidneys. We then used fluorescent cell sorting to isolate $CD4^+$ and $CD8^+$ T cells from obstructed WT and Twist1 TKO kidneys. Sorted $CD4^+$ T cells from Twist1 TKO kidneys expressed similar mRNA levels for TNFα and IL17A. Sorted $CD8^+$ T cells from obstructed Twist1 TKO kidneys expressed higher mRNA levels for TNFα (1.8±0.39 vs 1.0±0.19 au; p=0.03), but not IL17A than WT controls. To further explore the role of TNFα in T cells during fibrogenesis, we subjected TNFα TKO and WT mice to UUO. We found TNFα deletion in T cells exaggerated kidney fibrosis and injury as quantitated by real time PCR for fibronectin (1.4±0.09 vs 1.0±0.13 au; p=0.03) and NGAL (1.3±0.10 vs 1.0±0.05 au; p=0.01) mRNA expression, respectively.

Conclusions: Twist1 in T cells drives fibrosis in the injured kidney, possibly by limiting TNFα production.

Funding: NIDDK Support, Veterans Affairs Support

PO0659

Evaluation of the Effects of a Resistant Starch Diet and Metaproteomics Study of Microbiome-Host Interactions in a 5/6 Nephrectomy Murine Model of CKD

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Background: Chronic kidney disease (CKD), a progressive decline in kidney function, is a growing health problem: 13% of adults in the US have CKD. In 40% of cases, CKD leads to irreversible loss of kidney function, end-stage renal disease. Prebiotic Resistant Starch (RS) changes gut flora and alleviates CKD. However, mechanisms of RS action remain unclear.

Methods: Male mice (n=8) were used to reduce renal mass and to induce CKD. 8 mice served as healthy controls. Each of the two groups was further split in two subgroups (n=4, each), either supplemented with RS or regular diet. PEAKS was used to identify peptides via de novo sequencing in cecal content. To better understand the differences between CKD, CKDRS, HRS and H phenotypes we combined all bacteria that were differentially abundant in six comparisons to infer bacterial co-abundance (BCoA) network. Histopathological evaluation was used for kidney damage comparison.

Results: Histopathological evaluation showed that CKDRS mice had less kidney damage compared to CKD group. Using metaproteomics we found that the most abundant bacterium in HRS phenotype is indole-producing Oscillibacter sp. 1-3, confirming the result of Blast2GO that indole metabolism is upregulated in HRS phenotype as compared to CKDRS and CKD. The most connected network' hub Firmicutes bacterium ASF500 is significantly overrepresented in CKDRS as compared to CKD and is not significantly different between HRS and H. Firmicutes bacterium ASF500 belongs to 20 bacterial strains from human intestine that can induce Th17 cells in the mouse and rat intestine and have immunostimulatory effects. Experiments to validate effect of butyrate on host epithelial cells in germ-free mice are underway.

Conclusions: Resistant starch slows down the progression of chronic kidney disease in 5/6 nephrectomy model. For the first time we demonstrate decrease in kidney fibrosis during RS supplementation. Metaproteomics allows to discover molecular mechanisms and bacterial species responsible for beneficial effects of RS. MST2 analysis allows for clear visualization of the most important connections within the bacterial co-abundance network.

Funding: Other NIH Support - Center for Translational Pediatric Research (CPTR) NIH Center of Biomedical Research Excellence; Arkansas Biosciences Institute; Arkansas Tobacco Settlement Proceeds Act of 2000; NIH IDeA Networks of Biomedical Research Excellence, Other U.S. Government Support, Government Support - Non-U.S.

PO0660

Sex Differences in Renal Mitochondrial Function of Young Healthy Rats

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Background: Sex differences in mitochondrial performance have been linked to many pathologies. Premenopausal females are typically less prone to cardiorenal damage than males. Differences in the ability to manage oxidative stress, calcium uptake, fission/fusion cycles, and respiratory performance in mitochondria can affect the onset and progression of the diseases. While characteristic sex-related dissimilarities have been reported in renal function, nothing is known with regards to how sex may affect the performance of renal mitochondria. The goal of this study was to compare renal mitochondrial function in young healthy male vs female rats.

Methods: Mitochondria were isolated from the kidneys from Sprague Dawley (SD) rats (10-11 weeks). Mitochondrial membrane potential, superoxide and H_2O_2 levels were measured with luminescent (MCLA) or fluorescent (TMRM, Amplex Red) dyes, and seahorse analysis was performed. Antioxidant capacity was measured with a Trolox-based assay. Lipid peroxide radicals were detected using with spin resonance spectroscopy (ESR) with *in vivo* spin trapping.

Results: Kidneys from SD male (SD^M) and female rats (SD^F) were divided into cortex ($SD^{MC, FC}$) and medulla ($SD^{MM, FM}$). First, we report significantly higher membrane potential in SD^{FM} compared to SD^{MM} (p<0.001). H_2O_2 levels were elevated in both the SD^{FC} and SD^{FM} mitochondria compared to SD^M (p<0.01). Interestingly, mitochondrial superoxide production was increased in the medulla compared to the cortex for both SD^M and SD^F, while SOD2 expression was lower (p<0.001). Antioxidant capacity was lower in SD^{FM} tissues compared to all other groups, which is consistent with higher H_2O_2 level (p<0.05). Female mitochondria had significantly lower basal and ATP-linked respiration, as well as reserve and maximal capacity compared to males. In addition, we report that these parameters were lower in medullary vs cortical mitochondria, independent of sex. ESR analysis showed similar lipid peroxide radical levels in males and females, but detected a different radical adduct – an amine or amino acid-centered radical – in the medulla.

Conclusions: We report sex-related differences in mitochondrial function in the kidneys of young healthy rats. Further studies are needed to establish the mechanisms that they may affect the predisposition to kidney disease development later in life.

Funding: NIDDK Support, Other NIH Support - NHLBI, Commercial Support - Dialysis Clinics Inc

PO0661

Renal Involvement in Coronavirus Disease 2019 (RECORD): A Systematic Review and Meta-Analysis

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Background: COVID-19 caused substantial casualty worldwide. As the reported renal involvement varied across regions, we sought to review the global prevalence of renal manifestations among COVID-19 patients and determine the risk factors associated with AKI.

Methods: We systematically searched 6 databases for peer-reviewed reports and 7 data portals for grey literature for all trials, cohorts, case-control studies and case-series that reported the prevalence of renal manifestations including AKI, RRT, proteinuria and hematuria, and their associated risk factors. All papers were screened, assessed and extracted by at least 2 researchers independently. Quality was assessed according to NIH assessment tools. To avoid duplicate of patient data, we matched the location, institution and time period, and only included the largest data source if studies overlapped. Prevalence of renal manifestations was pooled from studies that consecutively recruited patients from the general population, and with clear definition of outcome. This review was prospectively registered at PROSPERO (CRD42020184621).

Results: 36 studies from 8 countries and over 50 cities with a total of 14,712 patients were identified. 34 and 2 were cohorts and case-control studies respectively. 24, 7 and 5 studies reported COVID-19 patients from the general population, severe / critical patients and patients with history of RRT. AKI occurred in 14.3% of all COVID-19 cases and was highest in New York City. 4.7% of hospitalized COVID-19 patients underwent RRT. Proteinuria and hematuria were present in 42.5% and 26.7% of all COVID-19 cases. The odds of mortality among COVID-19 patients who developed AKI was 15 times higher than non-AKI COVID-19 patients (pooled OR=16.85, 95% CI: 10.06 to 28.23, 2 cities, 6 studies, 9,297 patients) and was higher in Hubei. Such effect was not observed among kidney transplant patients (pooled OR=0.95, 95% CI: 0.12 to 7.22, 2 studies, 30 patients). Higher C-reactive protein, leukocyte count, serum lactate dehydrogenase and creatinine levels on admission were associated with AKI.

Conclusions: AKI was prevalent among COVID-19 patients and significantly associated with mortality. The odds of mortality among AKI patients varied significantly between cities, which could be associated with differences in healthcare infrastructure and delayed hospitalization and treatment initiation.

PO0662

Forecasting Continuous Renal Replacement Therapy Shortages During the COVID-19 Pandemic in the United States

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Background: The coronavirus disease 2019 (COVID-19) pandemic has increased continuous renal replacement therapy (CRRT) demand in the US, however total CRRT demand and capacity remain unclear. Our objective was to project national and statewide CRRT demand and capacity during the COVID-19 pandemic.

Methods: We projected CRRT demand using a model in which 4% of patients admitted with COVID-19 develop acute kidney injury (AKI) requiring CRRT for 12 days. To estimate non-COVID-19 CRRT demand, we applied the prevalence of AKI requiring CRRT among other ICU patients of 8.8%. We assumed capacity would be double this demand and that this demand would decrease to 25% during the pandemic. We compared CRRT demand and capacity to estimate shortage. In sensitivity analysis, we varied parameters influencing CRRT demand and capacity.

Results: We estimated a national CRRT shortage of 1529 (95% uncertainty interval:1264-3837) machines with a capacity of 9375 machines, and shortages in 8 states during the COVID-19 pandemic (Table 1 and Figure 1).

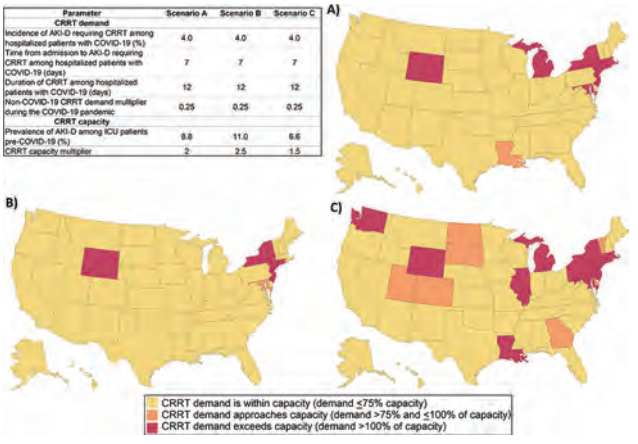
Conclusions: Several US states are projected to have CRRT shortages during the COVID-19 pandemic. A national strategy, such as the creation of a federal stockpile, is needed to mitigate CRRT shortages during this pandemic and future healthcare crises.

Funding: NIDDK Support

Model-generated results for 8 states with CRRT shortages

State	Total ICU beds	Occupied ICU beds	Pre-COVID-19 CRRT demand	CRRT capacity	CRRT demand at peak resource utilization (95% uncertainty interval)	CRRT shortage at peak resource utilization (95% uncertainty interval)
Connecticut	731	446	39	78	224 (171-503)	146 (92-425)
Maryland	1227	805	71	142	174 (128-391)	32 (0-249)
Massachusetts	1555	984	87	173	193 (143-464)	20 (0-291)
Michigan	2749	1773	156	312	313 (293-429)	1 (0-117)
New Jersey	1891	1045	92	184	575 (514-1011)	391 (330-827)
New York	4420	2750	242	484	1391 (1325-1565)	907 (841-1081)
Rhode Island	279	202	18	36	51 (24-207)	15 (0-171)
Wyoming	102	37	3	7	25 (2-114)	17 (0-107)

As noted, 8 US states are projected to encounter CRRT shortages with a total shortage of 1529 (95% uncertainty interval: 1264-3837) machines during the COVID-19 pandemic. Minor discrepancies in this table are due to rounding.



Heat maps demonstrating states with CRRT shortages during the COVID-19 pandemic under scenarios: A) base case, B) highest CRRT capacity estimate and C) lowest CRRT capacity estimate

PO0663

Acute Tubular Injury in Patients with Severe COVID-19 Infection

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Background: Novel coronavirus, severe acute syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread all over the world. SARS-CoV-2 enters host target via angiotensin-converting enzyme-2 which are ubiquitously expressed in many organs including proximal tubules in kidney. Indeed, autopsy cases with coronavirus disease-2019 (COVID-19) revealed the existence of coronavirus particles in the renal tubular epithelium. Several reports have shown COVID-19-associated acute kidney injury (AKI), however involvements of SARS-CoV2 in tubular injury has not been fully understood. Here, we evaluated tubular injury in patients with severe and non-severe COVID19.

Methods: We investigated the relationship between urinary levels of tubule markers (NAG, β2-MG, α1MG, and L-FABP) and laboratory markers in 17 COVID-19 patients without chronic kidney disease on admission. We also analyzed the relationship between the laboratory markers and respiratory status in severe (n=7) or non-severe (n=10) COVID-19 patients which were defined by requirements of supplemental oxygen.

Results: Although only 2 patients developed AKI in severe cases, serum Interleukin-6 (IL-6) level significantly increased in all of severe patients and correlated with levels of proteinuria (R2=0.37, p=0.01), NAG (R2=0.41, p=0.006), α1MG (R2=0.47, p=0.007), L-FABP (R2=0.57, p=0.001) on admission. In addition, severe patients had significantly higher levels of proteinuria (severe: 0.67 vs non-severe: 0.14g/gCr), NAG (33.3 vs 10.1U/L), β2MG (17134.4 vs 1168.5μg/L), α1MG (63.6 vs 12.4mg/L), L-FABP (57.9 vs 7.5μg/gCr) as compared to non-severe cases. Proteinuria and elevated tubular markers were observed only in 2 and 6 cases respectively in non-severe patients, despite those were found in all severe cases.

Conclusions: We found that acute tubular injury was associated with the severity of COVID-19 infection. Since the pathophysiological hallmark of COVID-19 is severe systemic inflammation, it remains obscure whether progressive damage of tubules in SARS-CoV-2 is the result of direct viral infection, ischemic injury, or exposure of any humoral factors. Further large scaled studies focusing on tubular damage should be needed to elucidate underlying mechanisms of renal complication in COVID-19 infection.

PO0664

Incidence of AKI and Its Association with Mortality in Coronavirus Disease 2019 (COVID-19) Patients: A Meta-Analysis

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Background: Acute kidney injury (AKI) is a common complication in medical practice accounting from 8-18% of hospitalized patients. However, although it has been well-established that AKI is linked to increased mortality in hospitalized patients, whether this knowledge would extend to Coronavirus Disease 2019 (COVID-19) patients remained unanswered. Thus, this study aimed to determine the incidence of AKI and its association with mortality in COVID-19 patients from available literatures using a systematic review and meta-analysis.

Methods: We search Ovid MEDLINE, EMBASE, and the Cochrane Library for eligible publications reporting the clinical characteristics of confirmed COVID-19 patients without language restriction. Incidence of AKI and mortality were reported. Because COVID-19 is an emerging pandemic, a large number of studies were published within a short period of time. Valid Institutional Review Board (IRB) number or approval by the National Health Commission of that country were screened to avoid studies with duplicated patients' population.

Results: From 26 studies (n = 5,497), the pooled incidence of AKI in COVID-19 patients was 8.4% (95% CI, 6.0-11.7) with a pooled incidence of renal replacement therapy of 3.6% (95% CI, 1.8-7.1). The incidence of AKI was higher in critically ill patients (19.9%) compared to hospitalized patients (7.3%). Critically ill patients had higher mortality than hospitalized patients. (33% vs. 16.1%, respectively). The pooled estimated unadjusted odds ratio for mortality from AKI was 13.33 (95% CI, 4.05-43.91). By using meta-regression analyses, the incidence of AKI was positively associated with mortality in an adjusted model (Q 26.18; p = 0.02). Moreover, our adjusted model showed that age (p < 0.01), diabetes (p = 0.02), hypertension (p < 0.01) and baseline serum creatinine levels (p = 0.04) were positively associated with the incidence of AKI.

Conclusions: AKI is present in 8.3% of overall COVID-19 patients and in 19.9% of critically ill COVID-19 patients. Presence of AKI is associated with 13-fold increased risk of mortality. Age, diabetes, hypertension, and baseline serum creatinine levels are associated with increased AKI incidence. More studies, including the ones from multi-national databases, are encouraged to confirm our findings.

PO0665

Prolonged Intermittent Renal Replacement Therapy for AKI in COVID-19 Patients with Acute Respiratory Distress Syndrome

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Background: Patients with COVID-19 associated acute respiratory distress syndrome (ARDS) frequently develop severe AKI. Although continuous renal replacement therapy (CRRT) is standard of care for critically ill patients, prolonged intermittent renal replacement therapy (PIRRT) is a feasible option.

Methods: Prospective analysis of 101 PIRRT treatments in a COVID-19 reference hospital in Mexico City (Mar-May 2020).

Results: Of 142 severe COVID-19 patients, 91 (64%) developed AKI, 42 (29%) Stage 3, and 14 (7%) initiated PIRRT; median age 51 y [IQR 51-59, range 40-73], male 11 [78%], diabetes 5 [36%], median BMI 31 kg/m² [27-51], SOFA score 10 [IQR 9-11], ferritin 888 [510-1374 ng/mL], and D-dimer 3076 [1929-5858 ng/mL]. In 81/101 (81%) PIRRT sessions, ultrafiltration (UF) goal was achieved. Duration of PIRRT was 6-8 h in 65/101 (64%) yet in 16/101, procedure was extended 2-4 additional h, to reach UF goal. In subjects with vasopressors, there was a mean norepinephrine dose increase of

0.067 mcg/kg/min (95% CI 0.047-0.101). Intradialytic hypotension (SBP decrease ≥20 mmHg) occurred in 39 (39%) of PIRRT procedures, and 13/101 (13%) PIRRT were discontinued due to severe hypotensive episodes, with 2 patients switched to CRRT. System clotting was a frequent event during the first weeks of March (7 events in the first 30 PIRRT procedures) until concomitant enoxaparin (0.5 mg/kg/day) and regional anticoagulation (unfractionated heparin 500 U/h) were employed. During follow-up, 5 patients (36%) recovered from AKI and respiratory failure, 3 (21%) died, and 6 (43%) are still hospitalized at the time of this report. In those who recovered renal function (9/14), the median number of PIRRT sessions was 6 [IQR 5-8]. Table shows changes in our PIRRT protocol during the COVID-19 outbreak.

Conclusions: PIRRT therapy was feasible and appropriate in most patients who exhibited an exuberant inflammatory response, severe hemodynamic instability, and hypercoagulability.

Recommendation	
"Early" placement of vascular access	Place CVC before adopting prone position in high risk patients for RRT
Timing for initiation of PIRRT	Do not reduce net positive fluid balance until complete fluid resuscitation is confirmed (consider high insensible losses due fever)
Limit COVID-19 exposure	Limit HD staff exposure (place patients close in the ICU to simultaneously deliver PIRRT and limit time of nursing staff to max 4-6 h per person)
Prothrombotic complications	Use of systemic and regional anticoagulation
Severe mixed acidemia	Increased dialysate base yet avoid sudden pH normalization

PO0666

COVID-19 AKI: Risk Factors and Markers of Disease from a Large UK Cohort

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Background: Acute kidney injury (AKI) is a significant complication of COVID-19 infection. UK NICE guidelines have been developed. Aim: to examine our local patient-level COVID-19 Hospitalisation in England Surveillance System (CHESS) database to elucidate potential risk factors for AKI vs guidelines.

Methods: 564 COVID positive admissions between 7 March-24 May 2020 at University Hospital Southampton were examined using Python (Anacondas distribution) and SPSS™. AKI was staged by RIFLE and AKIN criteria consistent with NICE guidance. X^2, t-test, Mann-Whitney U test and logistic regression were used to analyse the data.

Results: AKI was present in 177 patients (31%). At peak, 108 (61%) stage 1; 42 (24%) stage 2; 27 (15%) stage 3. There were no significant differences in cohorts with respect to white vs non-white ethnicity, gender, obesity or anti-COVID-19 treatment. 44% of patients with AKI died vs 19% in the non-AKI group ($p<0.001$). AKI was associated with ICU admission (27% vs 10% $p<0.001$), requirement of non-invasive (13% vs 4%) and invasive ventilation (14% vs 4%) (both $p<0.001$). Prior diabetes (18% vs 8%), hypertension (47% vs 34%), chronic respiratory and cardiac disease (both 25% vs 15%) were more common in the AKI group ($p<0.004$). Increased age was associated with AKI ($p=0.02$) and length of stay (LOS) positively correlated to AKI stage($p<0.001$). Peak levels of biomarkers: ferritin, D-dimer, C-reactive protein, high sensitivity troponin-I, neutrophil count and total white cell count, were all significantly raised ($p<0.001$) in the AKI group, increasing with stage of AKI ($p<0.001$). However, in multivariable analysis first clinical observations, neutrophil count, haemoglobin, D-Dimer and albumin came out as the most significant predictors of AKI: Specificity 88.7%, Sensitivity 43.6%.

Conclusions: AKI is a frequent complication of COVID-19 and we identified similar risk factors to those in the NICE guidelines. In addition, we found hypertension and chronic respiratory disease to increase risk of AKI whilst ethnicity, gender, obesity and COVID-19 treatments did not. Furthermore, AKI was associated with increased mortality, ICU admissions and LOS, concordant with previous studies. This data also points to several biomarkers as possible predictors of AKI development and severity. Further analysis of this data is ongoing.

PO0667

High C-Reactive Protein and D-Dimer on Admission Predict the Development of AKI in Patients Hospitalized with COVID-19

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Background: COVID-19 infection is characterized by an acute respiratory syndrome that causes severe symptoms in some patients including a high incidence of acute kidney injury (AKI), which is associated with poor prognosis. COVID-19 infection results in a complex host response including a cytokine storm and severe inflammation. We aimed to identify whether high inflammatory markers on admission predict the development of AKI.

Methods: We performed a cohort study utilizing data from 430 patients admitted with COVID-19 to the University of Colorado Hospital. We excluded patients with a known diagnosis of end stage kidney disease or chronic kidney disease or with missing data. A total of 203 patients were included in this analysis. The primary predictors were initial serum C-reactive protein (hsCRP) >100 mg/L and D-dimer >1000 ng/mL FEU on admission to the hospital. The primary outcome was AKI, defined by KDIGO definition of AKI based on serum creatinine levels. AKI diagnosis was confirmed by chart review. Multivariate logistic regression analysis was used to examine the association between CRP and D-dimer on admission and development of AKI.

Results: The mean age and body mass index of patients was 53.7 (16.9) years and 31.5 (8.4) kg/m2. Fifty-nine percent of patients were male, 40% were Hispanic and 22.7% were Black. 44.3% had hypertension, 35.0% had diabetes and 23% had underlying respiratory disease. Twenty-seven (13.3%) patients developed AKI. After adjustment for age, gender, race/ethnicity, diabetes, hypertension, respiratory disease, cardiovascular disease and ACEi/ARB use, admission CRP level >100 mg/L was associated with nearly a 4-fold increased odds of developing AKI (OR 3.8, 95% CI 1.4-9.8). After full adjustment, admission D-dimer level greater than 1000 ng/mL FEU was associated with a 5-fold increased odds of AKI (OR 5.0, 95% CI 1.8 to 13.5).

Conclusions: High CRP and D-dimer levels on admission were associated with a significantly higher risk of developing AKI, independent of underlying comorbidities. Thus, high CRP and D-dimer on admission should trigger due deliberation and avoidance of nephrotoxic medications and close monitoring for the development of AKI.

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PO0668

Hematuria and Elevated Lactate Dehydrogenase Are Associated with AKI in Hospitalized COVID-19 Patients

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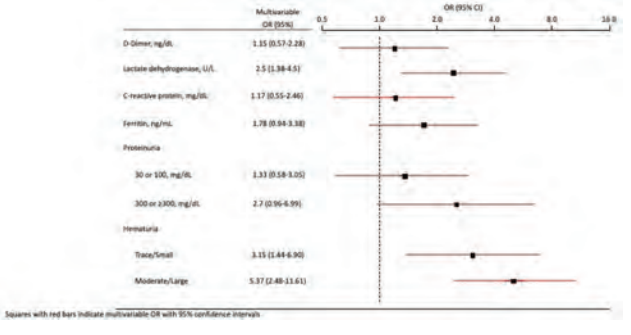
Background: Acute kidney injury (AKI) can be a severe complication of COVID-19, particularly in those who require intensive care. Its relationship to the incidence of proteinuria, hematuria, and elevated inflammatory markers has not been well characterized. Our objective is to describe the incidence of AKI in COVID-19, and its association with inflammatory markers.

Methods: Retrospective cohort study of adult patients hospitalized at the Cleveland Clinic with COVID-19. SARS-CoV-2 infection was confirmed by virus detection in respiratory specimens using RT-PCR. AKI was diagnosed per KDIGO serum creatinine-based classification. We selected stage 2 and higher as our primary endpoint for the study. Baseline creatinine was defined as the most recent pre-admission level available within 3 months of presentation. Acute lung injury was defined by the need for mechanical ventilation.

Results: The incidence of AKI was 14% in 621 hospitalized COVID-19 patients, with half requiring kidney replacement therapy (KRT). The incidence of proteinuria and microscopic hematuria were high in these patients (83% and 77% respectively). Seventy five percent of patients with AKI needed mechanical ventilation, and timing of KRT overlapped with time of mechanical ventilation. Inflammatory markers and acute phase reactants, including LDH, ferritin, and C reactive protein were significantly higher in patients with AKI compared to those with no AKI. On adjusted analysis, hematuria and elevated LDH levels were significantly associated with AKI (Figure).

Conclusions: Elevated lactate dehydrogenase levels and microscopic hematuria on presentation are independently associated with 50% probability of moderate to severe AKI. Our findings suggest a possible pathogenetic mechanism of endothelial cell injury and thrombotic microangiopathy as a cause of AKI in COVID-19 patients. Additional studies are needed to explore this potential mechanism of AKI in COVID-19.



Association of hematuria and LDH with AKI in COVID-19

PO0669

Renal Recovery in COVID-19 with AKI Managed on Peritoneal Dialysis

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Background: Acute peritoneal dialysis (AKI-PD) used to manage about 20% of our COVID-19 AKI patients requiring renal replacement therapy (RRT) of whom 45% had renal recovery.

Methods: Retrospective chart review of 11 consecutive patients undegoing bedside PD catheter placement from 4/1/2020 to 4/30/2020

Results: Median time from admission to the development of AKI was 1 day (IQR 0-3) (Table 1). In 73% of the patients, CRRT or intermittent HD was used as the initial RRT modality; CRRT circuit clotting was the primary reason for switching to PD in 2 patients. Median time from diagnosis of AKI to PD catheter insertion was 5 days (IQR 2-14). At one week, 10 catheters (91%) were functional with no leaks or bleeding detected. Only one patient was switched to CRRT due to primary PD catheter non-function; this

patient had BMI greater than 35 kg/m² and a history of appendectomy. Median duration of follow up from time of PD catheter placement was 37 days (IQR 32-37.5), death-censored median follow up was 35 days (IQR 30-37.5). The median time from AKI to death was 17 days (IQR 14-22). Median time from AKI to renal recovery was 34 days (IQR 21- 40).

Conclusions: In our AKI-PD cohort, the mortality rate was noted to be 36% and 45% had renal recovery during the follow up period. We hypothesize that preservation of residual renal function utilizing PD may have contributed to the high rate of renal recovery observed. Two of our patients converted from CRRT to PD due to repeated filter clotting. We did not observe any bleeding complications in our cohort. We hypothesize that hypercoagulable COVID-19 patients may be excellent candidates for PD potentially due to lower risk of bleeding complications.

Table 1.

Baseline Characteristics	Total N= 11
Age, Median (IQR)	65 (52, 76)
Male, N (%)	10 (91)
Race	
Asian, N (%)	6 (55)
White, N (%)	2 (18)
Black, N (%)	1 (9)
Declined, N (%)	2 (18)
Ethnicity	
Hispanic, N (%)	1 (9)
Comorbid Conditions	
Hypertension, N (%)	7 (64)
Diabetes Mellitus, N (%)	5 (45)
Chronic Kidney Disease, N (%)	2 (18)
Coronary Artery Disease, N (%)	2 (18)
History of Abdominal Surgery, N (%)	1 (9)
Body Mass Index kg/m², Median (IQR)	28 (23, 30)
Clinical Characteristics before PD initiation	
Oliguria[1], N (%)	7 (64)
Severity of ARDS[2]	
Mild, N (%)	8 (73)
Moderate, N (%)	3 (27)
Severe, N (%)	0
SOFA[3] score median (IQR)	9 (6, 10)
Initial PD prescription	
Time from PD catheter insertion to start of PD	
<24 hours, N (%)	6 (55)
24-48 hours, N (%)	5 (45)
Modality of PD	
Manual PD, N (%)	6 (55)
Automated PD, N (%)	5 (45)
Dwell Volume	
1000-1500ml, N (%)	6 (55)
2000ml, N (%)	5 (45)
Mean daily Ultrafiltration over one week in ml, Median (IQR)	708 (-162, 1068)
Patient Outcomes at 30 day follow up	
Renal Recovery[4] N (%)	5 (45)
Death, N (%)	4 (36)
Alive on HD, N (%)	2 (18)

1. Oliguria defined as urine output less than 400ml per 24 hours
2. Severity of ARDS defined per Berlin Criteria
3. Sequential Organ Failure Assessment score
4. Renal recovery was defined as no longer requiring renal replacement therapy

PO0670

Acute Peritoneal Dialysis in Patients with COVID-19 and AKI: A Single-Center Experience in a Time of Crisis in the United States

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Introduction: In developed countries such as the United States, intermittent hemodialysis (iHD) or continuous renal replacement therapy (CRRT) are the primary mode of renal replacement therapy (RRT) for the management of AKI. However, during the COVID-19 pandemic, the ability to provide HD in our hospital system was overwhelmed due to the surge in the number of patients with AKI requiring RRT combined with severe personnel shortages related to illness. Studies have shown no difference in clinical outcomes between HD and PD for AKI. We describe our rapid adoption of an acute PD program during the COVID-19 surge.

Case Description: At Montefiore Medical Center (MMC), in Bronx, NY, the first patient with COVID-19 was admitted on March 11, 2020. As the number of patients with AKI rose, we initiated an acute PD program starting on March 25th. As of April 13th, there were 2,015 patients with COVID-19 admitted to MMC. From April 1st to April 22nd, 30 patients were initiated on PD with the help of surgery and interventional radiology who placed Tenckhoff catheters at bedside and under fluoroscopy, respectively. Of those 30 patients, 14 died, 8 were discharged, and 8 were still hospitalized as of May 14, 2020. Of the 8 patients discharged, 3 were still on PD and 5 had renal recovery (all were able to stop dialysis and 4 returned to baseline creatinine). Of the 8 patients still hospitalized, 4 patients were switched to iHD (3 due to fluid retention and 1 due to PD catheter malfunction), and 4 patients had renal recovery and were able to stop dialysis. Challenges to this program included lack of nurse training, difficulty securing supplies and irregular therapy provision and underdosing due to staffing shortages. Patients on medical wards received more frequent exchanges and did not have significant volume overload and metabolic derangements like those patients requiring intensive care.

Discussion: Despite challenges, we demonstrate the feasibility of acute PD as an alternative to HD in patients with COVID-19-associated AKI. In this single-center experience, we found that acute PD was more effective for stable patients on the wards than for patients with severe illness requiring intensive care.

PO0671

Fluid Balance on CRRT and Association with Respiratory Status in Patients with COVID-19 and AKI

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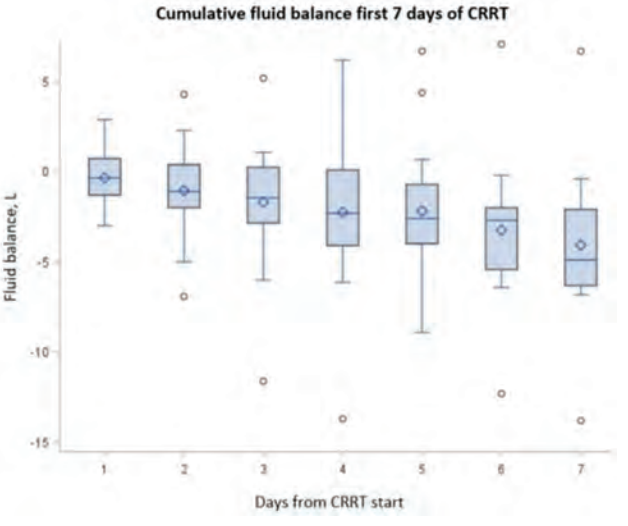
Background: Acute kidney injury is common among critically ill patients with COVID-19 (CoV-AKI), complicating the primary syndrome of ARDS. We report our single center experience with fluid management on CRRT in relation to respiratory parameters.

Methods: Retrospective chart review of 32 consecutive patients with CoV-AKI requiring CRRT admitted to the ICU at the University of Michigan between 3/23 and 4/26, with follow-up through 5/12/2020. All patients received post-filter continuous venovenous hemodiafiltration with regional citrate anticoagulation per institutional protocol. Daily cumulative fluid balance and respiratory parameters (P/F and PEEP) were recorded for the first 7 days of CRRT. We assess the relationship between cumulative fluid balance on CRRT and respiratory parameters (P/F and PEEP) with repeated measures modeling adjusted for fluid accumulation at CRRT start, height, weight, and age.

Results: Mean age 54.8, majority black (75%), and comorbidities included hypertension (90.6%), diabetes (56.2%), CKD (53.1%), and organ transplantation (18.8%). Median length of mechanical ventilation was 15.0 (12-25) days. Median cumulative fluid balance from admission to CRRT start was +3.3 (2.0- 5.6) liters. There was a trend toward increasingly negative fluid balance on CRRT (figure). When adjusting for age, weight, height and cumulative fluid balance at CRRT start, there was no association between cumulative fluid balance on CRRT and P/F (p=0.21) or PEEP (p=0.47). At end of data collection, 9 (28.1%) patients remained in the hospital, 10 (31.3%) survived to hospital discharge and 13 (40.6%) had died.

Conclusions: Cumulative fluid balance on CRRT did not correlate with change in P/F or PEEP, even after accounting for baseline fluid balance. Nevertheless, it is possible that more aggressive fluid removal is required to demonstrated an effect.

Funding: NIDDK Support



Mean Daily Fluid Balance

PO0672

Effect of Early Initiation of Blood Purification in ICU Adults with Severe COVID-19

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Background: Cytokine storm induced by SARS-CoV-2 was considered as one of the main mechanisms of multiple organs dysfunction in Covid-19. Blood purification could remove excess cytokines or other harmful substances and then attenuate target organs injury. In this prospective single-center cohort study, we aimed to assess the efficacy of early initiation of blood purification in ICU adults with severe Covid-19.

Methods: Sixty-two patients in early stage of severe Covid-19 in ICU(Tongji Hospital, Wuhan, China) from Feb.9.2020 to Mar.24.2020 were recruited and divided into two subgroups: 20 patients initiated blood purification including CVVH(/HP) after ICU admission, and the other 42 patients who had not received RRT unless reached traditional RRT indication, were served as control. The primary outcome was in-hospital all-cause mortality.

Results: The 20 patients initiated early RRT after 6.4±3.6 days from ICU admission. The mean cumulative treatment time was 50.0±42.2 hours, the net ultrafiltration rate was 65.5±65.2ml/h. One patient in control group also received RRT after ICU admission due to AKI. No statistic difference was found in the two subgroups in baseline. 61.3% patients died during hospitalization. The median survival time was 12 days and the average observation time was 19 days. Kaplan-Meier analysis showed that the in-hospital all-cause mortality of early RRT patients was lower than control group(50.5% vs 66.7%, *p*=0.040). Univariate analysis and Cox proportional hazard regression also confirmed that early initiation of RRT was an independent protective factor(HR 0.21, 95%CI 0.06-0.74, *p*=0.014) for in-hospital all-cause death of severe Covid-19 after adjusting by SpO_2, lymphocyte proportion, albumin, LogNT-proBNP, LogInterleukin-6, mechanical ventilation and use of glucocorticoid. A figure that shows the course of disease indicates that early initiation of blood purification may decrease the death without multiple organs injuries(39% vs 0%, *p*=0.037).

Conclusions: Early initiation of blood purification could probably reduce the mortality of severe Covid-19. It was implied that it could delay occurs and reduce degrees of target organs injuries by cutting the peak load of cytokine storm. Further research in basic and clinical were needed to clarify the mechanism of blood purification in cytokine storm-related diseases.

PO0673

Incidence of New-Onset Proteinuria in AKI Associated with COVID-19 Is Not Greater Than It Is in AKI from Other Causes

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Background: Early reports of acute kidney injury (AKI) associated with COVID-19 have claimed high incidence of proteinuria. If so, it may suggest an AKI pathogenesis not solely related to ischemic acute tubular injury (ATI). We hypothesized that those claims result from observation bias. Therefore, we sought to investigate the rate of *de novo* proteinuria in AKI associated with COVID-19 (CoV-AKI) compared to that of AKI in the pre-COVID-19 era (non-CoV-AKI).

Methods: Hospitalized patients with CoV-AKI entered the cohort (n=161). As a control non-CoV-AKI group (n=186), we accessed a database of patients with AKI who underwent urinary sediment microscopy due to suspicion of an intrinsic cause of AKI (Sedi-AKI cohort, 2017-2019). We examined the incidence of proteinuria of any degree (1+ dipstick), significant [urine protein-to-creatinine ratio (UPCR) ≥ 0.5–3.0 g/g or 2+ dipstick] or overt [UPCR ≥ 3.0 g/g + 3+ dipstick].

Results: Median age were similar: 65 (34-95) and 60 (20-88) years for CoV-AKI and non-CoV-AKI, respectively. Women were 62% and 63% (p=0.86). Black race was more common in CoV-AKI (75% vs. 35%; p=<0.0001). ATI (ischemic and/or toxic) was the presumed cause of AKI in 75% and 71% of CoV-AKI and non-CoV-AKI, respectively. Incidence of any, significant or overt proteinuria were 123/148 (83%) vs. 127/184 (69%) (p=0.003), 98/148 (66%) vs. 81/184 (44%) (p=0.0001) and 14/148 (10%) vs. 23/184 (13%) (p=0.39), for CoV-AKI and non-CoV-AKI, respectively. Among those with significant proteinuria, no difference in median UPCR was found [0.69 vs. 0.69 g/g (p=0.23)]. Using baseline UPCR when available, rates of *de novo* significant and overt proteinuria were similar [57/124 (46%) vs 57/123 (46%) (p=1.00) and 6/124 (5%) vs 7/123 (7%) (p=0.75)]. Among overt cases who underwent kidney biopsy, collapsing glomerulopathy was found in 3/4 (75%) in the CoV-AKI group compared to 0/11 (0%) in the control (p=0.002).

Conclusions: The incidence rate of new onset proteinuria was not found to be increased in CoV-AKI and is consistent with that of other forms of ATI. An observed overall greater incidence in significant proteinuria in CoV-AKI may be driven by preexisting proteinuria. While the rate of overt proteinuria is not greater in CoV-AKI, the primary cause of *de novo* glomerular disease may vary.

PO0674

AKI Perspectives and Practices in Latin America (LA) During COVID-19: Analysis from GlomCon Latin America Working Group

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Background: The epidemiology, clinical presentation, management and outcomes of COVID-19 comes from early reports from China and Europe with AKI prevalence ranging widely from 0.5% to 29%. However, knowledge about this pandemic is still emerging. With the epicenter now in the western hemisphere, we aim to determine the behavior and possible differences in presentation of AKI in COVID-19 patients in Latin America. To our knowledge, this is the first of such study.

Methods: Descriptive analysis extracted from an online survey carried out among nephrologists, renal pathologists and other health workers treating kidney diseases between May 20-27, 2020 from sixteen Spanish speaking Latin American countries divided into 6 categories. We present the results for the AKI category.

Results: 430 responses were obtained of which 360 (84%) were considered for analysis. 86% of the participants were nephrologists. 35% of the respondents reported the prevalence of AKI to be <5%, while 32% estimated it at 6-10%. The majority of AKI in these patients was stage 3 according to 31% of the respondents. Roughly half of the nephrologists witnessed new onset proteinuria which was almost exclusively (96%) sub-nephrotic. The majority (64%) reported no hematuria. Half of the participants (50.2%) reported that renal replacement therapy (RRT) was never or rarely required. Intermittent hemodialysis was the main RRT used reported by 88% of those surveyed followed by continuous renal replacement therapy (33%), peritoneal dialysis (24%) and prolonged intermittent RRT (19%). The most common complications during RRT were hypotension (60.3%) and circuit clotting (36.6%). Over one third of the participants (35%) estimated the mortality of patients with AKI and COVID to be <20%.

Conclusions: Our survey highlights potential differences in the presentation, management and outcomes of AKI in patients with COVID-19 in LA; among those, a lower prevalence, higher need for RRT and lower mortality. More studies are warranted to better understand AKI in hispanic COVID-19 patients as well as its distinct characteristics compared to the rest of the world.

PO0675

AKI due to COVID-19 in the Intensive Care Unit: Analysis of a Brazilian Center

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Background: The kidney may be affected by coronavirus (COVID) in the setting of acute kidney injury (AKI) or glomerular diseases. Data about AKI in Intensive Care Unit (ICU) patients of Latin-America are scarce. The aim of this study is evaluate the risk of AKI, dialysis (HD) and death in ICU patients diagnosed with COVID pneumonia in a brazilian center.

Methods: Analysis from medical records of ICU patients with diagnosis of COVID pneumonia in a brazilian single-center. AKI was defined according to KDIGO criteria.

Results: During the period of February 2nd to May 4th, 95 ICU patients diagnosed with COVID were analyzed. There was predominance of male (64.2%), median age of 64.9 years, previous diagnosis of hypertension, diabetes and obesity in 51.6%, 27.4 and 30.5% respectively. AKI was diagnosed in 54 (56.8%) patients and 32 (59.2%) of them required HD. Mortality rate was 17.9%. Patients with AKI, compared to no-AKI were statisticaly significant more frequently hypertensive and diabetic, worse SAPS3 and SOFA scores and need for organ support therapies. Laboratory tests depicted more anemia, lymphopenia, and higher levels of inflamatory markers as well as longer lenght of stay in ICU, hospital and death. Similar findings were seen in those ones who required HD compared to those with conservador treatment. Comparing patients who undergone death to survivors, they were older, more frequently diabetic, worse SAPS3 and SOFA scores and need for organ support therapies, AKI and dialysis. Multinomial logistic regression predicted that hypertension (p=0.01), mechanical ventilation (p=0.01) and use of hydroxychloroquine (p=0.009) were independent risks factors for AKI; hypertension (p=0.002), mechanical ventilation (p=0.03), use of vasopressor (p=0.04), and use of hydroxychloroquine (p=0.009) for HD patients; and age >65 years (p=0.03) and AKI (p=0.04) for death.

Conclusions: In our study, AKI was a common complication of ICU COVID patients, it was associated to hypertension, organ support therapies and use of hydroxichloroquine. As well as age >65 years, AKI was an independent risk fator to death.

PO0676

AKI in Patients with COVID-19 Infection: Preliminary Data from AKI COVID-19 Registry of the Spanish Society of Nephrology

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Background: SARS-CoV-2 coronavirus pandemic has significant impact on the general population, and chronic hemodialysis patients presented a poor prognosis with a mortality rate around 25%. Data from severe acute kidney injury(AKI) and acute renal replacement therapy(RRT) is scarce. We present the preliminary results of AKI COVID-19 Registry of the Spanish Society of Nephrology.

Methods: The online Registry began operating on May 21th. It collects epidemiological variables, contagion and diagnosis data, signs and symptoms, treatments and outcomes. Patients were diagnosed with SARS-Cov-2 infection based on PCR of the virus.

Results: One week after the AKI COVID registry started, 54 patients with AKI with RRT and COVID-19 from 11 Hospitals. Age was 64+9years and 55% men. 65% hypertension, 31% diabetes mellitus, 14% cardiovascular disease, 26% chronic kidney disease, 6% neoplasm, 29% obesity, 8% chronic obstructive pulmonary disease, and

6% smokers. Previous treatment: 10% immunosuppressive, 20% ACEi, 25% ARBs, 14% antiplatelets, and 10% anticoagulants. Clinical characteristics: 92% common respiratory symptoms, 96% pneumonia, 90% required intensive care unit(ICU) and 87% mechanic ventilation. 32% albuminuria, 18% hematuria, and 50% AKI with preserved urine output. Time from COVID-19 symptoms start to AKI 12.3+8days, time ICU 19.8+5days. APACHE at UCI admission 15+7. 81% lymphopenia. RRT was needed in 91% 13.4+12days: 55% received continuous RRT, and 72% anticoagulation. Kidney biopsy was not performed. Mortality 46.3% (60% males), and 4% remained under RRT. Time from AKI to renal function recovery 25+14 days. 65.2% death patients had hypertension. No differences were observed in comorbidities, chronic treatments, renal clinical characteristics, dialysis modality and mortality. Decreased lymphocyte count was associated with worse patient prognosis (dead 495±260 vs. survivors 789±460,p=0.023).

Conclusions: The mortality in AKI with RRT and COVID-19 is alarming high. Severe AKI associated with COVID-19 disease is more frequent in males. Interestingly, half of the patients preserved urine output. Severe lymphopenia was associated with mortality. More data from the AKI COVID-19 registry will help us to enlighten the prognosis and risk factors associated to mortality.

Funding: Government Support - Non-U.S.

PO0677

AKI in People Living with HIV Hospitalized with COVID-19

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Background: People living with HIV (PLWH) have an increased burden of kidney disease and unique factors that may place them at increased risk for acute kidney injury (AKI) in the setting of COVID-19. The aim of our study was to characterize the incidence, risk factors and outcomes of AKI among hospitalized PLWH with COVID-19.

Methods: We performed a retrospective study of adult PLWH hospitalized with laboratory-confirmed COVID-19 in a large healthcare system in Bronx, New York from March 10-May 11, 2020. Data collected included demographics, comorbidities, antiretroviral therapy (ART), initial laboratory data, and preadmission CD4 count and HIV viral load. AKI was defined and staged using KDIGO criteria. Fisher and Wilcoxon tests compared differences in those with and without AKI.

Results: During the study period, 77 PLWH were hospitalized with COVID-19. The majority were Black or Hispanic, 50% were men, 53% had hypertension, 31% diabetes mellitus, 22% chronic kidney disease (CKD) and 14% end-stage kidney disease (ESKD). Mean CD4 count was 470 cells/uL and 83% had a suppressed HIV viral load (<40 copies/mL). After excluding 11 with ESKD, AKI incidence was 50%. Those with AKI were older [63 (SD 9) vs 55 (SD 13) years, p=0.005], more were black (56% vs 37%, p=0.01) and more had CKD (42% vs 9%, p<0.0001) compared to those without AKI. There were no significant differences in CD4 count, HIV viral load, or use of tenofovir-containing ART between those with and without AKI. By AKI severity, 11/33 (33%) were stage 1, 4/33 (12%) stage 2 and 18/33 (55%) stage 3. Mechanical ventilation (33% vs 0%, p=0.0004) and in-hospital mortality (42% vs 3%, p=0.0002) were more common in those with AKI. Of 6 patients who required renal replacement therapy, 4 died and 2 remained RRT dependent. Admission white blood cell count, neutrophil/lymphocyte ratio, D-dimer, ferritin, C-reactive protein and lactate dehydrogenase levels were significantly higher in those with AKI.

Conclusions: The incidence of AKI in PLWH hospitalized with COVID-19 was high and associated with poor outcomes. We did not identify HIV-specific risk factors for AKI in the setting of COVID-19. Admission inflammatory markers may be predictive of AKI in PLWH with COVID-19.

PO0678

AKI Is Related to Mortality in COVID-19 Patients Without Underlying Kidney Disease

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Background: Due to its high infectivity and mortality, coronavirus disease 2019 (COVID-19) has become a global public health issue. The kidneys act as critical metabolic organs, therefore, whether COVID-19 can induce renal damage is of utmost importance but remains controversial, and the prognosis of COVID-19 encountering acute kidney injury (AKI) is unknown. Moreover, the efficacy of different treatments that COVID-19 patients undergo needs to be explored. In this study, we aimed to explore these questions.

Methods: A single-centered, retrospective study was conducted in which 96 patients with COVID-19 were enrolled. Epidemiological, clinical, and laboratory characteristics, as well as treatments and patient outcomes were described. Characteristics were compared between severe cases and critical cases. Relevant factors of AKI were filtrated, and the treatment efficacy was also evaluated.

Results: A total of 6 patients (6.3%) died during hospitalization. Four patients (4.2%) developed AKI, among which 3 patients (75%) died. Statistical analysis indicated that AKI was not common in COVID-19 patients without underlying kidney disease, but was related to mortality. Age, severity of disease, procalcitonin, C-reactive protein and interleukin-6 were correlated with AKI onset in COVID-19 patients, while lymphocyte count and estimated glomerular filtration rate at admission were inversely related to the development of AKI.

Conclusions: In conclusion, AKI is not common in COVID-19 patients without underlying kidney disease but related to mortality.

Funding: Government Support - Non-U.S.

The relationship between AKI and outcome of study population

	Total(n=96)	AKI(n=4)	Non-AKI(n=92)	P-value
outcome				0.001**
dead	6	3	3	
survivor	90	1	89	

**-P≤0.001

The relationship between AKI and outcome of study population

	Total (n=96)	AKI (n=4)	Non-AKI (n=92)	P-value
Outcome[a]				0.001**
Dead	6	3	3	
Survivor	90	1	89	

[a]-using fisher exact test, *-P<0.05, **-P≤0.01

The variables related to AKI by spearman correlation analysis

		condition	age	lymphocyte	CRP	PCT	eGFR	IL-6
AKI	r_s	0.275	0.213	-0.207	0.255	0.266	-0.237	0.307
	P-value	0.007**	0.037*	0.043*	0.012*	0.010**	0.020*	0.011*

AKI=acute kidney injury, r_s: correlation coefficient, CRP=C-reactive protein, PCT=procalcitonin, eGFR=estimated glomerular filtration rate, IL-6=interleukin-6, *-P<0.05, **-P≤0.01

PO0679

Acute Peritoneal Dialysis with Percutaneous Catheter Insertion for COVID-19-Associated AKI in Intensive Care: Experience from a UK Tertiary Centre

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Background: During the COVID-19 pandemic in 2020, high rates of acute kidney injury (AKI) in critically unwell patients are being reported, leading to increased demand for renal replacement therapy (RRT). There are considerable challenges providing RRT for large numbers of patients with COVID-19 and alternatives to continuous veno-venous hemodiafiltration therapies (CVVHDF) in intensive care units (ICU) are needed in both high and low-resource settings. Peritoneal dialysis (PD) can be initiated immediately after percutaneous insertion of the catheter, but there are concerns about impact on ventilation and RRT efficacy. We describe our recent experience of percutaneous catheter insertion and peritoneal dialysis in patients in ICU with COVID-19 infection.

Methods: Patients were selected according to local protocol and catheters inserted percutaneously using Seldinger technique by two experienced operators. Sequential Organ Failure Assessment score (SOFA) and ventilation requirements were recorded at time of insertion, and at 24 hours after insertion. Procedure complications, proportion of RRT provided by PD, renal recovery and RRT parameters during PD were assessed.

Results: Percutaneous PD catheters were successfully inserted in 32/39 (82.1%) patients after median of 10.0 (IQR 13.0, 19.0) days on ICU. No adverse events following insertion were reported, SOFA scores and ventilation requirements were comparable before and after insertion and adequate RRT parameters were achieved. Median proportion of RRT provided by PD following catheter insertion was 90.2% (IQR 77.5, 100).

Conclusions: PD provides a safe and effective alternative to CVVHDF in selected patients with AKI and COVID-19 infection requiring ventilation on intensive care.

Clinical Parameters of Patients Prior to and after Peritoneal Dialysis Catheter Insertion

Parameter, Median (IQR) N=31(1 Missing)	24 hours Prior to PD Catheter Insertion	24 hours After PD Catheter Insertion
Lowest PaO2: FiO2 Ratio	22.0 (18.3, 30.0)	22.5 (18.5, 31.0)
SOFA Score	16.0 (15.0, 16.0)	16.0 (15.0, 17.0)
Requirement for vasopressor support (N (%)) Median maximal dose of norepinephrine (μg/kg/min)	18 (46.2%) 0.13 (0.08, 0.22)	16 (41.0%) 0.17 (0.07, 0.32)

IQR: interquartile range; PD: Peritoneal Dialysis; PaO2 : FiO2 ratio (arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction)); SOFA: Sequential Organ Failure Assessment

PO0680

Adding Heparin to Citrate in Continuous Renal Replacement Therapy May Extend Filter Lifespan in COVID-Related AKI

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Background: COVID may predispose patients to thrombosis and lower filter lifespan. Association between D-dimer level (DD) and filter clotting in Continuous Renal Replacement Therapy (CRRT) has not been described.

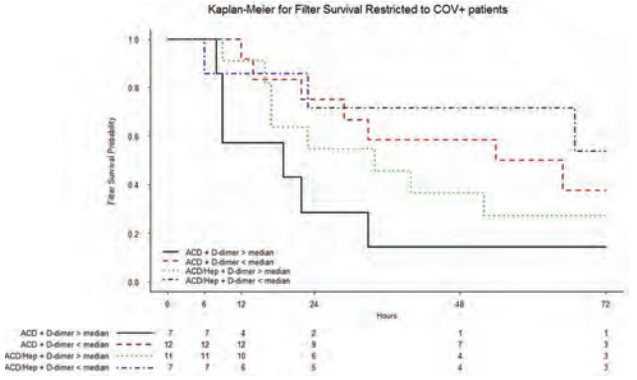
Methods: All patients who needed CRRT in Hospital das Clínicas (Brazil) during March to May 2020 (COVID related-AKI (COV+), n=37) and August to September 2019 (COVID unrelated-AKI (COV-), n=18) were studied. Anticoagulation in CRRT in COV+ was done with citrate 3mmol/L (ACD, n=19), or citrate 4mmol/L plus non-fractioned heparin 10U/Kg/h (ACD/Hep, n=18), while in COV- with citrate 3mmol/L only. Data are expressed in median [IQR]. We performed Spearman's correlation between DD and time-free of filter clotting (TFC), and Kaplan-Meier curve to study filter survival by anticoagulation method and DD.

Results: ACD/Hep group presented lower filter clotting in 72h when compared to other groups (ACD/Hep: 35% vs ACD: 100% vs COV-: 80%, p< 0.05). Analyzing

filter clotting per patient-day, ACD/Hep also presented less clotting than ACD group (ACD/Hep: 41% vs ACD: 100%, p< 0.05). In COVID patients, median TFC was 33.5 h [17.0;72.0] (ACD: 29.0 h [13.0;68.5], ACD/Hep: 40.0 h [17.0;62.0], p: NS). Clotting time from obese patients did not differ from non obese patients (obese: 31.0 h [18.5;57.2] vs non-obese: 56.0 h [16.8;72.0], p: ns). Median DD in all COVID patients was 3,519 [1420-13,883]. Patients with DD below median (<3,500) had higher TFC (ACD high DD: 19.0 h [9.00;27.5], ACD/Hep high DD: 34.0 [17.0;62.0], ACD low DD: 57.0 h [27.2;66.8], ACD/Hep low DD: 67.0 h [26.0;72.0]; Figure 1). There was statistically significance in correlation between DD and TFC in ACD patients, but not in ACD/Hep group.

Conclusions: Heparin may extend filter lifespan in CRRT, and this benefit seem to be greater in high DD patients.

Funding: Government Support - Non-U.S.



PO0681

A Retrospective Observational Study Comparing the Frequency of CRRT Clotting in COVID-19 Positive vs. Negative Patients

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Background: Coronavirus disease 2019 (COVID-19) emerged from China in late 2019 as a respiratory disease of unknown cause. A novel coronavirus 2019-CoV was implicated as the cause. A high proportion of patients goes into septic shock from COVID-19infection and develop acute kidney injury (AKI) which often requiring continuous renal replacement therapy (CRRT). Clinical experience has suggested that these patients are hypercoagulable with studies showing increased rates of thrombosis. This complicates the administration of CRRT as this leads to more frequent clotting of the dialysis catheter and sequelae of blood loss, time off dialysis, and increased use of resources

Methods: We retrospectively audited all patients admitted at our center from February to April 2020 who developed severe AKI requiring CRRT and compared the number of CRRT clotted in the first 7 days in COVID-19 negative (N = 49) and positive (N = 55) patients. Pediatric patients were excluded from this analysis. We also collected data on other variables which may influence rate frequency such as location of catheter, INR, and presence of systemic anticoagulation

Results: We found that patients who tested positive for COVID-19 had a higher number of clotting events in the first 7 days of CRRT (3.51 vs 1.63, p < 0.00008). This population had higher incidence of AKI vs ESRD, number of pressor, and PEEP. Also, COVID 19 patients on anticoagulation has decreased clotting frequency compare to COVID 19 positive patients not on anticoagulation (2.7 vs 4.3, P <0.05)

Conclusions: This data confirms our clinical experience that coagulopathy in COVID-19 positive patients lead to a greater incidence of CRRT clotting and the use of systemic anticoagulation was effective in reducing the number of clotting events

PO0682

A Retrospective Study of Critically Ill Patients with COVID-19 and Anticoagulation Used Throughout CRRT

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Background: Studies indicate that 5% of patients with COVID-19 develop critical illness, warranting ICU level of care. Up to 15% of these critically ill patients develop acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). COVID-19 also appears to generate a pro-thrombotic state in some patients and thrombosis during CRRT could prevent life sustaining clearance and fluid removal.

Methods: In this single center study, we performed a retrospective chart review of patients admitted to Montefiore Medical Center, with a confirmed diagnosis of COVID19 in an ICU requiring CRRT between 3/10/2020 — 4/28/2020. Subsequently, we categorized the different anticoagulation (AC) types that were used for each CRRT treatment: no AC, heparin, bivalirudin, apixiban. The primary outcome was to determine the percent of achieved versus prescribed CRRT in patients treated without AC, heparin, or bivalirudin (dosing > 0.25 mg/kg/hr, versus < 0.25 mg/kg/hr). The secondary outcome was to determine the percent reduction in BUN and potassium within 10 hours of CRRT.

Results: We excluded patients with renal failure requiring renal replacement therapy (RRT) that did not have a confirmed diagnosis of COVID19, as well as patients with a previous history of thrombosis. We were left with 69 patients, whom we analyzed the first three RRT treatments of each patient. The average age was 59.48 years, 81.2% male, 18.8% female. 15% of patients were African American, 5% Caucasian, 31% Hispanic, and 17% identified as other. The average BMI was 30.2. 40% of patients had diabetes mellitus, 49% hypertension, and 14% CKD or ESRD. We analyzed a total of 162 RRT treatments. Of these 162 treatments, 49% of patients received bivalirudin, 27% heparin, and 23.4% did not receive AC. We found that 84.5% of patients receiving bivalirudin completed their CRRT treatment, 77.7% receiving heparin completed treatment, and 59.3% of patients not on AC completed treatment.

Conclusions: Patients with a confirmed diagnosis of COVID 19 that are critically ill and receive CRRT are more likely to finish their CRRT treatment, and therefore achieved improved clearance, if they were given some form of AC to prevent clotting.

PO0683

Association of Ventilatory Time and AKI in a Bronx Cohort of COVID-19 Patients

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Background: The relationship of lung-kidney interactions in COVID19 has not been well described. AKI has been associated with increased mechanical ventilation times. Recent publications have shown a strong association of COVID19-AKI with mortality and a high incidence of AKI occurring peri-intubation. We hypothesized that mechanical ventilation (MV) time would be increased in patients with COVID19-AKI and longer in those with severe AKI.

Methods: We analyzed a cohort of incident COVID19 patients who required MV. Patients with end stage renal disease were excluded. AKI was defined using KDIGO criteria (0.3 mg/dL increase or greater than a 50% increase from the baseline Cr) between the maximum Cr and baseline Cr. AKI stage was defined by KDIGO criteria. Days of total MV was measured in days from date of initial intubation, including subsequent intubation/extubation events, until successful extubation or death. Censored data was not included. Linear regression models were utilized to evaluate associations.

Results: We analyzed 318 patients. 62% were male, 37% were black/African American and 33% were Hispanic/Latino. Hypertension was prevalent in the cohort (N=212) and over 50% were obese. Median MV time was 4.67 days (IQR 1.76, 9.95). AKI occurred in 89% (N=283) of the cohort. Stage 3 AKI developed in over 50% (N=161) of patients. In models adjusted for age, hypertension, diabetes and disease related group weight, patients with AKI had 3.46 more days of MV, however this finding did not reach statistical significance (95%CI 0.92-6.00). This association however was significant and increased linearly with stage of AKI (p for trend <0.001).

Conclusions: This is one of the first studies to evaluate the association of COVID19-AKI and MV time. Even after adjusting for severity of illness, patients with increased stage of AKI had longer MV times. This may be due to pathophysiologic kidney-lung interactions seen in non-COVID19 disease and/or direct effect of COVID19 on the kidneys. As few patients in our cohort were spared from kidney injury, inferences comparing those with and without AKI are difficult to discern. We plan to explore this question in a larger cohort to determine whether COVID19-AKI alone is associated with ventilatory time.

Funding: NIDDK Support

PO0684

Can the AKI Alert Staging Tool Help Manage Patients Admitted During the COVID Pandemic?

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Background: Basildon & Thurrock University Hospital has the second highest rate of hospital admissions with AKI stage 3 in the United Kingdom based on Renal Registry Hospital Episode Submission Data. Acute kidney injury (AKI) is common in hospitalized patients and carries a higher risk of mortality. Given the limitations of resources both personnel and equipment, a retrospective study was done to see if the AKI alert staging tool could help predict and direct resources to those patients who would benefit most from specialist intervention.

Methods: Data was reviewed from January - May 2020. This corresponded to the peak of admissions and by the end of the period, the hospital was on course to returning to pre pandemic activity. Relevant data including admission laboratory tests and imaging was collected. The admission stay was analysed for duration, the need for transfer to an intensive care environment to receive ventilator support and/or renal replacement therapy. Discharge destination was reviewed and whether the patient was discharged home, to another facility or did not survive the admission. For comparison we looked at the same period in the preceding year as this would represent the most matched population.

Results: Over 5000 AKI alerts were generated for this period for 4390 unique admissions. This compares to 3910 AKI alerts for 1098 unique admissions for the identical period in the previous year. The vast majority were for AKI stage one alerts none of which were in COVID positive patients. A significant proportion of patients with AKI Stage 2 and 3 alerts were positive for COVID. Those that were admitted to Intensive Care with Stage 3 AKI almost always required intubation and renal replacement therapy. Mortality was higher in this group.

Conclusions: The AKI alert system helps identify patients who are unwell and can benefit from Nephrologist input at an early stage. The Alert algorithm excludes haemodialysis patients, therefore this population was excluded. During the COVID pandemic there was a clear increase in AKI admissions and alerts creating a substantial demand on renal services. Specialist intervention should be directed to AKI alert stage 2 patients where intervention can help prevent progression into AKI stage 3 and subsequent ICU admission. AKI stage 1 patients who are COVID negative can be managed without specialist input.

PO0685

Characteristics and Outcome of AKI Needing Dialysis with COVID-19 Infection

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Background: COVID-19 infection has varying grades of mortality worldwide. Multi-organ injury, not uncommonly associated with AKI, portends a poor outcome. We studied AKI needing hemodialysis (HD) in the context of COVID-19 infection

Methods: From March 15th to May 25th 2020, for consecutive COVID-19 infections AKI needing HD in a large dialysis network age, gender, payer type, days:admission to HD start, urine output, S. Cr, comorbidities, other organ injuries, length of stay & outcome, dialysis session details: blood flow rate(BFR), dialysis flow rate(DFR), ultafiltration volume were reviewed. We compared survivors and non survivors using Mann Whitney/ Wilcoxon 2 sample test for medians and Fisher exact 2 tailed for association

Results: n = 20. Mean age: 56. 7 + 3.93 years. M:F 17:3, 9 survived, 11 expired. HD sessions=51; CRRT: 4, duration: 29.2 ± 25.4 hours. 47 sessions: Duration: 4.87 ± 1.11 hours, BFR: 195 ± 43 ml/min, DFR: 389 ±99 ml/mn, UF: 437ml/hour. No clotting reported.

Conclusions: AKI needing HD in COVID-19 infection is associated with significant multiorgan injury and high mortality; middle aged male predominate. No significant clinical characteristics were predictive of survival in a sample size

Comparison of survivors and non survivors of COVID-AKI needing HD

	Survivors (n= 9)	Non survivors (n=11)	p value
Age (yrs)	56	55	0.68
M/F (%)	88.9/11/.1	81.8/18.2	1.0
Self pay or povate Insurance/public Insurance (%)	77.7/22.2	81.8/18.2	
Htn (%)	33.3	27.3	1.0
DM (%)	11.1	36.4	.31
Altered Mentation	88.9%	63.6	.32
Vasopressor use (%)	22.2	45.5	.37
Ventilator (%)	47.37	52.63	1.0
Admission to HD start interval (days)	2	1	0.87
Oliguria (%)	88.9	90.9	1.0
S. Creatinine (mg%)	6.16	3.00	0.09
No of HD	2	2	0.65
Hb (g%)	9.6	10.8	.17
TC (/MM3)	9878 ± 4950	23962 ± 22221	
Hospital stay (days)	24	13	.60
Antivirals Rx (%)	66.7%	90.9%	.28
Steroid Rx (%)	66.7%	81.8%	.61

PO0686

Circuit Clotting on Continuous Venovenous Hemofiltration in COVID-19 Patients at New England's Largest Health Safety-Net Hospital

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Background: The pandemic of COVID19 led to a surge in critically ill patients with severe kidney failure requiring continuous renal replacement therapy (CRRT). Primary reports rapidly showed a hypercoagulable state associated with cytokine storm representing a challenge to conduct CRRT. We report our experience to face clotting on continuous venovenous hemofiltration (CVVH) with COVID19 patients.

Methods: We reviewed data on all admitted patients with COVID19 diagnosis and requiring CVVH at Boston Medical Center between March, 15th and May 7th, 2020. The study was approved by the institutional IRB.

Results: Twenty six patients were admitted to ICU with COVID19 disease and developed acute kidney injury requiring CRRT. The majority of patients were males (73%), and mean age was 64.3 (+/ 9.4) years. At dialysis initiation, patients showed marked inflammatory state with a median CRP of 239mg/dl (IQR 123-391.5), fibrinogen 609mg/dl (431-693), d-dimer 4,036 ng/ml (1,777-15,558). CVVH was conducted in predilution mode, with a median therapy rate of 3L/h (2.5-3.1) and a mean blood flow of 280 mL/min. The median cartridge half-life from CVVH initiation was 11.8 hours (3.5-20). Twelve patients (46%) experienced CVVH circuit clotting within the first 24 hours, including 6 patients (23%) with severe recurring clotting. Curative systemic anticoagulation by heparin was used in 12 patients (46%) based on hospital protocol. Its use was associated with mild improvement in cartridge half-life: 15h with curative heparin dosing compare to 11.25h with no/ low dose preventive anticoagulation (non-significant). Of note, heparin was held prior to CRRT initiation for dialysis catheter placement and was reinitiated without bolus, which could lead to early coagulation of the filter in patients with hypercoagulable state. The fatality rate was 76.9% with a median time from CVVH initiation to death of 2.5 days (1 - 8.75).

Conclusions: Conducting CRRT in patients with multiorgan failure secondary to COVID19 is challenging. Our experience suggests only a mild non significant improvement of clotting prevention with heparin anticoagulation at the time of cvvh initiation. Further studies are warrantied to determine the optimal anticoagulation regimen.

PO0687

Clinical Characteristics and Short-Term Outcomes of Severe AKI in COVID-19 in Bronx, New York

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Background: After the first reported case of COVID-19 in the U.S., New York City quickly became the epicenter of the pandemic. AKI has been reported in patients with severe COVID-19. The Bronx consists of a predominantly minority population with a high burden of comorbidities that may be at increased risk for AKI in the setting of COVID-19. We aimed to characterize risk factors and short term outcomes in patients hospitalized with COVID-19 and severe AKI.

Methods: We performed a retrospective study of 113 adults hospitalized with COVID-19 in a large healthcare system in the Bronx who required nephrology consultation for AKI from March 11-March 30, 2020. We extracted data on demographics, comorbidities, admission vital signs and labs, need for mechanical ventilation, renal replacement therapy (RRT), in-hospital death and discharge. AKI was defined by KDIGO criteria. Chi-square analyses and Wilcoxon tests were used. Data was censored on April 12, 2020. All patients had ≥ 14 days of follow up.

Results: Mean age was 63 (SD 12) years old; 69% were men and 33% were Black and 23% were Hispanic. Forty-five patients (39.8%) had chronic kidney disease, 58(51%) had diabetes mellitus and 87(77%) had hypertension. The majority presented with AKI within 24 hours of admission and 75% had Stage 3 AKI. Ninety-two (81%) patients had proteinuria and 53(47%) had hematuria. Intensive care unit (ICU) was required in 62(55%), 64(57%) required mechanical ventilation, 56(49.5%) required RRT and 18(16%) were not candidates for RRT. In-hospital death occurred in 68(60%) and 22% were discharged. Of those who required RRT, in-hospital death occurred in 35(62.5%) and only 6 patients were discharged, 5 of whom remained RRT dependent. Heavy proteinuria (3-4+ on urinalysis) and initial C-reactive protein (CRP) were higher in those with AKI who died [21.1 (IQR 14.3-29.6) versus 6.6 (3.2-16.3), p<0.001].

Conclusions: Severe AKI in the setting of COVID-19 is associated with increased utilization of ICU, mechanical ventilation, and RRT. Outcomes are poor in those with Stage 3 AKI, underscoring the need for palliative care involvement and early goals of care discussions. Elevated initial CRP and heavy proteinuria may be useful to risk stratify patients with COVID-19 and severe AKI at increased risk for mortality.

PO0688

Clinical Factors Associated with AKI in Patients with COVID-19 from a University Hospital in Brazil

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Background: Critically ill patients with COVID-19 frequently presents Acute kidney Injury (AKI) associated with increased mortality. However, there is paucity of data from Brazil. So, we analyzed factors in associated with AKI patients in a university hospital.

Methods: We conducted an observation with frequencies and association with binary logistic regression study in patients with COVID-19 hospitalized at Hospital Sao Paulo-Federal University of Sao Paulo. Diagnosis and classification of acute kidney injury (AKI) were by KDIGO. We examined the rates of renal function, mechanical ventilation (MV), renal replacement therapy (RRT), medications and in-hospital mortality.

Results: We observed a total of 172 in-patients with COVID-19. Patients were predominantly male (61,5%). We observed hypertension in 55%, diabetes 34%, smokers 27%, obesity (19%). Eighty-nine (52%) patients needed intensive care unit (ICU)], 70 (79%) cases of AKI were in ICU (31% of general ward admissions; p<0,001). In the ICU there were 78% needed mechanical ventilation, 36% in RRT, amine vasoactive 65% and mortality in 48%. AKI patients were older (61±15, 55±15; p=0.01), higher creatinine in admission (2.6±1.6, 1.3±0.7; p=002), higher RDW (14.7±1.5, 13.3±1.6; p=0.08), needed of MV (88%) and vasoactive amine (90%), RRT (88%) and higher mortality (87%). We used serum creatinine, age, RDW, mechanical ventilation and vasoactive amine in model of regression. We observed that MV (OR 1026 [CI95%, 1009-1038; p<0.001) and age (OR 1030 [CI95%, 1004-1056; p=0.002) were independently associated with AKI.

Conclusions: AKI is associated with high rates of RRT and death. Higher age and need of mechanical ventilation were associated with AKI in COVID-19 patients.

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PO0689

Community and Hospital-Acquired AKI in COVID-19

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Background: AKI is a frequent complication of COVID-19. We describe characteristics of patients with COVID-19 who developed both, community-acquired AKI (CA-AKI) and hospital-acquired AKI (HA-AKI) in a Mexico City reference COVID-19 center.

Methods: We included data from all consecutive patients hospitalized between March 16th - May 29th 2020, with pneumonia and positive SARS-CoV-2 by RT-PCR test. Only data from patients who finished follow-up (n=636) was analyzed. AKI was defined according to KDIGO and ESKD patients (n=6) were excluded. Clinical and demographic characteristics of those with CA-AKI, HA-AKI, and non-AKI were compared by non-parametric ANOVA.

Results: Of 630 COVID-19, AKI was detected in 164 (26%), 81 (49%) CA-AKI, and 83 (51%) HA-AKI. Among AKI, 84 (51%) were Stage 1, 38 (23%) Stage 2, and 42 (26%) Stage 3. Stage 3 was more frequently observed in HA-AKI (p<0.001). RRT was provided to 15 (9.1%) at a median 3 days from diagnosis. Fluid overload was the main indication for RRT initiation. In general, AKI was associated with higher severity of COVID-19 evidenced by several risk scores, ICU admission, mechanical ventilation, and vasopressor therapy. Recovery from AKI was more frequent in the CA-AKI group 66% vs 44 % (p<0.001), and often associated to volume depletion reverted with fluid management. Among patients with AKI, 92 (56%) died, 49% in the CA-AKI vs. 63% in the HA-AKI group (p<0.001). There were no differences in RAAS inhibitor use between groups.

Conclusions: CA-AKI and HA-AKI are frequent renal manifestations in COVID-19. AKI is associated with more severe COVID-19 and significantly higher mortality. Although more comorbidities were present in CA-AKI, outcomes were better for CA-AKI vs. HA-AKI, in spite the latter group being younger, as it represents ICU patients with severe COVID-19 disease and associated multiorgan failure.

Table 1. Characteristics and In-hospital outcomes for CA-AKI versus HA-AKI.

	Non-AKI (N=466)	CA-AKI (N=83)	HA-AKI (N=81)	*P* value
Age (yr), median (IQR)	51 (41-61)	61 (47-68)	51 (45-62)	<0.001
Male, n (%)	292 (63)	59 (71)	57 (70)	0.176
Comorbidities, n (%)				
Diabetes mellitus	116 (25)	33 (40)	28 (35)	0.008
Hypertension	117 (25)	37 (45)	24 (30)	<0.001
Chronic kidney disease	13 (3)	12 (15)	6 (7)	<0.001
BMI (kg/m²), median (IQR)	29.1 (26.4-31.8)	29.6 (25.9-33.3)	29.4 (27.2-32.9)	0.293
C-reactive protein (mg/dL)	13.1 (5.5-20.1)	18.8 (13.7-28.2)	20.0 (13.3-28.1)	<0.001
CPK (mg/dL)	97 (55-207)	120 (69-273)	180 (96-386)	<0.001
LDH (mg/dL)	348 (265-455)	477 (342-624)	468 (368-585)	<0.001
D-Dimer (ng/mL)	703 (426-1158)	978 (549-2042)	825 (566-1712)	<0.001
Days admission to AKI, median (IQR)	-	-	3 (2 -6)	<0.001
Renal replacement therapy, n (%)	-	2 (3)	13 (16)	<0.001
SLED	-	-	11 (85)	
CRRT	-	1 (50)	2 (15)	
IHD	-	1 (50)	-	
Need for ICU admission, n (%)	122 (26)	49 (59)	74 (91)	<0.001
Mechanical ventilation, n (%)	38 (8)	12 (15)	68 (84)	<0.001
Vasopressor, n (%)	37 (8)	9 (11)	64 (79)	<0.001
ICU length of stay (d), median (IQR)	3 (1-9)	3 (1-6)	11 (5-20)	<0.001
In-hospital length of stay (d), median (IQR)	6 (4-9)	6 (2-9)	13 (6-23)	<0.001
Renal recovery, n (%)	-	54 (66)	39 (48)	<0.001
Mortality, n (%)	92 (20)	41 (49)	51 (63)	<0.001

PO0690

Is AKI in COVID-19 Patients Associated with Increased Mortality?

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Background: Acute kidney injury(AKI) affects 22% of hospitalised patients and is associated with a 21.9% increased risk of mortality in non COVID-19 admissions. Based on reports from China the rate of AKI in patients hospitalised with COVID-19 is 3-9%. The study's objective was to identify AKI prevalence in COVID-19 patients and associated adverse outcomes.

Methods: This is a retrospective observational cohort study of patients admitted to hospital with positive COVID-19 PCR testing from 14th February to 7th May 2020. Demographic data, past medical history and blood results were obtained from health records. AKI was defined according to KDIGO criteria.

Results: 383 patients (220 Male) were included in the final analysis, with an age range of 18-99 yrs(median 69 yrs). AKI occurred in 153(39.9%) patients (103 male), with a median age of 74 years. 111(72.5%) patients had AKI on admission, 42(27.5%) developed AKI while hospitalised. Average clinical frailty score (CFS) in the AKI group was 4. Median creatinine kinase in the AKI group was 213iu/L(IQR 149-1260). Of all 153 AKI patients;100(65.4%) were in Stage 1, 29(19%) in Stage 2 and 24(15.7%) in Stage 3. 14(9.2%) patients required renal replacement therapy (RRT) with 7(50%) becoming dialysis independent. 3 patients died and 4 transferred to specialist units for treatment whilst on RRT. Mean peak serum creatinine of 246umol/L was observed on Day 5 of admission and Day 11 of symptoms on average. 90/153(58.5%) patients had recovery of renal function. 40/76(53%) patients who required CPAP or mechanical ventilation respiratory support had evidence of AKI compared to 113/304(37%) of non-ventilated patients. Of all 153 AKI patients, 61(39%) deaths occurred compared to 43/228(19%) in the non-AKI group. This difference was significant, p<0.01, OR= 2.89 (95% CI: 1.81, 4.58) suggesting that patients with AKI had a 74% chance of increased death. Univariate analysis showed that age, males, baseline eGFR, albumin, CFS and Charlson comorbidity index were predictors of AKI. Multivariate analysis showed that independent predictors of AKI included males, Black and Asian race, baseline eGFR and albumin. An increase in baseline eGFR by 1ml/min in COVID-19 patients was associated with a 2.4% risk reduction in death, p<0.01, OR= 0.976 (95% CI: 1.02, 1.03).

Conclusions: AKI is a common finding and a poor prognosticator in patients with COVID-19.

PO0691

Kidney Injury in ICU Adults with Severe COVID-19

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Background: The SARS-CoV-2 infected humans through the angiotensin converting enzyme (ACE-2) receptor. Kidney, which highly expressed ACE-2, became one of the main target organs attacked by SARS-CoV-2. In this cross-sectional study, we aimed to explore renal injury in ICU adults with severe coronavirus disease 2019 (Covid-19).

Methods: Fifty-three severe Covid-19 adults, admitted into ICU (Tongji Hospital, Wuhan, China) from Feb.9.2020 to Mar.24.2020, were finally included in analysis. Baseline demographic, clinical characteristics, laboratory examination data and prognosis were all recorded.

Results: Mean age of 53 patients was 67.5±15.2 yrs, including 34 men and 19 women. The predominant comorbid conditions were as follows: hypertension in 26 patients (50.0%), diabetes mellitus in 11 patients (21.2%), cardiovascular diseases in 5 patients (9.6%) and chronic kidney disease in 2 patients (3.8%). The mean serum creatinine at baseline was 67.2±26.7 μmol/L, while the baseline urine routine before hospitalization was uninformed. In the period of whole ICU stay, most patients presented abnormal urine routine: 93.2% of patients had proteinuria (+/- 9.1%, 1+ 40.9%, 2+ 31.8% and 3+ 11.4%, respectively) and 97.7% had hematuria. 20 of 53 patients (37.7%) with mean age of 72.2±9.9 yrs diagnosed as hospital-acquired acute kidney injury, according to KDIGO 2012 AKI diagnosis creatinine criteria. In those AKI patients, 5(25%), 7(35.0%) and 8(40%) reached AKI stage I, II and III, respectively. AKI was diagnosed after 25.0±12.8 days since onset of Covid-19 and after 7.8±5.6 days since ICU admission. The mean duration of AKI course was 7.9±7.1 days. Finally, 16 of 20 patients with AKI (80.0%) died in ICU. The survival time of AKI patients was 32.9±14.6 days since onset of Covid-19 and 15.7±9.4 days since ICU admission. The in-hospital all-cause mortality of AKI patients was higher than non-AKI patients (80.0% vs 29.4%, *p*=0.004). Only one (5.0%) patient recovered from AKI during ICU stay (serum creatinine reduced ≥50%).

Conclusions: Kidney injury including abnormal urine routine and increased serum creatinine presented in almost all severe Covid-19 patients. AKI event could predict poor prognosis with severe Covid-19. We should increase awareness of kidney injury in patients with severe COVID-19.

PO0692

Association of Antiplatelet and Anticoagulation Therapy with Dialysis-Requiring AKI in Critically Ill Patients with COVID-19

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Background: Critically ill patients with COVID-19 have a high incidence of thrombotic complications and dialysis-requiring acute kidney injury (AKI-D). COVID-19 hypercoagulability has been implicated as a possible contributor to AKI-D. Our hypothesis is that pre-existing antiplatelet (APT) or anticoagulation therapy (ACT) is associated with a lower incidence of AKI-D in critically ill patients with COVID-19.

Methods: Records of patients with COVID-19 admitted to the ICU from March 13th -April 1st 2020 were reviewed. Exclusion criteria included ESRD status, and ICU discharge or death prior to 14 days of follow-up. Groups were divided based on APT or ACT prior to ICU admission. AKI-D was defined as initiation of renal replacement therapy (RRT) of any kind during the 14 days. Groups were compared using 2-tailed Fisher's exact test and unpaired t tests.

Results: A total of 149 records were reviewed, and 98 patients were included (47 died and 4 discharged). Twenty-three patients (23.5%) were on APT or ACT and 39 (40%) required RRT. Table 1 compares characteristics by study group. Hypertension and cardiac conditions were significantly different between groups. Twelve (52%) of patients on APT or ACT required RRT and 27 (36%) not on either required RRT (p=0.22).

Conclusions: Pre-existing APT or ACT was not associated with AKI-D in critically ill patients with COVID-19 and 2 weeks of follow up. Our study confirmed a high incidence of AKI-D but was limited by significant differences in cardiac conditions between study groups. Future larger studies examining this association in groups with comparable cardiac conditions are needed.

Table 1: Demographic and Clinical Characteristics

Characteristic	On AP or AC (n=23)	Off AP or AC (n=75)
Age, mean (SD), years	62 (12)	58 (13)
Males, n (%)	12 (52%)	50 (67%)
Cr, mean (SD), mg/dL	1.8 (1.4)	1.6 (1.9)
Diabetes, n (%)	10 (43%)	23 (31%)
Hypertension, n (%)	17 (74%)	38 (50%)*
Cardiac condition	16 (70%)	4 (5%)**
Lung condition	3 (13%)	13 (17%)
BMI, mean (SD), kg/m^2	35 (12)	31 (8)
RRT requiring AKI, n (%)	12 (52%)	27 (36%)

AP, antiplatelet; AC, anticoagulation; Cr, admission creatinine; Cardiac condition = coronary artery disease, congestive heart failure and/or atrial fibrillation; Lung condition = chronic obstructive pulmonary disease or asthma; RRT, renal replacement therapy; AKI, acute kidney injury; * = p-value = 0.06; ** = *p*-value <0.01

PO0693

COVID-Related AKI Recovery Courses with Negative Fluid Balance and Related Electrolyte Disorders

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Background: Acute Kidney Injury (AKI) occurs in 3-37% of COVID patients; recovery is poorly described.

Methods: All patients who recovered from AKI in Clinics Hospital (São Paulo, Brazil) during April 2020 (COVID related-AKI (COV+), n=35) and September 2019 (COVID unrelated-AKI (COV-), n=25) were studied for 1.5 month each. Recovery was represented by spontaneous serum creatinine (sCr) drop in patients not submitted to dialysis, or by withdrawal of dialysis in those who needed the therapy. Serum creatinine, urea (sU), sodium (sNa), bicarbonate (bic), and fluid balance (FB) were analyzed during the first five days of recovery (5-Dr). Data are expressed in mean ± SD. Repeated mesaures ANOVA was used to compare different days on each parameter, and t test was used to compare groups. Categorical data were analyzed using Fisher's test.

Results: Among 88 COV- patients, 25 recovered from AKI, while 35 in 102 COV+ patients recovered during the time studied (86% COV+ were in KDIGO 3 classification). In COV+ group, COVID-AKI time was predictive of AKI duration: earlier AKI (≤ 7 days from COVID symptoms) lasted 5.6 ± 4.0 days (vs 11.9 ± 9.2 days in later AKI presentation, p< 0.05). Both COV+ and COV- patients coursed with sCr and sU drop during 5-Dr, except for diuretic users, who presented sCr drop without sU drop. COV+ patients presented negative overall FB during 5-Dr, while COV- patients presented positive FB (-516.2 ± 2730 vs 225.5 ± 5686 ml/24h). In COV+, sNa rose through 5-Dr (p< 0.05), and in COV- it did not. Among diuretic users, the same patern of FB was seen between groups (-194.9 ± 3163 in COV+ vs 163.5 ± 1080 ml/24h in COV-), and COV+ showed increased sNa through 5-Dr (p< 0.05), while COV- reduced sNa through 5-Dr (p< 0.05). Diuretic users had bicarbonate increase in COV+ (from 24.3 ± 3.6 to 27.0 ± 4.9 mmol/L, p<0.05), but not in COV-. In diuretic non-users, both groups have risen sNa through 5-Dr, but only COV+ reached statistical significance. Diuretic use at AKI-recovery was higher in COV+ patients (57% vs 28%, p< 0.05).

Conclusions: Later-onset COVID-related AKI seems to be more prolonged. Diuretics should be carefully used in AKI-recovering COV+ patients, once hypernatremia and metabolic alcalosis are more common than in other AKI etiologies.

Funding: Government Support - Non-U.S.

PO0694

CRRT Circuit Patency in Patients with COVID-19 and AKI

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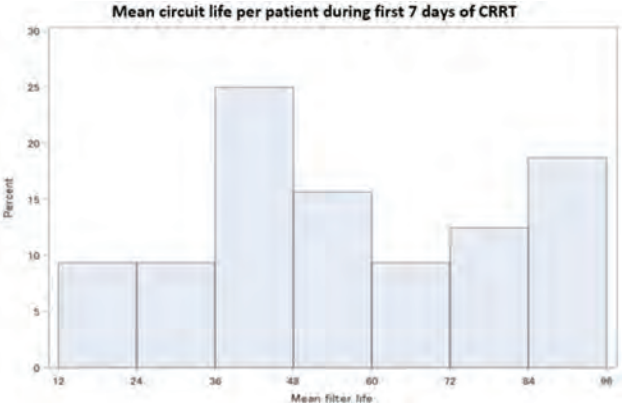
Background: COVID-19 is associated with AKI and hypercoagulable state, which may present challenges in delivering CRRT. We present our center's experience with CVVHDF with regional citrate anticoagulation (RCA) in COVID-19, with special attention to circuit life.

Methods: We performed a retrospective review of 32 consecutive patients with COVID-19 and AKI managed with CVVHDF-RCA at the University of Michigan. CVVHDF was prescribed according to institutional protocol consisting of a fixed blood flow to citrate ratio with target post-filter ionized calcium 0.2-0.4mmol/L. Replacement fluid was delivered post-filter. Primary outcome was mean circuit life per patient during the first 7 days of CRRT. We used Wilcoxon rank sum to examine whether systemic anticoagulation use associated with circuit life. We used univariate linear regression to assess the relationship between baseline inflammatory markers and circuit life.

Results: Prior to CRRT start, the median ferritin was 1587 (IQR 933-2219) ng/ml, d-dimer 6.0 (IQR 3.0-9.5) mg/ml and CRP 20.0 (IQR 8.6-33.0) mg/dl. The mean patient circuit life was 56.9 (SD 28.8) hours. Mean circuit life was 54.3 (SD 23.1) hours for those on systemic anticoagulation (n=23) and 63.6 (SD 29.1) hours for those without (n=9), p=0.39. There was no association between circuit life and inflammatory makers (ferritin p=0.92, CRP p=0.29, d-dimer p=0.24).

Conclusions: The circuit life in COVID-19 patients on CVVHDF-RCA at our institution was similar to our experience with non-COVID-19 patients, and longer than what has been reported in randomized controlled trials assessing anticoagulation protocols in CRRT. We found no association between systemic anticoagulation use or inflammatory markers and circuit life, further supporting that a standardized CVVHDF-RCA protocol with fixed blood flow to citrate rate provides an effective means of maintaining CRRT circuit patency in patients with COVID-19 infection at increased risk of clotting.

Funding: NIDDK Support



PO0695

Filter Clotting, Anticoagulation, and Duration of Sustained Low-Efficiency Dialysis in Patients with COVID-19 and AKI

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Background: There have been anecdotal accounts of shortened duration of renal replacement therapy (RRT) due to filter clotting in patients with COVID-19 and acute kidney injury (AKI) (CoV-AKI) requiring RRT (AKI-RRT). Thus, we examined the duration of runs of RRT in patients with CoV-AKI as well as in patients with AKI-RRT in the pre-COVID-19 era.

Methods: Among 161 patients with CoV-AKI, we identified patients with CoV-AKI who underwent RRT by sustained low efficiency dialysis (SLED) for ≥ 2 days (n = 52) (March-April 2020). As a control, we included patients with AKI without COVID-19 diagnosis who underwent SLED (n = 24) (non-CoV-AKI) in December of 2019, pre-COVID-19 era. We quantified the duration of RRT under various protocols of anticoagulation (AC) [no AC, citrate (CIT), regional heparin (rH), minimally intensive heparin (mIH), systemic low intensity heparin (sLH), systemic high intensity heparin (sHH) and sHH plus CIT (sHH+CIT)] by computing the duration (hours) of each SLED session (hrs of SLED/start) and the percentage of short SLED runs (< 6 hours).

Results: In CoV-AKI, the median hrs of SLED/start under each AC protocol were 6.1 for no AC, 5.4 for CIT, 10.6 for rH, 11.6 for mIH, 11.4 for sLH, 12.4 for sHH and 14.6 for sHH+CIT. As the AC intensified, the duration of SLED increased (chi-square for trend, p = 0.014). Pre-COVID-19, standard AC for non-CoV-AKI were no AC or CIT and had a longer median RRT duration compared to CoV-AKI under either no AC or CIT (10.2 vs 5.5 hrs of SLED/start, for non-CoV-AKI vs CoV-AKI, respectively, p = 0.021). Similarly, the proportion of patients with short runs was greater in CoV-AKI (under no AC or CIT) vs non-CoV-AKI (55% vs 19%, p = 0.01). When comparing the 3 more aggressive AC protocols (sLH, sHH and sHH+CIT) in CoV-AKI with non-CoV-AKI, the duration of RRT was similar (12.2 vs 10.2 hrs of SLED/start, p = 0.11) and the percentage of short SLED runs were also similar (10% vs 19%, p = 0.25).

Conclusions: RRT in CoV-AKI was associated with shorter duration of SLED compared to non-CoV-AKI, likely driven by increased filter and/or catheter clotting. Aggressive AC protocols with sHH with or without CIT in CoV-AKI were successful in restoring the duration of RRT back to that observed in patients with AKI-RRT in the pre-COVID-19 era.

PO0696

Impact of Renal Replacement Therapy Modality on Prognosis of SARS-CoV2 Infection

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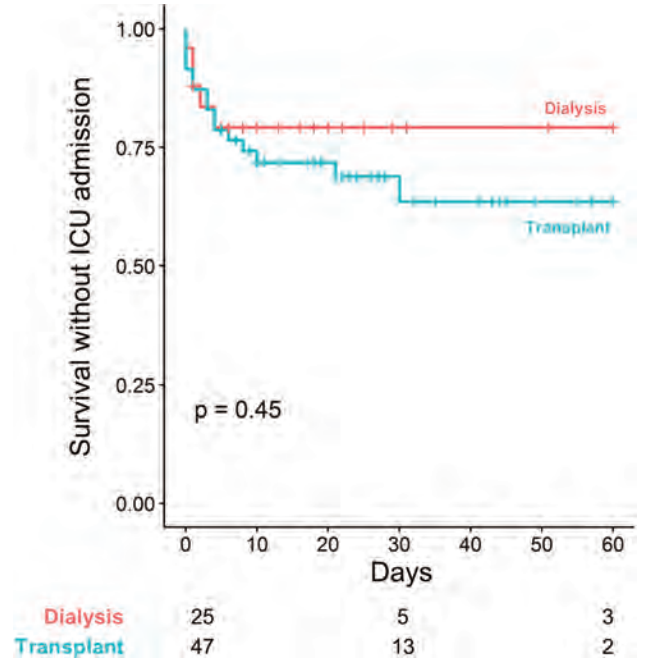
Background: Prognosis of SARS-CoV2 infection among patients with Chronic Kidney Disease (CKD) is poorly known. In particular, the impact of renal replacement therapy (RRT) modality on prognosis is undetermined. Patients with kidney transplant exhibit treatment-induced immunodepression, while patients on dialysis are usually older and exhibit higher frailty. We aim to determine the impact of RRT modality on the prognosis of SARS-CoV2 infection among patient with advanced CKD.

Methods: We conducted a retrospective cohort study using our institution's Clinical Data Warehouse. Health records of all patients with at least one hozpitalization or consultation in our nephrology department were screened based on ICD-10 codes. Inclusion criteria were: hospitalization in any of our institution's hospitals for SARS-CoV2 infection (national Public Health agency criteria). Patients were divided into two groups: «active kidney transplant» and «dialysis». A Cox model stratifying on age and medical history of coronary artery disease was used to determine adjusted Hazard Ratio (HR) for death or intensive care unit (ICU) admission.

Results: We included 72 patients: 47 in the «transplant» group and 25 in the «dialysis» group. First hospitalization was on 20/02/28 and last hospitalization on 20/05/19. Median follow-up was 21.5 days. Death or ICU admission occurred in 21 (29%) patients («transplant» group: 15 (32%), «dialysis» group: 6 (24%), p=0.45). In multivariate analysis, adjusted HR for death or ICU admission was 1.70 [95%CI:0.59–4.86] for transplant vs. dialysis (p=0.32).

Conclusions: In our study, among patients hospitalized for SARS-CoV2 infection, no significant difference in risk for ICU hospitalization or death was found between CKD patients on dialysis or with active kidney transplant. A trend for higher risk was noted among patients with active kidney transplant. Further studies are required to confirm those findings.



PO0697

Lower Continuous Venovenous Hemodialysis Replacement Rate and Its Effect on Patient Outcome in the COVID Crisis Time

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Background: Acute kidney injury (AKI) is a common problem encountered in COVID positive patients with incidence close to 23% and mortality close to 60% in this cohort of patients. Continuous Veno-Venous Hemodialysis (CVVH) plays a primary role in management of these patients. Nephrologists nationwide have been facing a compelling supply/demand mismatch dilemma. Lowering the rate of replacement fluid flow rate (RFFR) is one strategy that was used by our practice to mitigate this issue in selected patients. We hypothesize there is no difference in clinical outcome between the patients receiving high RFFR vs low RFFR.

Methods: This is a retrospective observational study from a single center experience. We analyzed data from March 2020 till the end of May 2020. We included patients with confirmed coronavirus disease 2019 (COVID-19) who required CVVH during their hospitalization. Patients were divided into two groups i.e Group 1 (> 20ml/kg/hr RFFR) vs Group 2 (< 20ml/kg/hr RFFR). Patients 18 years or older with at least 3 days of CVVH during their hospital stay were included. We compared percentage drop of blood urea nitrogen (BUN) and phosphorus as well as hospital stay and mortality between the 2 groups. We used ANOVA, t-test and Chi square for analysis, as appropriate.

Results: We enrolled 36 patients in the study, 20 in group 1 and 16 in group 2. Eighty percent of the patients enrolled were men. Mean weight was 100 ± 8kg in group 1 vs 107 ± 8 in group 2. There was no statistically significant difference in percentage reduction of blood urea nitrogen (BUN) or phosphorus (Po4) *P*= 0.2& 0.5 respectively (Means 25.4 vs 21.7 & 18.4 vs 17.1). Mean filtration fraction was similar between the two groups (17.9% vs 17%). Frequency of line clotting events was compared in the two groups using Chi square with *P* value 0.8. Mortality was not significantly different between groups, although it was actually lower in the groups treated with the lower RFFR.

Conclusions: Although our data analysis is still evolving, we found no difference in mortality, toxin clearance and frequency of line clotting between the two studied groups. No randomized control trial has assessed using a lower than 20ml/kg/hr RFFR in CVVH. Our study, thus far, showed no difference between the two groups. This finding needs to be further validated in a randomized control study.

PO0698

Low-Molecular-Weight Heparin Is a Superior Anticoagulant to Unfractionated Heparin for Renal Replacement Therapy in Patients with AKI due to Coronavirus Disease 2019

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Background: Severe coronavirus disease 2019 (COVID-19) not only causes acute pulmonary pathology leading to acute respiratory distress syndrome needing intubation, but also leads to acute kidney injury (AKI) requiring renal replacement therapy (RRT). Due to hemodynamic instability, these patients (pts) often need either continuous RRT (CRRT) or prolonged intermittent RRT (PIRRT). Accelerated Veno-Venous Hemodialysis (AVVHD), a form of PIRRT with typically 40-50 liter of dialysate used over 8-10 hours has been successfully used to treat hemodynamically unstable pts. In the past, we have published extracorporeal circuit clotting (ECC) to be low (5%) even without anticoagulation. However as hypercoagulability is extreme with COVID-19, we noticed a marked increase in ECC. Unfractionated heparin (UFH) was the initial anticoagulation of choice during the early phase of the pandemic but was ineffective in preventing ECC, prompting a trial of low molecular weight heparin (LMWH).

Methods: We conducted a single-center retrospective study to evaluate the efficacy and safety of LMWH vs UFH in preventing ECC in pts with AKI due to COVID-19 who received AVVHD from 3/25/20 through 4/30/20 at a large academic medical center. Data collected included pt demographics, type of anticoagulation and thrombolytic use, treatment characteristics including clotting frequency as well as bleeding complications. ECC was defined as any event that required an unexpected interruption in treatment or the use of thrombolytics.

Results: A total of 58 pts received 408 AVVHD treatments. The average pt age was 58 years, 65% were male, 66% were black and 69% were obese with body mass index >30 kg/m^2. 188/408 (46%) of AVVHD treatments received anticoagulation with UFH while 165/408 (40%) of treatments received LMWH. ECC occurred in 30% of AVVHD treatments who received UFH vs 15% in the LMWH group, a relative risk reduction of 50% (P = 0.001). 47.1% pts who were on UFH had ECC on the first RRT treatment compared to 13.6% on LMWH (P = 0.01). Only 1 pt experienced a major bleeding event in the UFH group and none with LMWH.

Conclusions: Anticoagulation with LMWH is superior to UFH in reducing ECC in pts receiving AVVHD for AKI due to COVID-19 without an increased risk of bleeding.

PO0699

Markers of Inflammation and Risk for AKI and Need for Dialysis in Patients with COVID-19

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Background: Acute kidney injury (AKI) is a reported manifestation of COVID-19 (CoV-AKI). Release of inflammatory cytokines has been recognized as a characteristic feature of COVID-19 and is linked to severity of illness. However, it has not been clearly determined if levels of serum markers of inflammation are associated with risk for development of AKI or its severity.

Methods: We conducted an observational study in patients hospitalized at Ochsner Medical Center over 1-month period with COVID-19 and diagnosis of AKI. We examined the relationship between the blood level of ferritin, C-reactive protein (CRP), procalcitonin (proCal), D-dimer and lactate dehydrogenase (LDH) and the incidence of AKI, as well as AKI requiring renal replacement therapy (AKI-RRT), by assessing comparison of means and proportions and by logistic regression analysis.

Results: Among 644 patients with COVID-19, we compared 161 (26%) with AKI vs 414 (64%) without AKI. Median serum creatinine on admission was higher in the AKI group (1.8 vs 1.1 mg/dL, p<0.0001). Preexisting chronic kidney disease rates were comparable (35% vs 28%, for AKI and no AKI groups). The median value of inflammatory markers on admission were higher in the AKI group [ferritin 1016 (516-2534) vs 680 (315-1416) ng/mL, p<0.0001; CRP 163 (93-243) vs 93 (46-165) mg/L, p<0.0001; proCal 0.37 (0.2-1.6) vs 0.12 (0.06-0.32) ng/mL, p<0.0001; D-dimer 1.57 (0.96-5.14) vs 1.13

(0.68-2.57) mcg/mL, p=0.0004; and LDH 532 (365-804) vs 428 (309-548), p=0.0004]. On multivariate logistic regression analysis, CRP (p=0.003) and ferritin (p<0.035) were associated with greater risk for AKI. In addition, ferritin ≥ 1200 ng/mL and CRP ≥ 300 mg/L were independently associated with AKI [adjusted odds ratio: 2.3 (1.3-4), p=0.003, and 2.5 (1.0-6.3), p=0.05; respectively]. Furthermore, ferritin, CRP, proCal and LDH levels were significantly higher in those with AKI-RRT compared to those not requiring RRT (p=0.022 to p=0.009).

Conclusions: Higher level of inflammatory markers were associated with CoV-AKI, and levels were even higher for those with CoV-AKI-RRT. In patients with COVID-19, magnitude of ferritin and CRP on admission could be used for AKI risk stratification.

PO0700

Morbid Obesity, Hypertension, and Male Sex Are Associated with Greater Risk for AKI in Patients with COVID-19

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Background: Acute kidney injury (AKI) is a reported manifestation of COVID-19 (CoV-AKI). However, there is paucity of data regarding risk factors for CoV-AKI. We examined the association of demographics and comorbidities with CoV-AKI risk and its severity at an academic hospital in New Orleans.

Methods: We conducted an observational study in patients hospitalized at Ochsner Medical Center over 1-month period with COVID-19 and diagnosis of AKI. We assessed the relationship between baseline demographic and clinical characteristics and the incidence of AKI, as well as AKI requiring renal replacement therapy (AKI-RRT), by assessing comparison of means and proportions and by logistic regression analysis.

Results: Among 644 patients with COVID-19, we compared 161 (26%) with AKI vs 414 (64%) without AKI. Male sex (62% vs 51%, p=0.02) and essential hypertension (HTN) (83% vs 70%, p=0.002) were more common in the AKI group. Median body mass index (BMI) was higher among those with AKI (34 vs 31 kg/m^2, p<0.0001). No difference was found in age, race, presence of diabetes, chronic kidney disease or heart disease respect to AKI rate. On multivariate logistic regression analysis, HTN was strongly associated with greater risk for AKI [OR 1.96 (CI 1.2-3.2), p=0.009]. Male sex [OR 1.72 (CI 1.1-1.9), p=0.005] and higher BMI [OR 1.04 (CI 1.02-1.07), p<0.001] were also associated with AKI. RRT was required in 89 (55%) of the patients with AKI. Those with AKI requiring RRT (AKI-RRT) had higher median BMI (35 vs 33 kg/m^2, p=0.048) and younger age (61 vs. 68, p=0.0003) compared to those with AKI not requiring RRT. Of note, higher BMI correlated with younger age (R=-0.53, p<0.0001).

Conclusions: HTN, male sex and higher BMI were associated with greater incidence of AKI in patients hospitalized with COVID-19. Higher BMI was further associated with AKI-RRT. Hypertensive, male and obese patients are at higher risk for CoV-AKI and should be more closely monitored during the COVID-19 pandemic.

PO0701

Mortality of AKI in Human Immunodeficiency Virus with and Without Co-Infection with COVID-19

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Background: Since the start of COVID-19 pandemic, concerns have been raised about specific populations being at potential higher risk for developing more severe diseases, and patients living with HIV (PLWH) are among them. SARS-CoV-2, a newly isolated virus from the Corona Virus family, is enveloped, positive-sense single-stranded RNA virus that causes multi-organ failure, especially acute kidney injury (AKI) which is proved to be associated with significantly elevated mortality rate. It dysregulates human immunity especially on T lymphocytes which is shared by HIV as the mechanism of causing related diseases. We reviewed our hospital data to examine if HIV infection resulted in worse outcomes in COVID-19 patients who developed AKI.

Methods: Retrospective chart review of all admitted patients to Kings County Hospital (KCH), a municipal hospital in Brooklyn, New York City between 3/1 to 5/15, 2020, from the electronic medical record. Patients were reviewed in groups of COVID infection without history of HIV, HIV patients admitted without COVID infection and patients with history of HIV who were admitted because of COVID infection. The rate of AKI and mortality were extracted and analyzed suing Chi-squared test in SPSS.

Results: A total of 1092 patients with confirmed COVID-19 diagnosis were admitted in the above time period, out of which 22 were diagnosed with COVID-19 and HIV. In the COIVD-19 without HIV diagnosis group, 450 patients developed AKI and 213 patients died, with a mortality rate of 47.3%; in the COVID-19 with HIV group, 9 patients developed AKI and 4 expired, mortality rate is 44.4%. There's no significant difference between these two groups (p=0.86). Compared to these two groups, 21 out of 93 PLWH without COVID infection had AKI during hospitalization with 2 patients deceased, and a mortality rate of 9.5% which is significantly lower (p=0.03).

Conclusions: Data from our hospital bewtween 3/1 and 5/15/2020 shows the mortality rates of patients with HIV and COVID-19 co-infection with AKI and COVID patients without HIV who developed AKI are not statiscally different, but significantly higher than patients with HIV who developed AKI.

Patients admitted to KCH from 3/1 to 5/152020

	COVID-19 without HIV	COVID-19 with HIV	HIV without COVID-19
Total N (& Mortality %)	1070 (29.6%)	22 (27.3%)	93 (3.2%)
Patients developed AKI (& Mortality %)	450 (47.3%)	9 (44.4%)	21 (9.5%)

PO0702

Phenotype and Outcomes of AKI Associated with COVID-19 in Urban New Orleans

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Background: Acute kidney injury (AKI) is a manifestation of COVID-19 (CoV-AKI). However, there is paucity of data from United States, particularly in a predominantly African American (AA) population. We report the phenotype and outcomes of AKI at an academic hospital in New Orleans.

Methods: We conducted an observational study in patients hospitalized at Ochsner Medical Center over 1-month period with COVID-19 and diagnosis of AKI by KDIGO. We examined the rates of renal replacement therapy (RRT) and in-hospital mortality as outcome measures. Adjudication of cause of AKI was independently performed via manual chart review by 3 study team members.

Results: Of 644 admissions with COVID-19, 69 were excluded due to ESRD or kidney transplant. Thus, 575 patients entered the cohort [173 (28%) to an intensive care unit (ICU)]. Patients were predominantly AA (71%). AKI was diagnosed in 161 patients (28% overall, 61% of ICU admissions), median age 65 (34 – 96), predominantly male (62%) and hypertensive (83%). Median follow up was 25 (1 – 45) days. Vasopressors and/or mechanical ventilation was required in 105 (65%) of them. In-hospital mortality rate for those with AKI was 50% (80/181). *De novo* AKI was diagnosed in 65%, whereas AKI over preexisting chronic kidney disease occurred in 35% of the cohort. Ninety-one (57%) patients arrived with AKI, whereas the remaining 43% acquired AKI during the hospitalization [median hospital day of AKI onset: 4 (2 – 10)]. RRT was required in 89/161 (55%) and 77/105 (73%) patients for all AKI cases and the ICU subset, respectively. The mortality rate for those with AKI-RRT was 72% (64/89). Hemodynamic instability leading to ischemic acute tubular injury (ATI) and rhabdomyolysis accounted for 66% and 7% of the etiology, respectively. Reversible prerenal azotemia occurred in 9%. In 13%, no obvious cause of AKI was identified aside from the COVID-19 diagnosis. Three (1.8%) patients had *de novo* collapsing glomerulopathy.

Conclusions: CoV-AKI is associated with high rates of RRT, ICU care and death. Hemodynamic instability leading to ischemic ATI is the predominant cause of AKI in this setting, but other etiologies contribute to the overall AKI burden.

PO0703

Presentation on Admission and Outcomes in COVID Patients Admitted with AKI

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Background: COVID-19 infection secondary to the SARS-CoV2 virus was defined by the WHO as a global pandemic. While the disease initially affects the respiratory system, a multi-systemic organ dysfunction of varying degrees has been described. Renal failure has been recognized as a significant part of the pathophysiology. Elmhurst Hospital Center (EHC) was described as the "epicenter of the epicenter" in New York City.

Methods: A retrospective chart review was undertaken of COVID positive adult patients (polymerase chain reaction testing of a nasopharyngeal sample) admitted to EHC from 3/7/20 - 4/7/20. Demographics, clinical characteristics, biomarkers, and outcomes were examined. AKI was determined by the KDIGO definition. Exclusion criteria: <18 years old, pregnant, ESRD, patients expired within first 5 days

Results: The average age was 59 years, 77.95% were Male; 55% had hypertension (HTN), 40% had diabetes (DM). Hispanics made up the most significant portion of the demographic with 62.05%, followed by Asians (24.1%). AKI occurred in 44.1% of patients and was associated with HTN ((p=0.011) but not DM (p=0.289). AKI was associated with an increased use of mechanical ventilation (p<0.001), and increased mortality (p<0.001). Hypertension (p=0.007), older age (p=0.003), and DM (p=0.018) were significantly associated with mortality. Ethinicity was not associated with mortality (p=0.231). Admission CPK did not have a significant association with AKI (0.065) or death (p=0.19).

Conclusions: Both HTN and DM are associated with increased mortality. AKI is significantly associated with increased respiratory failure requiring mechanical ventilation and mortality. Diabetes and admission CPK were not associated with AKI.

Demographics of patients admitted to EHC.

Demographics	n=195				
	Median	Interquartile range			
Age (years)	59	48 - 69			
		n	%	Death	P-value
Sex	Male	152	77.95%	69	0.339
	Female	43	22.05%	16	
Past Medical History	HTN	n=107	54.87%	56	0.007
	Diabetes	n=78	40%	42	0.018
	ESRD on HD	n=20	10.26%	7	0.413

Variable	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Age (year)	1.02 (1.00, 1.05)	0.03	-	-
HTN	3.24 (1.59, 6.62)	0.001	-	-
CKD	9.27 (3.51, 24.50)	<0.001	5.94 (1.78, 19.78)	0.004
DM	3.47 (1.74, 6.92)	<0.001	2.90 (1.15, 7.26)	0.02
CRP	1.01 (1.00, 1.01)	0.03	-	-
D-Dimer	1.23 (1.02, 1.48)	0.03	-	-
LDH	1.00 (1.00, 1.01)	0.03	-	-
Steroids	3.82 (1.76, 8.35)	0.001	5.33 (1.88,15.10)	0.002
Tocilizumab	3.35 (0.98,11.45)	0.05	-	-
ICU	2.43 (1.19, 4.95)	0.01	4.01 (1.60, 10.07)	0.003

PO0704

Refractoriness of Hyperkalemia and Hyperphosphatemia in Dialysis-Dependent AKI Associated with COVID-19

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Background: There have been anecdotal accounts of an unusual incidence of persistent hyperkalemia (hyperK) and hyperphosphatemia (hyperP) in patients with COVID-19 and acute kidney injury (AKI) (CoV-AKI) despite renal replacement therapy (RRT). However, an observation bias could not be discarded. Thus, we examined the rate and severity of hyperK and hyperP in patients with CoV-AKI actively treated with RRT.

Methods: Among 161 patients with CoV-AKI, we selected those who underwent RRT by sustained low efficiency dialysis (SLED) for ≥2 days (n=64). A database of patients with AKI on SLED who underwent urinary sediment microscopy (Sedi-AKI cohort, 2017-2019, n=60) served as control (non-CoV-AKI). We examined the rate of hyperK [serum potassium (sK) ≥ 5.5 mEq/L], severe hyperK [sK ≥ 6.5 mEq/L], hyperP [serum phosphate (sP) ≥ 4.5 mg/dL], moderate hyperP [sP ≥ 7.0-10.0 mg/dL] and severe hyperP [sP > 10.0 mg/dL] as % SLED-days with an event.

Results: Median age were similar: 60 (39-84) and 58 (22-88) years for CoV-AKI and non-CoV-AKI, respectively. Black race (77% vs. 30%; p<0.0001) and male sex (78% vs. 61%; p=0.04) were more common in CoV-AKI. Ischemic ATI was the presumed cause of AKI in 85% and 82% of the CoV-AKI and non-CoV-AKI, respectively. Along the duration of SLED, the incidence of hyperK was greater in CoV-AKI [mean 19 ± 2% vs. 14 ± 3% SLED-days, p=0.002]. The proportion of patients with ≥1 event of severe hyperK was greater in CoV-AKI [33% vs. 7%, p=0.0004]. The incidence of hyperP were similar between groups [mean 56 ± 4% vs. 53 ± 5% SLED-days, p=0.49]. However, the proportion of patients with ≥1 event of moderate and severe hyperP were greater in CoV-AKI [86% vs. 60% (p=0.001) and 50% vs. 18%, (p=0.0002)]. In CoV-AKI, sK and sP correlated with lactate dehydrogenase (LDH) [R=0.305 (p=0.044) and R=0.307 (p=0.043), respectively] but not with creatine kinase; and hyperP events correlated with shorter SLED runs (hours/run) (R=-0.268, p=0.055).

Conclusions: HyperK and hyperP refractory to RRT (by SLED) were more frequent in CoV-AKI compared to other forms of AKI in the pre-COVID-19 era. Because of the correlation of sK and sP with higher LDH and shorter SLED runs, intracellular ion release from cell injury due to cytokine "storm" and RRT interruptions may play a role.

PO0705

Risk Factors for AKI in Patients Hospitalized with COVID-19

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Background: We evaluated risk factors and prevalence associated with AKI in our early experiences with patients hospitalized with COVID-19, 32% of whom required ICU level care, at the University of Texas Southwestern and Parkland Hospitals in Dallas, Texas from 3/13/20-5/07/20.

Methods: Patients admitted with COVID-19 confirmed by SARS-CoV2 PCR test were screened for AKI. Univariate and multivariate logistic regression using backward selection identified factors associated with AKI.

Results: COVID-19 was confirmed in 145 patients, of whom 62 (43%) had AKI. Patients with AKI were older, mean (SD) age 60 (17) vs. 54 (15) years without AKI, p=0.03, and were more likely to have hypertension, 74% vs. 47%, p=0.002, and diabetes mellitus, 61% vs. 31%, p<0.001. CKD was present in 42% of those with AKI vs. 7% of those without, p<0.001. Race, ethnicity, and ACEI/ARB use did not differ between groups. Patients with AKI had higher CRP, median (IQR) 102 (44-161) vs. 59 (21-116) mg/L, p=0.009, and LDH on presentation, 365 (265-493) vs. 317 (228-385) U/L, p=0.04. Ferritin, IL-6, and D-dimer was similar between groups. A higher percent with AKI received steroids, 42% vs. 16%, p<0.001. Tocilizumab was administered in 15% of AKI vs. 5% of non-AKI groups, p=0.08 while rates of hydroxychloroquine and remdesivir use did not differ. Renal replacement therapy was required in 8 patients with AKI, of whom 7 received CVVHDF and 1 HD. There were 8 (13%) deaths in those with AKI vs. 5 (6%) in those without. Factors associated with AKI are listed (**Table**).

Conclusions: During the first weeks of COVID-19 outbreak at our hospitals, 43% of patients had AKI. Underlying CKD, diabetes, steroid use and illness severity were independently associated with AKI. Follow-up is needed to determine the long-term impact on kidney function and recovery.

PO0706

The Impact of COVID on CRRT Filter Lifespan

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Background: Patients with COVID are more likely to have systemic thrombotic events. Although it has been theorized that those on CRRT also have an increased rate of filter loss due to clotting. If COVID-positive patients are more likely to clot their filter than other patients on CRRT, a more aggressive anticoagulation strategy may be worthwhile. This could result in longer filter lifespan, less circuit down time, which would result in improved clearance, lower costs, less risk of iatrogenic blood loss, and less wasted nursing time. If there is no difference in filter lifespan between COVID positive and negative patients, then more aggressive anticoagulation would result only in added risk without a clear benefit.

Methods: We analyzed COVID data on patients in a related unblinded prospective randomized trial, in which patients are assigned to either pre-filter CVVH or CVVHD. The standard treatment protocol at the University of Iowa is to use citrate anticoagulation with a blood flow rate of 200 mL/min and a dose of 25 mL/kg/hr. The primary outcome is average filter life, and secondary outcomes are mortality, intensive care unit LOS, hospital LOS, and renal recovery.

Results: A total 30 patients using a total of 90 filters from March 25 to May 20, 2020 were evaluated (Table 1). The average filter life in COVID-positive patients was 37.4 +/- 35.8 compared to 33.1 +/- 26.7 in COVID-negative patients (p = 0.55). However, COVID-19 patients were more likely to receive heparin anticoagulation in addition to citrate.

Conclusions: Contrary to other reports, in this retrospective, unadjusted analysis of CRRT patients, the presence of COVID-19 did not decrease average filter life. Further research is needed regarding the appropriate anticoagulation strategy in COVID-19 positive patients.

Table 1: Patient characteristics

	COVID-positive (n = 8)	COVID-negative (n = 16)	p value
Age	53.6 +/- 13.9	59.2 +/- 16.0	0.41
Male (%)	8 (100%)	7 (44%)	0.0089
Caucasian (%)	1 (13%)	14 (88%)	< 0.01
Hispanic (%)	7 (88%)	0 (0%)	< 0.01
Black (%)	0 (0%)	1 (6.3%)	< 0.01
SOFA	9.25 +/- 1.98	10.4 +/- 2.85	0.32
CVVH (%)	5 (63%)	8 (53%)	0.65
Diabetes (%)	4 (50%)	11 (69%)	0.37
CAD / HF (%)	0 (0%)	5 (31%)	0.084

PO0707

Single-Center Experience of AKI in COVID-19-Infected Patients in West Kent Hospital, United Kingdom

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Background: The outcome of renal function and in COVID-19 positive patients is unclear. We studied the epidemiology of acute kidney injury (AKI) in the COVID-19 positive patients

Methods: Between 9th March 2020 and 26th April 2020 data was prospectively collected on 253 adult COVID-19 positive inpatients about co-morbidity, s. creatinine, demographics and AKI from digital records at our secondary care hospital. AKI stages were defined as per KDIGO Criteria

Results: Of the 253 patients, 58.9% were male with (mean ± stdev) age 71.9 ± 16.4 years. Common co-morbidities were Hypertension (54.1%), Cardiovascular Disease (34%), Diabetes Mellitus (28.3%), Chronic lung disease (23.3%), Dementia (20.5%), CKD (stage 3 - 5) 19.8% & 2 (0.8%) renal transplant. 2.8% (7) Patients on regular dialysis were excluded. 42.6% (105) patients had AKI. Of these 53.3% (56) had AKI 1, 20.9% (22) AKI 2 and 25.7% (25) had AKI 3. 2.4% (6) patient's needed acute haemofiltrated. The mean systolic BP at admission in non-AKI patients was 136 ± 22 mmHg (109 of 147 available) whilst in those with AKI it was 124 ± 25 mmHg (78 of 105 available). Thes, creatinine (median and range) in AKI patient at admission, peak and discharge or death was 126 (Range 30 - 1339), 173 (57 - 1339) and 113 (28 - 761) umol/L respectively. 52.4% (55) patients had recovered from AKI. The overall mortality rate in COVID-19 infected patient was 36.4% with mean age of 77.5 ± 12.4 years. Mortality in patients without AKI was 22% (31) & with AKI was 56.2% (59) with mean age of 77.7 ± 11.7 Years. The stage

wise AKI mortality was AKI1 25.7% (27), AKI2 10.4% (11) and AKI3 20% (21). 66.6% haemofiltration patients. 23% (25) AKI patients died with normal creatinine. Mortality in CKD patients as co-morbidity was 64%. All renal transplant patients survived without having AKI. 7.7% {19} patients required continuous positive airway pressure, 42.1% (8) patients developed AKI of these 75% (6) patients with CPAP died. A further 24 (9.75%) required mechanical ventilation with 62.5% (15) of these developed AKI with mortality of 80% (12).

Conclusions: Elderly patients were most commonly infected with COVID-19 infection. AKI was seen in 42.6% patients with COVID-19 infection. More than 60% COVID-19 infected patients died if they had AKI and were on any form of mechanical ventilatory support or had CKD as co-morbidity.

PO0708

Severe AKI in SARS-COVID-19 Patients from a Tertiary Hospital in Rhode Island

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Background: The clinical features & outcomes of COVID-19 patients who developed severe AKI are still being elucidated.

Methods: 42 patients with COVID-19 infection who developed KDOGI stage 3 AKI were identified from March 1 to May 15, 2020, at Rhode Island Hospital, a large tertiary teaching hospital. Their clinical presentations and outcomes are presented. The data in table 1 were presented as mean (± SD), median (IQR), or # (%).

Results: The baseline characteristics are outlined in table 1. Among them, 88% were admitted to ICU, 83% were intubated and needed pressor support. 71% received renal replacement therapy (RRT)(56% on CVVHDF). The mean duration of RRT and ICU stay were 6 and 14 days, respectively. 33 participants received treatment for COVID-19, among them 14 (33%) received Remdesivir(RDV), 6 (14%) received convalescent plasma(CP), 4 (10%) received hydroxychloroquine(HCQ), and 25 (60%) also received azithromycin. The mortality rates were 15% in the RDV group, 67% in the CP group, and 75% in the HCQ group. The mortality was 67% in those without any treatment. At the 60-day follow-up, 11 (26%) were discharged alive, 21 (50%) died. Those who died were older (mean age 71 vs. 61), having higher Charlson Comorbidity Index (4.7 vs 3.0), more likely to have diabetes (71% vs. 61%) and coronary artery disease (38% vs. 24%).

Conclusions: The mortality rate of SARS-COVID patients who developed severe AKI is high in our cohort. Future larger scale studies are needed to elucidate the causes of this high mortality.

Funding: Clinical Revenue Support

Table 1 Baseline and Presenting characteristics of the cohort

	Total Participants, n=42
Age	64(56-72)
Sex, Male	33(79%)
Hispanic	19(45%)
White	12(29%)
HTN	35(83%)
DM	28(67%)
HLD	26(62%)
CAD	13(31%)
CHF	6(14%)
COPD/Asthma	4(10%)
Atrial fibrillation	3(7%)
Baseline CKD	20(48%)
Charlson Comorbidity Index	3.7(±1.9)
Smoking, Never	18(43%)
BMI	31.4(±6.7)
Symptom. duration <1 week	30(71%)

PO0709

The Clinical Presentation of AKI Complicating COVID-19: Observations from Elmhurst Hospital, New York City

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Background: Early in March, NYC Hospitals became inundated, especially safety net public hospitals, The physicians at Elmhurst Hospital Center (EHC) encountered countless cases of respiratory failure often accompanied by AKI. Autopsy studies from China described an interstitial nephritis, with macrophage infiltrates and complement deposition along with fibrotic changes. We report our experience with COVID-19 and AKI.

Methods: We reviewed the charts of 137 SARS-CoV-2 positive patients (PCR of a nasopharyngeal sample) admitted to EHC 3/7/2020 - 4/7/2020. We categorized patients as having KDIGO defined AKI vs no AKI within the first seven days of admission. Co-morbidities, renal associated markers and inflammatory markers were anlayzed. Clinical outcomes were assessed. Exclusion criteria: <18 years old, pregnant, ESRD, mortality prior to day 7 of hospitalization. Welch T test and Chi square were used for AKI vs non-AKI

Results: Age was similar in both groups as was gender (male 74% vs 79%) and incidence of diabetes. Early AKI developed in 35% of whom 55% needed RRT; 85% of the AKI patients required mechanical ventilation vs 11.2% of the non-AKI group. Inflammatory markers (WBC, CRP, LDH); urine protein and urine white cells (but not CPK) were significantly higher in the AKI group. Procalcitonin and D-dimers as maximum levels became significant. We found that 20% of those not with early AKI developed late-onset AKI. Mortality was 76.7% in the AKI and 17.9% in the non-AKI group.

Conclusions: Early AKI developing in the first week of hospitalization was associated with overwhelming respiratory failure. The accompanying higher inflammatory markers, elevated urine WBCs and protein could implicate interstitial nephritis as an underlying pathology as described earlier.

	AKI (n:48)		*Non-AKI (n:89)*				
	Mean	SD	Mean	SD	t-value	df	p-value
Cr	1.49	1.08	1.66	1.42	1.481	117.40	0.140
Adm Procal	1.05	1.96	0.49	0.75	1.764	46.12	0.080
Max Procal	15.01	32.69	0.64	0.80	2.672	36.03	0.010*
Adm CRP	197.90	92.43	149.40	100.40	2.547	76.70	0.010*
Max CRP	252.50	76.37	181.10	88.41	4.709	100.10	0.001*
Adm D-Dimer	3197.00	7664.00	1080.00	4211.00	1.591	48.04	0.120
Max D-Dimer	15917.00	17676.00	3960.00	3960.00	4.172	56.76	0.001*
Adm IL-6	155.50	151.10	128.80	228.10	0.503	48.89	0.620
Max IL-6	681.30	953.90	368.70	646.70	1.109	18.98	0.280
U/A Adm Protein	185.10	256.00	82.50	92.20	2.182	52.53	0.030*
U/A Max Protein	199.00	254.50	82.50	92.20	2.488	52.57	0.020*

	AKI (n:48)		*Non-AKI (n:89)*			
	Count	%	Count	%	x^2	p-value
DM	20	27.08	31	34.83	0.62	0.42
HTN	33	68.75	37	43.82	7.77	0.005*

PO0710

Incidence of AKI in Hospitalized Patients with COVID-19

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Background: Preliminary reports indicate that acute kidney injury (AKI) is common in coronavirus disease (COVID-19) patients and is associated with worse outcomes. AKI in hospitalized COVID-19 patients in the United States is not well-described.

Methods: This is a retrospective observational study of patients aged ≥18 years with laboratory confirmed COVID-19 admitted to the Mount Sinai Health System between February 27 and April 15, 2020. We describe the frequency of AKI and dialysis requirement, AKI recovery, and adjusted odds ratios (aOR) for mortality while adjusting for age, gender, race, comorbidities, and admission labs and vital signs.

Results: Of 3,235 hospitalized patients with COVID-19, AKI occurred in 1406 (46%) patients and 280 (20%) with AKI required dialysis. The proportion with stages 1, 2, and 3 AKI overall was 35%, 20%, 45%, and 20% received dialysis (Figure 1A). In the 815 patients admitted to the intensive care unit (ICU), 553 (68%) had AKI and 34% required dialysis. The median peak serum creatinine was 2.2 (IQR 1.6-3.7) mg/dL in those that did not receive dialysis and was 8.6 (IQR 6.5-11.4) mg/dL in those that did receive dialysis. Urine studies were available for 581 (18%) patients of whom 338 (60%) patients had AKI. 558 (96%) of all patients had any urinary abnormalities of proteinuria, hematuria, or leukocyturia. Independent predictors of severe AKI were chronic kidney disease, systolic blood pressure, and potassium at baseline. In-hospital mortality in patients with AKI was 41%. The aOR for mortality for AKI was 9.6 (95% CI 7.4-12.3). 56% of patients with AKI who were discharged recovered kidney function back to baseline (Figure 1B).

Conclusions: AKI is common in patients hospitalized with COVID-19, associated with worse mortality, and nearly half of patients do not recover kidney function.

Figure 1A: Acute kidney injury stages overall and stratified by intensive care unit admission

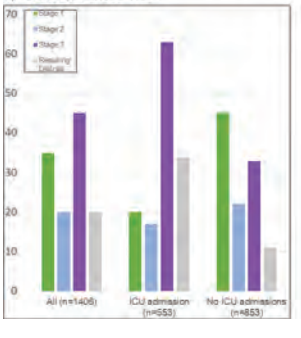
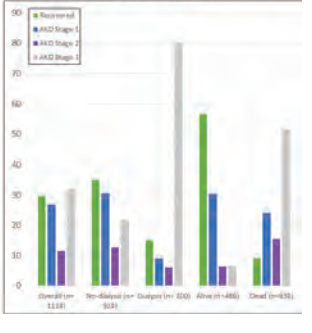


Figure 1B: Recovery and acute kidney disease overall, by need for dialysis, and by mortality status



PO0711

SARS-CoV-2 Infection and Outcomes in Chronic Dialysis Patients

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Background: The SARS-COV-2 pandemic (COVID) impacted ESRD patients on dialysis, categorized by the CDC as immunocompromised. We describe the characteristics and outcomes in patients treated by a non-profit dialysis provider.

Methods: From 2/17 to 5/29, 2020, Dialysis Clinic Inc. had identified 422 COVID+ patients from 90 clinics in 20 states. We compared their characteristics relative to the uninfected source clinic population (N=6,993) and tracked outcomes over the 15-week period.

Results: Comparative characteristics are shown in the table (*p<0.05). Hospitalization occurred in 295 (70%) with 75 deaths, 159 discharges and 61 still hospitalized. Ten patients died <30 days post-discharge. Another 11 deaths occurred in 116 non-hospitalized patients. Overall, 96 of 422 died (22.7%). While more black patients were infected, death rates were higher in white than black dialysis patients (31.5% vs. 18.8%, p=0.008).

Conclusions: Chronic dialysis patients with COVID have higher death rates than the general population. Infected patients tended to be older, with more comorbidity, particularly DM/CVD, and utilized respiratory inhalers/assistance. Group home residents were overrepresented with COVID while home dialysis patients were disproportionately spared.

Source: 90 DCI Clinics w/ 7,415 patients	COVID+	Non-COVID
N of Patients (%)	422 (5.7%)	6,993 (94.3%)
Age (years)	65.3±13.3*	62.1±14.9
% Male	60.2	57.3
% White	26.3*	36.0
% Black	56.9*	46.5
% Other Race	16.8	17.5
Vintage (days)	1,692 ± 1,699	1,668 ± 1,808
% Home Dialysis	3.3*	14.9
% CVC	25.6	22.0
% Group Home	38.9*	6.4
% Albumin <3.5 g/dL	19.2*	14.5
# Comorbid Dis.	3.3±1.9*	3.0±1.9
% DM	69.7*	57.7
% AHD	26.5*	21.7
% CVA	11.8*	8.5
% HTN	77.7*	81.7
% Inhaler Use	28.2*	19.9
% Wheelchair	3.6*	1.8
% ADL Help	0.9*	0.3
BMI	29.1 ± 7.4	28.8 ± 8.9

Note: % CHF, COPD, PVD, Smoking, ACEi-ARBs, Steroids, Flu/Pneumonia Vaccines similar.

PO0712

ESKD Patients Hospitalized with COVID-19: Early Outcomes in Bronx, New York

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Background: It is unclear whether end-stage kidney disease (ESKD) patients with COVID-19 are at increased risk for adverse outcomes due to impaired immune responses attributable to uremia. Alternatively, a weakened immune state could mitigate the cytokine surge observed in non-ESKD patients with COVID-19. The aim of our study is to describe the clinical characteristics and short term outcomes in ESKD patients requiring hospitalization for COVID-19.

Methods: We performed a retrospective study of 114 consecutive ESKD patients hospitalized at two major hospitals in the Bronx with COVID-19 from March 9, 2020 to April 12, 2020 in the midst of the coronavirus surge in New York City. Clinical and laboratory data were extracted from the medical record and short term outcomes were reported.

Results: The mean age was 63 years (range 30-87); 61.4% were men and 88.6% were Black or Hispanic. Most had hypertension (89.5%) and diabetes mellitus 66% and 30.7% were nursing home residents. Intensive care unit admission was required in 13(11.4%) patients and 17(14.9%) required mechanical ventilation. In-hospital mortality occurred in 23(20%) patients and was similar to mortality observed in non-ESKD patients. Mortality was 59% in those who required mechanical ventilation. At the time of data censoring, 47% had been discharged and 32% remained hospitalized. Initial procalcitonin, ferritin, lactate dehydrogenase and lymphocyte percentage were significantly higher in those who died.

Conclusions: Short term mortality in Bronx ESKD patients hospitalized with COVID-19 was similar to non-ESKD patients. Mechanical ventilation was associated with high mortality. Initial elevated inflammatory markers may be predictors of mortality in ESKD patients with COVID-19. To date, this is one of the largest studies describing outcomes in hospitalized ESKD patients with COVID-19. Further studies describing long-term outcomes in this population following COVID-19 are needed.

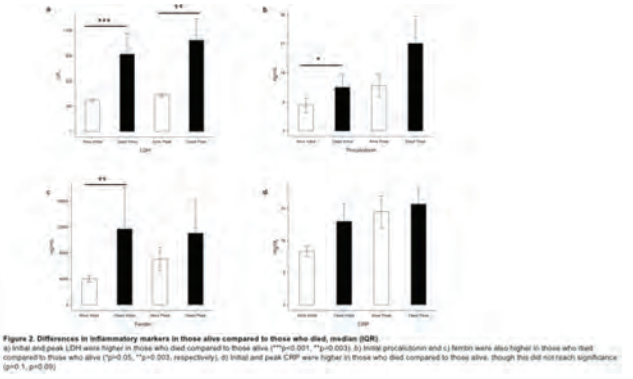

Figure 2. Differences in inflammatory markers in those alive compared to those who died, median (IQR):
a) Initial and peak LDH were higher in those who died compared to those alive (***p<0.001, **p=0.003). b) Initial procalcitonin and c) ferritin were also higher in those who died compared to those who alive (*p=0.05, **p=0.003, respectively). d) Initial and peak CRP were higher in those who died compared to those alive, though this did not reach significance (p=0.1, p=0.09)

PO0713

Trends in Fever and Respiratory Illness in Hemodialysis Patients During the COVID-19 Pandemic

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Background: Hemodialysis (HD) patients are vulnerable to the 2019 coronavirus disease (COVID-19) due to older age and common coexistence of comorbidities. Fever and respiratory illness (RI) are common symptoms of COVID-19. In order to create a disease surveillance tool and anticipate areas of COVID-19 outbreak, we aimed to assess the trends in fever and RI symptoms in HD patients treated at a national dialysis provider network in the United States during the pandemic.

Methods: We used data from HD patients actively treated between Jan 1 2018 ad May 16 2020 at a national dialysis provider network of large integrated health care company. If the body temperature of the patient either before or after the treatment was greater than 100 degrees Fahrenheit, then the patient was identified as exhibiting the symptom of fever. If the patient complained of shortness of breath, wheezing, runny nose, bloody cough, dry cough or purulent cough, then in this analysis the patient was identified as exhibiting the symptom of RI.

Results: The total patients count ranged from 196,774 to 209,475 per week while the total count of HD treatments ranged from 413,477 to 454,215. For the year 2020, a clear increase in trend for number of patients was observed after week 11 (03/08-03/14/2020) for RI symptoms (Figure 1A) and week 12 (3/15-3/21/2020) for fever symptom (Figure 1B). Both increasing trends spike at the week 15 (04/05-04/11/2020) and decline thereafter.

Conclusions: HD patients appear to exhibit a different trend in RI and fever symptoms during the year 2020 compared to concurrent periods in 2018 and 2019. which coincides with COVID-19 outbreak. Routine surveillance of dialysis patients may allow for early identification of COVID-19 outbreaks.

Funding: Commercial Support - Fresenius Medical Care

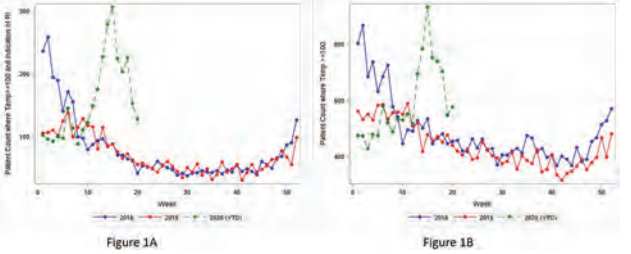

Figure 1A Figure 1B

PO0714

Implementation of Strategies for Prevention and Control of SARS-CoV-2 Infection at Dialysis Units in Latin America: Analysis from GlomCon Latin America Working Group (LGlomCon)

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Background: Patients on dialysis belong to the high-risk group to develop severe COVID-19 infection due to their multiple comorbidities. International societies have issued recommendations for the control and prevention of SARS-CoV-2 infection at dialysis units but implementing them may not always be feasible as many healthcare systems in Latin America (LA) have limited resources. This study aims to reflect the experience of nephrologists in LA at taking care of these patients and if the recommendations were adopted in their practices.

Methods: Descriptive analysis extracted from an online survey carried out among nephrologists, renal pathologists and other health workers treating kidney diseases between May 20-27, 2020 from sixteen Spanish speaking LA countries divided into 6 categories. We present the results for the ESRD category.

Results: 430 responses were obtained, 360 were considered for analysis. 276 (86.5%) of the participants were nephrologists and 178 (64%) of them practiced in dialysis units. 163 (92.6%) already implemented strategies to control and prevent COVID-19 in their units. 125 (71%) received training on it and 128 (72.7%) reported personal protective equipment availability. The most common implemented strategies were: education sessions about COVID-19 for patients and caregivers (68.5%), designated isolation areas (77.8%) or shifts (68.75%) for patients with suspected or confirmed COVID-19 and a 7-feet separation between hemodialysis (HD) machines (61.9%). 49 (28%) of the nephrologists reported an outbreak among patients and 60 (34.2%) among medical staff. Patient absenteeism to their HD sessions due to fear of infection, a decrease in the frequency and a shortening of the time of the sessions was reported in 41.7%, 30.2% and 36%, respectively. 29 (16.5%) of the respondents considered that those practices were associated with patient mortality.

Conclusions: Most dialysis units in LA are partially implementing the recommended strategies for control and prevention of COVID-19 but this seems to be insufficient since at least one third of them already faced outbreaks among patients and medical staff.

PO0715

Implementing COVID-19 Infection Control Procedures in Outpatient Dialysis in an Urban US Population

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Background: Emerging data reveal disparities in the burden and severity of disease among racial and ethnic minorities in the US. Emory Dialysis consists of 4 outpatient dialysis facilities, serving an older, urban and predominantly African-American population. These facilities are in counties with the highest number of COVID-19 cases in Georgia. We describe infection control measures implemented to prevent COVID-19 transmission, and the clinical characteristics of patients with COVID-19 in the facilities.

Methods: Based on CDC's recommended guidance, we implemented the following infection control procedure between February and April 2020: 1) screening; triaging all patients, and separating patients with symptoms of COVID-19; 2) monitoring staff for COVID-19 symptoms; 3) limiting healthcare personnel in the facilities; 4) universal masking in the dialysis units; 5) conducting PPE re-trainings; 6) assessing facility preparedness; 7) separating high risk patients (nursing home residents); and 8) cohorting patients with COVID-19 to a dedicated dialysis shift.

Results: Of the 745 patients followed at the Emory dialysis facilities, 18 (2.4%) were diagnosed COVID-19 between March 25—May 7, 2020. Among the 18 patients, 17 were receiving in-center hemodialysis and 1 was on peritoneal dialysis. The median age was 66.8 years (range 43–84) and 11 (61.1%) were female. Nine (50%) were residents of a skilled nursing facility. Sixteen (88.9%) patients had a diagnosis of hypertension, 10 (55.6%) had diabetes, and 10 (55.6%) had cardiac disease. Eight patients (44.4%) required hospitalization and 4 patients (22.2%) died from COVID-19 related complications. Two patients with COVID-19 were dialyzing at adjacent dialysis stations and the timing of their symptoms suggested possible transmission in the dialysis facility. In response, education, infection control audits and PPE re-trainings were conducted to bolster infection control practices.

Conclusions: In a high-risk patient dialysis population, we successfully implemented recommended infection control measures to mitigate the spread of SARS-COV-2 in our facilities. Dialysis facilities must stay vigilant and monitor for possible transmission of COVID-19. Regular audits of infection control practices remains critical.

PO0716

Canaries in the Coal Mine: Nursing Home Dialysis Patients as Sentinels During COVID-19

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Background: At least one-third of USA COVID-19 deaths are skilled nursing facility (SNF) residents. Since 2016, Dialyze Direct has brought staff-assisted home hemodialysis (HD) on-site to more than 7,000 patients in SNFs. HD is performed 5x per week in a den setting. Since 3/9/20, Dialyze Direct has screened patients for COVID signs or symptoms before every HD. Infection controls include, but are not limited to, patient masks, staff PPE, physical distancing, and cohorting by COVID symptoms or status. The penetrance of likely COVID in SNF HD patients in NY vs FL is presented.

Methods: A symptom diagnostic hierarchy tracked presumptive COVID infection and augmented the limited available COVID testing. At every HD, patient symptoms were recorded in an Electronic Health Record. Prevalent infection is defined as the proportion of patients with any of the symptoms during the pandemic living in the SNF during the week of interest. We report on weekly proportion from 3/9/20-5/16/20.

Results: Once COVID symptoms appeared among the HD population, penetrance increased over time. In NY, penetrance in week 1,5 (4/5/20), and 10 was 8, 52, and 64%. In FL, comparable data was 13, 15, and 25%. Prevalence differences (5/10/20) for NY (29/45) vs FL (23/92) (RR 2.6, CI 1.7-3.9; p=.000).

Conclusions: COVID symptom penetrance in SNF HD patients differed between NY and FL, likely attributable to differences in community disease prevalence, SNF's infection controls, their relationships to referring hospitals, and state health regulatory environment. On 3/25/20, NY mandated SNFs to accept COVID hospital returns and forbade SNFs to demand proof of negative test before accepting the return of suspected patients. COVID symptoms in SNF HD residents can serve as sentinel for COVID for the general SNF population as they are the most intensively monitored patients there. The more frequent 5x per week HD model in the SNF provides intense and relevant local surveillance compared to less frequent conventional off-site HD. This sentinel strategy can inform an urgent pivot of infection containment efforts by the SNF and larger regulatory agents so that lessons learned from successful containment strategies can be implemented early.

Funding: Commercial Support - Dialyze Direct

PO0717

Chronic Dialysis Access Management in the COVID-19 Era: The Need for Raising Awareness

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Background: Coronavirus Disease 2019 (COVID-19), an acute respiratory disease caused by novel coronavirus SARS-CoV-2, is particularly ominous to chronic dialysis patients as they are likely to experience more severe illness. However, these patients continue to require renal replacement therapy (RRT) during this time. To inform best practices for hemodialysis (HD) patients, we sought to determine the challenges regarding access placement during the pandemic era.

Methods: This is a retrospective single-center study of adult patients who received chronic dialysis at one of the University of Virginia dialysis units. Prevalence of central venous catheter (CVC) use were assessed in patients receiving chronic HD between the months of February-April 2020 (during the pandemic in our area) and compared to the three months prior (October-December 2019). The patients' relevant clinical and laboratory information were reviewed and recorded monthly. All patients who received RRT on HD were included.

Results: A total of 58 patients were evaluated, among whom 33 were male and 25 were female. The age range is 18-90 with a median age of 65. The number of patients using catheters in the pandemic months was 18 (31%), 19 (33%) and 22 (37%). The numbers pre-pandemic were 14 (25%), 19 (33%) and 17 (30%). The number of patients with central venous catheter for more than 90 days during the pandemic was 14 (24%), 16 (30%) and 16 (30%). The numbers pre-pandemic were 12 (22%), 15 (27%) and 15 (27%).

Conclusions: This single-center study reveals the impact of the pandemic on HD catheter use in our area. There is a large population of ESRD patients in the United States on HD that require vascular access. An AVF is the desired access type as it has the most extended access survival, the best patient survival outcomes, the lowest cost, and requires the fewest interventions. Early referral for AVF is important; however, during the Covid-19 pandemic era patients and providers are hesitant to refer patients, wanting to avoid any exposure to the virus while resources remain scarce. This study identifies the inherent difficulty for access placement in this high-risk population of patients during times like this and raises questions in the literature on the best choice of access for these patients along with the optimal timing of fistula placement to provide safe care for the patients.

PO0718

Clinical Characteristics and Outcomes in ESKD Patients with COVID-19 Infection in an Urban Community Hospital in Brooklyn, New York, During the Global Pandemic

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Background: The impact of coronavirus disease 2019 (COVID-19) on individuals with End Stage Kidney Disease (ESKD) receiving maintenance hemodialysis (MHD) is unknown. This study aims to describe clinical characteristics and outcomes in a cohort of patients with ESKD receiving MHD hospitalized with confirmed COVID-19 infection in an urban community hospital during the New York City peak of the global COVID19 pandemic.

Methods: Cases with a diagnosis of ESKD and COVID-19 based on positive PCR testing results were identified from retrospective review of electronic health records for patients hospitalized between March 4, 2020 and April 30, 2020. Electronic health records were reviewed in order to obtain demographic data, presenting symptoms, laboratory values, medical management, and outcomes.

Results: 29 patients with ESKD on MHD with confirmed COVID-19 infection were identified. 16/29 (55%) were over age 60 years, 20 (69%) were male and 14 (48%) were Hispanic. 18 (62%) had Diabetes and 26 (89%) were overweight or obese (BMI >25). All had hypertension. 68% were on Statin and 40% on ACE inhibitor or ARB at the time of admission. 25/29 (86%) were dialyzed via arteriovenous fistula or graft. The most common presenting symptoms were dyspnea (85%), cough (60%) and fever (28%). All initial chest radiographs showed abnormalities, with diffuse infiltrates on 21 (72.4%) and focal infiltrates on the remainder. All patients who required renal replacement therapy during hospitalization received conventional HD. 10 patients required mechanical ventilation during hospitalization (34%); all of these patients died. Overall, 13 patients (45%) died and 16 patients (55%) were discharged after a median of 6 and 7 days hospitalization, respectively. Three patients (10%) were readmitted during the period of observation. No significant associations were found between age, sex, race, or diabetes and mortality. Mechanical ventilation was the most consistent predictor of death.

Conclusions: 45% mortality was observed in a small cohort of patients with ESKD on MHD with confirmed COVID-19 infection hospitalized during the peak of the global COVID-19 infection. This high mortality rate reinforces the need for social distancing and infection control measures to reduce transmission in this high risk population.

Funding: Clinical Revenue Support

PO0719

Clinical Outcomes of Patients with ESKD Hospitalized with COVID-19

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Background: Patients with end-stage kidney disease (ESKD) comprise a vulnerable population to infections. COVID-19 has been responsible for high mortality worldwide. To-date, there is limited data regarding the impact of COVID-19 in the ESKD population. We report clinical outcomes of ESKD patients with COVID-19 admitted to an academic hospital in New Orleans.

Methods: We conducted an observational study in patients with ESKD and COVID-19 hospitalized at Ochsner Medical Center over a 7-week period. We compared rates of need for mechanical ventilation, shock, need for intensive care (ICU) and in-hospital mortality as outcome measures between patients with and without ESKD.

Results: Among 851 admissions (67% black) with COVID-19, 49 (6%) patients had diagnosis of ESKD. Patients with ESKD were mostly male [61% vs 49% in non-ESKD (n = 806), p = 0.10] with a median age of 64 (38 – 90) years. Median body mass index (BMI) were 32 vs 27 kg/m^2 (p = 0.11) for those admitted to ICU vs wards, respectively. Thirteen of them (27%) vs 293 (37%) in the non-ESKD group, p=0.16) were admitted to an intensive care unit (ICU). In-hospital mortality rate for the ESKD cohort was 32% compared to 24% for non-ESKD (p = 0.21). Compared to a subset with 161 patients with acute kidney injury (AKI) with 50% mortality, the 32% mortality rate in ESKD was significantly lower (p = 0.027). Shock and/or mechanical ventilation requirement were comparable between groups [12 (24%) of those with ESKD vs 213 (26%) of non-ESKD, p = 0.65]. Median serum ferritin level was significantly more elevated in ESKD compared to non-ESKD [2125 vs 633 ng/mL, p = 0.0019).

Conclusions: Clinical outcomes in individuals with ESKD with COVID19 appear to be grossly similar to that of non-ESKD population with COVID19. The similar mortality rate was seen despite higher levels of ferritin, suggesting that the interpretation of the significance of serum ferritin in ESKD has to be done with caution. Furthermore, the mortality in ESKD patients with COVID19 is lower than that observed in AKI. The observed lack of increased mortality in ESKD does not align with the outcomes of this patient population in other critical illnesses. The ability to mount and exaggerated inflammatory response in COVID19 might be somewhat restricted in ESKD.

PO0720

Clinical Symptoms in 44 Hemodialysis Patients Who Survived and Recovered from a Confirmed SARS-CoV-2 Infection and COVID-19 in Relation to Age and Hospitalization: An International Experience

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Background: A novel coronavirus (SARS-CoV-2) is now rapidly spreading throughout the world. Patients undergoing long-term in-center hemodialysis (HD) are highly vulnerable given kidney failure, comorbidities, and the need for frequent visits to a dialysis facility.

Methods: A total of 610 patients on maintenance HD at DaVita clinics in 6 countries were tested for presence of infection with SARS-CoV-2 using polymerase chain reaction (PCR) between March 28 and May 18. Of these, 115 HD patients (19%) were positive. Information up to May 25, 2020, show that 44 patients have recovered. Clinical symptoms during infection with SARS-CoV-2 are reported from these 44 recovering survivors (Germany 13 patients, Poland 12, Portugal 12, Colombia 2, Saudi Arabia 3, and Malaysia 2) and classified into 4 categories: no symptoms, mild, moderate, or severe symptoms. Hospitalizations and time to recovery were also analyzed. Statistical comparisons were made using Chi-2 analysis and Kruskal-Wallis tests.

Results: Of the 44 patients recovering from COVID-19, 22 patients were ≥70 years and 9 patients were >80 years. Symptoms in relation to age, hospitalization, and time to recovery are shown below.

Conclusions: The majority of HD patients (66%) who recovered from COVID-19 had no or mild clinical symptoms during the infection. There were no significant differences in the occurrence of symptoms from SARS-CoV-2 in relation to age, hospitalization, or time to recovery. Additionally, old and frail HD patients with confirmed COVID-19 may have mild symptoms of the disease.

Percentage of HD Patients Who Recovered From Clinical Symptoms During Infection With SARS-CoV-2

	No symptoms	Mild symptoms	Moderate symptoms	Severe symptoms
All patients	27.3	38.6	31.8	2.3
<70 years	36.4	40.9	22.7	0
>= 70 years	18.2	36.4	40.9	4.5
Hospitalized	36.1	36.1	25	2.8
Time to recovery (days)	27	25	30	41

PO0721

Comparison of Psychological Distress and Demand Induced by COVID-19 During the Lockdown Period in Patients Undergoing Peritoneal Dialysis and Hemodialysis: A Cross-Section Study in a Tertiary Hospital

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Background: Since the outbreak of COVID-19 in December 2019, it has spread rapidly and widely, bringing great psychological pressure to the public. In order to prevent the epidemic, lockdown was required in many areas of China, which led to inconvenience of treatment for dialysis patients. However, there are few studies on the mental health of dialysis patients with ESRD after health emergencies and the comparison between HD and PD is less. To explore the psychological distress and the psychological demand induced by COVID-19 in the patients undergoing dialysis and compare the difference between hemodialysis (HD) and peritoneal (PD) patients during the lockdown period.

Methods: Questionnaires were given to the dialysis patients in West China Hospital of Sichuan University. The Impact of Event Scale (IES) was used to investigate the patients' trauma-related distress in response to COVID-19. We investigated the patient characteristics, the impact of COVID-19 to the severity of illness and daily life, the IES scores and the psychological support during the epidemic period of COVID-19.

Results: 232 eligible respondents were enrolled in this cross-section study, consisting of 156 PD patients and 76 HD patients. The median IES score for all the enrolled patients was 8.00 (2.00-19.00), which belonged to the subclinical dimension of post-traumatic stress symptoms. HD patients had a significant higher IES score than PD patients (11.50 vs 8.00) (p<0.05). HD patients already got more psychological support from the medical staff. There was no significant difference on further demand of psychological support between the two groups. In the multivariate regression analysis, we found that dialysis vintage, the impact of COVID-19 on the severity of illness and daily life, and confidence in overcoming the disease contributed to IES score (p<0.05).

Conclusions: HD patients had more severe trauma-related stress symptoms than PD patients. When major public healthy events occurred, careful psychological estimate and sufficient psychological support should be provided to the dialysis patients, especially to the HD patients.

PO0722

COVID-19 Incidence and Outcomes in Hemodialysis Patients in Mexico

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Background: HD pts are at high risk for COVID-19. High incidence and death rate were reported in China and Europe with more than 20% of asymptomatics. We report incidence, features and outcomes of COVID-19 in HD patients in a network of 8 clinics in Mexico. A protocol was started on Mar 15 with hygiene measures; symptoms triage; separation by age; use of PPE and isolation of suspected cases. We use a more inclusive case definition, different from Mexico Health Ministry's(SSA). All cases are referred for PCR but most aren't tested.

Methods: Retrospective analysis of cases (suspect or PCR(+)) from mar 15 to may 22 2020 compared to controls. T-test and Chi² were used. Hospitalization, IMV and deaths were registered. Overall mortality from mar - may 2020 compared to same period of 2019. We compared the number of cases using our case definition with that using the SSA's. Incidence of COVID-19 in staff was also analyzed.

Results: Total 1276 pts; Of 102 suspects 25 (24%) had PCR and 16 (64%) were(-). 13 (12%) non-tested were discarded based on alternative dx. 2 pts with (-) PCR were cases based on CT. Total 75 cases (10 (+)PCR, 65 w/o test) were analyzed and compared to controls. No differences in HD vintage, DM, CVD, HD session length, VA, BUN or Kt/V. Less age, fem gender, HTN, more sessions/wk, ACEi/ARB and lower Hb were found in the cases. 7 (9%) hospitalized and 2 (3%) required IMV. There were 6 (8%) deaths, only 1 (1.3%) attributed to COVID-19. Overall mortality minimally higher than that of the same period of 2019 (1.35% vs 1.30%). 31% of cases had only 1 symptom. Only 1 PCR(+) and 14 PCR(-) cases fulfilled SSA's definition. Among 231 staff members, 31 cases (13.8%), 11 (35%) PCR(+) and 20 non tested.

Conclusions: Incidence of probable or confirmed COVID-19 was 5.9%; probably overestimated suggested by scarce testing and low mortality. ACEi/ARB use more frequent in cases, adjusted for HTN and age. Our protocol helps prevent in-clinic contagion. A more comprehensive probable case definition appears more useful for HD patients.

	COVID-19 (Susp / Conf) n 75 (5.7%)	Non - COVID-19 n 1,201	Total n 1,276	p
Mean age (S.E.)	44.7 (18.8)	49.7 (17.7)	49.4 (17.8)	0.019
Female (%)	45 (60)	471 (39.2)	516 (40.4)	<0.001
Hypertension (%)	67 (91.8)	804 (66.9)	871 (68.4)	<0.001
ACEi/ARB Yes (%)	45 (60)	366 (30.5)	411 (32.2)	<0.001
Hemglobin (g/dL)	9.30 (2.02)	10.4 (1.96)	10.3 (1.98)	<0.001
Mean sessions per week (S.E.)	2.80(0.46)	2.6 (0.67)	2.6 (0.66)	0.01

PO0723

COVID-19 Infection in Patients with ESRD Requiring Hemodialysis

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Background: This case series assesses characteristics and outcomes of patients with confirmed novel coronavirus (SARS-CoV-2, COVID-19) infection and end stage renal disease (ESRD) requiring hemodialysis during the COVID-19 pandemic.

Methods: This is a single center retrospective study of 24 ESRD patients on hemodialysis who were admitted to Saint Barnabas Medical Center, a 597-bed acute care hospital in Livingston, New Jersey, and with a confirmed COVID-19 diagnosis between February 1st to April 5th, 2020. The characteristics, clinical course, and outcome were assessed and compared. In addition, a subgroup analysis was made between patients who expired (n=8) versus those who lived (n=16).

Results: The overall mortality rate was 33.3% vs. 21% in the general population with COVID-19. Among the 4 (16%) patients who required ICU admission and prolonged pressor support and invasive mechanical ventilation, 2 (50%) patients were successfully extubated and discharged from the hospital while the other 2 (50%) patients died. There were no statistical differences in laboratory values between patients who survived versus patients who died except C-reactive protein (CRP), p=0.002.

Conclusions: We report a mortality rate of 33.3% in our case series of 24 patients with ESRD on dialysis with concurrent COVID-19 infection. There was a statistical difference in CRP value between patients who died versus survived. Fifty percent of intubated patients were successfully extubated and discharged.

PO0724

COVID-19 Infection Patterns in an Academic Inner City Dialysis Unit

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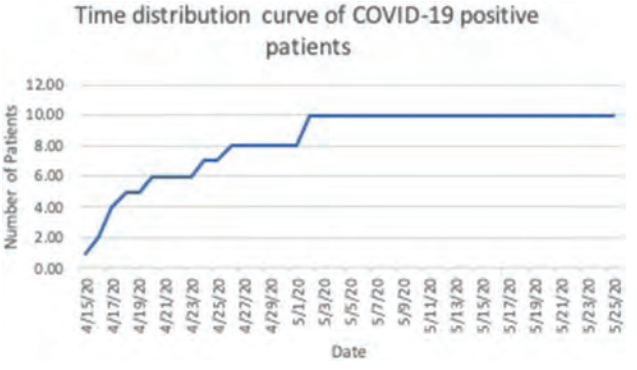
Background: COVID-19 remains a major public health emergency and in-center dialysis provides multiple opportunities for its spread. Elderly immunocompromised hosts pose a significant risk for infection as well as poor outcomes. We present a retrospective analysis of COVID-19 cases in our dialysis unit.

Methods: Retrospective analysis was done as a part of a quality improvement project using unidentified patient data including: demographics, distribution of dialysis shift, patient zip code, transportation mode (self, ride share or public transport), residence type (home, long term care facility or homeless shelter), etiology of ESRD and dialysis vintage. T-test and multivariate analysis (including logistic regression for binary and categorical data) were conducted using SPSS v23.

Results: There were 70 patients in the unit and 10 became positive for COVID-19. 65/70 (92%) of all patients were African American. Between COVID-19 positive and negative patients, there was no significant difference in age (62±15 vs 63±14 years p=0.2), dialysis vintage (7.6±8.7 vs 5.2±4.7 years p=0.31), male gender (7/10 (70%) vs 40/70 (58%) p=0.31). 5/10 (50%) of the positive patients were MWF 2nd shift. On multivariate analysis, this effect approached significance (p=0.051); however, there was no interaction of COVID-19 positive status with demographic characteristics, dialysis vintage, residence type, zip code distribution, or transportation modality. Of note, universal masking and temperature screening were implemented on March 5, 2020 in this unit and no new cases were noted after May 2, 2020.

Conclusions: Our analysis did not show any clear factor associated with COVID-19 infection among our dialysis patients although clustering approached statistical significance. Small sample size and demographic distribution are shortcomings of our study; larger scale epidemiological studies and data analysis are required for better understanding the risk of COVID-19 infection amongst in-center dialysis patients.



Chronological Distrubtion of COVID-19 Cases

PO0725

COVID-19 Infections in a Small Dialysis Organization in New York City

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Background: COVID-19 infected more than 1.6 million Americans (0.48%) and more than 15,000 of the 500,000 (3%) Americans with chronic kidney disease treated by dialysis. The Rogosin Institute operates nine dialysis centers in New York City (NYC), the epicenter of the COVID-19 US Public Health Emergency (PHE). We followed guidance from the Centers for Disease Control and Prevention and the New York State Department of Health throughout the PHE. We screened all patients and staff for signs and symptoms of COVID-19 by measuring temperature and inquiring about symptoms on presentation to our dialysis centers. Infected patients who did not require hospitalization were treated in our centers on a dedicated shift by dedicated staff. We used a symptom-based approach to discontinuing isolation.

Methods: We created a COVID-19 tool in REDCap to track the spread of Coronavirus. We surveyed our Electronic Health Record weekly using a direct data connection and automated scripting to identify patients infected with COVID-19. We reviewed demographic and clinical data for each infected patient. We used descriptive statistics to analyze our population of infected patients.

Results: On February 28, 2020, 1,559 patients received dialysis at our centers. By May 11, 241 (15.5%) had been infected. Our mortality rate was 22.8% compared to general populations in NYC (10-12%), US (6.0%) and worldwide (6.5%) and rates for dialysis patients reported between 7-20%. We had a disproportionate occurrence of COVID-19 among residents of Brooklyn (49% of infections, 44% of patients) and Queens (29%; 25%). Most of the infected patients were male (53%) and Black (51%). Common co-morbidities included hypertension (98%), diabetes mellitus (60%), heart failure (25%) and coronary artery disease (25%). Common outpatient medications included statins (64%) ACE inhibitors/ARBs (80%) and calcium channel blockers (63%). Fever was the only common presenting symptom (94% of patients). A significant proportion (12%) of patients were in the hospital within 14 days prior to diagnosis of COVID-19 infection.

Conclusions: COVID-19 infection was common and associated with high mortality rate in our NYC population of dialysis patients despite adherence to governmental guidelines for control of disease spread. We hypothesize community spread was common in our patients residing in the epicenter of the US COVID-19 PHE.

Funding: Clinical Revenue Support

PO0726

COVID-19 Outbreak and Experience in a Dialysis Unit in the Philippines

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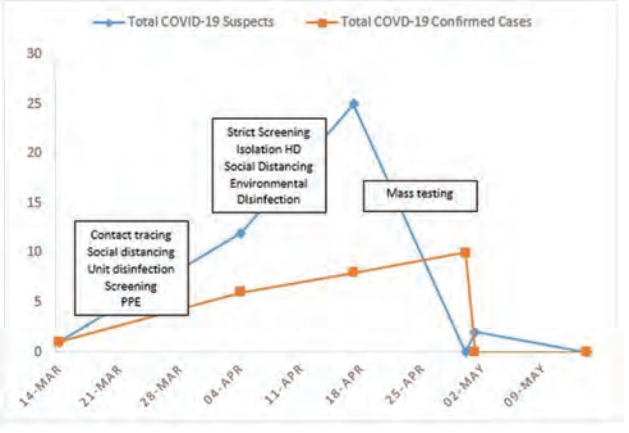
Background: Patients on regular dialysis are at an increased risk to COVID-19 due to their multiple comorbidities and exposure in the health care setting. The risk for virus transmission within a dialysis unit is also high emphasizing the importance of implementing infection control measures. The objective of this report is to describe the COVID-19 outbreak in a dialysis unit including interventions done.

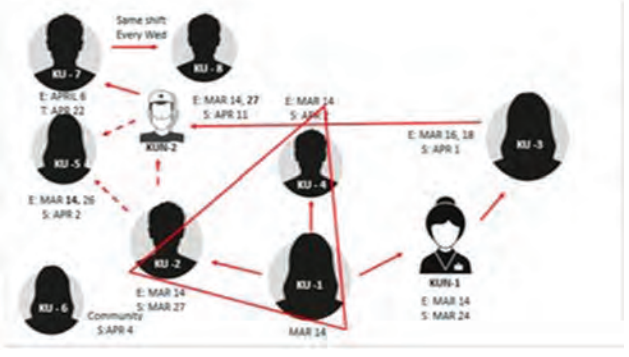
Methods: Review of the epidemic course with contact tracing was done from March 14 to May 14, 2020 in the dialysis unit of a tertiary hospital in the Philippines

Results: Of 167 patients, 20 became COVID-19 suspects. Eight were positive - 3 were exposed from the first confirmed case, 2 were handled by a COVID-19 infected healthcare worker (HCW) who was asymptomatic at time of contact while 2 asymptomatic patients tested positive during mass testing. Two of 67 HCWs tested positive were exposed to patients. Key interventions are (a) enhanced screening by mass testing using NPS/OPS RT-PCR of patients and HCWs after identifying 6 patients and 2 HCWs infected with COVID-19 (b) instead of cohort, dialysis of COVID-19 confirmed and suspected cases was done in isolation rooms separate from the dialysis unit (d) adequate personal protective equipment for HCWs and masks for all patients and (e) environmental disinfection especially in the waiting area with strict social distancing and daily screening.

Conclusions: The infection control and preventive actions done halted the increase in cases. Maintaining these strategies for the duration of the pandemic allowed further decline in the rate of infection.



COVID-19 Suspects, Cases and Interventions



Contact Tracing in the Unit

PO0727

Demographic and Clinical Characteristics of Patients with CKD and SARS-CoV2 Undergoing Hemodialysis Treatment

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Background: Patients on HD or PD are likely to be at increased risk of COVID-19 and its complications because they have multiple comorbid conditions. There is a lack of evidence about the optimal management and even clinical manifestations because clinical presentation is highly variable. The delayed diagnosis is because it's not recognized by the treating centers and the confusion with patients with fluid overload or uremic syndrome can be fatal in this population.

Methods: Retrospective, observational, single-center study in Mexico. We analyzed the clinical manifestations and outcomes of all maintenance HD patients hospitalized with COVID-19 from April 9th to May 31st, 2020 as confirmed by real-time polymerase chain reaction

Results: 20 patients followed in our hospital with median age of 45.2±13.8 years, 50% were men. All the patients have HTA (100%), DM (50%), the most common symptoms at admission were asthenia (75%), dyspnea (65%), cough (55%) followed by myalgias (50%) and fever (45%). Poor oxygen saturation (<95%) breathing room air was observed in 18 patients (90%) with mean oxygen saturation of 77± 9%. Lung abnormalities on initial chest X-ray were observed in all patients. Peripheral ground-glassopacities, the typical radiologic pattern, were bilateral in 13 patients and unilateral in 7. Laboratory studies with lymphopenia in 85% of patients with a mean of 0.7+0.38. There were no differences baseline leukocyte or lymphocyte from patients who survived vs from those who died. The mortality rate (40%) was much higher than that observed in the general population (8%). Mortality was higher in women.

Conclusions: The impact of this virus on patients with CKD is poorly understood. The evaluation of the nephrologist must be very detailed, most of the patients had mild dyspnea, however on physical examination, desaturation and radiological images were suggestive of infection by SARS-CoV2. The current situation provides a unique opportunity to gather vital information to process and learn from the experience worldwide. These results will allow us to treat them in a timely manner and reduce lethality in dialysis patients.

PO0728

Effect of COVID-19 on Dialysis Practices on the Ground: Early Results from an International DOPPS Program Survey

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Background: The COVID-19 pandemic caused unprecedented disruption to dialysis patients care globally. Facility surveys were distributed to assess the impact of COVID-19 pandemic on hemodialysis (HD) and peritoneal dialysis (PD) practices.

Methods: Medical Director (MD) and Nurse Manager (NM) Surveys (MDS, NMS) are being distributed in May/June 2020 to 723 clinics enrolled in the Dialysis (in-center HD, DOPPS) or Peritoneal (PDOPPS) Dialysis Outcomes and Practice Patterns Study in Canada, China, Japan, the United States, 7 European countries, 5 Gulf Cooperative Council countries, and China metropolitan areas (Beijing, Guangzhou, Shanghai). Surveys content includes the number of COVID-19 cases, testing, and clinical management, screening, infection control, staffing, patient transportation, and psychological support.

Results: As of 27 May 2020, we have 80 MDS (China, Europe, US = 33, 38, 5) and 101 NMS (45, 46, 9) responses from DOPPS sites. The following percentages are presented sequentially for China, Europe, and US. Among MDs, 0%, 67%, 67% reported at least one confirmed COVID-19 case among dialysis patients, and 85%, 70%, 66% reported being on the late phase of the COVID-19 curve. 40%, 23%, 100% of MDs were more likely to recommend home dialysis; 19%, 5%, 29% reported an increase in missed dialysis treatments; 30%, 24%, 50% were more likely to prescribe potassium binders; and 75%, 68%, 43% had greater challenges obtaining vascular access interventions. Among NMs, 30%, 9%, 40% reported current limitations in access to COVID-19 testing; and 61%, 51%, 29% reported having, or risk of, shortage in staffing.

Conclusions: Early results indicate many clinics in Europe and US have had COVID-19 cases, but sites in the three DOPPS-China cities have avoided COVID-19 to date. In all regions, shortages of human and medical resources were common, as were changes to dialysis delivery/practice including more skipped sessions, greater use of potassium binders, and preferentially recommending home dialysis. Over the next month, we expect hundreds more responses, and will compare approaches in PD and HD clinics. These data will inform guidance for dialysis care as the COVID-19 pandemic ensues.

Funding: NIDDK Support, Commercial Support - Support for the DOPPS Program (including CKDopps, DOPPS, and PDOPPS) is provided by Amgen (founding sponsor, since 1996), Kyowa Kirin Co. (since 1999, in Japan), and Baxter Healthcare (since 2011). Additional support is provided for specific projects and/or countries by Akebia Therapeutics, AstraZeneca, Bard Peripheral Vascular, Bayer Yakuhin, Chugai Pharmaceutical, DialyzeDirect, Japanese Society for PD, JMS Co., Kidney Research UK, Kidney Foundation Japan, Kissei Pharmaceutical Co., Medice, Nikkiso Co., ONO Pharmaceutical Co., Sanofi-Aventis Deutschland GmbH, Terumo Corporation, Torii Pharmaceutical Co., and Vifor Fresenius Renal Pharma.

PO0729

Factors Associated with SARS-CoV-2 Infection (COVID) Severity and Mortality in Chronic Dialysis Patients

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Background: From 2/17 to 5/29, 2020, Dialysis Clinic Inc. had 422 maintenance dialysis patients diagnosed with COVID from 90 clinics in 20 states. While prognostic factors in the general population have been reported, there is limited information regarding the US dialysis population.

Methods: Over a 15 week period of observation, 96 patients died (22.7%) and 116 (27.5%) were not hospitalized (for up to 30 days post-COVID diagnosis), likely with milder illness. We compiled univariable associations with p<0.1 into stepwise logistic regression models (forcing in age, sex. race) to determine factors associated with 1) Death from COVID; and 2) Moderate/severe illness (hospitalized or died without hospitalization <30 days post-COVID diagnosis).

Results: Candidate variables are listed in the table, with retained significant factors marked (a or b at p<0.05). Notably, 42% of all deaths occurred at age >75 years, increasing to 74% of all deaths at age >65 years. Wheelchair use also associated with higher death risk.

Conclusions: Dialysis patients with low albumin and vintage ≧1 year associated with increased illness severity. It was surprising that a history of pneumonia vaccine associated with more severe illness - whether this reflects "treatment by indication" bias vs. pulmonary immune activation by vaccination vs. chance finding is unclear. PVD also tended to increase illness severity but more importantly, was significantly associated with risk of death, independent of older age.

Each Model Total N=422	COVID Severity		COVID Death	
Model Entry Variables	Mod/Severe (N=306)	Mild Disease (N=116)	Died (N=96)	Alive (N=326)
Mean Age (years)	65.5	64.1	71.1[a]	63.4
% Male	62.1	55.2	63.5	59.2
% White	26.1	26.7	36.5[b]	23.3
% Black	56.9	56.9	46.9	59.8
% Other Race	17.0	16.4	16.7	16.9
% Vintage ≥1 year	84.0[a]	70.7	▪	▪
% Albumin <3.5 g/dL	22.2[a]	11.2	27.1	16.9
% Pneumonia Vaccine	85.0[b]	72.4	▪	▪
% ACE-Inh/ARBs	▪	▪	21.9	33.7
% Wheelchair	4.6	0.9	7.4[b]	2.6
# Comorbidities	3.4	2.9	3.8	3.1
% CHF	▪	▪	31.3	20.6
% Other CVD	▪	▪	45.8	34.4
% PVD	17.6[b]	9.5	25.0[a]	12.6

a: Significant in the multivariable model; b: Significant if age, sex, and/or race were not forced into the model.

PO0730

Fighting COVID-19: Experience from a Chinese Hemodialysis Center

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Background: COVID-19 has ravaged China and spread throughout the rest of the world. Since there is no effective treatment available at present time, patients with ESRD feel anxious and uncomfortable to come to dialysis center and receive dialysis treatments.

Methods: To help the patients deal with their anxiety without interrupting their treatments, we developed emergency response plans and offered following instructions during the pandemic of COVID-19.

Results: 1) We have immediately adopted a comprehensive epidemiological screening and symptom evaluation for all hemodialysis patients, family members and medical staff. Confirmed and suspected COVID-19 patients will be quarantined in the designated places for 14 days after they are cured and discharged from hospitals. 2) We emphasize scientific education and teach our patients about the scientific evidence-based protection measures. 3) Patients shall wear masks throughout the treatment and avoid gathering and talking. They are trained how to wash hands in the correct way. They are required to wash their hands before entering the hemodialysis center and after returning home. 4) Before entering the hemodialysis center, everyone shall scan the QR code and register his or her health information. Medical staff will screen patients and perform the risk stratifications as seen in **figure 1.** Medical staff will check the patients' temperature before, during and after dialysis treatment. 5) The environmental cleaning and disinfection measures will be strengthened for hemodialysis facility. The spaces between dialysis stations will be increased and the isolation curtains will be installed to keep social distance. Isolation treatment area will be set up to reserve for suspected COVID-19 hemodialysis patients.

Conclusions: Since we adopted above-mentioned instructions, we have zero infection case during the pandemic of COVID-19.

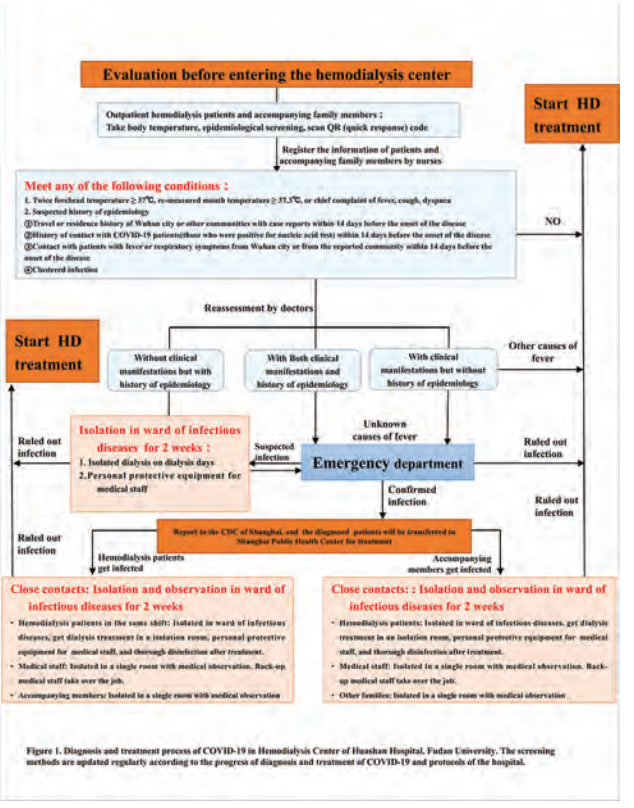

Figure 1. Diagnosis and treatment process of COVID-19 in Hemodialysis Center of Huashan Hospital, Fudan University. The screening methods are updated regularly according to the progress of diagnosis and treatment of COVID-19 and protocols of the hospital.

PO0731

Ferritin and Lymphopaenia as Markers of COVID-19 in a Haemodialysis Population

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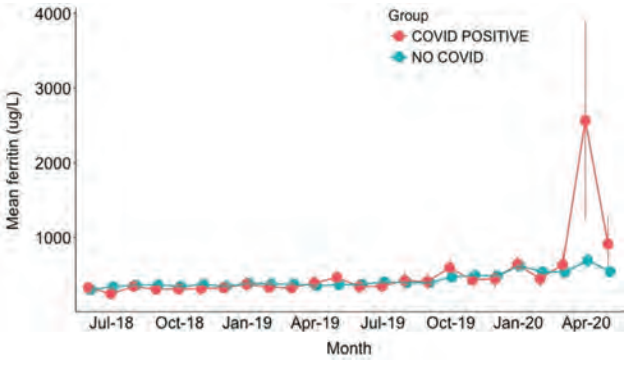
Background: The COVID-19 PCR swab test has low sensitivity and some infected people are asymptomatic, which makes it possible for inadvertent spread of the virus to occur. We reviewed laboratory data in haemodialysis (HD) patients to investigate the utility of routine blood tests as surrogate markers of COVID-19 infection.

Methods: Retrospective cohort study of data in prevalent patients on HD from 1st March 2020. Blood test results from June 2018 to May 2020 were analysed.

Results: There were 708 patients. 473 were on HD since June 2018. 150 had ≥1 PCR test for COVID-19: 69 were positive. 268 (37.9%) were female and 282 (39.8%) were of non-white race. Median age was 69 years (IQR 56-78). *Lymphocytes* Mean lymphocyte count at baseline was 1.5 (SD 4.3). Prior to March 2020, the mean monthly prevalence of lymphopaenia was stable at 32 %, but rose to 67 % in COVID +ve patients and 36 % in COVID -ve patients (p<0.001) during the peak of the COVID crisis in April. *Ferritin* Mean monthly ferritin at baseline was 395μg/L. Prior to March 2020, only 3% of patients each month had a ferritin of > 1000μg/L. In April, 68 % of COVID +ve individuals had a ferritin of >1000μg/L compared to 18 % of COVID –ve patients (p<0.001). No significant differences were noted in platelet count, neutrophils and CRP over the study period.

Conclusions: Our data show a high prevalence of lymphopaenia which was more pronounced in COVID +ve patients. There was no similar rise over the previous 2 winter periods, so we feel this was a COVID specific, rather than just a viral phenomenon. A low lymphocyte count has recently been associated with adverse prognosis in our patients with COVID-19. Our data support reports which suggest that ferritin could aid screening for COVID-19 in HD patients. The degree of elevation of ferritin during the 'COVID months' in our COVID +ve group suggests that the disease was contributing to this. This may be due to a cytokine storm and multi-organ involvement and ferritin may prove to be a prognostic factor for COVID-19.



PO0732

Impact of Undertaking Safeguards to Limit Exposure and Prevent COVID-19 Infection in Ambulatory Dialysis: A Single-Center Experience

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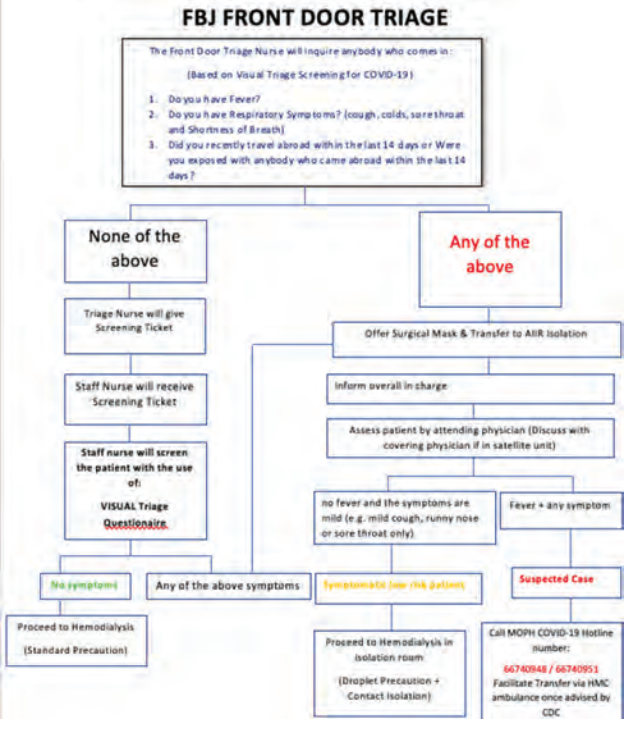
Background: Dialysis patients are considered at high risk to develop serious COVID19 complications. Taking extreme measures are necessary to prevent COVID19 transmission at the dialysis center. We are presenting outcomes of our COVID19 prevention project from our largest dialysis center in Qatar.

Methods: Our project was done at FBJKC (largest dialysis center in Qatar with about 60% of all hemodialysis (HD) and 90% of all peritoneal dialysis (PD) patients in Qatar)) between March 1st and May 25th 2020. We gradually implemented a bundle of measures and algorithm (attached) to properly triage and limit COVID19 exposure inside the center. New infection control protocol with specifications to COVID19 were implemented, including a new policy for reusing N95 masks in high risk areas. We tracked number of patients and staff who were infected during that period and source of infection.

Results: Our dialysis census during that period was 480 HD and 170 PD patients. Only 6 HD patients turned positive for COVID19 (0.9%) and 2 PD patients (1.2%) (compared to 1.3% general population in Qatar by May 25th). We had 3 dialysis staff infected out of 114 (2.6%). Our investigation showed that all cases of COVID19 (both in patients and staff) were likely contracted outside the center. All staff and patients exposed to positive cases of COVID19 inside the center turned out negative. Our infection control classified most exposures at low risk, especially after we fully implemented our precautions.

Conclusions: Preventive actions implemented inside a large dialysis center led to prevention of COVID19 transmission. Increase positive COVID19 cases (in staff and patients) were related to countrywide growth of infection.



PO0733

Outcomes of COVID-19 in ESRD Patients on Hemodialysis

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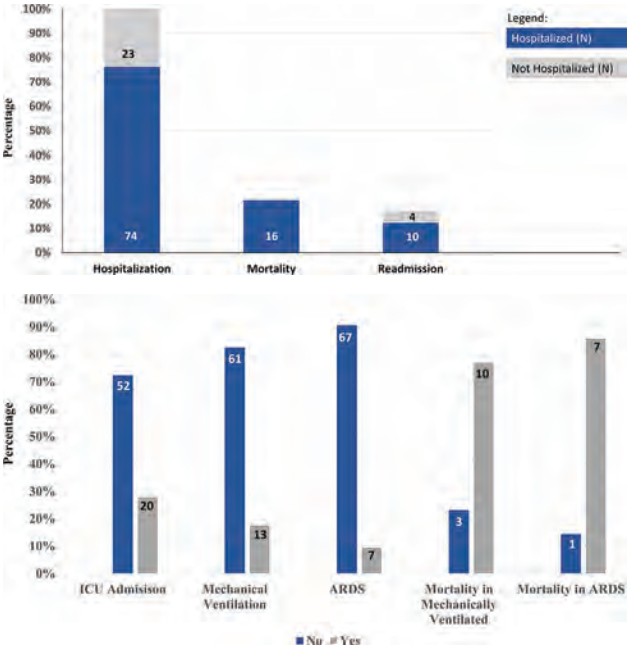
Background: The presentation, natural course, outcomes, and markers of COVID-19 among end stage renal disease (ESRD) have not been well defined. The objective of this study is to evaluate the outcomes of COVID-19 hospitalized and nonhospitalized outpatient ESRD patients. The secondary objectives are to evaluate mortality rate, hospital readmission rates, treatment methods, lengths of hospital stay, mechanical ventilation requirement, and acute respiratory distress syndrome (ARDS) between hospitalized and non-hospitalized patients.

Methods: This is a prospective, observational study evaluating the outcomes of hemodialysis patients who test positive for COVID-19 between March 10 to May 8, 2020 at a large regional health system in Southeast Michigan. Incenter hemodialysis patients, 18 years or older who tested positive for COVID-19 were included. Descriptive statistics are used, and continuous variables are presented as medians with interquartile ranges, and categorical variables are presented as percentages. Two-sided t-tests were used for exploratory analysis.

Results: 97 of 192 patients tested positive for SARS-CoV-2. Hospitalization rate among COVID-19 positive patients were 76.3%. The most common presenting symptom was fever (63%). Overall mortality and readmission were 16.5% and 14.4%. Median length of hospital and intensive care unit stay was 7.6 and 8 days. Of the hospitalized patients, 17.6% required mechanical ventilation, and 53.9% developed ARDS, with a mortality of 85.7% in this group of patients. Leucopenia, C-reactive protein, peak ferritin and D-dimer corelated with mortality among hospitalized patients.

Conclusions: ESRD pose a higher risk for hospitalization, overall mortality was acceptable, although survival among patients requiring mechanical ventilation was low.



PO0734

Outcomes of ESKD Patients Hospitalized with COVID-19

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Background: Patients with ESKD have a dysregulated immune system and a higher annual mortality rate compared with the general population. We aimed to describe the clinical characteristics and compare the outcomes of patients with and without ESKD, among those hospitalized with COVID-19 disease.

Methods: We reviewed the health records for all patients hospitalized with Covid-19 between March 1, 2020 and April 27, 2020 from 13 hospitals in New York. Patients < 18 years or admitted to inpatient obstetrics service were excluded. ESKD diagnosis was defined using ICD-10 code and manual adjudication. Patients were followed up through May 27, 2020.

Results: Of 10,482 patients admitted with COVID-19, 419 (4.0%) had ESKD. Among patients with ESKD, 408 (97.4%) were on hemodialysis and 11 (2.6%) were on peritoneal dialysis. When comparing baseline characteristics of the two groups, patients with ESKD were older, were predominately of Black race, and had greater proportions of comorbid conditions. The primary outcome was that patients with ESKD had a higher odds of in-hospital death than those without ESKD (rates, 31.7% vs 25.4%; OR 1.4, 95% CI 1.1 - 1.7). After adjusting for age, sex, race/ethnicity, the odds of

in-hospital death remained higher in the ESKD group (adjusted OR 1.5, 95% CI 1.2 - 1.8). The ESKD group did not have a significantly higher odds of needing mechanical ventilation than the non-ESKD group in both the crude analysis and after adjustment for age, sex, race/ ethnicity. The odds of having a length of stay of >7 days was higher in the ESKD group compared to the non-ESKD group, in both the crude analysis and the adjusted analysis (OR 1.62, 95% CI 1.3 - 2.1; adjusted OR 1.6, 95% CI 1.3 - 2.1). The independent predictors for death for non ESKD patients were age, male gender, cancer, CHF, elevated BUN, low albumin and being on a ventilator. The independent predictors of death for ESKD patients were age, lymphopenia, low albumin and being on a ventilator. Black race was associated with lower risk of death..

Conclusions: ESKD patients had a higher rate of mortality compared to non-ESKD patients hospitalized with COVID-19. Black race was associated with a lower risk of death among ESKD patients compared to white patients.

PO0735

Outcome of Hospitalized ESRD-COVID-19 (C19) Infected Patients

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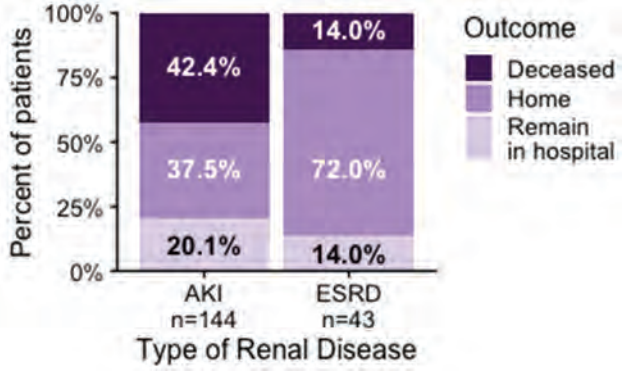
Background: Emory University affiliated hospitals serve the metro Atlanta area, where a significant number of C19 cases have ocurred. In this report we describe the outcomes of AKI and ESRD patients with confirmed C19 admitted to our health-system.

Methods: All patients seen by Emory Nephrology at 2 tertiary referral and one county hospital were categorized as **ESRD** if they required dialysis prior to C19 infection, or **AKI** if they developed acute kidney injury as a result of C19 infection. Outcomes of interest included patient survival and discharge from the hospital. Admission to Intensive care unit and use of mechanical ventilation were recorded. Comorbid conditions and outpatient use of medications were analyzed.

Results: From 3/1/20 to 5/26/20, 474 consecutive patients were seen in COVID-19 related consultation. 287 patients were considered PUI and eventually tested negative for C19. The remaining 187 patients were C19 positive by nasopharyngeal swab or tracheal aspirate and represent the study population for this report. There were 43 ESRD (23%) and 144 AKI (77%) patients. Age (64 vs 63 years), gender (63 vs 66% males) ethnicity (86 vs 82% African-americans) and comorbid conditions were similar in AKI and ESRD patients. AKI patients were more likely to be admitted to ICU (83 vs 35%) and to require mechanical ventilation (73 vs 20%) compared to ESRD patients ($p<0.05$). Figure 1 presents the outcomes based on the type of renal disease at presentation. The eGFR of AKI patients at time of admission was 50±34 ml/kg/m^2. 84 AKI patients required dialysis during their hospitalization (52.5%).

Conclusions: Patients with ESRD C19+ were less likely to require ICU admission or mechanical ventilation. Mortality of ESRD patients was 14% compared with 42% of AKI patients, ($p<0.002$). ESRD patients with C19 were also more likely to be discharged from the hospital compared to those with AKI. Despite similar demographics and co-morbidities, hospitalized C19 AKI patients had worse mortality than those receiving chronic dialysis.



PO0736

Non-Hospitalized Maintenance Hemodialysis Patients with COVID-19 Have Elevated Inflammatory Markers

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Background: In addition to an aggressive pneumonia, patients hospitalized with COVID-19 have marked inflammatory and hypercoagulable states, with downstream cardiovascular and thrombotic events. Hemodialysis patients have baseline increases in inflammation and hypercoagulability. However, to our knowledge, little is known about the level of inflammation and hypercoagulability among non-hospitalized in-center hemodialysis patients with COVID-19. We collected inflammatory and coagulation markers among hemodialysis patients with COVID-19 who were managed as outpatients.

Methods: Patients in our dialysis program with one positive nasopharyngeal swab PCR for SARS-CoV-2 were consecutively admitted to an outpatient COVID-19 hemodialysis shift. While receiving their usual dialysis prescription, the patients also had weekly measurements of D-Dimer, Fibrinogen, C-reactive protein (CRP), and Serum Ferritin, until they tested negative x 2 for SARS-CoV-2.

Results: 16 consecutive patients were admitted to the COVID-19 isolation shift over 30 days. Their average age was 60 yr, 56% were Black, 25% Hispanic, and 44% female. Causes of ESKD included diabetes (75%), glomerular diseases (19%), and hypertension (6%). No patients received intravenous iron supplementation while on the isolation shift. Table 1 displays the inflammatory marker levels in this group. Note, the 4-fold (D-Dimer), 6-fold (Ferritin) and 21-fold (CRP) increase in these biomarkers from normal levels.

Conclusions: Our initial, unique data show an increase in inflammatory markers in a cohort of non-hospitalized COVID-19 hemodialysis patients. Such an increase may be from the pro-inflammatory impact of COVID-19 in a group with pre-existing high levels of inflammation from uremia and oxidative stress. Additional investigation as to whether these elevated markers associate with cardiovascular and thrombotic events (dialysis circuit and vascular access clotting, sudden cardiac death) is needed.

Funding: NIDDK Support, Clinical Revenue Support

Inflammatory Markers among Non-Hospitalized HD Patients with COVID-19

	Mean ± S.D.	Observed Range	Normal Range(non-ESKD)
D-Dimer mcg/mL	2.0±1.0	0.4 - >4.0	0.0-0.5
Fibrinogen mg/dL	527.4±122.7	273-960	217-480
C-reactive protein mg/L	50.4±54.4	0.9-477	0.0-2.4
Serum Ferritin ng/mL	1954.6±1697.0	419-11066	22-322

PO0737

Network Analysis of In-Center Spread of COVID-19: A Single Dialysis Center Experience

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Background: The need to continue in-center hemodialysis (HD) during COVID-19 pandemic presents a risk of transmission for patients and staff members. The present study aimed to determine if the periodic interactions among patients and staff resulted in spread of COVID-19 in a HD center during a period of 2 months

Methods: This is a retrospective analysis on a HD center in New York City (172 patients, 32 staff members, 26 chairs, MWF and TTS schedules, and 4 shifts/day). From March 2nd to April 24th we recorded every HD treatment (chair, patient, and staff member involved in care). We kept dated records for positive COVID-19 cases (patients and staff). To estimate the patient-to-patient interaction, we obtained the location coordinates of each dialysis chair, calculated the Euclidian distance between them and weighted the interaction by proximity between chairs. We conducted network analysis to assess these interactions

Results: During the study period, 16 patients and 2 staff members became COVID-19 positive. As shown in Figure 1(a), there were 3 chairs (2, 24, and 25) that had more than 1 positive patient. Clusters in chairs 2 and 25 were ruled out based on a lack of direct contact between the involved patients (at least 2 shifts separating them at all times; no in-between patients became positive); chair 2 had a nonviable temporal direction of transmission. Based on schedule, shift, and a 14-day incubation period, the cluster in chair 24 was dismissed. This was corroborated by network analysis [Fig. 1(b)] where the purple dots represent the COVID-19 positive patients, the blue dots represent negative patients (same shift/schedule), and the edges represent the weighted patient-to-patient interaction. We reasoned that more exposed patients would have had a higher chance of becoming infected. Similar information was found for staff-to-patient interaction

Conclusions: Based on our analysis we consider that for patient-to-patient, staff-to-patient, and staff-to-staff interactions, in-center spread of COVID-19 was unlikely

Funding: Private Foundation Support

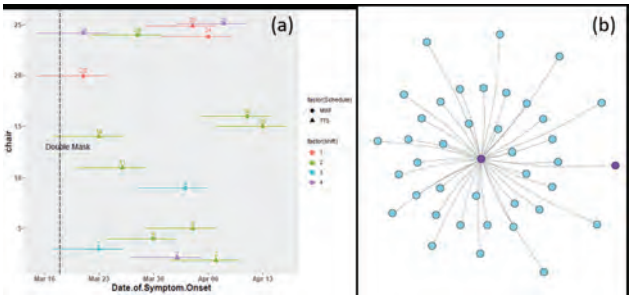


Figure 1(a)infection history;(b)network analysis patient interaction

PO0738

Outcomes of Patients on Chronic Dialysis Hospitalized with COVID-19

Lili Chan, Suraj K. Jaladanki, Lewis Kaufman, Shuchita Sharma, Staci A. Leisman, John C. He, Barbara T. Murphy, Steven G. Coca, Girish N. Nadkarni. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Preliminary reports find that patients with end stage renal disease (ESRD) on dialysis who test positive for SARS-CoV-2 have fewer symptoms and require less intensive care than expected. However, there are no reports regarding the outcomes of ESRD patients who are hospitalized with coronavirus disease 2019 (COVID-19).

Methods: This is a retrospective observational study of patients aged ≥18 years with laboratory confirmed COVID-19 admitted to the Mount Sinai Health System between February 27 and May 20, 2020. ESRD patients were identified by International Classification of Disease codes for ESRD. ESRD patients were propensity matched (5:1) to non-ESRD patients by age, gender, race/ethnicity, comorbidities, body mass index, and facility and week of hospital admission. Multivariate analysis was performed to test the association of ESRD with mortality after adjustment for age, diabetes, hypertension, stroke, coronary artery disease, and congestive heart failure.

Results: 122 ESRD patients were admitted during the study period and matched to 610 non-ESRD patients from the same study period. Patients with ESRD were well matched on age, sex, race/ethnicity and most comorbidities except ESRD patients had a higher prevalence of diabetes (55% vs 43%, P=0.02) and hypertension (66% vs. 55%, P=0.03). ESRD patients had higher inflammatory markers of ferritin and procalcitonin. There was no significant differences in d-dimer, fibrinogen, C reactive protein, or interleukin-6 (Figure 1A). ESRD patients were significantly less likely to receive mechanical ventilation (3% vs. 10%, P=0.01) or be admitted to the intensive care unit (9% vs. 21%), and had similar in-hospital mortality (9% vs 13%, P=0.5). ESRD status was associated with lower odds of intubation and intensive care admission, but not significantly associated with mortality after adjustments for age and comorbidities (Figure 1B).

Conclusions: While ESRD patients had higher prevalence of comorbidities and higher inflammatory markers, they had similar in-hospital mortality as matched non-ESRD patients.

Figure 1A: Boxplot for maximum inflammatory markers between ESRD and non-ESRD patients

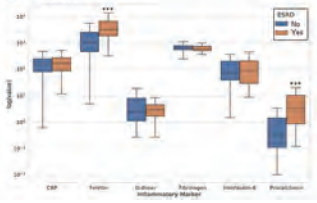
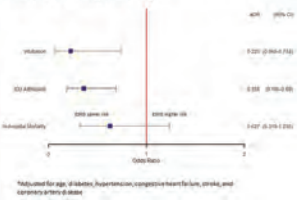


Figure 1B: Forest Plot for association of ESRD with intubation, ICU admission, and in-hospital mortality*



PO0739

Outpatient Hemodialysis Unit Preparedness During COVID-19 Pandemic in Several Dialysis Units in New York State

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Background: HD units are clustered close contact environments where prolonged and repeated exposure to blood borne pathogens occurs. Weeks into the CoVID-19 pandemic, wide disparities in rates of death and exposure of staff and patients amongst HD units in the same zip code of an epicenter in New York regions emerged.

Methods: Random HD units surveyed as to when and what infection control measures they implemented. Direct input into RedCap and SAS 9.0 analysis of the data conducted.

Results: 15 HD units (average census 18-240) responded. Survey compiled exposure rates from 3/1/20 - 4/30/20. The 1st reported case of CoVID-19 by a facility was 3/2/20. Most facilities reported outbreaks (4-30 cases per facility) by 3/21/20. Missed HD sessions due to CoVID varied from 2-100, hospital stays for such patients varied from 2-20 days and death rates from 0-15 per facility. 4 of 15 facilities reported deaths of family members of exposed patients and impediments in logistics of single person transportation forcing carpooling. Home dialysis programs reported minimal deaths and exposures. 20% of facilities had no infection preventionist and 26% no patient educator. Reported waiting area cleaning and hand sanitizer refill rates ranged from 1-5 times per day. 20% of the facilities have < 6 feet distance between patients. Implementation of infection control practices such as wearing of masks by patients varied widely amongst units. Some started March 1st-March 16th, some later due to mixed messages of its importance. Lack of personal protective equipment (PPE)(in 13% of facilities), staff, and housekeeping shortages (6.7-13.3%) compounded the problems. Positive CoVID results had 1-10 staff members infected per facility with sick call rates from 7-30 days, and no staff death. 46% of the HD units don't belong to the CDC coalition.

Conclusions: Maintenance of strict hand hygiene, proper air flow, repeated environmental surface cleansing, availability of PPE, and patient and staff education remain the corner stone in preventing infections from spreading. Lack of leadership support and failing to share best practices between dialysis units in the US remains prohibitive but must be encouraged and standardized.

PO0740

Outpatient Initiation of Dialysis for AKI Requiring Dialysis Following Diagnosis of COVID-19

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Background: COVID-19 has been associated with the development of AKI, and the incidence of AKI-D may be as high as 3-5% in patients hospitalized with COVID-19. We examined the initiation of outpatient (OP) dialysis for AKI-D following a diagnosis of COVID-19.

Methods: We identified patients who were diagnosed with COVID-19 prior to initiating OP dialysis for AKI-D in a Fresenius Medical Care North America (FMCNA) dialysis facility between March 30, 2020 and May 22, 2020. COVID-19 diagnosis was based on information provided at the time of referral or data collected within FMCNA. We assessed demographics, geographic location, and select initial outpatient lab values. We followed patients from initiation of OP dialysis until the earliest of recovery of kidney function, transition to ESKD, death, loss to follow-up (typically, transfer to another dialysis provider), or May 24, 2020, and estimated the cumulative incidence of these outcomes.

Results: The cohort comprised 127 patients who were diagnosed with COVID-19 prior to initiating OP dialysis for AKI-D. Mean age was 56.3 ± 14.7 years and 64% were male. Initiation of OP dialysis for AKI-D was observed in regions with a known high incidence of COVID-19 disease (Figure). The median hemoglobin, platelet count and albumin at dialysis initiation were 8.9 g/dL, 271,000 per microliter, and 3.2 g/dL, respectively. During a median follow-up period of 19 days, 18 (14.2%) patients recovered kidney function, 2 (1.6%) transitioned to ESKD, and 2 (1.6%) died.

Conclusions: In an approximate 7-week period, 127 adults started OP dialysis for AKI-D following a diagnosis of COVID-19. Unfortunately, information regarding the clinical course of COVID-19 preceding OP initiation of dialysis was not available and using information at the time of referral may have resulted in misclassification of COVID-19 disease. Nevertheless, these are important findings and warrant further study, especially with respect to long-term outcomes in this population.

Funding: Commercial Support - Fresenius Medical Care

PO0741

Impact of the COVID-19 Pandemic on In-Center Intermittent Hemodialysis Treatment Adherence

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Background: Studies have shown that 7.9% of patients miss one to two hemodialysis session per month and 35% miss hemodialysis at least once every three months.[1] During current COVID-19 pandemic there has been a decrease in utilization of emergency medical services due to fear of contagion. We hypothesized that patients undergoing in-center hemodialysis might have increased compliance with their dialysis prescription to avoid emergency department visits or hospitalizations. We therefore evaluated the effects of the COVID-19 pandemic on patient adherence to their dialysis prescription.

Methods: This is a retrospective analysis of in-center hemodialysis patients treated in the seven American Renal Associates (ARA) dialysis facilities in Dallas, Texas. COVID-19 was declared a pandemic on March 11, 2020 and pandemic related changes were mandated in ARA hemodialysis facilities on March 13, 2020. We used existing clinical data and examined patient compliance with their dialysis prescription between January 1 to March 14, 2020 (pre-COVID) and March 15 to May 18, 2020 (COVID).

Results: The study enrolled 754 eligible patients. Significantly fewer patients missed a single treatment in the COVID vs pre-COVID periods (35.5% vs 49.9%; p<0.001). The percentage of patients who were hospitalized was lower during COVID vs pre-COVID (12.5% vs. 19.6%; p<0.001). The percentage of patients who shortened hemodialysis time was lower during COVID vs pre-COVID (36.2% vs. 40.9%; p=0.06) although not statistically significant. Finally, significantly more patients achieved a weight within1 kg of their estimated dry weight at the end of the dialysis sessions COVID vs. pre-COVID (28.5% vs. 34.5%, p=0.01).

Conclusions: These data suggest that during current COVID-19 pandemic, hemodialysis patients have become more adherent to their dialysis prescription. Retrospective studies have suggested that patients are avoiding seeking medical care due to fear of contacting the SARS-CoV-2 virus[1]. Our data suggest that similarly, hemodialysis patients have significantly increased their adherence to hemodialysis prescription in order to avoid hospital visits. Additional studies are ongoing to determine the causes for the observed improved compliance.

PO0742

Accuracy of Lower Temperature Thresholds in Detecting COVID-19 in Hemodialysis Patients

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Background: Patients receiving in-center hemodialysis (HD) are uniquely vulnerable to COVID-19 yet identifying infected individuals may be challenging. They may not present with typical symptoms and low basal body temperature may impair detection of fever. We studied the accuracy of temperature thresholds in detecting COVID-19 in HD patients.

Methods: We retrospectively studied all patients between March 24-May 14, 2020 from a single HD unit (Hôpital du Sacré-Coeur) in Montreal, Canada, where COVID-19 is highly prevalent. All patients who presented with symptoms or contact exposure were tested by nasopharyngeal swab. Prompted by an outbreak, systematic testing of all HD patients was started on April 18th. Basal temperature was defined as the average pre-dialysis temperature from weeks -1 to -3 before testing. Diagnostic performance was determined for various temperature thresholds defined *a priori*.

Results: Of 205 in-center HD patients, 34 developed COVID-19 during the study period. Of these, 21 (61%) were hospitalised, 4 (11%) required intensive care and 9 (26%) died. Baseline characteristics are presented in Table 1. Less than a third had typical symptoms. Thresholds of ≥ 37.3 °C and "basal temperature +0.5 °C" had similar moderate sensitivity and high specificity in predicting COVID-19 (Table 2). Combining symptoms and either of these thresholds improved sensitivity to 85%.

Conclusions: Less than one third of HD patients have typical symptoms of COVID-19 or fever >38.0°C. Pre-dialysis temperature >37.3°C or 0.5°C above basal temperature markedly improves sensitivity for detection of COVID-19 in asymptomatic HD patients. A screening strategy combining symptom questionnaires and pre-dialysis temperature monitoring should be used in HD units in regions of high COVID-19 prevalence.

Table 1: Baseline characteristics in HD patients without and with COVID-19

Characteristics	COVID-19 negative (n=171)	COVID-19 positive (n=34)	p-value
Male sex	59%	56%	0.7
Age	71 (60, 81)	76 (68, 85)	0.03
Black race	20%	38%	0.02
Living in long-term care facilities	11%	32%	0.001
Primary kidney disease			0.5
Diabetic	47%	32%	
Hypertensive	22%	47%	
Glomerulonephritis	14%	9%	
Diabetes	54%	47%	0.4
Ischemic heart disease	37%	32%	0.6
Heart failure	9%	24%	0.01
Indication for screening			<0.001
Symptoms without fever	2%	24%	
Fever (at home, or >37.5 in HD)	1%	47%	
Contact with positive case	4%	9%	
Systematic screening	94%	21%	
Temperature at screening (°C)	36.5 (36.3, 37.0)	37.5 (37.0, 38.0)	<0.001
Basal temperature (°C)	36.5 (36.3, 36.7)	36.6 (36.4, 36.9)	0.1
Change from basal (°C)	0.1 (-0.3, 0.5)	0.9 (0.3, 1.5)	<0.001
Above 37 °C	28%	77%	<0.001
Above 37.3 °C	8%	65%	<0.001
Above 37.5 °C	4%	59%	<0.001
Above 38 °C	0%	27%	<0.001
Above basal	56%	87%	0.001
Above basal + 0.5 °C	25%	70%	<0.001
Above basal + 1 °C	1%	43%	<0.001

Presented as Percent and median (25th-75th percentiles)

Table 2: Diagnostic performance of various thresholds

Pre-dialysis temperature	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Above 37 °C	77%	72%	35%	94%	2.7	0.33
Above 37.3 °C	65%	92%	61%	93%	7.9	0.38
Above 37.5 °C	59%	96%	74%	92%	14.3	0.43
Above 38 °C	27%	100%	100%	87%	∞	0
Above basal + 0.5 °C	70%	93%	33%	93%	10.7	0.32
Above basal + 1 °C	43%	91%	93%	91%	4.7	0.62

PO0743

Assessment of a Laboratory-Based SARS-CoV-2 Antibody Test Among Hemodialysis Patients: A Quality Improvement Initiative

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Background: The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Assessment of newly developed anti-SARS-CoV-2 antibody tests in hemodialysis patients is needed.

Methods: As part of a quality improvement (QI) initiative, nasopharyngeal swabs and predialysis blood samples were collected on the same day from adults receiving routine dialysis care at clinics managed by a large dialysis organization in the Miami, Florida, region (April 23-30, 2020). Polymerase chain reaction (PCR) tests for SARS-CoV-2 (Fulgent Genetics, Temple City, California) and chemiluminescence immunoassays (Diazyme Laboratories, Inc, Poway, California) were performed according to manufacturer protocols. For antibody tests (IgM and IgG), a reading of >1 arbitrary unit/mL was scored as positive.

Results: Of 715 participants in the QI initiative, 38 had symptoms consistent with COVID-19 prior to or during the initiative. Among these, COVID-19 was confirmed in 14 and ruled out in 20, with 4 being inconclusive. Among the 34 patients with known COVID-19 status, the sensitivity and specificity of the antibody test were 57.1% and 85.0%, respectively, when both IgM and IgG were considered. The remaining 677 patients had no record of symptoms consistent with COVID-19 or any known exposure. Of these, 38 (5.6%) tested positive for anti-SARS-CoV-2 antibodies; none of the antibody-positive patients with available PCR results (N=33) tested positive for SARS-CoV-2.

Conclusions: The operational characteristics of the laboratory-based antibody test make it sufficient to rule in, but not rule out, SARS-CoV-2 infection in the appropriate clinical circumstance. A substantial proportion of dialysis patients may have had asymptomatic SARS-CoV-2 infection.

PO0744

Clinical and Psychosocial Impact in Mexican Hemodiafiltration Population During the COVID-19 Pandemic, Twice Weekly Sessions: Is This Safe?

Jose S. Lopez Gil, Hector Alejandro P. Garza, Magdalena Madero, Daniela Xavier. Division of Nephrology *Instituto Nacional de Cardiologia Dr Ignacio Chavez, Mexico City, Mexico*.

Background: There is evidence that in patients with residual kidney function (RKF) could benefit switch thrice to twice weekly sessions. In patients without RKF, the evidence is limited. We evaluate the clinical and psychosocial impact of the Covid-19 pandemic in Mexico City.

Methods: At the beginning of the Covid-19 pandemic, the on-line posdilutional hemodiafiltration (OL-HDF) sessions were adjusted from 3 to 2 times per week. 2 months later, we determine hemoglobin, urea, serum creatinine, sodium, potassium, calcium, phosphate, albumin, ferritin and C reactive protein. Likewise psychological evaluation using Hamilton test were carried out and characteristic of sessions were collected. We divide in two groups according to thrice versus twice weekly schedule

Results: 25 patients were evaluated, 16 (64%) were female, mean age was 42.04±18.02 years, 21 (84%) did not have RKF. The length session between thrice vs twice were 181.74± 9.94 vs 196 ± 9.19 **(p<0.001)**. When we analyzed the anuric patients we found a significant difference in post-session systolic and diastolic blood pressure when compared between groups **(p = 0.014).** We did not find difference in dry weight **(p = 0.5)**. We found significance difference between total substitution volume between groups (24.43±10.9 L vs 26.5± 12.48 L, **p =0.042**) and no difference in Kt/V (1.67 ± 0.25 VS 1.73 ± 0.34, p = 0.35). We found significance difference between groups in serum creatinine (8.68±3.55 vs 10.04±2.94, **p=0.03**) in the rest of molecules we did not find difference. 32 and 44% of the patients developed depression and anxiety, respectively. 36% of patients lost their jobs and 80% use public transport. There was a moderate correlation between anxiety episodes and economic limitation due to Covid-19 (**r = 0.40 p = 0.04**). There was no significant inverse correlation between pharmacological adherence and economic limitation (r = -0.29 p = 0.29).

Conclusions: Change of the schedule in patients without RFK did not show significant differences in terms of biochemical parameters, on the other hand, improvement in replacement volumes. We considered a safe strategy to reduce the risk of transmission among our population. Pharmacological and attending adherence to sessions was not modified despite the psychological findings due to the Covid-19 pandemic.

PO0745

Clotting of Hemodialysis Catheters in Patients with Renal Failure with COVID-19

Mary C. Mallappallil,[1,2] Jie Ouyang,[1,2] Sabu John,[1,2] John D. Wagner,[1] Mariah W. Thaxton,[1] Ernie Yap,[1,2] Siddhartha D. Bajracharya.[1,2] *[1]Health and hospital corporation New York City - Kings County Hospital, New York, NY; [2]State University of New York at Downstate Medical Center, Brooklyn, NY.*

Background: We are an inner-city hospital in New York that had a surge of patients diagnosed with COVID-19. Many of these patients had acute kidney injury (AKI) and required renal replacement therapy (RRT). NYC Health + Hospitals/Kings County has 40 adult intensive care unit (ICU) beds. ICU capacity expanded to a potential of 150 beds during the COVID-19 surge. The surge included patients transferred from other NY inner-city hospitals for critical care and RRT. Sequential obstacles were faced in providing hemodialysis (HD) to this expanded pool of AKI patients. Additional machines, supplies, staffing and organization were helpful. Clinicians noted that COVID-19 complications included hypercoaguability and we observed an increased frequency of clotting of hemodialysis catheters (HDC).

Methods: We examined the percentage COVID-19 tested renal failure patients with clotting of HDC access during the period March 1, 2020 to May 15, 2020. We collected data on 146 patients during the above period who had HD. We then compared those who were COVID-19+ positive confirmed by testing to those who were not COVID-19+ by testing. HDC clotting was identified by the use of alteplase. We compared our findings of the two groups to historical controls during a similar time period prior to the COVID-19 surge, between January 1 to February 29, 2020.

Results: We had 3,665 admissions between March 1 and May 15, 2020, of which 1,075 patients had a confirmed COVID + test during the admission. Of these, 773 patients were noted to have AKI from diagnosis codes in the electronic medical record. Of the146 patients who needed HD (including patients with AKI and CKD) 97 were COVID-19+ and 49 were negative. HDC clotting identified by the use of alteplase was noted in 27% of those who were COVID-19 + compared to 10% of those who were COVID-19 negative. (P value= 0.02 by Chi-square using SPSS Version 24). The percentage of patients with clotting of catheters in the non-COVID-19 group was comparable to historical controls.

Conclusions: Significantly more COVID-19+ patients had HD catheter clotting compared to non-COVID-19 patients. Increased clotting was noted as a barrier to providing optimal HD therapy. For this and other reasons, we initiated an urgent start acute peritoneal dialysis program to mitigate the challenges in delivering HD to COVID-19 patients.

PO0746

Contingency Planning for COVID-19: Feasibility of Twice Weekly Hemodialysis in a Large Canadian Cohort

David Clark, Kenneth A. West, Karthik K. Tennankore. *Dalhousie University Faculty of Medicine, Halifax, NS, Canada.*

Background: Reducing hemodialysis treatments from three times weekly to twice weekly is a potential strategy to lessen potential exposure/transmission of COVID-19 while allowing hemodialysis units to operate with fixed/reduced resources. As part of contingency planning at a large Canadian center, all facility-based hemodialysis patients were reviewed in advance for candidacy of a reduced "twice weekly" schedule.

Methods: All prevalent patients receiving at least thrice weekly, facility-based hemodialysis - affiliated with the QEII Halifax, Nova Scotia, Canada - were systematically reviewed in a stepwise manner, using accepted criteria for implementing twice weekly hemodialysis (Fig. 1).

Results: Of 473 patients assessed, only 18 (4%) fulfilled criteria for twice weekly hemodialysis (Fig 1.) Of these patients, average age was 63 ± 12 (SD) years, 61% were diabetic, 95% Caucasian; and at least 67% receiving dialysis for 6+ months prior to assessment. 83% of qualifying patients missed 0 treatments in the preceding month, and none missed >1 treatment. Average for serum albumin was 36 ± 4 g/L, Urea reduction ratio, 72.7, and residual urea clearance, 5.7 ± 2.7 mL/min/1.73m^2.

Conclusions: Although feasible, a twice weekly hemodialysis strategy applied to a small proportion of our patient population, potentially reflecting an 'intention to defer' strategy for initiating dialysis.

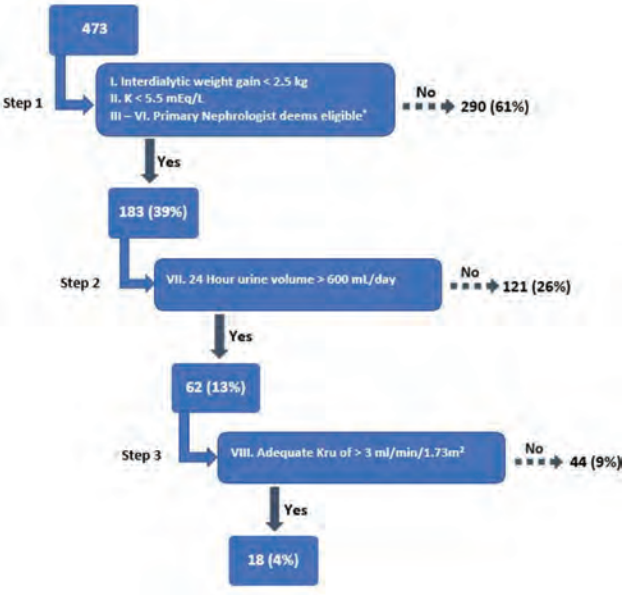

Figure 1. Stepwise approach and selection criteria to review all facility-based hemodialysis patients for candidacy of twice weekly hemodialysis (N=473). *Patients who fulfilled interdialytic fluid gain and serum potassium criteria were assessed by primary nephrologist for eligibility using each of: III. good nutritional status, IV. no clinical evidence of fluid overload, and VI. infrequent hospitalization/easily manageable co-morbid conditions (cardiovascular and pulmonary).

PO0747

Impact of the COVID-19 Pandemic on Virtual Care in Home Dialysis

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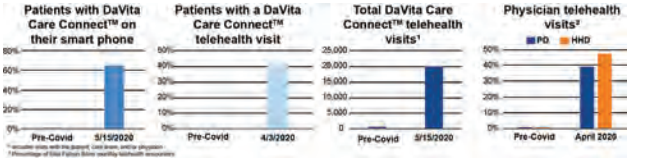
Background: While almost every provider and the majority of patients in the United States (US) possess the technology needed to conduct a telemedicine visit, prior to the current pandemic utilization in home dialysis was relatively low. The current study examined trends in telehealth utilization before and during the COVID-19 pandemic in US home dialysis patients treated by a large dialysis organization in the US.

Methods: Telehealth was delivered using a proprietary multiparty, video, secure messaging (HIPAA compliant), scheduling, and educational resource telehealth platform DaVita Care Connect™ (DCC™) application. IT systems data were utilized to develop ongoing reports depicting patient, facility, and physician adoption rates across 1750 home dialysis programs. Data were segmented by geographic areas (9) and by time of COVID-19 dissemination within locales.

Results: A meaningful increase in telehealth utilization was observed since the start of the pandemic (prior to March 2020). Among 28,500 home dialysis patients treated, the DCC™ application was installed on 18,300 patient cell phones (65.3%). Overall, 16,000 peritoneal dialysis (PD) patients and 2,200 home hemodialysis (HHD) patients participated in a telehealth visit. Fifteen thousand visits were performed in April 2020. There were 18,000 messages sent between the care team and patient and 6000 educational resources viewed by patients at home since the COVID-19 pandemic (mid-March). The numbers of social worker and dietician visits and interdisciplinary team rounds also increased over time. There was significant variation DCC™ app download and utilization across geographic regions.

Conclusions: The COVID-19 pandemic has dramatically increased the use of telehealth management for home dialysis patients in the US. Examining the impact of virtual visits on patient outcomes going forward will be critical in designing post-COVID care. Balancing the integration of telehealth visits and face-to-face visits to optimize care will necessitate advancing a new care model for patients with end-stage kidney disease.



PO0748

Abstract Withdrawn

PO0749

Mental Health Status During the COVID-19 Pandemic of Hemodialysis Patients

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Background: Patients receiving hemodialysis (HD) treatment are a particularly vulnerable population as previous studies have shown that they are at higher risk to develop anxiety, depression, and diminished health-related quality of life. During the COVID-19 pandemic patients and health professionals are under insurmountable psychological pressure which may lead to various psychological problems. The aim of this study was to assess the effect of this pandemic on mental health and quality of life in low-income HD patients.

Methods: Observational, cross-sectional study done in low-income HD patients and matched healthy controls from March-April 2020. The survey collected basic demographic and laboratory data. To assess mental status 3 different scales were used: Generalized Anxiety Disorder (GAD-7), Insomnia Severity Index (ISI), and the Kidney Disease Quality of Life (KDQOL-36). An evaluation of media interest was added.

Results: 152 HD patients and 33 control subjects were included. The median age was similar in both groups (HD 51±17 vs 48±10 yrs p=NS). Literacy was significantly higher in the control group. The control group showed significantly higher interest media (p=0.03); 60.5% of HD patients showed none or low emotional impact with this pandemic (42% in control group p=0.02). Severe anxiety was more prevalent in the control group (22.6 vs 0% p= 0.01). The ISI scale showed also significantly higher sleep impairment in control subjects (42.6 vs 20.5% p=0.04). In the HD group, the prevalence of GAD symptoms was higher in females than men (p=0.005), and one of the most influential factors associated with GAD symptoms was to live in a rented home. Patients ≤50 years had significantly higher GAD symptoms (0.01). Unemployed HD patients showed the lowest K-DQOL scores.

Conclusions: HD patients had less emotional impact, lower GAD-7 and ISI scores symptoms than healthy controls. To live in a rented home and unemployment were important risk factors associated with a higher prevalence of anxiety and sleep disorders.

Funding: Government Support - Non-U.S.

PO0750

Monitoring Trends of COVID-19 Among ESKD Patients in a Large Dialysis Organization

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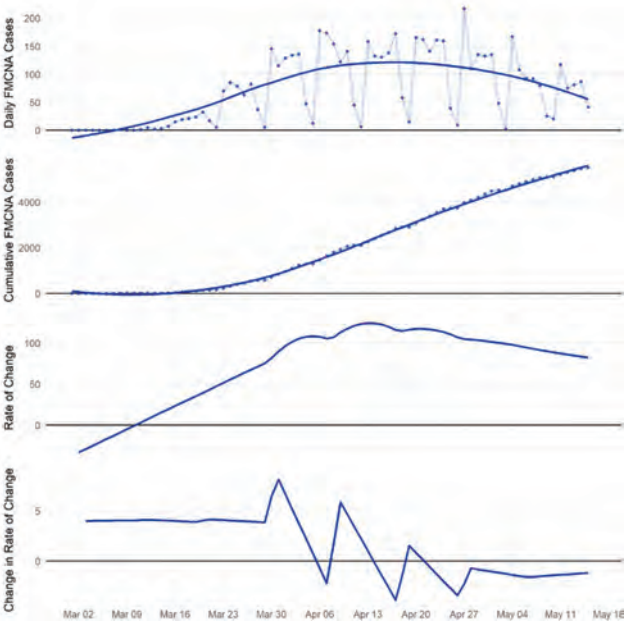
Background: Monitoring real-time acceleration, plateaus, and deceleration of infection rates is important for healthcare planning during a pandemic. We implemented methodology to continuously monitor daily cases and changes of COVID-19 case rates among individuals with ESKD receiving care in a large dialysis organization.

Methods: We identified patients with ESKD receiving dialysis in a Fresenius Medical Care North America (FMCNA) dialysis facility who tested positive for COVID-19. We fit a loess curve to the daily cumulative number of identified cases and computed the first and second derivative of the fitted curve to assess rate of change and change in rate of change, respectively, over time. We used these visualization techniques to monitor trends in case rates at the national and state levels.

Results: By May 15, 2020, there were 5,513 confirmed COVID-19 cases among patients receiving dialysis in an FMCNA facility. Mean age was 63.6 years, 57% were male, and 71% of confirmed cases had diabetes. Nationally, during the peak infection period in early April, new cases routinely exceeded 150 per day and there was a steady acceleration in growth of cases until the second week of April. As of May 15, 2020, among states with sufficient data, 2 states demonstrated continued acceleration, 10 demonstrated deceleration, and 13 plateaued in rate of growth.

Conclusions: The timing of the acceleration in growth of COVID-19 cases among individuals with ESKD followed national trends in the general population. Varying patterns of plateauing and deceleration of cases at the state level were observed in the ESKD population. Real-time monitoring of disease rates in high-risk populations, such as individuals with ESKD, is needed to plan for continuously changing healthcare demands during a pandemic.

Funding: Commercial Support - Fresenius Medical Care



PO0751

Psychological Impact of COVID-19 and Implementability of Prevention and Control Measures in Hemodialysis Centers: A Provincial Questionnaire Survey in China

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Background: This study investigated the psychological status of patients and staff and implementabilty of prevention measures in hemodialysis centers in Guangdong Province of China during the Coronavirus disease 2019 (COVID-19) pandemic.

Methods: An electronic questionnaire survey was performed in an anonymous manner between March 28 and April 3, 2020. Two questionnaires were designed to investigate the psychological status for hemodialysis patients and general staff (doctors, nurses, technicians, and other staff), respectively. And an additional questionnaire for administrators (directors or head nurses) of hemodialysis centers was designed to address the implementabilty of prevention measures, including strengthened patient triage management, restricting caregiver visits to patients during dialysis, strengthened prevention amongst staff, and improved patient education and protection. All the 516 hemodialysis centers registered in Guangdong Province were voluntarily invited to join the survey.

Results: Total 1,782 patients, 3,400 staff, and 420 administrators responded for this survey. Patients living in rural areas reported a higher incidence of severe anxiety compared to those living in other areas. Medical staff reported better mental health than non-medical staff. With respect to implementabilty of prevention measures, hemodialysis centers in general hospitals outperformed independent blood purification centers, and tertiary hospitals outperformed other level hospitals. However, restricting acceptance of non-resident patients was lower in tertiary hospitals than that in other hospitals. Under this condition, only one patient imported from Hubei Province was diagnosed with COVID-19.

Conclusions: The outbreak did not significantly affect the psychological status of most patients and medical staff. Due to the successful implementation of comprehensive prevention measures, the COVID-19 epidemic was controlled effectively. This provincial survey may provide experience for other countries and regions with similar epidemic.

PO0752

Persistent Viral Shedding and Antibody Response to the SARS-CoV-2 Virus in Chronic Hemodialysis Patients

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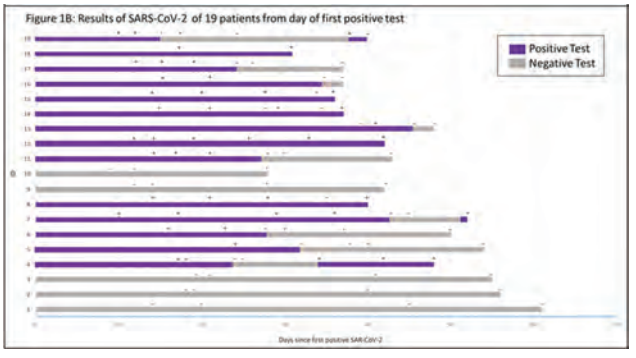
Background: The duration of SARS-CoV-2 viral RNA shedding and antibody response of chronic HD patients to the SARS-CoV-2 virus is currently unknown

Methods: This is a retrospective case series of chronic HD patients who tested positive for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2 RNA) on nasal or nasopharyngeal specimen between March 20 and May 28, 2020 at the James J. Peters VA Hospital. Patients were tested at varying intervals to document clearance of virus or for surveillance purposes. SARS-CoV-2 Virus IgG Antibody (Ab) testing was performed on all HD patients with COVID-19 (using the Abbot IgG nucleocapsid antibody test and i2000SR machine, Ref. range of the Ab titer: >1.39 positive)

Results: Of 84 chronic HD patients, 26% (22) were diagnosed with COVID-19. Mean age of those with COVID-19 was 72±9 years old, 86% were Black, 77% had diabetes and all had hypertension. Of these patients, 59% (13/22) required hospitalization and 18% (4/22) died. IgG Ab testing was performed on 19 out of 22 COVID-19 patients. All 19 patients tested positive for IgG Ab with an average Ab titer of 7±1.2. 20 days after the first SARS-CoV-2 RNA positive test, 68% (13/19) patients remained positive on repeat RNA testing. 3 patients tested positive for SARS-CoV-2 RNA on repeat surveillance testing, despite testing negative on 2 prior consecutive nasal or nasopharyngeal specimens (Fig. 1). None of these 3 patients were symptomatic at the time their repeat swabs were positive for SARS-CoV-2 RNA

Conclusions: All HD patients with a confirmed diagnosis of COVID-19 developed IgG Ab to the SARS-CoV-2 virus, but the SARS-Cov-2 RNA was detectable in the swab specimen for a prolonged duration of time. In a few cases, the SARS-CoV-2 RNA became detectable after 2 consecutive negative RNA specimens. It is unknown if the IgG antibodies confer immunity against the SARS-CoV-2 virus. Additionally, the significance of persistent viral RNA shedding in patients who have recovered from COVID-19 remains to be elucidated



PO0753

Screen for Initial assessment of COVID-19 Infection Using Lung CT and Lymphocyte Count in Patients Under Hemodialysis

Cuifang Li, Xiangning Yuan, Hui Xu. *Xiangya Hospital, Central South University, Changsha, China.*

Background: The maintenance hemodialysis (MHD) patients with elder age and more comorbidities are more susceptible to SARS-CoV-2 than the general population. There is a clear need to effective assessment of COVID-19 infection status in these patients in hemodialysis center in order to prevent virus spread and decrease mortality in MHD patients.

Methods: MHD patients in the hemodialysis center and patients screening for COVID-19 in the fever clinic were enrolled from February,21 2020 to February,29 2020. Baseline characteristics, lung CT, blood routine and COVID-19 nucleic acid test results were collected.

Results: 276 MHD patients and 313 patients screening for COVID-19 in the fever clinic were collected. After matching for age and gender, 136 MHD patients and 136 patients in fever clinic were included. Compared with patients screening for COVID-19 in fever clinic, more MHD patients showed decreased white blood cell count and lymphocyte count (18.4% VS 5.9%, P<0.001; 59.6% VS 36.8%,P<0.001; respectively). 48.5% of the MHD patients and 41.2%of patients in the fever clinic with positive CT findings. Compared with the MHD patients, patients screening for COVID-19 in fever clinic showed more ground glass opacity (GGO) (80.3%VS 98.2%,P=0.002), more consolidation (16.7% VS 67.9%, P<0.001), and less pleural effusion (40.9% and 19.6%, P=0.01). Among them, centrally distributed GGO was more common in MHD patients than patients in the fever clinic (42.4% vs 23.2%,P=0.03), while diffuse GGO was more common in patients with pulmonary infection in the fever clinic than MHD patients (37.5% vs 4.5%; P<0.001). There was no significant difference in the proportion of peripheral GGO distribution between the two groups (33.3% vs 39.3%,P=0.5). Thirteen patients in the fever clinic and none of the MHD patient were positive for SARS-CoV-2 by RT-PCR analysis. 109 pairs of MHD patients underwent CT examination before and after dialysis were analyzed, results showed no significant difference between the CT lesion detection rate pre- and post-dialysis (48.6% vs 47.7%, P=0.89).

Conclusions: Lymphocyte count decrease is common in MHD patients, and pulmonary CT of MHD patients may show signs similar to that of COVIP at some time. RT-PCR is of great significance for the differential diagnosis, while pulmonary CT are conducive.

Funding: Government Support - Non-U.S.

PO0754

Rates of Asymptomatic Carriage and Antibody Positivity for SARS-CoV-2 in a Large Haemodialysis Cohort

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Background: Haemodialysis patients represent a unique challenge in the COVID-19 pandemic, balancing infection risk while safely providing life-sustaining haemodialysis. Asymptomatic infection rates in haemodialysis patients are unknown. **Aims:** 1 - To define rates of asymptomatic swab positivity in a cohort of prevalent haemodialysis patients 2 - To define rates of antibody positivity in patients known to have been historically swab positive 3 - To define rates of antibody positivity in patients without prior symptoms or clinical suspicion of COVID-19

Methods: A programme of COVID-19 screening using a validated nasopharyngeal PCR analysis was carried out across a prevalent cohort of 1253 haemodialysis patients. Concurrently all patients were offered antibody testing for Anti-SARS-CoV-2 IgG/IgM (Roche) and a total of 848 tests were completed.

Results: 1 – Routine screening over a 4 week period from 4/5/20 to 1/6/20 confirmed 7 cases of asymptomatic swab positivity (0.6%). 2 – In our cohort there were 197 confirmed swab positive cases of COVID, and of the 153 survivors 124 were antibody positive (81%). 10 patients were highly clinically suspicious of COVID and managed as such; of those 3 were antibody positive (30%). 3 – Of the remaining swab negative patients who had antibody testing (n=710) 82 were antibody positive (11.5%).

Conclusions: In a large inner-city London haemodialysis where the population prevalence of COVID has been high, we demonstrate 1 – low asymptomatic rates of virus carriage at this later stage in the pandemic 2 – significant proportions of swab positive patients seroconverting to be antibody positive 2 – suggestion that 11.5% of patients had previous been asymptomatic carriers and had seroconverted to be antibody positive

PO0755

Providing Multidisciplinary Renal Care in the Time of COVID-19

Ollie Fielding,[1] Jung Hoon Son,[1] Tia Y. Yu,[1] Andrew Bohmart,[2] Frank Liu,[2] Jeffrey I. Silberzweig.[2] The PEAK team *[1]pulseData, New York, NY; [2]The Rogosin Institute, New York, NY.*

Background: New York City (NYC)-based Rogosin Institute has provided a specialty case management to patients via its Program for Education in Advanced Kidney Disease (PEAK) since 2015. PEAK aims to educate patients about options for renal replacement therapy and encourages adoption of home dialysis modalities and transplantation. The global pandemic due to the novel coronavirus SARS-CoV-2 (COVID-19) hit NYC at the beginning of March 2020 and has resulted in over 40,000 hospital admissions and claimed the lives of 15,000 NYC residents.

Methods: A city-wide requirement to adopt social distancing caused us to adapt our approach so we could continue our patient management and delay dialysis starts where possible. Our multidisciplinary team continued to provide regular consults via a telehealth platform. pulseData built a query to look at the standard deviation of lab results for creatinine and potassium over the prior six months leading to decreased need for patients to leave their homes for venipuncture. We also built a query to identify those patients at high risk of poor COVID-19 outcomes (those over age 65, with COPD or other respiratory conditions, and other comorbid risk factors). These high risk patients were discussed in a weekly care plan meeting.

Results: The Rogosin team delivered 481 telehealth appointments between January 1 and May 1 2020. We identified 17 of 189 patients seen in PEAK over the last 12 months as high risk for poor COVID-19 outcomes. The standard deviation (SD) of the last six months of serum creatinine measurements for PEAK patients was 0.24 (IQR 0.16-0.44), patients with an SD in the top quintile were considered to be in need of repeat lab tests and home-based venipuncture was used where possible. Only 12 PEAK patients began dialysis treatment between January 1 and May 1 2020 compared with 28 patients in the same period in 2019. Most of these patients (67%) began dialysis optimally (as an outpatient and with venous access) in Jan-May 2020 vs. only 43% in the same period 2019 (a 56% increase).

Conclusions: Responding to the challenges of the COVID-19 crisis were acutely felt in NYC and represented a major disruption to our ability to deliver nephrology care. Adopting a coordinated, data driven approach we were able to continue to deliver multidisciplinary care to patients and improve renal replacement therapy outcomes.

Funding: Commercial Support - pulseData

PO0756

Enhanced Sentinel Surveillance System for COVID-19 Outbreak Prediction in a European Dialysis Clinics Network

Francesco Bellocchio,[3] Paola Carioni,[3] Mario Garbelli,[3] Francisco Martínez-Martínez,[1] John W. Larkin,[2] Len A. Usvyat,[2] Franklin W. Maddux,[2] Stefano Stuard,[1] Luca Neri.[3] *[1]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care North America, Waltham, MA; [3]Fresenius Medical Care Italia SpA, Palazzo Pignano, Italy*.

Background: Accurate predictions of epidemic dynamics may enable timely organizational interventions in high risk regions. We exploited the interconnection of the EMEA Fresenius Medical Care (FMC) dialysis clinic network to establish a sentinel surveillance system where the occurrence of new cases in a clinic propagates distance-weighted risk estimates to proximal dialysis units. The surveillance system is embedded in an artificial intelligence model which predicts COVID-19 outbreak occurrence in HD clinics from trends in clinical practice patterns and regional COVID-19 epidemic metrics. The system stratifies clinics by their risk of new local outbreak.

Methods: The risk prediction model is computed considering a cohort of 640 clinics belonging to the FMC network. We trained a model to predict outbreak in each clinic in a 2-week prediction horizon (i.e. two or more COVID-19 cases). In addition to sentinel distance-weighted risk estimates, the model included 73 variables (i.e. regional-level epidemic data from open source datasets and clinical practice data from the EuCliD® database). We generated the training set on data available on 04/01/2020 and tested prediction accuracy at 4/15/2020 and 4/20/2020.

Results: In the training set there were 58 (9.1%) clinics with two or more patients with COVID-19 infection in the two-week prediction window. In the validation samples there were 27 (4.2%) and 12 (1.9%) clinics with two or more patients with COVID-19 infection during the two-week prediction window. The performance of the model was suitable in both testing windows (AUC=0.86 and 0.80 respectively). The model is used to construct risk maps highlighting geographical clusters of clinics at risk (figure).

Conclusions: A sentinel surveillance system together with the wealth of information collected in EuCliD® and state of the art modeling strategies allows prompt risk assessment and timely response to COVID-19 epidemic challenges throughout networked European clinics.

Funding: Commercial Support - Fresenius Medical Care

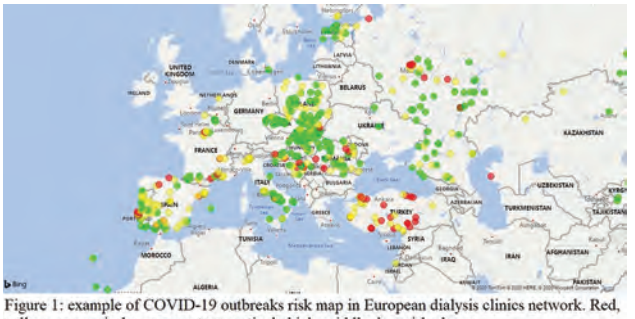

Figure 1: example of COVID-19 outbreaks risk map in European dialysis clinics network. Red, yellow, green circles represent respectively high, middle, low risk classes

PO0757

Trajectories of Clinical and Laboratory Characteristics Before COVID-19 Diagnosis in Hemodialysis Patients

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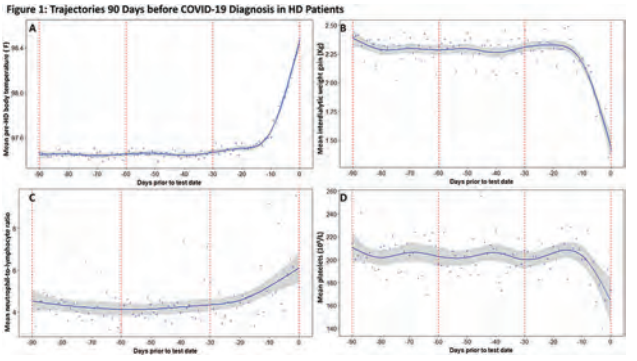
Background: The frequency of evaluations in hemodialysis (HD) care affords opportunities to assess profiles that may characterize onset of the 2019 coronavirus disease (COVID-19). We aimed to characterize the trajectories of clinical/laboratory assessments before COVID-19 diagnosis in HD patients.

Methods: We assessed data from HD patients with known COVID-19 dialyzed at Fresenius Kidney Care in the United States between 02 Mar and 09 Apr 2020. We computed mean daily values for 40 variables 90 days before a positive rRT-PCR test (COVID-19+). Nonparametric smoothing splines were used to fit data of individual trajectories and estimate the mean change over time.

Results: There were 1294 HD patients with COVID-19 (mean age 64±14 years, 60% male, 47% white race, 69% had diabetes, and 24% had coronary artery disease). Mean pre-HD body temperature (primarily oral) increased by about 1° Fahrenheit (F) over 10 days before COVID-19+ test and approached 99° F at diagnosis (**Fig 1A**). Mean interdialytic weight gain decreased by about 0.75 kg (**Fig 1B**) over 14 days before COVID-19+ test; concurrent decreases of about 20 minutes were seen in HD treatment time. Mean neutrophil-to-lymphocyte ratio had mild increases (**Fig 1C**), while mean platelet counts decreased by about 40×10^9/L over 14 days before COVID-19+ test (**Fig 1D**). Trajectories of many variables (vitals, heparin, hematology, nutrition, bone, anemia) were observed to change before COVID-19+ test, yet alternations were generally minor.

Conclusions: The trajectories of several clinical/laboratory parameters appeared to change before COVID-19 diagnosis in HD patients. Many changes were small and may not be independently useful in identifying onset of COVID-19. Mean pre-HD body temperature before SARS-CoV-2 infection was 97.4° F and should be considered in screening. Findings may have utility in prediction model development. Further comparisons to patients without COVID-19 are needed.

Funding: Commercial Support - Fresenius Medical Care



PO0758

Distribution of SARS-CoV-2 Positive Tests, Dialysis Stations, and Household Poverty Within Cook County, Illinois

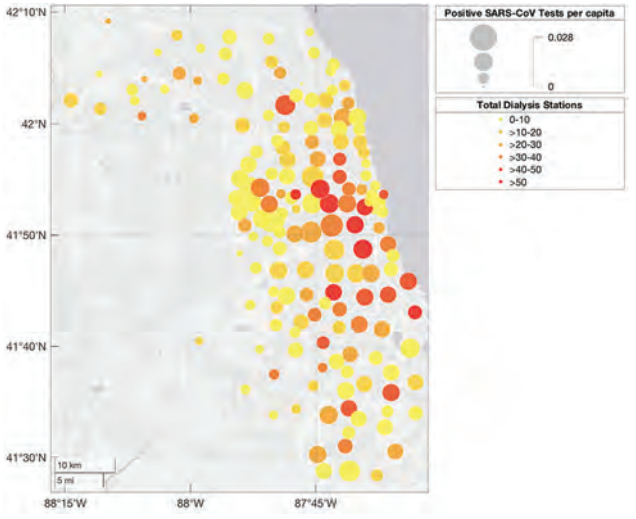
Siddharth Bhayani,[1] Ranit Sengupta,[2] Talar Markossian,[2] Mohammad samie Tootooni,[2] Amy Luke,[2] David A. Shoham,[2] Richard Cooper,[2] Holly J. Kramer.[3] *[1]Loyola University Chicago Stritch School of Medicine, Maywood, IL; [2]Loyola University Chicago, Chicago, IL; [3]Loyola University Medical Center, Maywood, IL*.

Background: End stage renal disease (ESRD) shows higher prevalence in poor urban communities, areas with high SARS-CoV-2 exposure risk. This ecological analysis examined the correlation of SARS-CoV-2 positive tests per capita with number of dialysis stations, demographics and income data of the residents within ZIP codes (n=163) in Cook County, Illinois.

Methods: Data on SARS-CoV-2 positive tests per capita within a ZIP code were merged with ZIP code data on number of dialysis stations (sum of dialysis stations per dialysis center), demographics and household income, during a period from January 21-May 16, 2020 in Cook County (5,231,852 residents). Spearman's rank correlation coefficients were calculated to examine the linear correlation of SARS-CoV-2 positive tests per capita with dialysis stations, demographics and household poverty. We mapped SARS-CoV-2 positive tests per capita and total dialysis stations by ZIP code in Cook County.

Results: Positive tests per capita correlated significantly with number of dialysis stations ($r = 0.23$; 95% CI 0.18, 0.28; $P < 0.005$), number of households living in poverty ($r= 0.58$; 95% CI 0.54, 0.61; $P < 0.005$) and percentage of residents reporting Black race ($r = 0.34$ $p < 0.005$, CI = 0.30, 0.39) or Hispanic ethnicity ($r = 0.60$ $p < 0.001$, CI: 0.57-0.63). Figure 1 show several areas within Cook County with both high number of SARS-CoV-2 tests per capita and number of dialysis stations.

Conclusions: SARS-CoV-2 tests per capita correlates positively with number of dialysis stations, and poverty status of that ZIP code. These findings highlight the high risk of SARS-CoV-2 exposure for patients with ESRD living in poor urban areas.



PO0759

Kidney Patient Mortality due to COVID-19 in Ecuador: The Experience in Guayas Province

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Background: Ecuador is a country of seventeen million population located in the west coast of South America. In late February 2020, Ecuador had its first Covid-19 case in the city of Guayaquil, followed by massive growth of infections in Guayas Province (14000 of 39000 cases), the current epicenter. Due to the lack of official information in this population, and the significant impact in mortality saw in other countries, a need for data is warrant.

Methods: There are approximately 15000 patients on renal replacement therapy in Ecuador, 94% of them on hemodialysis. At Guayas Province, the estimation of 5200 people on hemodialysis accounts for the 34% of the country's patients. A simple telephone-based questionnaire was performed at the first week of May, directed to the owner, medical director, or head of nurses of each center in the Guayas Province.

Results: From the 35 centers in Guayas, it was possible to collect data from 29 locations (82.5%) -mostly private centers-, that represents approximately 4719 patients, 89.8% from the total of patients in Guayas Province. Just 2 / 8 public centers provide information. Results are summarized in Table 1.

Conclusions: The 11.91% Covid-19 mortality in Guayas Province was high, especially if the expected monthly mortality is around 0.8-1.1%; the lethality was very high, and this could be explained by the fact that renal patients are considered as high-risk patients in this disease. The low mortality in PD patients could be attributable to the lockdown and stay-in-home measures. It is necessary to implement specific protocols in order to avoid high mortality, if a second peak of Covid-19 is expected.

Results from Guayas Province in Covid-19 pandemic.

	Global Results	N	Range
Mortality (HD)	11.91%	(n= 562/4719)	5-35%
Lethality	55%		43-62%
Mortality (PD)	2.88%	(n= 6/208)	
Mortality (TX)	2.06%	(n= 9/436)	

HD Hemodialysis, PD Peritoneal Dialysis, TX Kidney transplant patients. Range represents the % variation between centers

PO0760

Clinical Characteristics, Management, and Outcomes in COVID-19-Positive Dialysis Patients from Three London Renal Centres, United Kingdom

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Background: Dialysis patients, with frequent co-morbidities, advanced age and frailty, visiting treatment facilities frequently are perhaps more prone to SARS-Cov-2 infection and related death - the risk-factors and dynamics of which are unknown. The aim of this study was to investigate the hospital outcomes in SARS-CoV-2 infected dialysis patients.

Methods: This prospective, observational, multi-centre study collected data on SARS-CoV-2 infected HD patients between 29/02/2020 and 15/05/2020. Data was collected on demographics, comorbidities, WHO performance status, clinical symptoms, laboratory parameters, hospital management and outcomes. Treatment was predominantly supportive, unless patients were part of an approved clinical trial. The study was approved by NHS Research Ethics Committee 20/SW/0077 and Heath Research Authority IRAS 283130.

Results: Of 1737 HD patients at the 3 renal centres, 224 (13%) were COVID-19 positive over the study period. The characteristics of the COVID-19 HD patients were: mean age 65.8; 59% male; 38% Caucasian; 81% hypertension; 54% diabetes; 25% chronic lung disease; 29% ischaemic heart disease and 22% cerebrovascular disease. The most common symptoms at presentation were fever (62%) and cough (53%). About 143 (64%) patients were managed as an inpatient and 81 (36%) as an outpatient. Of 9 patients that required mechanical ventilation: 6 died, 1 patient was discharged and 2 are still under clinical care. Overall 51 patients died (23%), 154 (69%) were discharged alive and 19 (8%) were still under clinical care as of 15/05/2020. Preliminary analyses suggested that those that died were significantly older (p=0.0028), more likely to have ischaemic heart disease (p=0.003), cerebrovascular disease (p=0.019), smoking history (p=0.006), WHO performance status 3-4 (p=0.004), higher neutrophil: lymphocyte ratio at presentation (p=0.0001) and higher CRP at presentation (p=0.0021).

Conclusions: This large cohort of COVID-19 positive haemodialysis demonstrates a high case fatality ratio, which increased significantly with age, cardiovascular disease, smoking history, frailty and markers of inflammation.

PO0761

COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Experience

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Introduction: The SARS-CoV-2 (COVID-19) pandemic presents significant challenges to kidney transplant recipients (KTRs) with risk for higher mortality yet sparse available data. We present our single center experience of COVID-19 infection in KTRs.

Case Description: Methods We reviewed the electronic health records of KTRs with confirmed COVID-19 infection using rt-PCR testing via nasopharyngeal swabs, at our transplant center. Results We identified four KTRs with diagnosed COVID-19 infection in our institution. Details of individual cases are summarized in table 1. Patient A died of complications while patients B, C and D fully recovered. Patient A initially recovered from COVID-19 pneumonia but then was readmitted three weeks later and developed features closely resembling macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) leading to death despite treatment with dexamethasone, IV immunoglobulin and anakinra. Patient C had minimal symptoms without cytokine storm possibly related to complement blockade from revulizumab, a C5 inhibitor, which was being used for treatment of aHUS.

Discussion: Our single center case series of COVID-19 infections in KTRs is small but highlights two important aspects: 1) development of MAS/HLH like features in patient A which to our knowledge has not been described in the setting of COVID-19 infection in KTRs; 2) development of minimal symptoms without cytokine storm in patient C likely related to use of C5 blocking agent revulizumab. Further studies are needed to shed light on these phenomenon.

Case series of varied clinical manifestation of COVID 19 infection at our center

aHUS – atypical hemolytic uremic syndrome; DCD – donation after cardiac death; LURD – living unrelated donor; MMF – Mycofenolate Mofetil; THYMO – rabbit antithymocyte globulin, Cr- Creatinine

PO0762

Incidence of COVID-19 Disease in Pediatric Kidney Transplant Recipients: A Report of the Improving Renal Outcomes Collaborative

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Background: The impact of COVID-19 disease on previously healthy children has been minimal, yet there is limited data on the impact of COVID-19 on children and adolescents with kidney transplants.

Methods: We used the existing infrastructure of the Improving Renal Outcomes Collaborative (IROC) learning health system to develop and rapidly implement a web-based registry for collecting clinical and outcomes data about COVID-19 disease in pediatric transplant recipients. We distributed the registry to 32 U.S. pediatric kidney transplant centers and requested clinical and outcomes data from all recipients suspected of having COVID-19 disease. Here, we present an interim analysis of the first 6 weeks of registry data.

Results: Between April 6 and May 27, 2020, 18 IROC centers entered data on 99 pediatric kidney transplant recipients who had PCR based testing for COVID-19. 54 patients were tested due to symptoms of COVID-19 (most commonly fever and cough), 7 asymptomatic patients had a known COVID exposure. 34 patients were tested per hospital policy (e.g. pre-anesthesia), and 4 did not have a reported testing indication. Overall, 10/99 (10%) tested positive for COVID-19, 6 of whom had any symptoms, 3 had a known exposure with a COVID+ individual, and 1 was diagosed by a pre-anesthesia screen. Thus far, the clinical course and outcomes are known in 8/10 COVID-19+ patients: 5 received outpatient supportive care alone, 2 were admitted to intensive care and 1 was admitted to a non-intensive care inpatient unit. Transplant outcomes were excellent in all COVID-19+ patients. There were no cases with respiratory failure, acute kidney injury, or allograft rejection/failure. There were no deaths due to COVID-19 disease.

Conclusions: In this interim analysis of the IROC learning health system, pediatric kidney transplant recipients had a relatively low incidence of COVID-19 disease and excellent short-term outcomes.

PO0763

Living Organ Donor Perspectives on Organ Donation During the COVID-19 Pandemic

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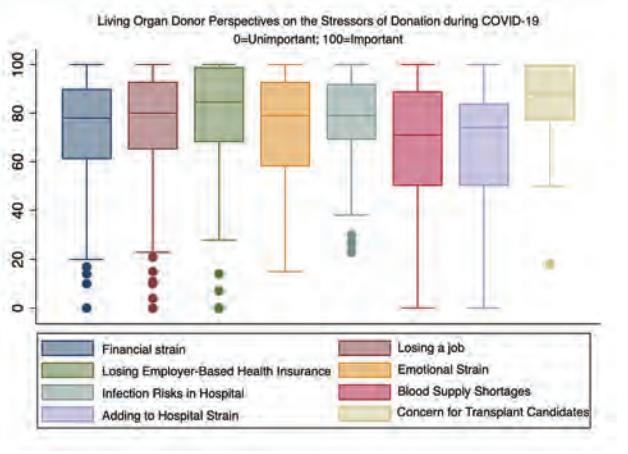
Background: Due to the COVID-19 pandemic, transplant programs across the U.S. postponed living donor surgeries and transplants. We examined perspectives of former and prospective living organ donors on the risks and excess burdens of organ donation during the COVID-19 pandemic.

Methods: In late April 2020, we disseminated an IRB-approved survey to a national online forum of over 1300 living donors and those in workup for donation. Using visual analog scales, respondents rated sources of information about COVID-19, burdens on donors due to the pandemic, and what factors should determine whether living donation should proceed during the pandemic (0=unimportant, 100=very important).

Results: After 4 weeks, there were 101 respondents from 35 U.S. states; 63% were between 31-50 years old, 95% were non-Hispanic white, and 90% were female. Respondents included 68 living donors (72% kidney) and 33 people in work-up to donate (73% kidney). The most and least important sources of information about COVID-19 were personal doctors (median importance 88, IQR 73-100) and social media (median 26, IQR 12-54), respectively. Nearly half (41%) were unsure of their transplant program's policy for living donation during the pandemic, and 58% reported that the decision to donate during COVID-19 should depend on factors such as transplant candidate health (median 100, IQR 90-100) and availability of COVID-19 tests (median 84, IQR 70-95). Respondents rated concern for transplant candidates and loss of employer-based health insurance as the most important pandemic-related stressors for donors (Figure).

Conclusions: Many living organ donors were uncertain about their transplant program's approach for donation during the pandemic. Donors were concerned about the health of transplant candidates and financial stressors, and prioritized availability of COVID-19 testing to determine when living donation should proceed during the pandemic.

Funding: NIDDK Support



PO0764

Clinical Outcomes of Hospitalized Kidney Transplant Recipients with COVID-19 in a Predominantly Minority Population

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Background: COVID-19 has been associated with increased morbidity in kidney transplant recipients. We aimed to identify risk factors for mortality in hospitalized kidney transplant recipients with COVID-19

Methods: We retrospectively reviewed the medical records of 75 kidney transplant recipients admitted for COVID-19 at our institution.

Results: Among the 75 patients, 28 (37%) died at a median 8 days (range, 1-36) after admission to the hospital. The Table summarizes the demographics and initial labs values of both groups. Most of our patients were Hispanic (54%) and African American (32%) and 97% had hypertension and 65% had diabetes mellitus. There was no difference between the two groups in terms of sex, type of transplant, time from transplant, immunosuppressive medications, medical comorbidities, presenting symptoms, temperature, or pulse oximetry values on admission. Non-survivors were older and had higher BMI. On admission most patients were lymphopenic, had low CD3/CD4/CD8 counts and had higher inflammatory markers (ferritin, d-dimer, CRP, procalcitonin, interleukine-6 levels). Non-survivors had statistically significant higher procalcitonin, IL-6 and pro-BNP levels on admission. More non-survivors required ICU stay (64% vs. 13%, $p < 0.001$), intubation (57% vs. 11%, $p < 0,001$) and renal replacement therapy (32% vs. 17%, $p=0.17$) compared to survivors. There was no difference in secondary bacterial infections, CMV viremia, DVT or stroke between the two groups. In a multivariate analysis, BMI (OR 1.15, CI 1.04-1.30, $p= 0.017$ per unit increase), higher procalcitonin (OR 4.16, 1.09-18.87, $p=0.046$) and proBNP levels (OR 1.017, 1.002-1.034, $p=0.039$, per 100 unit increase) on admission were associated with increased mortality.

Conclusions: COVID-19 is associated with increased mortality (37%) in our kidney transplant recipients and higher BMI, procalcitonin and proBNP levels at admission are associated with mortality.

	Hospitalized N =75	Survivors N = 47	Non-survivors N = 28	P-value
Sex, Male	47 (63%)	33 (70%)	14 (50%)	0.09
Age, median [range]	61 [21-84]	61 [21-79]	65.5 [44-84]	0.04
Race				0.55
Hispanic	40 (53%)	25 (53%)	15 (54%)	
African American	24 (32%)	17 (36%)	7 (25%)	
Type of transplant,				
Deceased donor	57 (76%)	34 (72%)	23 (82%)	0.34
Time after transplantation, median (range) months	58 [1-356]	55 [1-248]	77 [1-356]	0.23
Transplant < 12 months	6 (8%)	5 (11%)	1 (3.5%)	0.28
Body Mass Index (kg/m2)	28.7 [17.9-45.6]	27.5 [19-37.4]	30.4 [17.9-45.6]	0.04
Comorbidities				
Hypertension	71 (97%)	45 (96%)	26 (100%)	0.27
Diabetes mellitus	49 (65%)	28 (60%)	21 (75%)	0.17
Heart disease	14 (19%)	9 (19%)	5 (18%)	0.89
Lung disease	9 (12%)	4 (9%)	5 (18%)	0.21
Cancer	9 (12%)	5 (11%)	4 (14%)	0.64

Labs values on admission (median [range])	Total N=75	Survivors N=47	Non survivors N=28	P-value
Lymphocytes	1 [0.1-2.6]	0.6 [0.1-2.6]	0.7 [0.1-1.3]	0.92
Lymphocytes < 1,000	63 (84%)	38 (81%)	25 (89%)	0.48
Serum creatinine	2.23 [0.7-10.4]	2.05 [0.7-9]	2.3 [1.2-10.4]	0.28
Ferritin	562 [43-14256]	1265 [154-9259]	5529 [43-18758]	0.45
Ferritin > 1,000	28 (53%)	26 (55%)	12 (43%)	0.54
D-dimer	2 [0.32-20]	1.69 [0.32-20]	1.71 [0.39-16.66]	0.30
D-dimer > 3.0	20 (27%)	12 (26%)	8 (29%)	0.87
C-Reactive Protein	9 [0.5-48.7]	6.4 [0.5-35.7]	11.25 [1.4-48.7]	0.11
CRP > 10	34 (45%)	29 (62%)	15 (54%)	0.54
Procalcitonin	0.3 [0.1-44]	0.2 [0.1-5.1]	0.4 [0.1-44]	0.02
Procalcitonin > 0.2	50 (67%)	28 (60%)	22 (79%)	0.013
Interleukine 6 levels	51 [2.04-1374]	46.94 [2.1-769.4]	132.3 [10.7-1373.6]	0.02
IL6 > 50	34 (45%)	17 (36%)	17 (61%)	0.009
CD3 count	284 [10-1819]	350 [10-1819]	243 [14-916]	0.26
CD3 count < 706	39 (52%)	24 (50%)	15 (54%)	0.60
CD4 count	147 [4-976]	178 [4-976]	120 [4-614]	0.12
CD4 count < 344	37 (49%)	23 (49%)	14 (50%)	0.21
CD8 count	121 [4-954]	126 [4-954]	121 [17-380]	0.75
CD8 count < 304	18 (24%)	11 (23%)	7 (25%)	0.81
Pro-BNP	1795 [140-150000]	1217 [140-150000]	2380 [476-15000]	0.80

PO0765

COVID-19 and Kidney Transplantation: Results from the TANGO International Transplant Consortium

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Background: Chronic immunosuppression and comorbidities may expose kidney transplant recipients to an increased risk of developing critical coronavirus disease 2019 (COVID-19), but data in transplantation have been limited so far to single centers. To determine the clinical presentation, outcomes, and mortality risk factors in transplant patients with COVID-19, we analyzed retrospective data from a large international transplant consortium (TANGO Study).

Methods: Retrospective cohort study included kidney transplant recipients admitted with COVID-19 in 11 centers participating in the international TANGO consortium. We included all adult (≥18 yeas) kidney transplant recipients with a functioning kidney allograft who were admitted to a hospital between March-April, 2020. Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using an ad hoc designed data collection form.

Results: Among 9,697 kidney transplant recipients followed at 11 transplant centers, 145 (1.5%) were hospitalized due to COVID-19. 65% were male and more than half were over 60 years old (55%). Median time since transplant was 5 years (2-10) and only 16% were transplanted less than one year from the presentation. Prevalent comorbidities included hypertension (95%), obesity (41%), heart disease (25%) and lung disease (19%). Common symptoms at the onset of illness were fever and dyspnea (71%), followed by myalgia (54%) and diarrhea (35%). Management of anti-rejection therapy varied across centers: antimetabolites were withdrawn in 69% of patients and calcineurin inhibitor in 26%. Other treatments used during hospitalization included hydroxychloroquine (83%), antibiotics (76%), tocilizumab (13%) and antivirals (10%). During a median follow-up of 13 days (IQR: 7 - 21) after diagnosis of COVID-19, mortality was 30% and occurred at a median 10 (5-16) days after admission. Acute kidney injury (AKI) occurred in 46% and respiratory failure requiring intubation in 29% of cases. No rejection events were observed.

Conclusions: Our large international consortium indicates that kidney transplant recipients with COVID-19 have increased mortality (30%) upon hospitalization compared to the general population with a high rate of AKI (46%) and significant respiratory failure (29%).

PO0766

Atypical Clinical Presentation of COVID-19 in a Kidney Transplant Recipient with Tacrolimus Toxicity

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Introduction: Kidney transplant recipients represent a unique challenge to manage amidst the Coronavirus disease 2019 (COVID-19) pandemic as they have reduced innate ability to fight the viral infection due to immunosuppression. However, calcineurin inhibitors such as tacrolimus, may offer an advantage in reducing the effects of cytokine storms in transplant patients with viral pneumonia. We present an atypical case of COVID-19 in a kidney transplant recipient with toxic levels of tacrolimus that presented with mainly fever and diarrhea.

Case Description: A 76-year old African American male kidney transplant recipient presented to the Emergency Department (ED) after five days of fever (temperature of 101.8°F), nausea, vomiting, diarrhea and urinary frequency on March 27, 2020. His vitals were noted with a temperature of 96.9°F, respiratory rate of 40/min, and heart rate of 166 beats/min, blood pressure of 110/75 mmHg and pulse oxygen situation was 85% at ambient air. Admission labs were significant for a rise of serum creatinine to 3.1 mg/dL from a baseline of 1.5 mg/dL, lactic acid of 4.4 mmol/L, and a tacrolimus level of 26.9 mcg/L. He was transferred to the ICU following increased oxygen demands and elective intubation for impending respiratory failure on hospital day 2. His blood pressure transiently improved with a decrease in lactic acid to 1.4 mmol/L and serum creatinine down to 1.6 mg/dL following IV fluid resuscitation. On hospital day 4, he continued to require high ventilator support and initiated on vasoconstricting agents for hemodynamic support. His serum tacrolimus level continued to increase to 32.9 mcg/L with concordant increase of serum creatinine to 2.1 mg/dL with oliguria. Tacrolimus levels sustained super therapeutic levels >8 mcg/L despite cessation of the drug.

Discussion: It is possible that Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection may cause hepatic dysfunction and diarrhea, which reduced drug metabolism and lead to toxic levels of tacrolimus—perpetuating cytokine storm. It is important that in this particular transplant patient population to closely monitor drug levels due to SARS-CoV-2 infection on its metabolism, as well as preventing toxic levels, which further reduces the body's innate immunity and may indirectly worsen cytokine storm.

PO0767

Late Rejection of Failed Renal Allograft Precipitated by COVID-19 in a Hemodialysis Patient (HD)

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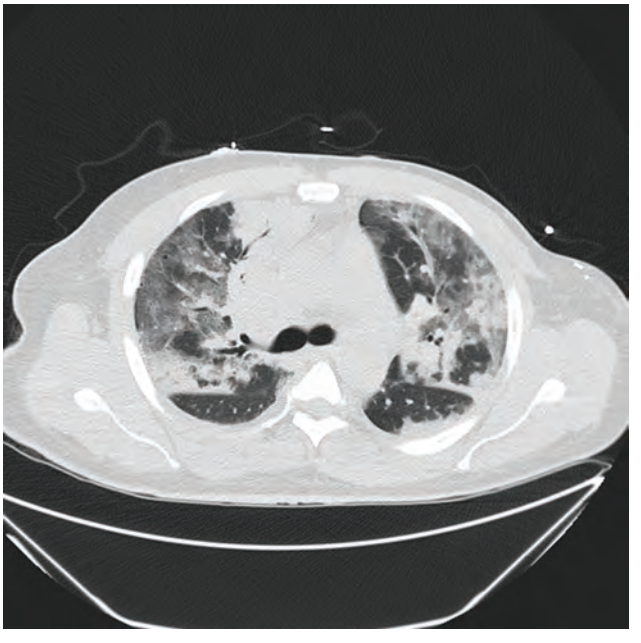
Introduction: We present a case report of an HD patient with a failed allograft that had been stable off immunosuppression who presented with acute allograft rejection in the setting of COVID-19 infection.

Case Description: 50 y/o male with a history of hypertension, living-related kidney transplant in 2005 E.S.R.D after his allograft failed in 2018. The patient's allograft remained stable off immunosuppression on HD until 3/2020, when the patient presented with severe allograft tenderness with no fever or evidence of urinary tract infection. An abdominal CT was consistent with allograft rejection. Abdominal pain resolved after IV steroids and initiation of low dose tacrolimus. He was discharged but returned 4 days later, with recurrent abdominal pain, fever and shortness of breath. CT chest was consistent with COVID19 pneumonia with a positive swab. His condition was complicated by acute respiratory failure and cytokine storm. Despite receiving Ankinra for COVID-19, our patient died.

Discussion: Failed allograft rejection for patients who initiate HD usually occurs within the first 6-12 months. Unless allograft failure occurs within a year of transplantation, many nephrologists complete withdrawal of immunosuppression in failed grafts after 4 months to decrease the risk of infections. In our case, the development of allograft rejection after stable long-term HD, is very unusual. We propose that the cytokine storm from COVID-19 in our patient provided the appropriate "danger signals" that triggered innate inflammation and augmented effector responses against the allograft. COVID-19 infection triggers a pro-inflammatory immune response, with IL-6 being a key cytokine that potentially drives T-cell effector responses and inhibits T-regulatory responses to donor allograft.



PO0768

Risk Factors for Mortality in Kidney Transplant Recipients with COVID-19

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Background: There is limited information on the presentation and risk factors for poor outcome in kidney transplant recipients with COVID-19.

Methods: We reviewed data of admitted kidney transplant recipients at 12 system hospitals with COVID-19 between March 1, 2020, and April 30th, 2020. We analyzed risk factors for mortality.

Results: 31 patients were identified, 30 were admitted. Median age was 58 (IQR 53-68), 61% male, 32% Caucasian, 29% African American, 29% multiracial and 6% Asian. Median time from transplant to COVID-19 testing was 1178 days (IQR 252-2897). The most common symptom was cough, followed by fever, shortness of breath and fatigue. Chest X-ray/CT revealed multifocal patchy opacities. Ten patients required mechanical ventilation. Laboratory markers can be seen in the table. Acute kidney injury occurred in 39% of patients. The majority of patients were on triple immunosuppression (94% on tacrolimus, 90% on mycophenolate, and 74% on prednisone). During the hospital course 87% had the antimetabolite stopped while 35% had CNI stopped. Treatments utilized included hydroxychloroquine (93%), azithromycin (50%), convalescent plasma (14%), IL-6 inhibitor (10%) and 1 received remdesivir. At a median follow up of 19 days (IQR 8 – 26) 10 patients died. Risk of death was greater if the patient was admitted to a non-transplant hospital (80% vs 23%, p=0.027), lymphopenic at presentation (47% vs 8%, p=0.013 or had O2 saturation less than 94% upon admission (100% vs 57%, p=0.03). During hospitalization mortality was also higher in patients with higher peak serum creatinine (3.2 mg/dl vs 1.5 mg/dl, p=0.013), or if requiring intubated (70% vs 14%, p<0.001). Increase in inflammatory markers including peak D-dimer, peak CRP, ferritin and procalcitonin were also predictive of mortality.

Conclusions: Kidney transplant recipients with COVID-19 should be monitored closely in a transplant center. Mortality is high, particularly in patients presenting with lymphopenia and hypoxemia.

	Total	Survived	Died	p-value
	N=31	N=21	N=10	
Creatinine presentation	1.5 (1.2-2.3)	1.4 (1.1-1.9)	1.7 (1.6-2.6)	0.057
WBC count presentation	6.8 (5.2-9.2)	6.8 (5.2-8.6)	7.9 (5.7-11.1)	0.42
WBC nadir	5.9 (4.4-7.5)	5.9 (4.5-7.2)	5.3 (4.4-9.4)	0.66
Lymph	0.8 (0.4-1.1)	1.0 (0.7-1.2)	0.4 (0.3-0.6)	0.013
Neutrophil presentation	5.3 (4.4-7.7)	5.3 (4.4-6.9)	6.7 (4.9-8.9)	0.25
Peak Creatinine	2.0 (1.4-3.5)	1.5 (1.2-2.5)	3.2 (2.0-4.5)	0.013
Pulm support				<0.001
None	32.3%	47.6%	0.0%	
Intubation	32.3%	14.3%	70.0%	
Nasal Cannula	25.8%	38.1%	0.0%	
Non rebreather	9.7%	0.0%	30.0%	
D-Dimer	703.0 (285.0-2480.0)	424.0 (200.5-2184.0)	1783.0 (627.0-9190.0)	0.082
Peak D-Dimer	2705.0 (467.0-8539.0)	842.0 (333.0-6288.0)	4413.0 (2705.0-15421.0)	0.033
Ferritin	817.0 (627.0-2871.0)	758.0 (325.0-1778.0)	2432.5 (817.0-2996.0)	0.054
Peak Ferritin	1081.0 (746.0-2871.0)	783.0 (647.0-2557.0)	1907.0 (846.0-3658.0)	0.19
CRP	10.5 (4.5-18.2)	8.7 (3.9-17.5)	15.7 (5.8-24.4)	0.054
Peak CRP	13.7 (5.1-26.1)	12.2 (4.3-22.5)	24.2 (13.2-46.6)	0.048
Procalcitonin	0.3 (0.2-0.9)	0.2 (0.2-0.5)	1.0 (0.3-2.3)	0.040
ESR	84.5 (50.5-102.5)	89.0 (56.0-107.0)	69.5 (45.0-98.0)	0.70

All data presented in median (IQR) unless otherwise noted

PO0769

Living Donor Kidney Transplant Practice in the COVID-19 Era: A Survey of US Transplant Programs

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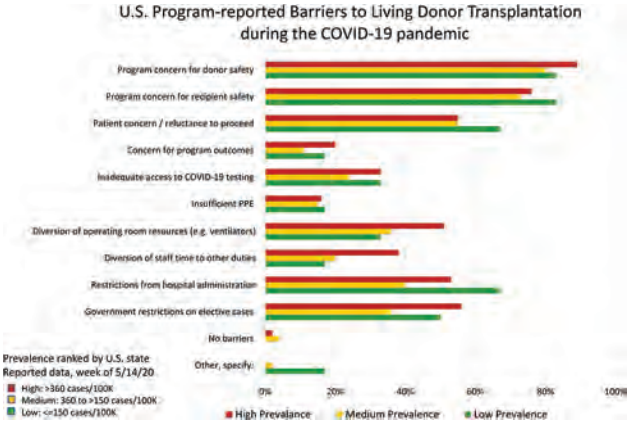
Background: We surveyed U.S. transplant programs to assess practices, strategies and barriers related to living donor kidney transplantation (LDKT) in the context of the COVID-19 pandemic.

Methods: After IRB approval, the survey was launched 5/9/20 by email and postings to professional society list-servs, using the Qualtrics platform. Data are reported through 5/27/20, and examined by state COVID-19 prevalence.

Results: Staff at 117 unique centers responded, representing 58% of U.S. living donor recovery centers and 75% of LKDT volume in the year before pandemic declaration. Overall, 66% reported LDKT surgery was on hold (82% in high vs. 50% in low prevalence states). 36% reported that evaluation of new donor candidates had paused, 27% reported evaluations were very decreased (>0% to <25% typical) and 23% reported evaluations were moderately decreased (25% to <50% typical). Barriers to LDKT surgery included program concerns for donor (84%) and recipient (75%) safety, patients concerns (54%), restrictions on elective cases (47%) and hospital administrative restrictions (47%). Programs with higher local COVID-19 prevalence reported more barriers related to staff and resource diversion (**Figure**). Most centers continuing donor evaluations used remote strategies (video 82%; telephone 43%). 61% of centers plan to continue more telehealth after the pandemic. 32% plan to resume some LDKT within 2 wks and 27% within 1 month. When surgery resumes, all will screen for COVID-19 before donation surgery, although timeframe and modalities vary.

Conclusions: COVID-19 has created many barriers to LDKT, especially in areas of highest prevalence. Transplant centers are planning to restart LKDT cautiously. Consensus-building is needed to reduce barriers, guide optimal practice, and facilitate safe restoration of LDKT across centers.



Barriers to LDKT during COVID-19 pandemic

PO0770

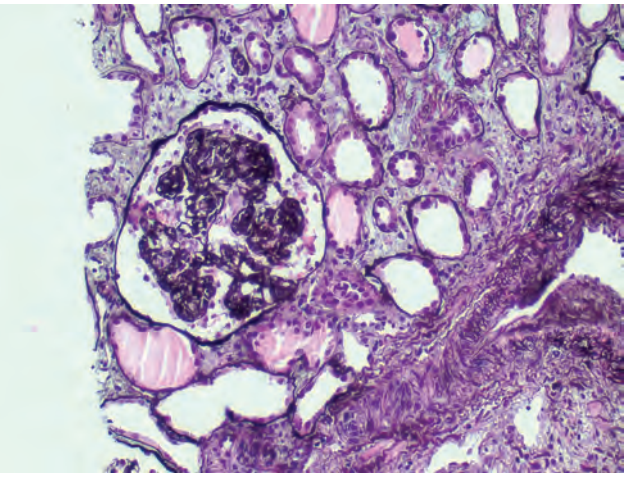
Collapsing/Sclerosing Glomerulopathy (CSG) and Acute Tubular Injury (ATI) in Patients with COVID-19

Sunil Sherchan, Mohamed Kahila, Jamrose K. Durrani, Isha Puri, Ibrahim A. Mohamed, Yohannes Melaku, Ernie Yap, Robert F. Leonardo, Subodh J. Saggi, Moro O. Salifu, Anthony D. Nicastri. *SUNY Downstate Health Sciences University, Brooklyn, NY.*

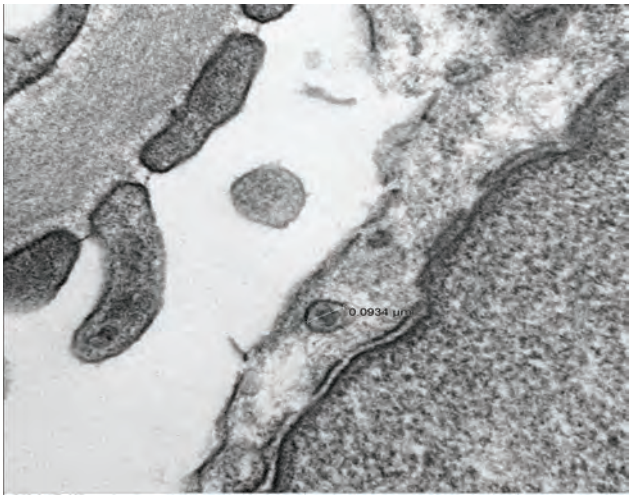
Introduction: AKI in patients with COVID-19 may be due to ATI from hemodynamic instability or inflammatory responses. We present two cases of CSG and ATI in patients admitted for COVID-19

Case Description: Case 1 25-year-old black obese female admitted with fever, cough, dyspnea and serum creatinine of 1.4 mg/dL, discharged next day with home quarantine. Re-admitted 26 days later due to nausea, fatigue, and bilateral foot swelling. Serum creatinine 28 mg/dl and urine protein to creatinine ratio (uPCR) of 10.4 g/g Case 2 42-year-old black female with hypertension, diabetes mellitus admitted with fever, dyspnea, cough, and diarrhea. Patient found to have diabetic ketoacidosis, serum creatinine 12.7 mg/dl. She developed deep vein thrombosis and pulmonary embolism and uPCR 15.4 g/g. She was started on hemodialysis Kidney biopsy showed global and segmental capillary collapse with a variable degree of sclerosis and severe renal tubules injury. Electron microscopy showed spherical structures in the podocytes, endothelial cells, and tubular epithelium similar to Coronavirus particles

Discussion: Our experience above is part of a growing literature describing the direct visualization of SARS-CoV-2 in causing ATI and CSG. Pathogenetic pathways remain to be elucidated



Capillary collapse.



Viral particles with preserved foot processes

PO0771

What Do Data Tell Us About Patients Receiving Calcineurin Inhibitors (CNIs) and Contracting a Coronavirus

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Background: We hypothesized that patients taking CNIs, cyclosporine and tacrolimus would be less susceptible to coronavirus infections because of antiviral and anti-cytokine-storm effects and compared the occurrence of positive coronavirus test rates in a population receiving a CNI and non-CNI treatment population. This is of high importance as CNIs are being trialed as a treatment for severe acute respiratory syndrome coronavirus 2 (COVID-19) immune response (NCT04341038). Transplant nephrologists recommend continuing CNIs through the COVID-19 pandemic.

Methods: We analyzed longitudinal EHR system data from the Rogosin Institute's nephrology clinic to identify a population of 5,144 patients with a record of respiratory viral panel (RVP) testing for any coronavirus strain between December 2012 and May 2020. We identified 1,195 patients receiving cyclosporine or tacrolimus and compared positive test rates of any coronavirus stain in those receiving CNIs to those not receiving CNIs.

Results: A total of 51 patients tested positive (1.05%) Of the 1,195 CNI recipients, 21 tested positive (1.76%); of 3,949 patients with no record of CNI treatment, 33 tested positive (0.84%). Given an age distribution difference between the two cohorts (CNI cohort median 58; non-CNI cohort median 68). We therefore calculated an age-adjusted positive test rate for both populations, with results of 1.76% for the CNI cohort and 0.83% for the non-CNI cohort. A z-test comparing the population proportions testing positive had a z-value of 2.71 (p-value 0.003), indicating significant difference. 8.47% of positive tests on an RVP for any of coronavirus, rhinovirus or respiratory syncytial were for a coronavirus in the CNI group vs. 6.48% in the non-CNI group (z 2.37, p 0.009). Using a logistic regression model to examine the probability of testing positive for a coronavirus (features for age, gender, whether the test was conducted in flu season (Dec-Feb) and whether the patient was receiving CNIs) we found that CNIs were statistically significant (p 0.007).

Conclusions: Based on the data, as far as we can tell being on a CNI does not offer protection from a symptomatic coronavirus infection. It remains to be seen if it decreases severity of the illness because of the potential for cytokine storm effects.

Funding: Commercial Support - pulseData

PO0772

ESKD Patients with COVID-19 vs. Kidney Transplant Recipients with COVID-19

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Background: The Covid-19 pandemic has had significant impact on the ESKD population with reduction in kidney transplantation due to decreased organ availability and temporary cessation of transplant procedures. To better understand the impact on patients with ESKD, we compared the outcomes of Covid-19 positive patients on the Waitlist with those with a functioning kidney transplant.

Methods: Our center developed a dashboard and active surveillance of Waitlisted and Kidney transplant recipients tested for SARS-CoV-2. From 3/13/20 to 5/20/20, we identified 55 Waitlisted patients who tested positive for SARS-CoV-2, and compared their clinical characteristics and outcomes with those post kidney transplant. Primary outcomes included hospitalization and mortality rates.

Results: Presenting symptoms and hospitalization rates were similar in waitlisted ESKD and kidney transplant patients with Covid -19. Azithromycin and doxycycline use was similar in both groups. Hydroxychloroquine use was more frequent in kidney transplant patients (62% vs 36%), as were other experimental therapies. Mortality was greater in waitlisted ESKD compared to kidney transplant patients (29% vs 13). Of the waitlisted ESKD patients who died, most were males, Black or Hispanic, and 81% had T2DM and/or HTN as the cause of their ESKD. None of the non-hospitalized patients died in either group.

Conclusions: Waitlisted ESKD patients on dialysis with Covid-19 are comparatively at higher risk for mortality compared to kidney transplant recipients with Covid-19 despite similar demographics and similar burden of comorbidities. Whether the ability of immunosuppressive therapy to prevent the cytokine storm contributed to better survival among kidney transplant recipients remains to be determined.

COVID-19+	Waitlisted ESKD (n=55)	Kidney Transplant (n=54)
Age- median years (range)	61 (38, 86)	57 (29, 83)
Gender, Male- n (%)	37 (67)	38 (70)
Race/Ethnicity- n (%)		
Asian	9 (16)	6 (11)
Black	26 (47)	13 (24)
Hispanic	14 (26)	17 (31)
White	6 (11)	17 (31)
Middle Eastern	0 (0)	1 (2)
Cause of ESKD- n (%)		
Diabetes	23 (42)	11 (20)
Hypertension	18 (33)	14 (26)
Glomerulonephritis	6 (11)	13 (24)
Lupus	0 (0)	2 (4)
Polycystic Kidney Disease	3 (5)	3 (6)
Other	5 (9)	11 (20)
Cardiovascular disease- n (%)	26 (47)	19 (35)
Pulmonary disease- n (%)	8 (15)	8 (15)
BMI- median (range)	26.5 (18, 42)	28 (18, 43)
Presenting symptoms	(n=50)	(n=54)
Fever	37 (74)	40 (74)
Cough / upper respiratory symptoms	34 (68)	32 (59)
Shortness of breath	24 (48)	28 (52)
Fatigue / myalgia	32 (64)	23 (43)
Diarrhea	18 (36)	21 (39)
Nausea / vomiting	6 (12)	5 (9)
Confusion	10 (20)	6 (11)
Treatment	(n=42)	(n=54)
Azithromycin	11 (26)	12 (22)
Doxycycline	7 (17)	8 (17)
Other antibiotic	26 (62)	21 (39)
Hydroxychloroquine	15 (36)	32 (62)
Remdesivir	0 (0)	2 (4)
IL-6 receptor inhibitor	1 (2)	2 (4)
Convalescent Plasma	0 (0)	1 (2)
Hospitalization- n (%)	44 (80)	39 (72)
Patient death- n (%)	16 (29)	7 (13)

PO0773

Kidney Transplant Practices in Latin America During the COVID-19 Pandemic: Analysis from GlomCon Latin America Working Group (LGlomCon)

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Background: Latin America (LA) is the current epicenter of a global pandemic that has never been seen in the era of transplantation and immunotherapy. We aimed to describe their nephrologists' practices and experiences regarding kidney transplant (KT) management in the context of COVID-19 pandemic.

Methods: Descriptive analysis extracted from an online survey carried out among nephrologists, renal pathologists and other health workers treating kidney diseases between May 20-27, 2020 from sixteen Spanish speaking LA countries divided into 6 categories. We present the results for the kidney transplant category.

Results: 430 responses were obtained of which 360 (84%) were considered for analysis. 139 (49%) respondents routinely participate in the care of transplant patients at centers that perform up to 50 KT per year (70% of them). The transplant activity was suspended in 90% of the centers at the time of the survey. Bigger centers continued their activity but not at full capacity. For transplant recipients who developed COVID-19, 52% of physicians continued the same maintenance immunosuppression for the ones with mild disease (outpatient). For moderate cases (inpatient but not requiring mechanical ventilation or vasopressors), 72% decreased maintenance therapy starting with the antiproliferative drug. For severe cases (ICU admission for mechanical ventilation or vasopressors), 74% stopped all the immunotherapy with the exception of steroids. ICU admission and need for renal replacement therapy were reported in less than 20% of their cases. Nephrologists from centers that continued their transplant activity during the pandemic reported that only 32% performed routine COVID-19 tests to donors and 51% to recipients before KT surgery.

Conclusions: Kidney transplants programs are almost closed throughout LA during the COVID-19 pandemic. The disproportionate resource allocation to COVID-19 will have unintended consequences for those already carrying the burden of health inequality with the potential to disadvantage marginalized patients further. Reported immunosuppression management is in line with transplant societies' recommendations.

Funding: Private Foundation Support

PO0774

A Machine Learning-Based Predictive Model for Outcome of COVID-19 in Kidney Transplant Recipients

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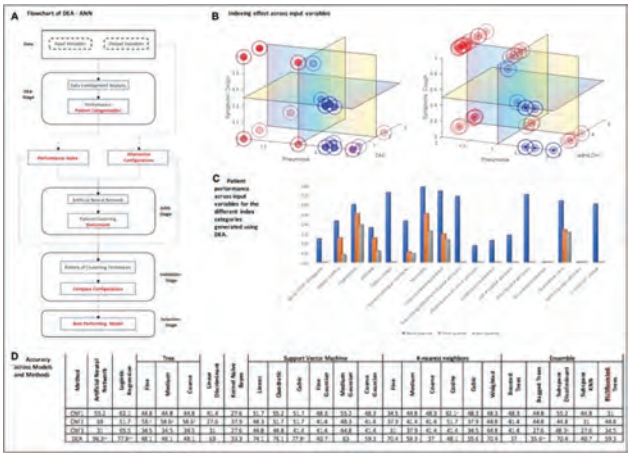
Background: Health systems need tools to deal with COVID-19, especially for high-risk population, such as transplant recipients. Predictive models are necessary to improve management of patients and optimize resources.

Methods: A retrospective study of hospitalized transplant patients due to COVID-19 was evaluated(March 3-April 24,2020). Admission data were integrated to develop a prediction model to evaluate a composite-event defined as Intensive Care Unit admission or intensification treatment with antiinflamatory agents. Predictions were made using a Data Envelopment Analysis(DEA)-Artificial Neural Network(ANN) hybrid, whose accuracy relative to several alternative configurations has been validated through a battery of clustering techniques.

Results: Of 1006 recipients with a planned or an unscheduled visit during the observation period, thirty-eight were admitted due to COVID-19. Twenty-five patients(63.2%) exhibited poor clinical course(mortality rate:13.2%), within a mean of 12 days of admission stay. Cough as a presenting symptom(P=0.000), pneumonia(P=0.011), and levels of LDH(P=0.031) were admission factors associated with poor outcomes. The prediction hybrid model working with a set of 17 input variables displays an accuracy of 96.3%, outperforming any competing model, such as logistic regression(65.5%) and Random forest(denoted by Bagged Trees, 44.8%). Moreover, the prediction model allows us to categorize the evolution of patients through the values at hospital admission.

Conclusions: The prediction model based in Data Envelopment Analysis-Artificial Neural Network hybrid forecasts the progression towards severe COVID-19 disease with an accuracy of 96.3%, and may help to guide COVID-19 management by identification of key predictors that permit a sustainable distribution of resources in a patient-centered model.



PO0775

Outcomes of COVID-19-Positive Kidney Transplant Recipients

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Background: Kidney transplant recipients (KTR) are at increased risk of infections due to immunosuppression (IS). COVID-19 has posed unique challenges due to its evolving symptomatology and lack of effective treatment options. Current data published about the impact of COVID-19 in KTR comes from severely impacted areas. The aim of our study was to review course and outcomes of KTR at our center.

Methods: Retrospective chart review of KTR diagnosed with COVID-19. Descriptive statistics were summarized as absolute numbers for categorical data and as median with interquartile range (IQR) for skewed distribution.

Results: We had 20 KTR diagnosed with COVID-19. Median age of 53.5 years(47-63), 10 males, and 12 blacks. Median time from KT to presentation was 70.7 months(17.25-158.75), with 1 pt in 1st year post KT. Thirteen (65%) pts were obese with BMI≥30kg/m^2, 2 pts had chronic obstructive pulmonary disease, and 5 had cardiac disease. Most common presenting symptom was cough in 14 pts, followed by fever-13 pts, shortness of breath-9, and diarrhea-6pts. During the study, 15 pts were hospitalized, and 9 of them had chest x-ray findings of bilateral opacities consistent with pneumonia. Inflammatory markers were elevated in all pts but did not correlate with disease outcome. Acute kidney injury was seen in 9 pts, with 3 requiring continuous renal replacement therapy. Four pts required mechanical ventilation. Ten pts had reduction of their IS. Hydroxychloroquine was used in 11 pts, and azithromycin in 4. Four hospitalized pts received convalescent plasma as part of an ongoing COVID-19 trial in our center. Donors were 4-6 weeks post recovery from confirmed severe acute respiratory syndrome coronavirus 2 infection. Enrollment was offered to pts at high risk of progression to severe disease. We had 3 deaths, 2 pts remain hospitalized, and the remaining 15 were either discharged or managed as outpatients. Median follow up time from presentation was 25 days(13-38) for the entire cohort.

Conclusions: In our cohort, 45% of patients presented with acute allograft dysfunction highlighting impact of SARS-CoV-2 infection on kidney function. Our center utilized investigational convalescent plasma in 4 pts successfully while the clinical trial outcomes are awaited. Ultimately, the development of a safe and efficacious vaccine targeting SARS-CoV-2 may better equip us to fight this pandemic.

PO0776

COVID-19 in Kidney Transplant Recipients at New England's Largest Safety-Net Hospital

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Background: The coronavirus disease 2019 (COVID-19) has led to a global pandemic as announced by the World Health Organization. Kidney transplant patients are thought to constitute a unique high risk group for severe COVID19 infection. Furthermore, disparities in health care have led to COVID-19 disproportionately affecting minority groups including African Americans and Hispanics.

Methods: We identified adult kidney transplant recipients who were admitted with COVID-19 between March, 15th and May 1st, 2020. We evaluated the demographic, clinical and laboratory data of all admitted patients. We also evaluated the presence of co-infections as well as decisions regarding immunosuppressant management.

Results: 23 kidney transplant recipients who were hospitalized for COVID-19 were evaluated. 91% of our patients were of minority groups. 35% of patients required ICU admission, and 30% required mechanical ventilation. 40% of patients had associated coinfections in addition to COVID19. 87% of patients had variable degrees of AKI, 26% of patients with AKI required renal replacement therapy. Mortality rate in our population was 22%. Upon admission to the hospital, our immunosuppressant therapeutic approach included stopping the antimetabolites and continuing with the calcineurin inhibitors (targeting trough level of 4 to 6 ng/dl for tacrolimus and 50 ng/dl for cyclosporine), and prednisone if patients were on steroids.

Conclusions: This report demonstrates higher rate of AKI, coinfection and mortality in kidney transplant patients in the setting of COVID19 as compared to general population.

Baseline Characteristics	Patients (N= 23)
Admissions	23
Mean age - year (range)	51 (24-68)
Sex – no (%)	
Male	19 (83 %)
Female	4 (17 %)
Body-mass index	26.1 (18.6-41)
Ethnicity/Ancestry	
African	9 (39%)
Hispanic	12 (52%)
Caucasian	1 (4%)
Arabic	1 (4%)
Co-existing disorder – no (%)	
Asthma	1 (4%)
Current or former smoker	3 (13 %)
Coronary Artery Disease	2 (9 %)
Congestive Heart Failure	11 (48 %)
Diabetes mellitus	10 (43 %)
Hepatitis B	1 (4 %)
Hypertension	21 (91 %)
Obstructive sleep apnea	3 (13%)
Type of transplant	
Cadaveric	20 (87 %)
Living	3 (13%)

Table 2 – Hospital Data	
Systemic symptoms at admission	
Fever	19 (83%)
Headache	2 (9%)
Diarrhea	8 (35%)
Nausea/Vomiting	3 (13%)
Respiratory symptoms at admission	
Cough	13 (57%)
Shortness of breath	10 (43%)
Requiring oxygen	15 (65%)
Requiring Intensive Care	8 (35%)
Requiring intubation	7 (30%)
Requiring Renal Replacement Therapy	6 (26%)
Survival	20 (87%)
Chronic Immunosuppressive therapy	
Calcineurin inhibitor	23 (100%)
Antimetabolite	23 (100%)
Prednisone	12 (52%)
Length of Stay (days)	9.2

PO0777

Identifying Scenarios of Benefit or Harm from Kidney Transplantation During the COVID-19 Pandemic: A Simulation Study

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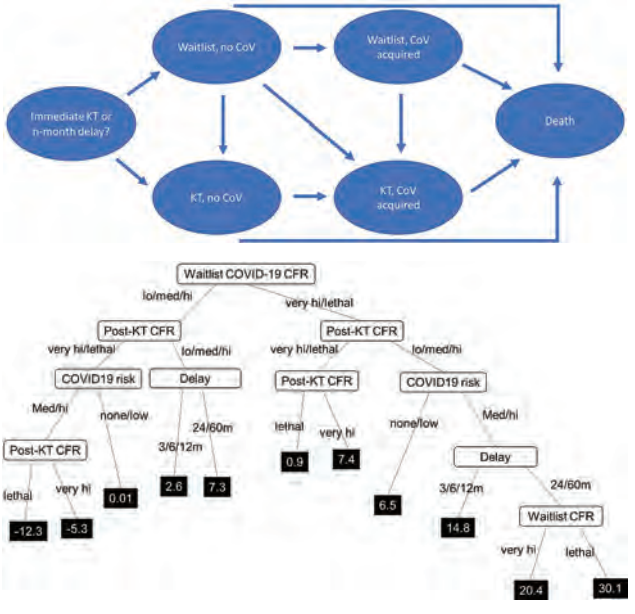
Background: Clinical decision-making in kidney transplantation (KT) during the COVID-19 pandemic is a challenge: both candidates and recipients may face increased acquisition risks and case fatality rates (CFRs). Given our poor understanding of these risks, many centers have paused or reduced KT activity, yet data to inform such decisions are lacking.

Methods: To quantify the benefit/harm of KT in this context, we conducted a Markov simulation study of immediate-KT vs delay-until-after-pandemic for different patient phenotypes under a variety of potential COVID-19 scenarios (Figure 1), simulating expected life-months gained from transplant over 5 years. A calculator was implemented (http://www.transplantmodels.com/covid_sim), and machine learning approaches were used to evaluate the important aspects of our modeling.

Results: Characteristics of the pandemic (acquisition risk, CFR) and length of delay (length of pandemic, waitlist priority for DDKT) had greatest influence on benefit/harm (Figure 2). In most scenarios of COVID-19 dynamics and patient characteristics, immediate-KT provided survival benefit; KT only began showing evidence of harm in scenarios where CFRs were substantially higher for KT recipients (e.g. ≥50% fatality) than for waitlist registrants.

Conclusions: Our simulations suggest that KT remains beneficial under COVID-19 in many scenarios. Our calculator can help identify patients who would benefit most. As the pandemic evolves, our calculator can update these predictions.

Funding: NIDDK Support



Partial summary of simulation output. Black boxes denote life-months gained from transplant; a negative value denotes harm from transplantation.

PO0778

COVID-19 in Patients with CKD in New York City

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Background: Coronavirus disease 2019 (COVID-19) has affected millions of people, and several chronic medical conditions appeared to increase the risk of severe COVID-19. However, limited data are available about the outcomes of COVID-19 in patients with chronic kidney disease (CKD).

Methods: This was an observational study of patients with CKD at three affiliated hospitals in New York City who were diagnosed with COVID-19 by reverse-transcriptase polymerase chain reaction of nasopharyngeal swab specimens collected in the emergency departments between March 3rd and April 21st, 2020. We stratified patients into three groups: pre-dialysis CKD, dialysis, and transplant. Data are shown as median (interquartile range). Logistic regression was used to identify CKD characteristics associated with non-survival.

Results: Of the 372 confirmed COVID-19 patients with CKD, 182 were pre-dialysis, 149 were on dialysis, and 41 had functional kidney transplant. The median age of the pre-dialysis group was 75 (63-85) years, dialysis group 66 (58-74) years, and transplant group 63 (48-71) years. Men comprised 62.4% of the cohort. Baseline serum creatinine was 1.5 (1.2-2.2) mg/dL in the pre-dialysis group. By the end of the observation period, 78.5% of patients were discharged or had died. Of these patients, mortality was highest in the pre-dialysis group (26.9%), followed by dialysis (24.2%), then transplant (9.8%) groups. Almost half of the cohort was receiving ACE-inhibitors or ARBs pre-COVID-19, which was not associated with non-survival. In the pre-dialysis group, baseline serum phosphorus was associated with non-survival (OR 1.5 per each 1.0 mg/dL of increase in serum phosphorus). Anemia, defined as hemoglobin <10 g/dL, was also associated with non-survival (OR 3.1) in that group. Body mass index (BMI)<25 kg/m^2 was paradoxically associated with non-survival (OR 2.7) in patients with pre-dialysis CKD.

Conclusions: Our data demonstrate that mortality in this cohort, particularly in patients with pre-dialysis CKD, was substantially higher than in the general population in New York City. Poorly controlled CKD complications, including CKD-mineral and bone disorder and anemia, as well as low BMI were associated with mortality. Ongoing control of CKD complications may serve as an opportunity to improve outcomes of COVID-19 in patients with CKD.

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PO0779

COVID-19 in CKD: Retrospective, Propensity Score-Matched Cohort Study

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Background: The prognostic factors for COVID-19 in patients with chronic kidney disease (CKD) are uncertain. We conducted a propensity score-matched study to compare clinical and prognostic features between hospitalized COVID-19 patients with and without CKD.

Methods: Patients with estimated creatinine clearance below 60 ml/min/1.73 m^2 for more than three months, were included in the CKD group. Fifty-six patients and the propensity score-matched fifty-six control patients were followed-up at least 15 days or until death after diagnosis of COVID-19. All demographic data and diagnostic and therapeutic methods were evaluated. The endpoints were all-cause mortality and acute kidney injury (AKI).

Results: Patient and control groups were reviewed retrospectively over a median follow-up of 44 days (IQR, 36-52 days) after diagnosis of COVID-19. Patients in the CKD group had higher intensive care unit follow-up and mortality rates than the other group, but these results did not reach statistical significance (16 [28.6%] vs. 19 [33.9%]; p=0.54 and 11 [19.6%] vs. 16 [28.6%], p=0.269, respectively). The frequency of AKI was significantly higher in predialysis patients with CKD compared to the other group (8 [14.3%] vs. 5 [45.5%]; p<0.001), but there was no significant difference between the groups in terms of cytokine release syndrome and respiratory failure (13 [23.2%] vs. 8 [14.2%]; p=0.226, 25 [44.6%] vs. 22 [39.3%], p=0.566, respectively). Multivariate logistic regression analysis revealed that respiratory failure (39.283 [95% CI, 7.296 to 211.519; P<0.001] and AKI (10.961 [95% CI, 1.688 to 71.186; P=0.012] were independent risk factors for the mortality.

Conclusions: The prognosis of COVID-19 in patients with CKD is worse than non-uremic patients. Also, AKI and respiratory failure are independent risk factors for mortality.

Table 1. The laboratory results, treatment regimen, and outcomes of the patients

		Control group (n=56)	Patients with CKD (n=56)	p-value
Laboratory results at admission (Median-IQR 25-75)	Lymphocyte count (/mm3)	1150 (758-1478)	940 (520-1355)	0.055
	Serum CRP levels (mg/L)	39 (17-93)	55 (18-154)	0.027
	Serum Ferritin levels (ng/ml)	247 (149-580)	731 (723-2860)	<0.0001
Anti-viral treatment (N, %)	Favipiravir	26 (46.4%)	15 (27.3%)	0.037
Anti-cytokine agents (N, %)	Tocilizumab	5 (8.9%)	1 (1.8%)	0.324
	Anakinra	3 (5.4%)	4 (7.3%)	
	Tocilizumab+Anakinra	5 (8.9%)	3 (5.5%)	
Outcomes (N%)	Number of died patients	11 (19.6%)	16 (28.6%)	0.269

Abbreviations; CKD, chronic kidney disease; CRP, C-reactive protein.

PO0780

Kidney and Clinical Outcomes of COVID-19 in the Mexican Population

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Background: Coronavirus Disease 2019 (COVID-19) is a new disease of pandemic proportions. Currently, there are no reports about kidney involvement and the association with mortality in Mexico. Our aim was to describe the characteristics in our population, clinical and renal outcomes.

Methods: Prospective, descriptive, single-center study in patients diagnosed with COVID-19 (positive RT-PCR tests), admitted to our hospital from April 2020 to date.

Results: 48 patients (60.41% men) with an average age of 54.33 years were included. 23 (47.9%) had a previous diagnosis of HTN and DM, 11 (22.9%) had obesity, 5 (10.4%) had neurological diseases, 4 (6.3%) had heart disease, 3 (6.3%) had malignancies and 1 (2.1%) had liver disease. 9 (18.8%) patients with a history of smoking. At admission, the mean oxygen saturation was 85.76%. The main reason for consultation was dyspnea in 35 patients (72.9%). Regarding symptoms, 81.3% (39) had dyspnea, 87.5% (42) fever, 54.2% (26) headache, 72.9% (35) cough and, to a lesser extent, odynophagia, myalgia and malaise in 33.3% (16), 45.8% (22) and 41.7% (20) respectively. The mean creatinine, urea and bicarbonate was 1.34 mg/dl, 56.69 mg/dl, and 18.49 mmol/l respectively. 25% of the patients required ICU admission and 27.1% mechanical ventilation. During the study period, 19 patients (39.6%) developed AKI, 20.8% classified as KDIGO stage 1 and 18.8% as stage 3. At the end of this study, 56.3% (27) had a complete recovery, 35.4% (16) died and 8.3% (5) are still admitted. Regarding the patients that had an AKI, 6 (31.57%) had a complete recovery, 3 (15.7%) required intermittent HD but eventually died, for a total of 13 death patients (68.4%). There was a statistically significant difference in mortality between patients with AKI vs patients with normal kidney function (p=0.002), with a RR of 3.47.

Conclusions: This study showed a higher prevalence of AKI in the Mexican population compared to reports from other countries, with a significantly higher risk for death. Special attention should be paid to this outcome and as nephrologists, we must take an active role in the care of these patients.

PO0781

Association Between Kidney Dysfunction at Admission and Outcomes in Hospitalized Patients with COVID-19

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Background: AKI is a major predictor of mortality in patients with coronavirus disease 2019 (COVID-19). Data regarding association of renal dysfunction (AKI, hematuria and proteinuria) at the time of admission with hospital outcomes is limited.

Methods: In this retrospective single-center study, we analyzed electronic medical record data on 300 patients admitted with COVID-19. Data collection included history of comorbidities, medications, vital signs, and admission and peak laboratory values. Outcomes included inflammatory burden (calculated using composite scores for multiple markers of inflammation), AKI during hospitalization, admission to the intensive care unit (ICU), need for invasive mechanical ventilation, mortality and length of stay. For multivariate analyses, generalized linear model (continuous outcomes) and logistic regression (dichotomous outcomes) were used. Machine learning algorithms (XGBoost classifier with 3-fold cross-validation) were performed to develop a predictive model for in-hospital AKI.

Results: No significant associations between admission AKI and hospital outcomes were observed. Admission proteinuria was associated with increases in in-hospital AKI, ICU admission, death, peak inflammation score, and length of stay on descriptive analysis; however, on multivariate analysis (after adjusting for multiple covariates), only in-hospital AKI remained statistically significant (OR=4.71, 1.28–17.38, p=0.02). Admission hematuria was associated with increases in in-hospital AKI, ICU admission, invasive mechanical ventilation, and death on descriptive analysis; and on multivariate analysis it still predicted increased rates of ICU admissions (OR=4.56, 1.12-18.64, p=0.03), invasive mechanical ventilation (OR=8.79, 2.09-37.00, p=0.003), and death (OR=18.03, 2.84-114.57, p=0.002). Using machine learning algorithms, an area under the receiver operating curve (AUROC) of 87.4% with an accuracy of 87.6% was obtained for predicting in-hospital AKI using only admission data.

Conclusions: In patients with COVID-19, admission hematuria and proteinuria are associated with adverse hospital outcomes, and admission data can be used to predict AKI during hospitalization.

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PO0782

COVID-19 in CKD Patients: Lessons from 553 CKD Patients with Biopsy-Proven Kidney Disease

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Background: COVID-19 is a novel coronavirus currently at the centre of a global pandemic, and patients with cardiovascular risk factors such as hypertension and diabetes are at risk of a serious complication such as hospitalization and death. Chronic kidney disease (CKD) increased cardiovascular risk and >90% of CKD patients presented hypertension. The prognosis and lethality of COVID-19 in patients with biopsy-proven kidney disease has not been previously studied.

Methods: Data included patients who underwent a kidney biopsy at the Vall d'Hebron Hospital between January 2013 and February 2020 with diagnostic confirmation and those with high clinical suspicion of SARS-CoV-2 infection during the period from March to May 2020.

Results: Of 553 patients, 39(7%) were diagnosed with SARS-CoV2 infection. The mean age was 63.4±15 years. 48.7% were male, 31 hypertension, 19 diabetic, 12 obese and 18 patients had lung disease. The renal histological diagnosis of glomerulonephritis with extracapillary proliferation in 10.3%, allergic interstitial nephritis in 10.3 %, secondary GSFS in 8.5% and diabetic nephropathy in 10.3%. 4 patients were on hemodialysis and 6 had a kidney transplant. Creatinine before infection was 1.52mg/dL±0,66. 17 patients were under immunosuppressive treatment (14 with prednisone, 8 mycophenolate, 6 tacrolimus, 1 rituximab). 26 patients had confirmation of SARS-CoV2 infection with RT PCR obtained from nasopharyngeal swab. 22 patients required hospital admission [average hospital stay was 16 days±11], of which 4 in the ICU and 6 (15%) died. 15 patients received lopinavir/ritornavir; 23 patients, azithromycin; 20 patients, hydroxychloroquine; 6 patients, tocilizumab; 9 patients, intravenous corticosteroids. 11 patients presented impaired renal function, of which 3 were transplanted and 8 with CKD. CKD patients under RAS blockade had less mortality than patients without RAS blockade treatment (29% vs 0%, p=0.014).

Conclusions: COVID-19 was diagnosed in 7% of our CKD patients with kidney biopsy. The mortality was 15%, lower than the reported in hemodialysis patients. RAS blockade is not exerting a deleterious effect in our CKD patients with COVID-19 infection, suggesting that they should not be withdrawn.

PO0783

Renal Dysfunction, COVID-19 Infection, and Mortality

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Background: Critically ill patients with the SARS-CoV-2 virus (COVID-19) infection have diverse clinical manifestations including renal dysfunction which can determine their short-term outcomes. We assess if renal dysfunction on day one of hospital admission is associated with increased mortality risk of patients with severe COVID-19 infection.

Methods: We conducted a retrospective review of records of patients with severe COVID-19 infection admitted to the Intensive Care Unit between March 4 and April 11, 2020. Patients were divided into two groups based on serum creatinine level on day one of hospital admission. Group 1 included patients with normal serum creatinine (SCr) 1.10 mg/dl while group 2 included patients with high SCr > 1.10 mg/dl. The primary outcome was mortality. Secondary outcomes were the need for renal replacement therapy (RRT), duration of RRT, development of adult respiratory distress syndrome (ARDS) and need for mechanical ventilation. Comparisons between groups were done using Mann-Whitney U-tests for continuous variables and chi-square tests for categorical variables. Mortality was evaluated with a Kaplan-Meier Survival Analysis.

Results: A total of 47 patients were included: 27 in group 1 and 20 in group 2. Patients in group 2 compared to group 1 were older (67 vs. 56, p=0.04), more frequently African Americans (11% vs 45%, p=0.02), hypertensives (80% vs 52%, p=0.05) with chronic kidney disease (25% vs 0%, p=0.01), without significant differences sex, diabetes mellitus, smoking status or use of renin-angiotensin antagonists. 8 patients in group 2 and 3 patients in group 1 died, with significant difference in cumulative survival (Figure 1). Need for RRT (55% vs 41%, p=0.33), duration of RRT (6 vs 3 days, p=0.08), development of ARDS (85% vs 81%, p=0.75) and need for mechanical ventilation (65% vs 61%, p=0.89) were not significantly different between groups 2 and 1.

Conclusions: The presence of renal dysfunction on the day of hospital admission is associated with increased hospital mortality in patients with severe COVID-19 infection.

Funding: Other NIH Support - No funding

PO0784

Kidney Involvement and Outcome of COVID-19 Patients Admitted from a Federal Medical Facility

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Background: Correctional facilities face unique challenges with the COVID-19 pandemic. A COVID-19 outbreak was reported in the Federal Medical Center (FMC) in Lexington, Kentucky, a prison for inmates requiring medical and/or mental health care. We aimed to compare clinical characteristics and kidney related outcomes in inmates from this FMC to other COVID-19 hospitalized patients.

Methods: A total of 86 COVID-19 patients were admitted to our hospital between March 1st and June 1st, 2020. Among those, 37 patients were from the same FMC. We examined demographics, clinical and laboratory characteristics, along with the outcomes of this cohort and compared it to other COVID-19 non-prisoners. AKI was determined by KDIGO criteria.

Results: All inmates were men and their mean age was 59.8±10.6 years. The majority of them were white (60%) and required ICU admission (54%), while 39% of patients required mechanical ventilation. The prevalent comorbidities were hypertension (81%), obesity (62%), diabetes (41%) and coronary artery disease (CAD) (38%). Stage 3 CKD was present in 22% of inmates. The mean eGFR was 68±26 ml/min/1.73m^2 at time of admission. Significant hematuria and proteinuria were found in 17% and 25% of patients, respectively. Hypertension, heart failure, CAD, COPD, hepatitis C infection, and AKI were more prevalent in the FMC cohort (P= 0.030, 0.001, 0.024, 0.001, 0.017, and 0.011, respectively). The difference in mortality rates was not statistically significant between groups (12% for inmates vs.17% for non-inmates, p=0.520). Incident AKI was higher in inmates vs. non-inmates (68% vs. 38%, p=0.006) and there was no difference in acute dialysis need (14% vs 12%, respectively). The overall mortality rates were higher in patients that required dialysis (80% vs. 6% for those who did not, p<0.001). The need for acute dialysis was independently associated with mortality in multivariable models.

Conclusions: Incidence of AKI was higher in hospitalized inmates with COVID-19 vs. non-inmates. The need for acute dialysis was strongly associated with mortality in overall COVID-19 hospitalized patients.

PO0785

Can Urine Biomarkers Predict Severity of COVID-19? A Preliminary Study

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Background: Early detection of coronavirus disease (COVID-19) in patients likely to develop severe manifestations enables appropriate interventions, including rapid intensive care unit admission. This study was conducted to determine whether non-invasive urine biomarkers can predict the clinical severity of COVID-19.

Methods: Design A retrospective case series. **Setting** Single-center study, national center hospital designated for infectious disease. **Patients** Fifty-eight patients who tested positive for SARS-CoV-2 in respiratory specimens through real-time reverse transcription-polymerase chain reaction (RT-PCR) were retrospectively studied. **Measurements and main results** Urinary β2-microglobulin (β2MG), liver-type fatty acid-binding protein (L-FABP) were serially measured. Serum interferon γ and monocyte chemotactic protein-1 were also evaluated.

Results: The 58 patients were assigned into three groups. Patients requiring intensive care were assigned to the severe group (N = 12). Patients treated with oxygen were assigned to the moderate group (N = 13). Other patients were assigned to the mild group (N = 33). Urine tests revealed that low β2MG and L-FABP levels on admission were associated with mild disease, whereas high levels were associated with severe disease. In severe cases, L-FABP tended to be persistently high. The resulting cutoff values were β2MG; Severe vs. Moderate+Mild: 2457 μg/dL (Specificity 76.9% and Sensitivity 90.0%, AUC 85.9%), L-FABP; Severe vs. Moderate+Mild: 22.0 μg/gCre (Specificity 84.6% and Sensitivity 90%, AUC 91.8%). Urinary β2MG and serum IFN-γ/MCP-1 showed a similar trend.

Conclusions: Evaluating urinary biomarkers such as β2MG and L-FABP may allow determination of COVID-19 patients with active cytokines and recognition of patients likely to become critically ill and requiring careful observation and early intervention.

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PO0786

Urinary Sediment Microscopy in COVID-19-Associated AKI

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Background: Acute kidney injury (AKI) is a complication of COVID-19 that is not fully understood. Microscopic examination of the urinary sediment (MicrExUrSed) is a valuable diagnostic tool in AKI. Thus far, there has been scarcity of data about MicrExUrSed in COVID-19-associated AKI (CoV-AKI). We hypothesized that MicrExUrSed provides diagnostic clues in CoV-AKI.

Methods: We conducted a prospective observational study in patients seen for inpatient nephrology consultation with KDIGO AKI stage ≥ 1 and COVID-19 over a 1-month period. Urine specimens were collected with personal protective equipment to perform MicrExUrSed. Slides were assessed for presence of white blood cells (WBC) [≥ 2+ dipstick, ≥ 6 per low power field (LPF)], red blood cells (RBC) (≥ 2+ dipstick, ≥ 8 per LPF), acanthocytes, granular casts (GC), renal tubular epithelial cell casts (RTECC) and waxy casts (WxC). Slides were assigned to a category of acute tubular injury (ATI) based on either a Perazella cast score ≥ 2 or a Chawla cast score ≥ 3.

Results: Among 161 cases of AKI, MicrExUrSed was performed in 20 (12.4%). Anuria and contact precautions were barriers to obtain specimens. GC were found in 17 (85%) of which 16 (80%) had "muddy" brown GC (MBGC). A median 5 MBGC per LPF (1-20) were found in a median 40% (10-95%) of LPFs. WxC were found in 10 (50%) cases with a median 2 (1-5) per LPF, all of whom had MBGC also present. RTECC were found in 3 (15%) cases with a median 1 (1-4) per LPF. Altogether, ATI score was assigned to 17 (85%) patients, of which 12 (60%) had AKI either after a hemodynamic/ischemic insult (9) or after a toxic insult (3) (rhabdomyolysis, vancomycin, contrast) and 3 (15%) had biopsy-proven ATI along with collapsing glomerulopathy; for a total of 15 (75%) patients with either clinical or histological evidence on ATI matching the MicrExUrSed findings. Ten (50%) and 5 (25%) had WBCs and RBCs, respectively. Acanthocytes were found in 1 (5%) patient with presumptive proliferative endocapillary glomerulonephritis.

Conclusions: MicrExUrSed in most patients with CoV-AKI showed overt evidence of ATI with an abundance of MBGC and WxC, including in cases of coexisting glomerulopathy. Pyuria was observed in half. The diagnostic utility of MicrExUrSed in CoV-AKI was comparable to that demonstrated in other forms of AKI.

PO0787

COVID-19 Infection in Kidney Transplant Recipients: A Multicenter Experience in Istanbul

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Background: Management of COVID-19 in kidney transplant recipients (KTR) should include treatment of infection and regulation of immunosuppression but there is no consensus on this issue yet. In this study, we aimed to describe our experience in KTR with COVID-19.

Methods: In this retrospective cohort study, we included KTR who diagnosed with COVID-19 from five centers. The patients were categorized into two groups for the analysis. Patients had respiratory failure and multiple organ dysfunctions were defined as severe pneumonia. All other cases were classified as moderate pneumonia. The primary endpoint was all-cause mortality.

Results: 40 patients (20 female) were reviewed over a median follow-up of 32 days (IQR, 14-51 days) after COVID-19. 5 patients died during the follow-up. The frequency of graft dysfunction was similar between groups (n=12 and n=2; p=0.615, respectively). The frequency of previous induction (n=18 and n=7; p=0.016, respectively) and rejection therapy (n=4 and n=3; p=0.023, respectively) was significantly increased in the group with severe pneumonia compared to the moderate pneumonia group. None of the patients using cyclosporine A developed severe pneumonia. Also, multivariate logistic regression analysis revealed that previous anti-rejection therapy (9.75 [95% CI, 1.223 to 77.724; P=0.032]) was the independent predictor for mortality.

Conclusions: COVID-19 more commonly causes moderate or severe pneumonia in KTR. Immunosuppression should be carefully reduced in KTR. Induction therapy with lymphocyte depleting agents should be carefully avoided in KTR during the pandemic period.

The demographic characteristics, treatment regimen, and outcomes of the patients

		All patients (n=40)	Moderate pneumonia (n=33)	Severe pneumonia (n=7)	p-value
	Age (Mean±SD, year)	44.9±14.8	43.3±14.9	49.3±14.8	0.388
Type of Donor (N, %)	Living Deceased	35(87.5%) 5 (12.5%)	30 (90.9%) 3 (9.1%)	5 (71.4%) 2 (28.6%)	0.204
	Duration of Hospitalization (Median-IQR 25-75, days)	9 (5-12)	7 (4-12)	13 (11-28)	0.002
Laboratory results at admission (Median-IQR 25-75)	Serum ALT levels Serum LDH levels	16 (10-27) 257 (198-370)	15 (8-23) 249 (174-340)	27 (23-39) 559 (275-666)	0.015 0.048
Withdrawal of agent (N, %)	Calcineurin inh. Antimetabolites	11 (27%) 40 (100%)	7 (21.2%) 33 (100%)	4 (57.1%) 7 (100%)	0.075 1
Treatment of infection (N, %)	Favipiravir	18 (45%)	12 (36.4%)	6 (85.7%)	0.024
Anti-cytokine agents (N, %)	Tocilizumab Anakinra	5 (12.5%) 3 (7.5%)	2 (6.1%) 3 (9.1%)	3 (42.9%) 0	0.024

Abbreviations; ALT, alanine aminotransferase; LDH, lactate dehydrogenase. P-values compared moderate pneumonia and severe pneumonia.

PO0788

COVID-19 and Kidney Transplant Outcomes

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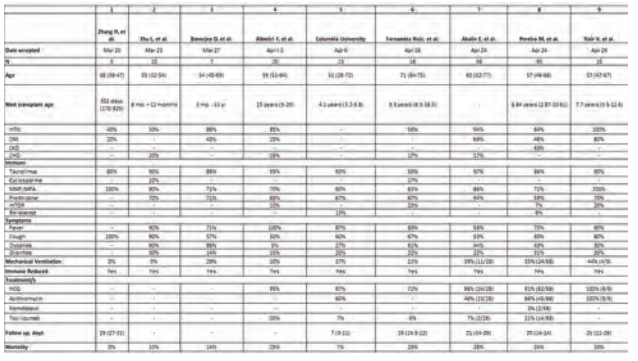
Background: Recent publications report great variations in the clinical course and mortality of COVID-19 in solid organ transplant (SOT) recipients. It is unclear whether these differences are related to study methods, treatment choices, or variables associated with patient populations.

Methods: We reviewed and summarized 9 published articles of COVID-19 in solid organ transplant recipients. We contrasted difference between study design and compared outcomes.

Results: All studies included kidney transplant recipients while study 6 and 8 included non-renal SOT. Four come from the United States. Results can be seen in the attached table. Most studies had a median age in the 50's, with hypertension and diabetes being common comorbidities. Tacrolimus, mycophenolate analogs and prednisone was the most common immunosuppression regimen. Presenting symptoms were usually fever, cough, dyspnea, and diarrhea. Immunosuppression was either reduced or discontinued in all studies. The majority of patients received hydroxychloroquine. Azithromycin, remdesevir, leronlimab, lopinavir/ritonavir, darunavir, oseltamivir, and tocilizumab were also used. Mortality ranged from 0% to 30%. All studies described hospitalized patients. A third of reports also included outpatients. The median follow up was approximately 3 weeks for most studies (range of 7 to 29 days). All but one series with reported patient deaths under 20% either did not include or had follow-up periods of less than 10 days.

Conclusions: Presentation of COVID-19 and immunosuppression strategies are similar among transplant centers. Differing outcomes may be related to small number of cases, potentially varying acuities of illness and follow up periods. Given that cytokine storm occurs late in the course of COVID-19, it is plausible that mortality may increase in studies with short follow up. When excluding short or missing follow up, mortality appears to be between 20-30%, which suggests that transplant recipients have a higher mortality than their non-immunocompromised peers.



PO0789

Thrombotic Microangiopathy (TMA) in a Patient with COVID-19

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Introduction: We describe a patient with COVID-19 and clinically significant kidney biopsy proven TMA

Case Description: 69-year-old Caucasian female with medical history of asthma came to the ED with productive cough, fever and dyspnea for 2 weeks. She was afebrile, tachypneic and hypoxic. Initial laboratories showed a normal WBC, hemoglobin level and platelet count. Inflammatory markers were elevated. SARS-CoV-2 infection was confirmed by PCR assay. CXR showed bilateral diffuse patchy opacities. Treated with hydroxychloroquine, enoxaparin and oxygen was started. Patient received anakinra and tocilizumab. On day 12, the patient developed thrombocytopenia, anemia and worsening kidney function concerning for microangiopathic hemolytic anemia. Due to worsening hypoxemia, patient received convalescent plasma. On day 17, she was intubated due to worsening respiratory failure. Findings suggestive of hemolysis were present. Urinalysis showed hematuria and proteinuria. Patient's kidney function worsened requiring initiation of CRRT. On day 20, the patient underwent a kidney biopsy that revealed severe acute TMA with cortical necrosis. Beta 2 glycoprotein-1 IgM levels were elevated, anti-phospholipid antibodies were absent. A disintegrin and ADAMTS13 level were not low. C3,C4 were in normal range. Heparin induced antibody testing was negative. Coagulation parameters were normal. Kidney doppler was unremarkable. No other systemic findings of macro thrombi were found. Low factor H complement antigen, elevated plasma CBb complement and plasma SC5b-9 complement levels suggesting an activation of the alternative complement pathway were found. Genetic testing was not done. Plasma exchange was not performed, but received a single dose of eculizumab on day 21. Unfortunately, she died on day 23.

Discussion: Coagulopathy associated with SARS-CoV-2 has been widely reported. Profound hypoxia, inflammation, disseminated intravascular coagulation(DIC) have all been implicated as potential causes, but were not present in our patient. To the best of our knowledge, we report the first case of TMA associated with SARS-CoV-2 with presence of diffuse cortical necrosis and widespread microthrombi in kidney biopsy. It is not clear if the virus played a direct pathogenic role or unmasked a latent complement defect leading to widespread endothelial damage and micro thrombi

PO0790

Renal Artery Thrombosis with Infarction in a Patient with Mild COVID-19

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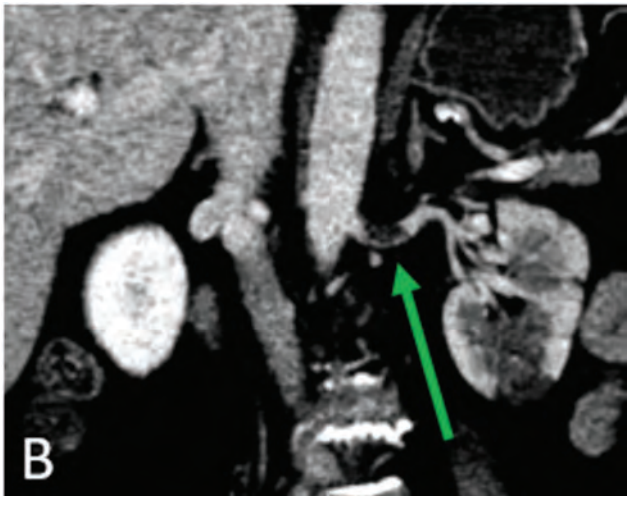
Introduction: There has been increased focus on the microvascular and macrovascular complications of COVID-19. Here we present a case of renal arterial thrombosis in a woman with mild symptoms of COVID-19.

Case Description: A 69 year old female with diabetes, hypertension, coronary artery disease, and acute embolic cerebrovascular event post cardiac catheterization in 2016 presented to the emergency department with acute diffuse intermittent abdominal pain and nonbloody emesis. Prior to this, she had been evaluated for cough, shortness of breath and myalgias which were conservatively managed with improvement. Her medications included aspirin, clopidogrel, furosemide, and insulin. Examination was significant for diffuse nonspecific abdominal tenderness without rebound or guarding. Laboratory assessment revealed preserved renal function with creatinine of 1.10 mg/dL and PCR positive for SARS-CoV-2. A computed tomography of the abdomen and pelvis with intravenous contrast revealed a non-occlusive thrombus in the left renal artery with several large wedge-shaped areas of decreased enhancement consistent with multiple left renal infarctions. On interdisciplinary discussion, the patient was managed conservatively with anticoagulation without acute intervention and was discharged home on apixaban.

Discussion: To our knowledge, this is the first description of renal artery thrombosis with renal infarction in the setting of COVID-19 infection. Patients who present with a COVID-19 infection, regardless of disease severity, should be evaluated for coagulopathy and development of thrombi as these may potentially contribute to infarction and end-organ damage. Although it requires a high index of suspicion, renal infarction should be considered part of the differential when evaluating a patient with COVID-19 infection presenting with abdominal pain or acute kidney injury. Initiation of anticoagulation should be considered with consideration of risks involved.



PO0791

A Case of Severe Thrombocytopenia in a Patient with COVID-19 Receiving Continuous Venovenous Hemodialysis

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Introduction: Thrombocytopenia is a rare complication of renal replacement therapy with most of the cases reported in intermittent hemodialysis patients. There is limited data regarding the incidence of thrombocytopenia caused by continuous renal replacement therapy (CRRT). We report a case of thrombocytopenia in patient treated with CRRT for severe AKI from COVID-19 sepsis unrelated to heparin.

Case Description: A 73-year female with history of type 2 diabetes mellitus was admitted for Coronavirus Disease 2019 (COVID-19) pneumonia. Patient developed acute hypoxic respiratory failure requiring mechanical ventilation despite treatment with hydroxychloroquine, azithromycin and convalescent plasma. Hospital course was complicated by septic shock and acute kidney injury with serum creatinine rising from a baseline of 0.8 mg/dl. Continuous veno-venous hemodialysis (CVVHD) without any anticoagulation was initiated due to severe fluid overload. Significant thrombocytopenia below 50,000/mm3 was noted 2 days after CVVHD treatment. Patient received multiple antibiotics and heparin drip before CVVHD and platelet counts were above 150,000/mm3. Heparin induced thrombocytopenia (HIT) was ruled out with negative serotonin release assay and platelet counts remain low despite the discontinuation of all potential agents. Disseminated intravascular coagulopathy was excluded based on coagulation tests. Platelet counts finally went up to 160,000/mm3 on subsequent CVVHD holidays and again dropped to 70,000/mm3 after CVVHD was resumed.

Discussion: The rate of rise in platelet count more than 150,000/mm3 in 2 days after cessation of CVVHD supports the diagnosis of thrombocytopenia caused by CVVHD. Although the exact mechanisms remain unclear, previous studies suggested that the mechanical destruction of platelets by the hemofilter or allergic reaction to dialyzer membrane as some of the reasons. Some studies have found that severe decline (more than 50%) in platelet count was associated with increased mortality and decreased rate of renal recovery. Thrombocytopenia on CVVHD unrelated to HIT is an under-acknowledged complication. Understanding the multiple etiologies of thrombocytopenia will help prevent the excessive use of blood products, fluid overload state and the potential clotting issue of CVVHD due to transfusion.

PO0792

Case Study: Kidney Transplant Patient with COVID-19: Impact of Viral Infection on Background Cell-Free DNA in a Donor-Derived Cell-Free DNA Rejection Assay

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Introduction: Donor-derived cell-free DNA (dd-cfDNA) assays are clinically validated to detect kidney transplant injury, reporting the donor fraction as a percentage of the total, or background, cfDNA. Various clinical factors can cause a significant increase in recipient cfDNA, contributing to higher background cfDNA and lower donor fraction, which may result in a false negative test result.

Case Description: A 50+ year old woman with end-stage renal disease secondary to polycystic kidney disease presented with 4 days (d) of diffuse muscle pain at 11 months post-kidney transplant. In the emergency department she had a fever to 101°F, bilateral infiltrates on chest x-ray, and a positive COVID-19 (SARS-CoV-2) test. She remained febrile for 3d before developing acute respiratory distress requiring oxygen supplementation; her creatinine level was 3 mg/dL. Due to worsening of her respiratory status, she was intubated and started empirically on vancomycin, meropenem, and azithromycin; mycophenolate mofetil was discontinued. She rapidly progressed to septic shock requiring vasopressor therapy. Her renal function deteriorated, and she was started on continuous renal replacement therapy on hospital d7. She received leronlimab on hospital d7 and d14 and convalescent plasma on hospital d11. Tacrolimus was discontinued on hospital d10 and she continued prednisone at 5 mg/d. Dd-cfDNA testing to assess allograft injury and to rule out active rejection was performed. At hospital d20, her dd-cfDNA was 0.07% with an elevated background cfDNA of 28,569 arbitrary units (AU, ~57X median value). At the second blood draw at hospital d25, her dd-cfDNA was 0.25% with a background cfDNA level reduced to 7,503 AU (~15X median value).

Discussion: In this case, infection with the SARS-CoV-2 virus was associated with a very elevated background cfDNA level, likely due to cellular apoptosis due to the immune process and/or tissue ischemia due to sepsis-associated hypoperfusion. Although this patient was not known to have active rejection of her allograft, the very high background levels complicate the interpretation of results, especially when donor fraction were reported.

PO0793

COVID-19 AKI to ESRD: A New Cohort of Dialysis-Dependent Patients

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Introduction: The Covid-19 pandemic has resulted in a massive number of hospitalizations with widespread effects on the global healthcare system. More research is needed to understand the implications of the disease, particularly its effects on renal function. Although initial studies from China suggested otherwise, there is growing evidence for an association between Covid-19 and AKI.

Case Description: A 66-year old man with history of CKD IIIb presented to the ED with fever and dry cough for several days. On admission the patient was febrile and tachypneic. Labs were showed elevations in BUN, SCr and inflammatory markers. Chest CT revealed bilateral ground glass opacities and NP swab was positive for SARS-CoV-2. The patient was initially treated with hydroxychloroquine, levofloxacin, and IV fluids. Clinical status worsened, eventually requiring intubation and vasopressors. Renal function progressed to anuria. Bicarbonate, potassium binders and loop diuretics were attempted to treat renal failure. On hospital day 4 the patient was placed on CRRT however he remained anuric. CRRT was complicated by clotting episodes managed with circuit anticoagulation with unfractionated heparin. The patient slowly improved, was extubated 17 days later, and transitioned to IHD. The patient underwent tunneled catheter placement and was discharged 30 days after admission and remains on IHD.

Discussion: It is theorized that renal impairment in Covid-19 is due to virus entry into host cells via the ACE-2 receptor present in lungs and kidneys. Post-mortem kidney biopsies suggest that renal damage in Covid-19 is mediated through multiple mechanisms including direct cytotoxicity, immunologic deposition, and microthrombi-related tubular damage. Although our patient recovered after a prolonged hospital course, he remained anuric requiring IHD far sooner than anticipated with natural progression of CKD, illustrating the unforeseen consequences of Covid-19 on healthcare resource utilization. Early use of CRRT may have a role as a therapeutic modality via inflammatory cytokine removal, however consideration must be made for future resource utilization including alternative RRT measures such as acute PD for critically ill patients as supplies dwindle. As the cases of Covid-19 increases, a higher number of patients may not see a return of renal function despite recovery and RRT resource management will need to be prioritized.

PO0794

Rhabdomyolysis as a Complication of COVID-19: A Report of Five Cases

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Introduction: COVID-19virus pandemia has caused more than 5million infected and 330thousand deaths worldwide. The incidence of acute kidney injury (AKI) is variable, from 0.5%to29.8%. Rhabdomyolysis(Rb) is a life-threatening emergency, usually manifesting as myalgia, fatigue, pigmenturia, and AKI. One of its leading non-traumatic causes are viral infections. We report 5cases of Rb associated with COVID-19.

Case Description: Of a total of 460 positive cases of COVID-19infection (real-timePCR), at the NationalMedicalCenter20deNoviembre in MexicoCity, 5were diagnosed with Rb and associated AKI(Ck>5,000U/l and KDIGO AKIcriteria). Characteristics of patients are presented in(Fig.1). Age range was from 29to64 years, only one female, all withBMI>25 kg/m2, time from admission-diagnosis of Rb was on average oneweek. Most common symptoms were fever, cough, and dyspnea(5/5), as well as abdominal pain(4/5). Only(1/5) was oliguric at diagnosis. Average Ck at diagnosis was7845 (18-165µg/L) and all cases had high levels of interleukin-6. They were managed with aggressive hydration, 2of them required renal replacement. At the time of this report, 2 had been discharged, 2 remain hospitalized(one still on RRT), and one died.

Discussion: COVID-19patients can develop AKIprimarily due to low oral intake, sepsis, andcytokine storm. Patients with COVID-19have multiple risk factors for Rb development: viral muscle cytotoxicity, continuous hyperthermia, andcytokine storm among others. This results in a high risk ofAKI via 3mechanisms: renal vasoconstriction, tubular obstruction and direct tubular toxicity. Of note, in the described cases, abdominal pain was a common symptom and only one was oliguric. Early identification allowed timely fluid resuscitation, which underscores the importance of having a high index of suspicion. Further observations will be needed to understand the full spectrum of association between COVID-19and Rb, but is clear that these patients are at highrisk for developing AKI by these mechanisms.

Table 1. Patient clinical and laboratory characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5
Clinical Characteristics					
Age (years)	45	56	29	44	64
Sex	Male	Male	Female	Male	Male
Comorbidities	Overweight	Hypertension Obesity	Overweight	Hypertension Diabetes	Overweight Hypertension
Time to Rhabdomyolysis diagnosis (days)	6	5	10	4	9
Signs and symptoms					
Fever	Yes	Yes	Yes	Yes	Yes
Dry cough	Yes	Yes	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes	Yes	Yes
Abdominal pain	No	Yes	Yes	Yes	Yes
Temperature (°c)	39	40	40	41	39
Urinary output > 0.5 (ml/kg/hr)	Yes	Yes	Yes	No	Yes
Laboratory characteristics					
Creatinine (0.7-1.2 mg/dL)*	0.86 / 1.6	0.5 / 2.3	0.6 / 1.8	0.9 / 3.3	0.9 / 2.8
Creatine kinase (18-164 U/L)*	26 / 5830	210 / 10852	20 / 6990	280 / 9553	130 / 6000
Myoglobin (0-140 µg/L)	500	900	711	1169	500
Interlukin-6 (0.5-4 pg/ml)	112	47	86	783	N/A
PO_2 (83-103 mmHg)	55	63	67	51	58

*At admission/ at Rhabdomyolysis diagnosis.

PO0795

Corticosteroid Treatment in a Case of COVID-19-Associated Collapsing FSGS

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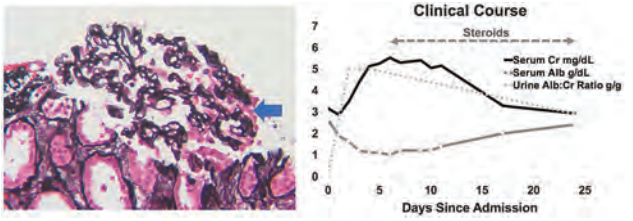
Introduction: Collapsing FSGS (cFSGS) is associated with viral infections including HIV, parvovirus B19 and CMV. Recent reports describe cFSGS in patients infected with coronavirus (COVID-19). While reports on idiopathic cFSGS suggest early institution of steroids improves renal outcomes, there are little data to guide treatment of cFSGS associated with infection. We present a case of AKI with severe abrupt nephrotic syndrome in a COVID-19 patient with cFSGS on biopsy and a rapid response to steroids.

Case Description: A 51 y/o black woman with no known medical history presented with 8 days of fever and SOB. COVID-19 testing was positive. Admission serum creatinine (sCr) was 3.2 mg/dL with an albumin of 2.6 g/dL. A urinalysis showed moderate blood and 3+ protein on dipstick along with granular casts. A urine albumin:Cr (UAC) ratio was 0.19 g/g. Despite volume resuscitation, her sCr continued to rise. Workup included negative HIV, hepatitis panel, and parvovirus B19. ANA, ANCA, anti-dsDNA, C3, and C4 were neg/nl. On day 5, she was afebrile with resolution of her symptoms, but sCr was further elevated at 5.3 mg/dL and albumin was 1.1 g/dL. Repeat UAC ratio was elevated over lab measurable range. A biopsy showed cFSGS and ATN. She was started on 60mg of prednisone/day. Two weeks later, her sCr was 2.9 mg/dL, albumin 2.4 g/dL and her UAC ratio was 3.0 g/g (Fig 1).

Discussion: The optimal treatment for viral related cFSGS is unknown. Because diffuse foot process effacement typically accompanies this lesion, it is tempting to give steroids. However, there is concern that this may exacerbate the infection, and cFSGS may improve along with clearance of the virus. Still, steroids may hasten recovery and reduce morbidity associated with the nephrotic syndrome. The rapid improvement in

proteinuria despite an increase in GFR suggests that steroids played a role in the recovery. A randomized trial would be necessary to determine the safety and efficacy of steroids for COVID-19 related cFSGS.



(Left) Jones stain highlighting collapse of glomerular tuft. Arrow pointing to the proliferation of visceral epithelial cells. (Right) Lab values: Admission to 2 weeks post discharge.

PO0796

Remote Peritoneal Dialysis Training in a COVID-19-Positive Patient

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Introduction: Training patients in peritoneal dialysis (PD) traditionally requires up to fourteen in-person clinic visits to cover all aspects of care. The COVID-19 crisis has created an unprecedented challenge in educating patients to perform PD safely while minimizing exposure to staff. Telemedicine has been well-received by staff and patients in other aspects of PD care. We present a case of a COVID-19 positive patient who was fully trained in PD using telemedicine.

Case Description: The patient is a 21-year-old man with VATER Syndrome who progressed to ESRD with uremic symptoms. He chose PD as his dialysis modality while awaiting a kidney transplant. Prior to his PD catheter insertion, he tested positive for COVID-19. He was deemed an ideal candidate for PD training via telemedicine and agreed to proceed. For the first two training sessions, he presented to the PD clinic and was placed in a designated isolation room with his personal computer. His PD nurse was in an adjoining room and trained him via video conferencing with the option to enter his room if needed. The patient quickly mastered the procedure in this monitored environment. He completed the remainder of the required education remotely in his home via telemedicine. Currently, he is fully trained and has initiated his full PD prescription.

Discussion: There are several advantages of telehealth in COVID-19 patients. The risk of viral exposure to healthcare staff and other patients is reduced by limiting trips to the PD clinic. Additionally, reducing the burden of travel saves time and expense for the patient. Patient selection for telehealth learning is critical: the ideal patient must be motivated and technologically savvy. The patient, PD nurse, and nephrologist must jointly determine whether proceeding with tele-learning is feasible and safe. Although remote videoconferencing is not the conventional or optimal method for PD education, it can be used successfully to train patients while minimizing exposure of COVID-19 to staff.

PO0797

Calciphylaxis and COVID-19-Associated Thrombotic Retiform Purpura in a Peritoneal Dialysis Patient

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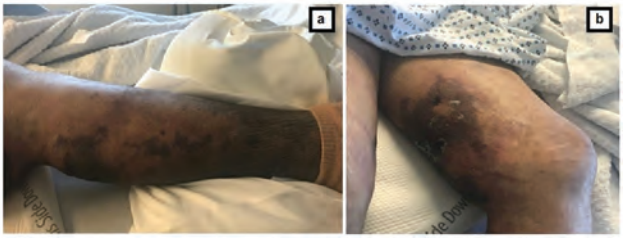
Introduction: The Coronavirus disease (COVID-19) pandemic has posed diagnostic and management challenges for nephrologists. We report an atypical manifestation of COVID-19 presenting as a case of Calciphylaxis and COVID-19 Associated Thrombotic Retiform Purpura in a peritoneal dialysis patient.

Case Description: A 62-year-old female presented to the emergency room with leg pain and edema for 4 weeks. She had recently been started on peritoneal dialysis. Examination revealed tender, indurated retiform dusky plaques on thighs and bilateral lower legs (Figure 1). Laboratory findings are summarised in Table1. Her SARS-COV-2-RT-PCR was positive. Imaging revealed no evidence of thrombosis. Skin biopsy showed severe ischemic dermopathy syndrome consistent with an overlap of COVID-associated thrombotic retiform purpura and calciphylaxis (Figure 2). The SARS-CoV-2 envelope protein was seen in endothelial cells within dermal blood vessels. The patient was transitioned to intermittent hemodialysis and started on intravenous sodium thiosulfate 25 grams three times weekly.

Discussion: In COVID-19 era, coagulation abnormalities are becoming increasingly evident. Management of calciphylaxis in PD patients is difficult under current circumstances due to limitations in the ability to provide regular infusions and multi-interventional care. We hypothesize that our patient had an underlying predisposition for calciphylaxis given risk factors of secondary hyperparathyroidism and an additional insult (COVID-19) caused a so-called "second hit" resulting in clinically apparent disease. Atypical presentations of COVID-19 due to a combination of procoagulant state, as well as any preexisting risk factors for calciphylaxis, must be kept in mind.

Table 1. Laboratory investigations

Sodium	122mmol/L
Potassium	2.9mmol/L
Chloride	79mmol/L
Blood urea nitrogen (BUN)	38 mg/dL
Creatinine	8.32mg/dL
Calcium, corrected	10.7mg/dL
Phosphorus	4.2mg/dL
Hemoglobin	10.7mg/dL
Hematocrit	32.3%
Platelets	217 x 103/uL
Alkaline phosphatase	140U/L
Parathyroid hormone (PTH)	1554pg/mL
Vitamin D 25 hydroxy (OH)	68.5ng/mL
Vitamin D 1,25 dihydroxy	79.7pg/mL
C-reactive protein	19mg/dL
Erythrocyte sedimentation rate	122
Creatine kinase	516 U/L
D dimer	953ng/mL
Lactate dehydrogenase	529U/L
Complements, C3 and C4	133mg/dL and 40.3mg/dL
HIV, Hepatitis B and C serologies	Negative



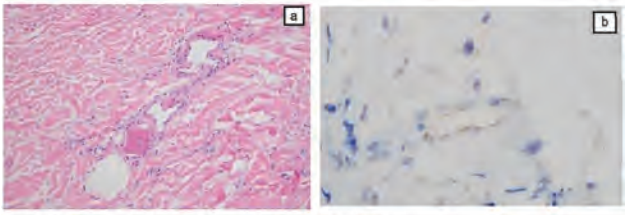


Figure 2. Skin biopsy showing severe ischemic dermopathy syndrome
(a): Illustrated is a dilated venule occluded with fibrin unaccompanied by a significant mural inflammatory cell infiltrate. A few background neutrophils secondary to ischemia are observed. (200X, hematoxylin and eosin).
(b): There is evidence of endocytosis of viral particles within the microvasculature of the dermis and subcutaneous fat. Illustrated is the SARS-CoV-2 envelope protein decorating the endothelium. There is, however, no evidence of active viral replication as revealed by the negative SARS-CoV-2 viral RNA studies(not illustrated). (1000X, Diaminobenzidine).

PO0798

Successful Recovery of COVID-19 Pneumonia in a Kidney Transplant Recipient with a Regimen Consisting of Favipiravir, Azithromycin, Nafamostat Mesylate (NM), and Intravenous Immunoglobulin (IVIg)

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Introduction: The SARS-CoV-2 virus has caused a worldwide pandemic of coronavirus disease 2019 (COVID-19) since end of 2019. Although COVID-19 has been widely reported, little is known about its impact on transplant recipients. We report a case of an interstitial pneumonia due to SARS-CoV-2 viral infection in a kidney transplant recipient. We also investigated how treatment of COVID-19 influenced the changes of lymphocyte subset and the number and activity of NK cells.

Case Description: This is a 49-year-old man who received kidney transplantation 13 months ago. His first clinical symptoms were of high fever, general fatigue, and myalgia. He had no complaints of cough nor shortness of breath, but his chest CT revealed interstitial pneumonia with SpO2 90 - 92 mmHg. Nasopharyngeal swab for SARS-CoV-2 RT-PCR assay was reported positive. He also showed acute kidney injury (AKI), whose serum creatinine level got elevated from 1.33 mg/dL to 1.67 mg/dL. We stopped tacrolimus and mycophenolate mofetil and continued low dose of methylprednisolone. The COVID-19 pneumonia and AKI were successfully treated with the regimen consisting of favipiravil, azithromycin, NM, and IVIg. On the 14th hospital day, the SARS-CoV-2 RT-PCR had become negative and simultaneously had acquired IgG antibody against SARS-CoV-2 virus. Regarding lymphocyte subset, the percentage of CD19^{+} B lymphocytes has been extremely low level because of administration of rituximab 13 months ago due to ABO-incompatible living related-donor kidney transplantation. On the day of admission, the total number of lymphocytes was only 482/μL and most of them were CD4^{+} lymphocytes and the number of NK cells were very few (6.8%). As the symptoms improved, the number and activity of NK cells increased and the proportion of CD4^{+} lymphocytes decreased.

Discussion: We successfully treated the patients with 4 off-label drugs against COVID-19, consisting of favipiravil, azithromycin, NM, and IVIg. Our current regimen seems to be successful, in particular, NM seems to block cytokine storm, thus preventing from serious illness, but a larger cohort of patients is required. Activation and expansion of NK cells are important in the treatment of COVID-19.

PO0799

Severe Hypernatremia as an Unintended Consequence of COVID-19-Related Social Distancing

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Introduction: COVID-19 is primarily a respiratory infection which can have adverse effects on multiple organ systems. There is limited information concerning the harmful effects of social distancing in patients with chronic illnesses who avoid seeking medical attention due to fear of contracting the novel COVID-19 disease.

Case Description: A 64-year-old African American female with a past history of HIV- related dementia and seizure disorder was residing with family members, requiring assistance with activities of daily living. She was ambulatory but needed assistance with hygiene and meals. The family reported that over the past 7-10 days, she had become less interactive, remaining bedbound and resisting oral intake. There was an initial reluctance to bring her to the Medical Center due to the fear of contracting COVID-19 infection, given her immune-suppressed status. Despite family efforts to provide social distancing and home care, mental status progressively worsened, prompting presentation to the emergency department. The patient had a GCS of 10. The patient was nonresponsive, did not follow commands, and only withdrew from noxious stimuli. Vital signs were prominent for fever 37.7° C and blood pressure was 94/64 mmHg. Pertinent laboratory results included: serum sodium, 201 mEq/L, plasma osmolality, 431 mOsm/kg, BUN 107 mg/dl, and creatinine of 4.8 mg/dL. CT head showed no acute intracranial pathology. Her condition required ICU care, including mechanical ventilation. COVID-19 screening was negative, while culture of lower respiratory secretions was positive for Staphylococcus aureus. With treatment of the respiratory infection and gradual hydration with 0.9 % sodium chloride solution which was shifted to Dextrose 5% after 3 days, the serum sodium concentration decreased to167 mEq/L. The patient was extubated and mental status gradually improved toward her baseline level. Serum sodium improved to 140 mEq/L and serum creatinine improved to 0.7 mg/dL over a 10 day period. The patient was subsequently transferred to a rehabilitation unit.

Discussion: Despite the pivotal role of social distancing in preventing the spread of the novel Coronavirus, reluctance in seeking medical attention can lead to serious and even life threatening consequences.

PO0800

Bilateral Renal Artery Thrombosis in a COVID-19 Patient with Anuric AKI

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Introduction: AKI is common in COVID-19. Hypercoagulability has been described. We present the case of a COVID-19 patient with anuric AKI who was found to have bilateral renal artery thrombosis (RAT) while on systemic anticoagulation.

Case Description: A 66-year-old woman with a past medical history of paroxysmal atrial fibrillation on apixaban (continued on admission), hypertension, and heart failure presented with 2 days of shortness of breath and a productive cough. She was found to be in hypoxic respiratory failure in the setting of COVID-19 pneumonia. Admission laboratory evaluation was significant for a white blood cell count of 36.8 x 10^3/mL, creatinine 6.04mg/dL, blood urea nitrogen 53mg/dL, lactate dehydrogenase 2,600U/L, and urine protein ≥ 500mg/dL. A renal ultrasound showed bilateral echogenic kidneys. She required initiation of hemodialysis then transitioned to peritoneal dialysis. Dialysis accesses and peritoneal fluid were complicated by bleeding with a subsequent drop in hemoglobin to 5.5g/dL (from 13.6g/dL, 48 hours prior). A contrast-enhanced CT angiogram of the abdomen and pelvis showed bilateral RAT, and thrombosis of the proximal celiac artery, with no evidence of acute arterial extravasation. She underwent bilateral renal artery aspiration thrombectomy and thrombolysis with stent placement in the right renal artery. Restoration of blood flow was achieved but she remained dialysis-dependent - her hemodynamic instability with continued blood loss may have played a role in this. A hypercoagulable work-up showed elevated prothrombin time, activated partial thromboplastin time, and INR. Fibrinogen was normal with an elevated fibrin degradation dimer, and low antithrombin III antigen, Protein C and S. These results are difficult to interpret in the setting of active anticoagulation and AKI

Discussion: We present a case of anuric AKI with bilateral RAT in a COVID-19 patient necessitating initiation of dialysis. Although her history of atrial fibrillation increases the risk of thromboembolic events, renal arteries are affected in only 2% of the cases. Complete occlusion and bilateral involvement is even rarer, moreover, our patient was on anticoagulation before and during the event. Given that COVID-19 can result in vascular injury and thromboembolic complications, assessing renal perfusion in oligoanuric COVID-19 patients with AKI may have merit.

PO0801

Severe Rhabdomyolysis in the Time of Coronavirus

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Introduction: Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has become a global pandemic with alarming numbers of morbidity and mortality. COVID-19 primarily presents as a lung infection, with symptoms of fever, cough, myalgia, and fatigue. The severity of the disease may range from a mild upper respiratory infection to severe pneumonia, ARDS, and death. This novel disease can also present with involvement of multiple organ systems including the kidneys. Acute kidney injury (AKI) has been reported in up to 37 % of cases. Here we report a case of a woman with COVID-19 presenting with rhabdomyolysis and AKI.

Case Description: A 48 y/o Hispanic woman with history of HTN, hyperlipidemia and DM type 2 who presented to the ED complaining of shortness of breath, fever, cough, and myalgias. Four days before presentation she had been diagnosed with COVID-19 and was self-isolating at home. Her symptoms worsened prompting her visit to the ED. Vital signs showed fever of 103.1 F, pulse 86, respirations 37, blood pressure 106/58 and O2 Sat 85% at room air, 95% with nasal canula at 4 L. PE was normal except for tachypnea and coarse breath sounds bilaterally on lung auscultation. Admission labs were remarkable for AKI and rhabdomyolysis. Serum creatinine was 3.61, BUN 83, and total CK 106,193. U/A with blood, 5-10 RBC, 5-10 WBC and many bacteria. FeNA was 0.3%. Toxicology panel was negative. Respiratory viral panel was negative. Influenza A and B are negative. She initially received 2 L bolus of IV NS and then continued with balanced crystalloid solutions for volume expansion over the next 3 days. She received treatment with hydroxychloroquine, azithromycin and ceftriaxone for COVID-19 pneumonia. Her symptoms improved and serum creatinine and CK gradually decreased until back to normal levels.

Discussion: Rhabdomyolysis can be seen associated with viral infections. We presented a patient with COVID-19 and rhabdomyolysis. There are no studies establishing a mechanism for COVID-19 induced rhabdomyolysis. Patients with COVID-19 pneumonia are generally kept with negative fluid balance to avoid overload and worsening of ARDS. On the other hand, volume expansion is mainstay management for rhabdomyolysis. Clinicians should have a high suspicion for rhabdomyolysis in patients with COVID-19 presenting with myalgias and AKI. Early recognition of and appropriate treatment is crucial to improve outcomes.

PO0802

Plasma Exchange in Critically Ill COVID-19 Patients

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Introduction: The spectrum of coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to respiratory failure and death of patients. Severely affected patients may develop a cytokine storm-like clinical syndrome with multi-organ failure and a mortality rate of up to 90%.

Case Description: Here we report on five COVID-19 patients with a median age of 67 years who were treated at the intensive care unit due to respiratory failure. Prophylactic antibiotic, antimycotic, and antiviral/immunomodulatory therapy was initiated in all patients upon admission. During the course of the disease, patients developed circulatory shock and persistent fever together with increased interleukin 6-levels compatible with the cytokine storm-like clinical syndrome. In addition, all patients had multi-organ failure with acute respiratory-distress syndrome (ARDS, 4 severe, 1 moderate) and acute kidney injury of at least KDIGO stage 2. A single PE with a median of 3.39 L of fresh frozen plasma was initiated in all patients followed by one additional treatment in patients 1, 3, and 5. During the PE, striking reduction of inflammatory markers C-reactive protein (-47%, P=0.0078) and interleukin 6 (-74%, P=0.0078), as well as significant reduction of ferritin (-49%, P=0.0078), LDH (-41%, P=0.0078), and D-Dimer (-47%, P=0.016) were observed. Due to circulatory shock, four patients received vasopressor treatment at the start of the PE that could be substantially reduced during treatment (-71%, P=0.031). Biochemical and clinical improvement continued over the following days together with an increase in the oxygenation index in 4 out of 5 patients. These improvements were achieved with only 1 to 2 PE, which might be a possible indication of a direct pathophysiological influence of PE on the COVID-19-associated cytokine storm-like clinical syndrome. Three of the 5 most critically ill patients are alive, while a 71-year-old male and a 76-year-old female patient died after the therapy was limited due to persistent severe ARDS.

Discussion: PE improved inflammation, microcirculatory clot formation, and hypotension, thereby improving clinical outcomes. Further studies to test whether (repeated) PE can alter the course of critically ill COVID-19 patients are clearly indicated.

PO0803

A Case of Severe Hyponatremia in a Patient with COVID-19

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Introduction: Hyponatremia is a common electrolyte disturbance seen in association with conditions such as malignancy and infections. In the recent literature, hyponatremia has been linked to SARS-CoV2 infection. To date, the most likely reported etiology of hyponatremia in setting of COVID-19 has been SIADH. We describe a severe case of hyponatremia, not due to SIADH, seen in a patient with COVID-19

Case Description: 49-year-old male with history of hypertension, hyperlipidemia, positive novel coronavirus nasopharyngeal swab done as outpatient, presented to the emergency department with fever, cough and dyspnea for a week. On admission, he was afebrile with respiratory rate of 18 and oxygen saturation of 84% on ambient air. His BP was not low, and heart rate ranged from 95-105 beats per minute. Pulmonary examination revealed rales bilaterally. Initial laboratory test showed serum sodium of 104 mEq/L and serum creatinine 0.58 mg/dL. Additionally, C-reactive protein was elevated to 7.19, serum ferritin elevated at 1798 and D-dimer was 158. CXR showed bilateral infiltrates. Serum osmolality was low at 217, and urine studies showed elevated urine osmolality (328) and low urine sodium (< 35), suggestive for diagnosis of hypotonic hyponatremia from volume depletion. He received treatment with 3% hypertonic saline with a subsequent

decrease in urine osmolality to 83. Serum sodium rapidly corrected to 118 requiring hypotonic fluids to manage overcorrection. Subsequently, serum sodium improved to a level of 133 mEq/L in the next 5 days after admission

Discussion: As the COVID-19 pandemic continues to evolve, cases of related hyponatremia in this setting are being reported, mostly SIADH being the underlying etiology. Various mechanisms for SIADH development, including cytokine storm, and hypoxic pulmonary vasoconstriction have been postulated, however, the common aspect of volume depleted state in setting of viral infection, leading to appropriate ADH release should not be forgotten

PO0804

Extracorporeal Cytokine Reduction Using Oxiris Blood Purification in COVID-19

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Introduction: Severe COVID-19 infection can cause "cytokine storm" and end-organ dysfunction. OXIRIS, a blood-purification filter, was recently approved by the FDA under emergency use authorization for this indication due to its ability to remove cytokines and endotoxin through its AN-69ST membrane. We describe our experience with the first two cases treated at our institution.

Case Description: Case 1: 58 year-old female patient with a baseline creatinine of 0.8 mg/dL & history of hemoglobin SC disease was admitted with respiratory failure due to COVID-19 infection. She deteriorated on hospital day (HD) 6 and was intubated. She received broad-spectrum antibiotics and convalescent plasma. On HD 15 she had increasing vasopressor requirement, anuric AKI and was started on continuous renal replacement therapy (CRRT). Due to worsening clinical status on HD18 she was started on the OXIRIS hemofilter through the CRRT circuit for 48 hours. Oxygenation improved and there was some improvement in inflammatory markers (IM) (table 1), however, the family withdrew care on HD 20. Case 2: 29-year-old male with no prior past medical history apart from morbid obesity presented with fever and dry cough in the setting of recent COVID-19 exposure. He was found to be COVID-19 positive and rapidly deteriorated with resultant intubation on HD4. He received hydroxychloroquine, doxycycline, remdesivir and convalescent plasma. OXIRIS hemoperfusion was initiated on HD8 due to worsening hypoxia despite high FiO2. Oxygenation improved by HD10 (table 1) and he was successfully extubated on HD16.

Discussion: We present our first 2 cases using the OXIRIS hemofilter. We treated the patients for 48 hours with a scheduled filter exchange at 24 hours. We used a blood flow of 250 ml/min and dialysate flow of 25 ml/kg/hour with either systemic heparin or regional citrate anticoagulation along with 1L/hr of pre-filter saline. For hemoperfusion we used the same parameters without dialysate. We observed rapid improvements in oxygenation (Figure 1). The findings are hypothesis generating though more data is needed to determine optimal timing and efficacy of this filter.

Table 1. Inflammatory and Respiratory Parameters.

	Case 1			Case 2		
	Pre	Mid	Post	Pre	Mid	Post
Hospital (ICU) day	19 (14)	20 (15)	21 (16)	9 (5)	10 (6)	11 (7)
Prone	No	No	No	No	No	No
CRP	10.5	12.2	28.6	11	5.5	3.6
Ferritin	12639	10623	8156	359	328	304
D Dimer	7.73	14.37		2.34	2.68	2.5
Endotoxin	0.63		0.62	0.7	0.45	0.36
IL 6	36.1		57.2	15.6		21.9
CD-4/ CD8	1.75 (263S/150B)			2.53 (374/148)		2.780 (395/142)
Pa/FIO2 Ratio	68	90		75		
FiO2	100	70	60	60	45	50
PEEP	12	12	12	22	22	22

PO0805

Rhabdomyolysis as a Late Complication of COVID-19 Infection

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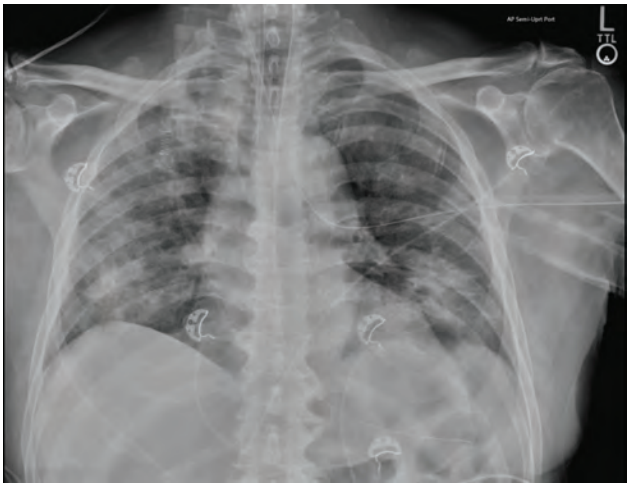
Introduction: The 2019 novel Coronavirus (COVID-19) is a betacoronavirus which typically presents with fever, cough, myalgia, and fatigue and can be associated with acute kidney injury (AKI). Recently, several cases of rhabdomyolysis (with and without AKI) have been reported with COVID-19 infection. We present a case of a patient with COVID-19 infection who developed rhabdomyolysis on hospital day 22.

Case Description: A 74-year-old man presented with several weeks of progressive malaise, dyspnea, fatigue, and nausea. He was hypoxic to 87%, febrile (38.8 C) and had diffuse bilateral infiltrates on chest x-ray [Figure 1]. He was intubated on hospital day 1. Testing for COVID-19 by PCR was positive. Creatinine improved from 1.6 to 0.9 mg/dL with 2L of IV fluids. He did not require vasopressors. On hospital day 22, while still intubated, his creatinine increased from 1.4 to 3.8 mg/dL. The level of creatinine phosphokinase (CPK) had was 7393 U/L from 118U/L on admission, and his plasma free myoglobin was 34,640 mcg/L. Urinalysis was positive for 3+ occult blood, few red blood cells, and many granular casts. His serum creatinine peaked at 6.67 mg/dL on hospital day 26 and subsequently declined to 1.6 by hospital day 33.

Discussion: Rhabdomyolysis is an infrequent complication of COVID-19 infection. When observed, rhabdomyolysis is typically present on admission. This is, to our knowledge, the latest that rhabdoymyolysis has been observed in COVID infection. The patient's inflammatory markers were not re-checked at the time of this event, though worsening inflammation may have provoked this event. Their troponin was mildly elevated; a TTE was not performed. No bed sores were observed, and the patient had no access to illicit substances. No medications known to cause rhabdomyolysis were given prior to this development. This case report suggests that rhabdomyolysis-related AKI may be a late complication of COVID-19 infection.



Chest XR

PO0806

Collapsing FSGS in COVID-19

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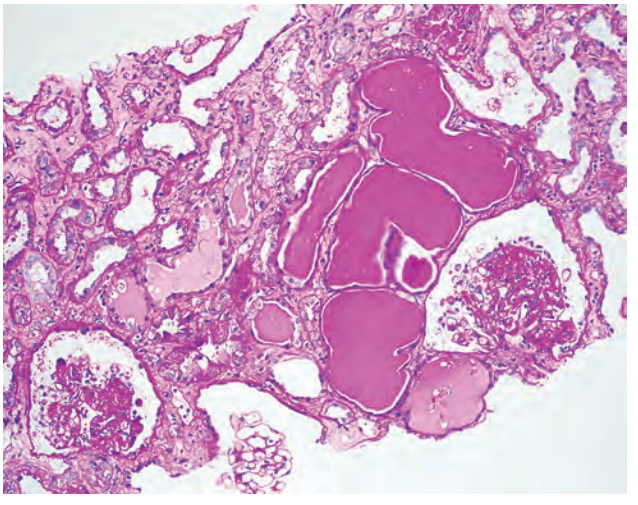
Introduction: The pandemic of novel coronavirus disease (COVID-19) has been complicated by high incidences of acute kidney injury (AKI). A virus-associated focal segmental glomerulosclerosis (FSGS) has been reported. We present a case of collapsing FSGS in a patient with severe acute respiratory syndrome coronavirus 2.

Case Description: A 56-year-old African-American (AA) man with hyperlipidemia and new diagnosis of COVID-19 the week prior, was admitted for vomiting, abdominal pain, and non-oliguric AKI with creatinine (Cr) of 4.97 mg/dL. Labs done within the year showed Cr of 1.1 mg/dL and microalbuminuria of 44 mcg/mg. An ER visit 3 days prior for fever and cough revealed a serum Cr of 1.47 mg/dL. CT abdomen/pelvis with IV contrast showed no obstruction. Urinalysis showed +2 protein and 2 RBCs/hpf. A 24-hour urine protein showed proteinuria of 15 grams. HIV and drug screen was negative. Renal biopsy showed FSGS with collapsing features, no cellular crescents, and severe acute tubular injury. Electron microscopy did not show viral particles. Two months later, the patient remained on hemodialysis.

Discussion: A challenge facing this pandemic is lack of knowledge of the pathology of COVID-19. Reports from post-mortem renal biopsies in China showed the majority were due to acute tubular injury with only 2 of 26 cases due to FSGS, none of the collapsing variant. However, there are at least 5 reports in the literature of COVID-19 complicated by de novo collapsing FSGS in patients of African descent, of which 2 tested positive for the *APOL1* genotype. The collapsing variant of FSGS is known to occur more commonly in AA patients, who are high risk for *APOL1* genotype. In viral infections, this genotype can be upregulated and promote development of FSGS. Although not directly tested, it cannot be excluded as a predisposing factor in our patient. In patients with COVID-19 and proteinuric AKI, especially in African-Americans, collapsing FSGS should be considered.



Renal Biopsy

PO0807

Attenuation of Circuit Longevity in COVID-19 Critical Illness with AKI on Continuous Venovenous Hemodiafiltration Despite the Use of Regional Citrate Anticoagulation (RCA) and Heparin-Bonded AN 69 (Oxiris®) Filter

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Introduction: Critical illness in SARS-CoV-2 (COVID-19) infection can result in acute kidney injury (AKI). Continuous renal replacement therapy (CRRT) is part of the overall supportive ICU management.

Case Description: CRRT was delivered as Continuous Veno-venous Haemodiafiltration (CVVHDF) using the Prismaflex (Baxter Inc.) system with heparin-bonded AN69 filter (oXiris®). The filters were electively changed every 12 hours for first 5 days to augment cytokine adsorptive capacity. Regional citrate anticoagulation (RCA) was used to ensure filter longevity. Initial citrate dose was prescribed at 3.0 mmol/L. All 3 consecutive patients were male aged 66.7 ± 6.02 years. APACHE II score was 32.7 ± 6.51 and predicted mortality was 71%. Mean initial creatinine was 264.7 µmol/L, and urine output was 6.7 mL/hour. All patients were on vasopressor support, broad spectrum antimicrobials and mechanical ventilation. 30 oXiris filters were studied in the 3 patients. 6/30 (20%) filters clotted spontaneously before scheduled change. Mean filter lifespan (24/30) was 689.6 ± 42.3 min before elective change. For the filters that clotted, mean circuit longevity was 515.7 ± 126.2 min. The observed difference was significant, p = 0.002. Importantly, filter clotting occurred despite adequate citrate dose of 3.0 mmol/L and mean post-filter ionized calcium of 0.34 ± 0.06 mmol/L. Vascular access issues were excluded by review of access, return pressures. Citrate dose was increased to 3.2 mmol/ L for all patients and this reduced the frequency of filter clotting subsequently. Two patients were extubated and had full renal recovery - mean duration of CRRT dependence was 9.5 days. However, the third patient remained CRRT dependent until demise on the 28th day of ICU stay.

Discussion: Attenuation of circuit lifespan was observed despite adequately dosed RCA and heparin bonded oXiris filters. We theorize that this could be due to a pro-coagulant state induced by the SARS-CoV-2 infection. Possibly, higher citrate dose to target even lower post-filter ionized calcium may be required to optimise anticoagulation and filter lifespan, thereby ensuring optimal effluent dose and solute clearance, for critically ill COVID-19 patients.

PO0808

SARS-CoV-2 Infection in the Early Post-Transplant Period After a Living Donor Kidney Transplant

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Introduction: Coronavirus disease 2019 (COVID-19) pandemic presented multiple challenges for living and deceased donor kidney transplant programs with the likelihood of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report the course of COVID-19 and immunosuppression within 3 months of living donor kidney transplant (LDKT) which has not been described previously.

Case Description: Three LDKT recipients developed COVID-19 in the early post-transplant period and were detected positive for SARS-CoV-2 at day 7, day 19 and 2 months post-transplant. Patients 1 and 2 had received 1 mg/kg of anti-thymocyte globulin (ATG) as induction and patient 3 had received no induction at the time of transplant. Patients 1 and 2 had minimal symptoms at diagnosis, whereas patient 3 had high grade fever, cough and shortness of breath. All 3 patients had lymphopenia at diagnosis and none required supplemental oxygen or intensive care unit monitoring. All 3 patients received azithromycin and hydroxychloroquine. Mycophenolate mofetil dose was reduced in patient 1 and was stopped in patients 2 and 3. Patient 3 developed acute kidney injury with a peak serum creatinine of 2.4 mg/dL, whereas other 2 patients did not develop kidney allograft dysfunction. All 3 patients recovered from SARS-CoV-2 infection with normal renal function at discharge.

Discussion: Limited experience of SARS-CoV-2 infection in early post-transplant period is available in deceased donor kidney transplant (DDKT) with serious morbidity and mortality implications. Lymphopenia described in patients with severe illness due to SARS-CoV-2 can be aggravated by recently used higher dose of lymphocyte depleting agent, especially to cover for delayed graft function in DDKT. As compared to previously reported cases of DDKT, our relatively young recipients of LDKT had a milder course, minimal complications and recovered from SARS-CoV-2 infection. We suggest consideration of recipient age, pretransplant isolation and using induction agent basiliximab or lower dose of ATG for a LDKT program during COVID-19 pandemic.

PO0809

COVID-19-Related Collapsing Focal Segmental Glomerulosclerosis and Apolipoprotein L1: A Report of Two Cases

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Introduction: Acute kidney injury has been seen in approximately 15% of the patient with COVID-19 infection. Acute tubular injury was presumed to be the most common cause of AKI, but it did not explain significant proteinuria and hematuria. We present the case report of 2 patients with collapsing focal segmental glomerulopathy with COVID-19.

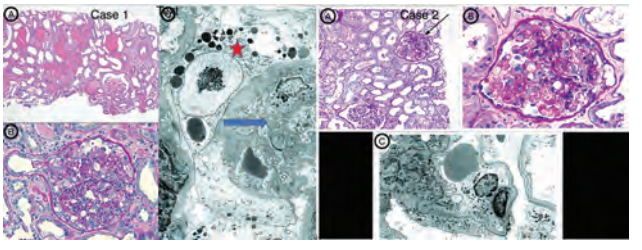
Case Description: Case 1, a 28 years old African American female and Case 2, a 58 years old African American male with baseline CKD III, admiited with COVID-19 infection and had acute kidney injury with significant proteinuria with hypoalbuminemia. Patients had kidney biopsies. Please see table for all the details.

Discussion: Possible etiologies of acute kidney injury in COVID 19 are tubular injury due to cytokine storm, direct cytopathic effect and immune mediated glomerulonephritis. Both the patients had collapsing FSGS in addition to tubular injury suggesting injury to the podocytes. Viral particles were not seen on both the biopsies, and hence direct cytopathic effect was not considered to be the mechanism of renal injury, although viral level below the detection threshold could not be excluded. Collapsing FSGS has been seen with other viral infections including Parvo-virus infection, Cytomegalovirus infection and HIV. Variant of apolipoprotein L1 (APOL1) gene in African Americans have been shown to be associated with FSGS. These two patients had genetic susceptibility due to APOL1 and COVID infection caused interferon surge leading to a second hit. Teaching Points: Renal biopsy should be consedered in patients with COVID-19 and Nephrotic range proteinuria. APOL1 testing should be done in patients with African American descent.

Demographic, clinical, laboratory, biopsy findings and follow up.

Patient No.	Age/Sex/Race	Onset of AKI	Risk Factors	Urinary findings	Chemistry	serology	Renal biopsy	APOL1	50 day follow up
1	28 Years Female AAa	7 days after the onset of fever	Asthma, Obesity	Proteinuria 2 grams on spot UPCRb No hematuria No eosinophils No casts	Cr: 0.9 to 8.05 mg/dl Albumin 3.3 to 1.3 g/dl Mild transaminitis Mild Rhabdomyolysis CRPd 15.7 mg/dl	Complements normal. Hepatitis B/C serologies negative. HIVe PCR negative.	LMf: Tubular injury ++. Collapsing FSGS. Mild IFTA IFg: No IF pattern EMh: No immune deposits Global podocyte foot process effacement.	Homozygous for G1 allele	Patient is off dialysis, but renal functions are not at baseline
2	56 years Male AA	7-10 days after the onset of fever	CKD 3 HTN, Obesity	Proteinuria 20 grams on UPCR, No hematuria No eosinophils No casts	Cr: 3.37 to 7.72 mg/dl Albumin 2 to 0.8 g/dl Mild transaminitis Mild Rhabdomyolysis CRP 9.0 mg/dl	Complements normal. Hepatitis B/C semologies negative. HIV PCR negative.	LM: Tubular injury ++. Collapsing FSGS. Mild IFTA IF: No IF pattern EM: No immune deposits Global podocyte foot process effacement.	Heterozygous for G1 and G2 alleles	Patient is off dialysis, but renal functions are not at baseline

a. AA: African American; b. UPCR: urine protein to creatinine ratio; c. Cr: Creatinine; d. CRP: C-reactive protein; e. HIV: Human immunodeficiency virus; f. LM: Light microscopy; g. IF: Immunofluorescence; h. EM: Electron microscopy.



PO0810

Diagnosing Vasculitis in the Era of COVID-19: A Diagnostic Dilemma for House Staff Officers

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Introduction: During our current pandemic, physicians must exclude COVID-19 in every patient presenting to the hospital with a febrile illness. However, every patient should have a complete work-up done to not miss other disease processes. Here we describe a case of microscopic polyangiitis with symptoms mimicking COVID-19.

Case Description: The patient is a 69 yo female with history of HTN who presented with four weeks of polyarthralgia and fevers; this was accompanied by a dry cough and morning stiffness in her shoulders and hips, for which she heavily used ibuprofen. Vital signs were within normal limits. Physical exam showed clear breath sounds with 2+ pitting edema in the lower legs and no rashes. Labs reveled a WBC of 20,000 cells/ microliter, with creatinine of 2.29 mg/dL, bicarbonate of 17 mmol/L, and C-reactive peptide of 204 mg/L. UA showed moderate leukocyte esterase, trace protein, and large blood. Serum C3 and C4 levels were normal, and a spot urine/protein ratio was 600 mg. Urine microscopy had several non-dysmorphic RBCs with occasional RBC and WBC casts. Infectious work-up via COVID-19 screening, blood cultures, hepatitis, and HIV was negative. The patient's creatinine trended up, peaking at 2.8 mg/dL. She was started on empiric solumedrol at a dose of 60 mg TID for possibilities of polymyalgia rheumatica or vasculitis or NSAID-induced acute interstitial nephritis. She had a positive MPO ANCA with titer of 1:320. Kidney biopsy confirmed pauci-immune crescentic glomerulonephritis, with clinical diagnosis of microscopic polyangiitis. She was placed on prednisone 40 mg daily and rituximab 375 mg/m 2 weekly for four weeks and was discharged home in stable condition.

Discussion: Systemic vasculitis remains to be a diagnostic challenge, especially in the era of COVID-19, given the overlap in symptoms. The diagnosis is made via clinical history and histopathological findings coupled with positive ANCA. Despite treatment, almost a quarter of these patients will progress to ESRD. In the era of COVID-19, great care must be taken to diagnose the kidney manifestations of systemic vasculitis.

PO0811

Low-Sodium Disorders and the 2019 Novel Coronavirus Disease (COVID-19)

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Introduction: COVID-19 have been well characterized with hallmarks of pneumonia and respiratory failure. Hyponatremia is a well reported finding in patients with pneumonia. However only few reports of sodium disorders have been directly attributable to the disease. We report three different presentations of hyponatremia in COVID19 patients.

Case Description: 1. 70 year old man with hypertension, diabetes presented with dyspnea. He was clinically euvolemic. Chest X-ray (CXR) showed bilateral interstitial and airspace opacities. Laboratory data revealed, serum sodium 122 meq/L, serum osmolality 264 mosm/kg, urine osmolality 579 mosm/kg and urine sodium 153 mmol/L. A diagnosis of hyponatremia secondary to the Syndrome of inappropriate Antidiuretic Hormone (SIADH) was made and the patient was treated with oral urea and fluid restriction. 2. 50 year old man with chronic alcohol abuse presented with bilateral calf soreness. CXR revealed increased interstitial markings. Laboratory data showed serum sodium 113 meq/L, serum osmolality 251 mosm/kg, urine osmolality 426 mosm/kg and urine sodium 14 mmol/L. Hyponatremia was attributed to a low solute state. Serum sodium improved with normal saline infusion. 3. 69 year old female with hypertension admitted with vomiting and diarrhea. CXR showed diffuse pulmonary infiltrates. Initial laboratory data revealed serum sodium of 126 meq/L, serum osmolality 260 mosm/kg. Serum sodium recovered as diarrhea resolved. However, eight days after starting therapy with Selinexor, a nuclear transport inhibitor, serum Na declined to 128 meq/L, serum osmolality 275 mosm/kg, urine sodium 29 mmol/L, urine osmolality 372 mosm/Kg. SIADH was attributed to Selinexor therapy. Sodium improved with oral sodium chloride therapy and fluid restriction

Discussion: Incidence of Hyponatremia due to SIADH in community acquired penumonia is 8-31% in adult patients. To the best of our knowledge, there have only been two case reports of SIADH in COVID-19 disease from Switzerland. Hence, it is unclear if SIADH is the predominant presentation of hyponatremia with COVID-19. The etiology of hyponatremia could be multifactorial as seen in the cases above. Clinical assessment of volume status and urine studies including osmolality and sodium with a thorough review of medications is the key to differentiate causes of hyponatremia and determining adequate management.

PO0812

COVID-19 Short-Term Outcomes of AKI and Chronic Hemodialysis

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Introduction: Acute kidney injury (AKI), albuminuria and hematuria are common and increase mortality in Covid-19 in addition to viral pneumonia, hypercoagulability and hyperinflammation. We present short-term outcomes of 21 Covid-19 patients with AKI and CRRT and the clinical course of 40 chronic hemodialysis (HD) patients with Covid-19.

Case Description: Twenty-one non-CKD Covid-19 infected patients with AKI required mechanical ventilation and CRRT at the ICU, 20 were males, average age was 59.7 years (y), average BMI 29 kg/m2, 33 % had diabetes. The typical scenario was a normal/slightly elevated creatinine level at admission, normalizing after iv fluids, but rising creatinine from day 3-4 and start of CRRT on day 8 (median). Urine analysis was available in eight patients, of which seven had albuminuria and/or hematuria. So far eight patients (38 %) have died. Dialysis has been discontinued in nine patients (43 %), median time 17 days in dialysis (range 1-35 days), follow up of 1-4 weeks. Patients 3-4 weeks after CRRT discontinuation have a creatinine level of 50-161 μmol/L (ref < 90-100 μmol/L). Four patients are still dialysis dependent (median time in dialysis 7-22 days). Forty out of 520 patients on chronic HD in Stockholm had symptomatic Covid-19 in March-April 2020, of these 24 patients (60 %) required hospitalization, 16 patients (40%) did not. Nine patients died (22,5 %), of whom eight were men. The average age (78 y) was significantly higher (p = 0.003) and median time in dialysis (11.5 y) was longer (p = 0.01) in the non-survivors compared to the survivors. CRP at admission was significantly higher in the non-survivors (p=0.0003), but there were no differences regarding prior cardiovascular disease or diabetes (56 vs 55 %). Only three patients had a BMI > 30 kg/m2. Among survivors, the number of patients with ACE inhibitor/ARB treatment did not differ from non-survivors (p = 0.08), 13 out of 15 patients continued their treatment, without more serious disease.

Discussion: The AKI mortality in Covid-19 with CRRT is high, but a substantial number of patients have survived and recovered kidney function although follow-up for long-term CKD prognosis is important. Fewer chronic HD patients than expected suffered severe disease, however patients older than 70 y in combination with longer time (> 10 y) in HD and high CRP at admission were at a higher risk of dying from symptomatic Covid-19.

PO0813

ANCA-Associated Vasculitis Under a COVID-19 Mask

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Introduction: Ground glass opacities (GGO) on CT scan are the hallmark of COVID-19. GGO can also be seen in ANCA-associated lung injury. Additionally, both can present with kidney injury. We report a case of presumed COVID-19 with AKI which was actually severe ANCA-associated vasculitis.

Case Description: A 74-year old female with a history of hypertension and diabetes, who presented with a week of chills, cough, dyspnea, and watery diarrhea, and a creatinine of 10.2 mg/dl (baseline creatinine 1.02 mg/dl). A month prior to admission, she was treated for presumed bacterial conjunctivitis, followed by otitis media, and then bacterial sinusitis with oral ciprofloxacin. Despite a negative swab, she was admitted with suspicion of COVID-19 given GGO seen on CT scan and an exposure history at her senior home. She was treated per the COVID-19 protocol: IV methylprednisolone 125mg, azithromycin, and ceftriaxone. She had microscopic hematuria and 4 grams of proteinuria. ATN was suspected as urine microscopy showed granular casts and no dysmorphic RBC or cellular/WBC/RBC casts. After a repeat negative swab and improvement in respiratory symptoms yet worsening renal function requiring hemodialysis, a full serologic workup was performed. Positive results include p-ANCA (1:320), MPO (49), and ANA (1:160 homogeneous) without hypocomplementemia. Other autoimmune markers including anti-GBM antibody were negative. A kidney biopsy was performed and showed pauci-immune crescentic glomerulonephritis (GN) with cellular crescents in more than 80% of the glomeruli with minimal interstitial fibrosis and tubular atrophy. Given the frailty of this patient, she was treated with oral prednisone and rituximab instead of cyclophosphamide. She remained on intermittent hemodialysis and tolerated the treatment well.

Discussion: This case emphasizes the importance of detecting pulmonary-renal syndrome in the time of COVID-19. Given the current global pandemic and a high volume of infected patients coupled with the lack of sensitivity of the SARS-CoV-2 assays, it is possible to miss this relatively rare ANCA-associated vasculitis. Patient with rapid proliferative GN feature and lung symptoms should be further worked up to avoid missing an ANCA-associated vasculitis. COVID-19 may actually provoke ANCA-associated vasculitis and further testing is underway.

PO0814

Antineutrophil Cytoplasmic Antibody (ANCA) Vasculitis with Glomerulonephritis in COVID-19

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Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it inflicts, coronavirus disease 2019 (COVID-19), has become a global pandemic in 2020. To date, only one case of ANCA associated vasculitis (AAV) with COVID-19 has been reported from Iran. We describe the first two cases of AAV and glomerulonephritis in the United States.

Case Description: Case one: 64 year old African American male with a distant (> 10years) history of cryptogenic organizing pneumonia presented to the hospital with hypoxic respiratory failure secondary to COVID19. He had an acute kidney injury(AKI) with elevated creatinine(Cr) of 7.87mg/dL. Urinalysis revealed active sediment with 55 RBC/hpf, 65 WBC/hpf, and nephrotic range proteinuria: 5 gm/gm of creatinine. He was initiated on renal replacement therapy and received convalescent plasma along with Tocilizumab for the treatment of COVID-19. Serologic testing revealed a positive perinuclear (p)-ANCA (1:320), myeloperoxidase (32.5). Kidney biopsy was consistent with a pauci immune glomerulonephritis; cellular crescent present in 40% of glomeruli. He received pulse dose steroids and Rituximab. The patient had a good clinical response and was able to discontinue hemodialysis and serum Cr decreased to 3.5mg/dL. Case Two: 46 year old South Asian male presented with rash from leukocytoclastic vasculitis and was diagnosed with COVID-19. He had an AKI, serum Cr peaked at 4.0mg/dL with proteinuria, leukocyturia, and microhematuria on urinalysis. Cytoplasmic(c)-ANCA and proteinase-3(PR-3) were positive. A kidney biopsy was performed which revealed a necrotizing glomerulonephritis. He was treated with steroids and Rituximab with a positive response, Cr decreased to 2.0mg/dL.

Discussion: It is now well known that SARS-CoV-2 affects organs outside of the respiratory system, with the kidneys being a usual target. The most commonly reported presentation of COVID-19 and the kidneys is AKI, the etiology of which is predominantly acute tubular necrosis (ATN). Collapsing GN is by far the most described glomerular lesion. Clinicians should be aware of AAV with GN as another potential pathology, and concurrent use of immunosuppression with treatment of infection, can lead to favorable clinical outcomes.

PO0815

Hemodialysis Refractory Hyperkalemia in a Case of SARS-CoV-2 Infection

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Introduction: Severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) is a newly identified virus that affects respiratory tract with varying severity. Renal disease is not uncommon, but the etiology is multifactorial and still not well understood. We present a case of hemodialysis refractory hyperkalemia in a patient with SARS-CoV-2 infection.

Case Description: 56-year-old African American male with past medical history of hypertension presented with cough, dyspnea and fever. On admission, he had a temperature of 104F, BP of 149/90 mmHg, HR of 104 bpm, and oxygen saturation of 92%. Physical examination was remarkable for diminished and diffuse coarse breath sounds. Lab work-up showed serum creatinine of 2.99 mg/dl (baseline 1.19 mg/dl) with an estimated GFR of 26 ml/min. Urinalysis revealed protein > 500 mg/dl, RBC 25, and presence of coarse granular casts. Urine protein-creatinine ratio was 3.2. Serology was negative for ANA, ANCA, and anti-proteinase antibodies, as well as hepatitis and HIV panels. Serum C3 and C4 levels were within normal limits. Viral PCR of nasopharyngeal aspirate was positive for SARS- CoV-2. Home medications lisinopril and hydrochlorothiazide were held on admission, and he was started on intravenous fluids, azithromycin, and hydroxychloroquine. On day 4, serum creatinine trended up to 3.29 mg/dl and potassium was 4 mmol/L but since the patient was oliguric, hemodialysis (HD) was started. Serum creatinine then trended to a high of 15 mg/dl, urea nitrogen to 102 mg/dl and serum potassium level to 6.9 mmol/L despite multiple HD sessions. Meanwhile, his oxygen requirement also increased to 15L. After 10 days of daily HD sessions, serum potassium came down to 4.3 mmol/L but he ultimately required HD post discharge.

Discussion: Previous literature has discussed SARS-CoV-2 association with effects on ACE2 of RAS and proximal tubular cells causing hypokalemia. To the best of our knowledge this would be the first documented case of hemodialysis refractory hyperkalemia seen with SARS-CoV-2 infection. One of the mechanisms for kidney injury is a direct viral induced cytopathic effect, which we believe held true for our patient. As viremia cleared, the kidney function improved though it did not return to baseline. In our case, development of hyperkalemia despite hemodialysis makes it more interesting, but it remains unclear how.

PO0816

Rhabdomyolysis in COVID-19 Patient Requiring RRT

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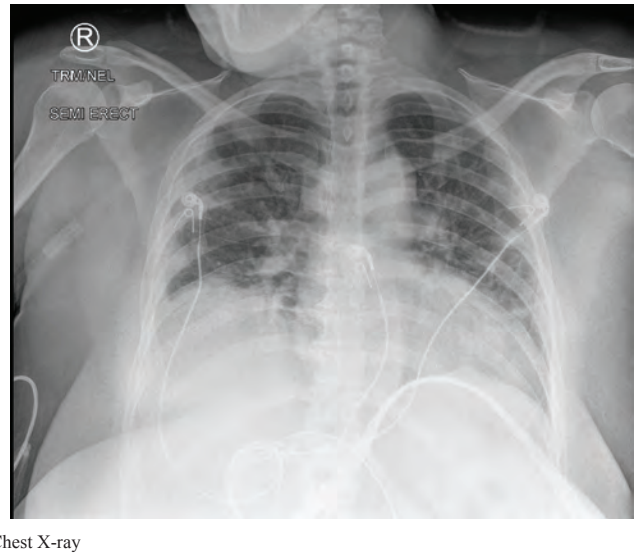
Introduction: Rhabdomyolysis is characterized by the release of intracellular muscle contents into the circulation. Of the 1099 patients affected by Covid-19 in China, only 0.2% had rhabdomyolysis.

Case Description: A 52 year old African American female with past medical history of Diabetes and hypertension presented to the ER with 7 days of worsening fever, chills, myalgias, nausea, vomiting, dyspnea, loss of sense of taste and smell. Her home medications included metformin and Candesartan-HCTZ, however, she had been off these medications for the last seven days. She was not on statins. She was a healthcare worker at a nursing home that had a recent outbreak of the novel Coronavirus with 51 positive cases. In ER, she was febrile, tachypneic with WBCs of 11.8 thousands/mm3, Creatinine of 6.68 mg/dl, BUN 76mg/dl, and creatinine kinase (CK) of 167,770 U/L. Urinalysis showed large amount of blood with 17 RBCs. Chest X-ray significant for mild patchy airspace opacity in the Lingula. She also tested positive for Covid-19. She was adequately volume resuscitated and alkalinized. Due to her severe AKI, she did not meet criteria for Hydroxychloroquine and Azithromycin. Sarilumab was contraindicated due to transaminitis. Patient was started on hemodialysis on day 3 of admission as her creatinine continued to rise. On the 10th day after admission, her transaminitis improved and Sarilumab was administered. Repeat Covid-19 test before administering Sarilumab was positive. Her IL-6 levels checked before initiating the drug were <5 pg/mL. Her CK levels had started to trend down and were at 4880 U/L the day before starting Sarilumab. She remained oliguric and on hemodialysis with no signs of renal recovery at the time of discharge.

Discussion: Coronavirus has a huge range of presentation from asymptomatic to severe ARDS. Our goal is to highlight one of the complications of the novel corona virus leading to acute renal failure requiring hemodialysis.



Chest X-ray

PO0817

The Role of Point-of-Care Ultrasound in the Management of Dialysis Patients with COVID-19

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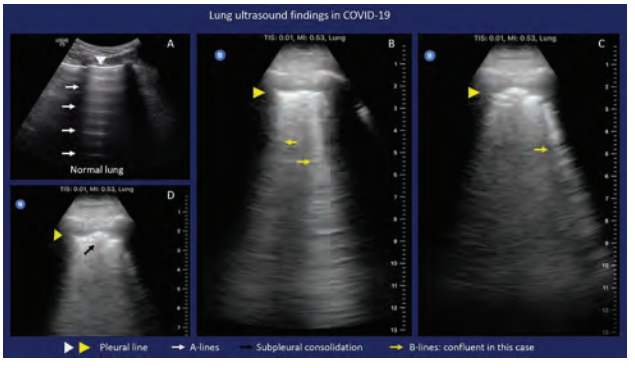
Introduction: Much of the burden for management of outpatient dialysis patients with suspected or confirmed Coronavirus Disease 2019 (COVID-19) has fallen to the dialysis units. Symptom recognition is not straightforward as these patients often have multiple putative etiologies for dyspnea especially given concomitant pulmonary congestion due to fluid overload. In this context, point-of-care ultrasonography (POCUS), particularly lung ultrasound (LUS) is a valuable diagnostic tool for nephrologists taking care of these patients. POCUS is free of ionizing radiation, can be performed at the bedside, and has comparable diagnostic accuracy to chest CT scan for most lung pathologies. We present a case study to illustrate the role of POCUS in dialysis patients.

Case Description: A 79-year-old woman with a history of ESKD on maintenance hemodialysis was found to be hypoxemic with an oxygen saturation of 90% on room air. Bedside LUS demonstrated patchy areas of pleural thickening and irregularity as well as confluent B-lines and scattered consolidations consistent with viral pneumonia [Figure]. Focused cardiac US did not reveal any overt signs of fluid overload. She tested positive for COVID-19 and improved with supportive care. She continued to receive dialysis on a separate shift for COVID-19 positive patients.

Discussion: In addition to aiding in diagnosis, POCUS limits staff exposure to the virus during transportation and avoids the downtime for radiology room decontamination unlike CT. Most handheld US devices can be completely encased in a standard plastic transducer cover that can be discarded after each use. We propose that dialysis units adopt LUS as a bedside tool to diagnose and monitor the extent of pulmonary involvement in patients with COVID-19 and differentiate from other causes of dyspnea. CT scan can be reserved for those with equivocal LUS findings or underlying chronic lung disease that interferes with interpretation.



PO0818

Severe AKI from Thrombotic Microangiopathy and Acute Tubular Necrosis in a Patient with COVID-19 and Gemcitabine Chemotherapy Use

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Introduction: Thrombotic microangiopathy (TMA) is a known but rare complication of gemcitabine therapy. However, gemcitabine-associated TMA has not been reported in a patient with concurrent COVID-19. Here, we present an interesting patient with COVID-19 who developed severe acute kidney injury (AKI) from acute TMA and acute tubular necrosis (ATN) following gemcitabine therapy.

Case Description: 45-year-old AA female with history of recurrent metastatic cervical cancer, peritoneal carcinomatosis, small bowel resection, colo-vesical fistula, colostomy and bilateral nephrostomy tubes was hospitalized for severe symptomatic anemia, fever and AKI. A week prior to hospitalization, patient had received her third outpatient dose of gemcitabine. Four weeks prior to presentation, serum creatinine (Scr) was 0.77. On admission labs, Scr was elevated at 7.36 and hemoglobin was low at 4.8. Patient also tested positive for COVID-19 on admission labs. There was no evidence of hydronephrosis on CT scan. Patient found to have clinical and labs findings of TMA (hypertension, thrombocytopenia, elevated lactate dehydrogenase and low haptoglobin) during hospital stay. Peripheral smear showed multiple schistocytes. Urinalysis was significant for microscopic hematuria and proteinuria. Spot urine total protein to creatinine ratio was 4.6. Complement C3 and C4 were not low. Patient was Coombs IgG positive and was initiated on high dose intravenous corticosteroids. Our patient also received one dose of rituximab therapy as per inpatient oncology team. Patient was initiated on hemodialysis for uremic symptoms. Kidney biopsy subsequently performed during hospital stay showed acute TMA and acute tubular injury with focal tubular necrosis.

Discussion: Our patient developed severe AKI in the setting of gemcitabine chemotherapy use and COVID-19. Kidney biopsy showed findings of both TMA and ATN. While the kidney biopsy findings are very interesting, it is unknown if either gemcitabine or COVID-19 or both were responsible for the severe AKI seen in our patient. Our patient remains oliguric and dialysis dependent.

PO0819

First US Case Series: Continuous Renal Replacement Therapy with Adsorbent Oxiris Filter in the Setting of COVID-19 Infection

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Introduction: Many COVID-19 hospitalized patients sustain acute kidney injury (AKI) requiring CRRT. Multisystem hyperinflammatory response plays a large role in their infection leading to enhanced morbidity and filter clotting. Oxiris filters have been used for years in Europe in septic patients due to their properties of reducing cytokines and inflammatory mediators but have not been available in the United States until late April 2020. Use of these filters in COVID-19 patients has been very limited, and has not yet been reported. We report the first U.S. experience in 3 COVID-19 patients requiring mechanical ventilation for their respiratory failure and continuous venous to venous hemodiafiltration (CVVHDF) using oXiris dialyzers for their (AKI).

Case Description: Case 1: A 73 year old male with laboratory tests revealing: creatinine 1.79mg/dl, C-Reactive Protein 1.01mg/dl, D-dimer 597, ferritin 13,000 ng/ml and Interleukin-6 (IL-6) 96 pg/mL. He was started on CVVHDF with M150 filter and then switched to oXiris filter. He remained on oXiris CVVHDF for 9 days with no reported clotting events, a decline in ferritin by 90% to 1437ng/mL and a decline in IL-6 levels to 73 pg/mL. Case 2: A 55 year old male on CVVHDF with the M150 filter had a serum ferritin level progressively increasing to 2377 ng/ml and multiple clotting events. The dialyzer was switched to oXiris. He had no clotting events while on CVVHDF for six days and his serum ferritin level decreased to 1759 ng/ml. Case 3: A 40 year old male on extracorporeal membrane oxygenation (ECMO). He was initiated on CVVHDF to the ECMO circuit using a M150 filter for 7 days and was switched to oXiris filter with no reported clotting events thereafter.

Discussion: The COVID-19 cytokine storm leads to activation of pro-inflammatory mediators leading to severe morbidity including coagulopathic events. Optimal treatment is still unknown. ECMO and CVVHDF with oXiris dialyzer in critical COVID-19 infection may play a role in decreasing inflammatory markers, which confers overall clinical improvement. Once switched to oXiris, our patients showed improvement in inflammatory markers and had no clotting of their dialyzers. In these patients, convective clearances (CVVHDF) may be more beneficial than diffusive therapies (CVVHD).

PO0820

Pre-Filter Argatroban for Coronavirus Disease 2019

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Introduction: Coronavirus disease – 2019 (Covid-19) has been implicated in a pro-thrombotic state. This has been well documented in numerous articles and has posed to be a difficult obstacle for those caring for Covid-19 positive patients. This has been particularly challenging for Nephrologist managing patients on continuous renal replacement therapies (CRRT). Amongst other things, filter clotting has been associated with an increased number of transfusions and interruptions in sustained therapy, as well as increased costs to the healthcare systems and patients.

Case Description: We present the case of a 73-year old African American male with a past medical history of underlying chronic kidney disease, hypertension, diabetes mellitus, heart failure, and atrial fibrillation who was admitted from his nursing facility after being found to be altered. Upon presentation to the hospital, the patient was screened for SARS-CoV-2 and found to be positive. He was transferred to the intensive care unit due to septic shock requiring vasopressors. Given oliguria, worsening acidosis, and metabolic derangements the patient was started on CRRT. Hospitalization was complicated by acute lower limb ischemic. Direct thrombolysis was unable to be performed due to thrombocytopenia and the patient subsequently underwent a guillotine amputation of the right lower extremity. CRRT was continued however multiple issues with filter clotting were noted despite systemic anticoagulation with heparin. The patient was transitioned to Argatroban as thrombocytopenia worsened and there was a concern for heparin-induced thrombocytopenia. Following the transition to Argatroban, the patient's filter life was exponentially increased and only replaced per hospital protocol. No further issues with clotting were reported with the dialysis circuit.

Discussion: The pathogenesis of hypercoagulability associated with Covid-19 is not fully understood. Techniques utilized to minimize the risk of clotting include increasing the blood flow rate, regional and systemic anticoagulation, and running replacement fluids pre-filter. The role of Argatroban, a direct thrombin inhibitor, in treating Covid-19 patients has not been well documented. We report the case of a patient who was successfully anti-coagulated with Argatroban being run pre-filter. Pertinent outcomes included prolonging filter life, elimination of filter clotting events, and fewer interruptions in CRRT.

PO0821

Efficacy of Acute Continuous High-Volume Peritoneal Dialysis on the Respiratory Mechanics of a Mechanically Ventilated Patient with Acute Respiratory Distress Syndrome due to COVID-19

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Introduction: Acute renal failure (ARF) is a common issue in mechanically ventilated patients diagnosed with acute respiratory distress syndrome (ARDS) due to COVID-19. Renal replacement therapy (RRT) is often required for volume overload. Such patients may not tolerate hemodynamic shifts induced by hemodialysis (HD). Continuous renal replacement therapy (CRRT) while better tolerated is a limited resource. Acute peritoneal dialysis (PD) remains a feasible RRT modality in patients on mechanical ventilation. Some hesitate to use PD for fear of increasing intra-abdominal pressure (IAP) with dwells leading to altered respiratory mechanics. Our case demonstrates that acute PD has no adverse respiratory outcomes in a COVID-19 patient.

Case Description: A 42 year-old Hispanic male with end stage renal disease newly initiated on urgent start PD for 1 week presents with acute hypoxemic respiratory failure secondary to ARDS from COVID-19. Upon presentation, he was intubated and initiated on lung protective ventilator strategies. Due to high ventilatory requirements (PEEP 15, FiO2 100%) with severe volume overload HD was selected in lieu of PD. He underwent daily HD but remained overloaded due to high daily intake. Due to limited availability of CRRT, he was transitioned to acute continuous PD via cycler (fill volume 2L, every 4hr). FiO2 reduced to 40%, peak and plateau pressures did not change, and he was able to maintain adequate ventilation with unchanged tidal volumes while on PD. He eventually received a tracheostomy.

Discussion: COVID-19 has challenged providers with managing critically ill patients in the setting of limited resources. In our case of ARDS with ARF, we transitioned from HD to acute PD in order to facilitate fluid removal in lieu of CRRT. The ICU team feared increased IAP from PD would worsen lung compliance and hypoxemia from atelectasis. A prospective study by Almeida et al showed that acute PD in mechanically ventilated patients was associated with increased IAP, but lung compliance, oxygenation, and PaO2/FiO2 increased. Our case noted similar observations without adverse event. Acute PD was able to meet the demands on his daily intake without any compromise to ARDS lung protective ventilator strategies.

PO0822

Methemoglobinemia and AKI in Patients with COVID-19: Don't Forget G6PD Deficiency

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Introduction: Patients with COVID-19 can be asymptomatic or have severe illness. Oxidative stress may be a cause of increased severity and mortality in COVID-19 patients. Methaemoglobinaemia (MetHb) and haemolysis can occur as a result of oxidative stress. MetHb is associated with sepsis, exposure to drugs and inborn errors of metabolism. Glucose-6-phosphate dehydrogenase (G6PD) deficiency may also manifest with MetHb and severe haemolysis.

Case Description: A 31-year old man, originally from West Africa, with no co-morbidities, presented with dyspnoea, cough, anosmia and oligo-anuria. He had type 1 respiratory failure and stage 3 AKI, which led to critical care admission for intubation, ventilation and haemofiltration. COVID-19 pneumonia was confirmed by nasopharyngeal swab and radiological imaging. He developed haemolytic anaemia. The MetHb was 3.5% (normal <1.5%). It rose to a peak of 10.7% with persisting anaemia and further investigations showed G6PD deficiency. He had no exposure to medications known to trigger haemolytic crises, such as Hydroxychloroquine. He was treated with supportive management including red cell transfusions and also with Tocilizumab for COVID-19. He was extubated after 15 days and recovered renal function. Data on 9 other patients admitted during this period to the ITU with COVID-19 and AKI showed 7 had normal MetHb levels and 2 had modest elevations (<3%).

Discussion: Triggers of G6PD deficiency include stress from infections, fava beans, or drugs e.g Hydroxychloroquine. It typically presents as haemolytic anaemia, jaundice and AKI. Although MetHb is linked to severe illness including sepsis, little is known about a possible association with COVID-19. Our report highlights the importance of considering alternative diagnoses of very high MetHb levels such as G6PD deficiency in COVID-19 patients. This is of particular relevance as Hydroxychloroquine has been used as experimental treatment for COVID-19 and in the current climate, G6PD deficiency should be suspected in COVID-19 patients with AKI, acute haemolytic anaemia and signikficantly elevated MetHb, particularly in those from regions of high prevalence and those treated with known triggers such as Hydroxychloroquine.

PO0823

Rhabdomyolysis and High Catabolic State in Patients with COVID-19 Who Develop Dialysis-Requiring AKI

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Introduction: Covid-19–associated rhabdomyolysis has not been clearly established; therefore, clinicians might have low clinical suspicion for rhabdomyolysis

Case Description: We are presenting five cases where Covid-19 patients became very catabolic and developed rhabdomyolysis associated with acute kidney injury (AKI). Symptoms were shortness of breath, fever, generalized malaise one week before the presentation. At the time of admission all patients had fever, tachycardia, tachypnea and were hypoxemic. One day later they were intubated for tachypnea and worsening oxygen saturation. They were admitted to the intensive care units and were treated with intravenous hydration. All the patients eventually required pressor support. AKI developed 10 days after onset of the symptoms and it was attributed to cytokine storm, ischemic acute tubular necrosis, and rhabdomyolysis. Intravenous furosemide was attempted with poor responses. Renal replacement therapy (RRT) was needed approximately three days after development of AKI. Continues renal replacement therapy (CRRT) was the modality used. After 3 days of interrupted therapy due to clotting, there was not improvement and overall high mortality.

Discussion: Rhabdomyolysis has been associated with many infectious diseases, including viral infections. The direct viral invasion and circulating viral toxins may directly destroy muscle cell membranes leading to rhabdomyolysis. However the

excessive immune response and cytokine storms which often seen in COVID-19 can promote to high catabolic state and rhabdomyolysis and therefore it will contribute to rapid worsening on renal function. Early detection and promptly supportive treatment with RRT may help to improve the vital prognosis of COVID-19.

Characteristic	1	2	3	4	5
Age – yr	34	42	45	70	72
Sex	Male	Male	Female	Male	Male
BMI – kg/m²	61.7	54.1	20	25.5	27.7
Comorbidities	Alcoholic cardiomyopathy	Ischemic cardiomyopathy, and polycystic Kidney Disease	None	None	Hypertension
Baseline Creatinine (mg/dl)	0.97	2.0	0.7	0.96	1.0
Laboratory data on diagnosis of AKI					
Potassium (mmol/l)	4.8	4.0	6.9	6.7	5.7
Phosphate (mmol/l)	6.8	5.3	10.6	8.2	6.9
Creatinine (mg/dl)	4.94	4.2	6.95	2.6	4.2
Blood urea nitrogen, mmol/l	50	78	110	73	76
Creatine Kinase (U/liter)	10,726	10,174	16,018	7,606	1304
Peak creatinine (mg/dl)	8.4	5.17	6.9	2.56	4.2/ 9.45
Peak blood urea nitrogen, mmol/l	177	160	131	150	159
Peak Creatine Kinase (U/liter)	14,266	10,174	20,666	15,750	>30,000
Days of Hospitalization	62	41	20	37	12
Death	No	No	Yes	Yes	Yes

PO0824

Severe Hypertriglyceridemia Leading to CRRT Malfunction in a COVID-19 Patient

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Introduction: Continuous renal replacement therapy (CRRT) is a therapy used in critically ill patients and is of particular importance with COVID-19. We present a patient with COVID-19 on propofol for sedation with persistent filter clotting issues found to have severe hypertriglyceridemia (SHT) corrected with lipopheresis. This case highlights the importance of managing all aspects of CRRT, the highly inflammatory state of COVID-19 and supply chain management during high utilization periods.

Case Description: A 41-year-old male with severe obesity and T2DM presented to the hospital with shortness of breath and fevers found to have COVID-19. The patient was intubated on presentation due to hypoxemic respiratory failure and admitted to the ICU. The patient was placed on Propofol for sedation. The patient presented with normal kidney function but peri-intubation had a rapid rise in creatinine to 4.00 mg/dL and was started on CRRT. It was noted that the CRRT circuit was continuously clotting within 30 minutes of initiation. The patient was also noted to have rising CPK levels and a concern for Propofol Infusion Syndrome (PRIS) was raised. A triglyceride level was checked and found to be 3286 mg/dL. The patient was initiated on insulin and heparin drips however due to CRRT issues and inadequate clearance a decision was made to perform lipopheresis to rapidly correct SHT. Patient underwent lipopheresis and the triglycerides dropped to 426 mg/dL. The heparin drip was continued and filter life greatly improved. The patient was continued on CRRT and adequate clearance was achieved.

Discussion: This case highlights important points for CRRT, COVID-19 and supply chain management. This patient was found to have PRIS however COVID-19 is a highly inflammatory state with a particularly robust response in patients with higher central adiposity. In this patient with metabolic syndrome, the addition of Propofol was a particular risk for SHT. With respect to the CRRT, a big indication to check triglycerides was the clotting of filters. Lipopheresis was indicated not only for the SHT but in order to help correct issues with CRRT and to achieve adequate clearance. Finally, during the COVID-19 crisis supply chain management was important with a shortage of CRRT machines, fluids and filters. In order to achieve optimal use of CRRT supply, adequate clearance, and correct SHT, lipopheresis was indicated.

PO0825

COVAN, COVID-Associated Nephropathy: An Evolving Epidemic of Kidney Disease

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Introduction: We highlight COVID-19 related renal characteristics in 6 African American patients with positive nasopharyngeal RT-PCR for SARS-COV-2 infection, presenting without severe respiratory symptoms but with acute kidney injury and nephrotic range proteinuria.

Case Description: One of the patients was a transplant recipient. None required mechanical ventilation and no COVID-19 specific therapy was prescribed. All underwent a renal biopsy that showed varying combinations of collapsing glomerulopathy, podocytopathy and protein overload tubulopathy (Fig 1A). Additionally, tubulo-reticular inclusions and virions (suspected to be SARS-COV-2 virions) were seen in electron micrographs (Fig 1B). *APOL1* genotype was tested in 3 patients who were all found to carry high-risk genotypes, suggesting possible susceptibility of patients with high-risk *APOL1* alleles to kidney involvement in SARS-Cov-2 (Fig 1C)

Discussion: There was discordance between the high risk G1/G1 genotype of the transplant recipient and the low risk G1/G0 donor kidney genotype, suggesting the important possibility of a systemic APOL1-related mechanism in kidney injury. In conclusion, these 6 cases draw attention to proteinuric kidney disease in COVID-19 infection, possibly associated with a milder form of respiratory disease and high risk *APOL1* genotype, emphasizing the need for ongoing vigilance and further investigation into this phenomenon

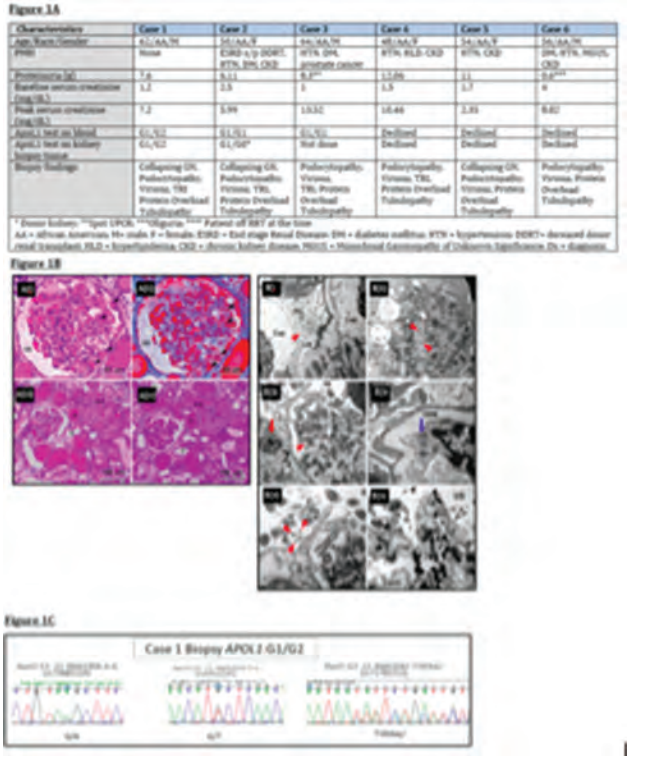

Figure 1: 1A: Demographic and Clinical features of the Six Cases. 1B:Biopsy findings. 1C: ApoL1 genotyping for Case 1

PO0826

AKI and Purpuric Rash in a COVID Patient

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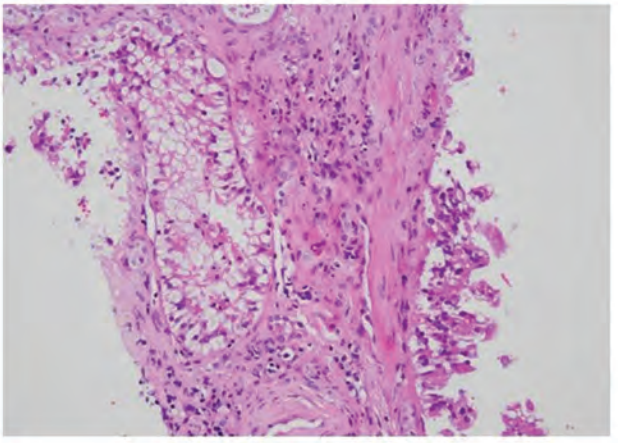
Introduction: AKI in COVID-19 patients are reported in several studies with an incidence of 23%. We report a case of COVID-19 pneumonia with AKI and purpuric rash.

Case Description: A 54 y/o female with hypertension, CKD stage 3, with a COVID+ swab, presented with CT chest findings consistent with COVID-19 pneumonia, purpura of the lower limbs concerning for leukocytoclastic vasculitis and non-oliguric AKI. Creatinine on admission was 8.5mg/dl, (baseline of 1.6mg/dL), CBC showed a wbc 26.9, Hb 6.9, platelets 196 and eosinophilia. Serologies were notable for elevated direct coomb, low haptoglobin, low C3/C4, and rheumatoid factor of 26. UA had no hematuria, UPCR 0.75 mg/mg. Home medication, naproxen was stopped one month ago. Renal biopsy showed severe acute tubular injury (ATI), coarse vacuolization of tubular epithelial cells, severe leukocytic infiltration of lymphocytes, neutrophils, eosinophils, severe vascular hyalinosis, global glomerular sclerosis (11 out of 30 glomeruli), severe (60%) interstitial fibrosis & tubular atrophy. Per institutional protocol, Immunofluorescence could not be performed in COVID+ patients. Renal function improved significantly after a 5 day course with IV steroids alone and patient remained stable with a creatinine of 3.4 mg/dL.

Discussion: This case features multiple potential mechanisms for AKI in a COVID-19 patient. Viral effects include, acute interstitial nephritis (AIN), severe ATI, and endothelial inflammation leading to vasculitis and purpuric rash. Recently, vasculitis similar to Kawasaki disease has been described in COVID-19 patients. Our case suggests that immune dysregulation from COVID infection may result in autoimmune findings such as elevated RF and hemolytic anemia. AKI improved in our patient after steroids, suggesting that a biopsy with features of AIN should be treated and could change the course of the disease.



PO0827

Unforeseen Complications of Delayed Vascular Access Intervention: A Case Report in the Wake of the COVID-19 Pandemic

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Introduction: Well-functioning dialysis access is of utmost importance as the lifeline of those with end stage kidney disease (ESKD). With the evolvement of COVID-19 pandemic, elective procedures were placed on hold. The American Society of Diagnostic and Interventional Nephrology (ASDIN) and Vascular Access Society of the Americas (VASA) issued a joint position statement on March 24, 2020, designating dialysis vascular access procedures to be "essential". We present a case with a series of complications that could have been prevented had the patient undergone a timely thrombectomy procedure.

Case Description: A 62 year old woman with ESKD undergoing hemodialysis through an upper arm arteriovenous fistula (AVF) presented with a thrombosed AVF in early March 2020 (before the ASDIN statement was issued). She was evaluated by the surgical team; however, due to restrictions to surgical procedures at the time, she did not undergo a thrombectomy and had a right internal jugular tunneled dialysis catheter (TDC) inserted instead. This was complicated by a superior vena cava thrombosis a few weeks later. The TDC was then removed and she had a right femoral TDC placed. She was started on anticoagulation. Her right femoral TDC was complicated by tunnel infection, necessitating its removal and subsequent placement of a left femoral TDC.

Discussion: This case illustrates the complexity of dialysis vascular access and some of the potential complications that are associated with it. It also highlights the importance of timely action to rescue any failed access. As outlined by the statement of ASDIN and VASA, dialysis vascular access should always be treated as a priority, and procedures to salvage it ought to be considered essential. This should also be the case in any future unforeseen restrictions to surgical procedures, such as pandemics or natural disasters.

PO0828

Does Cyclophosphamide Exposure in Patients with Vasculitides Lead to Better COVID-19 Outcomes?

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Introduction: COVID 19 is a pandemic disease caused by novel coronavirus called SARS-CoV- 2. End Stage Renal Disease patients are at high risk for developing severe manifestations of the disease often associated with high morbidity and mortality. Excessive and uncontrolled immune response is thought to be one of the important underlying mechanism for severity of the disease. We present 3 ESRD patients with underlying vasculitides who were admitted with respiratory distress due to COVID 19.

Case Description: All 3 patients presented with shortness of breath and had typical features of COVID 19 including hypoxia, fever; extensive bilateral interstitial infiltrates on Chest X rays, lymphocytopenia, elevated LDH; and ferritin. The first patient is a 37-year-old Hispanic male with ANCA -PR3 related vasculitis resulting in ESRD, on hemodialysis. He had been treated with Cyclophosphamide and prednisone induction therapy and is on maintenance prednisone. The second patient is a 40-year-old male with ESRD secondary to crescentic IgA nephropathy. He had been treated with cyclophosphamide and prednisone induction. The third patient is a 43-year-old female with SLE; ESRD secondary to lupus nephritis. She had been treated with cyclophosphamide and prednisone induction and is on maintenance prednisone. All 3 patients recovered in the hospital with oxygen supplementation and did not require NIV or intubation.

Discussion: We hypothesize that due to residual immunosuppressive action of cyclophosphamide, the inflammatory response in these patients was probably blunted. And this could have led to better outcome in these patients. Due to lots of unknowns related to COVID 19, further prospective/retrospective studies should be done looking at outcomes of COVID 19 in patients who had received cyclophosmide previously.

PO0829

Renal Biopsy Findings in Patients with COVID-19 Infection

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Introduction: COVID-19 infection is caused by severe acute respiratory syndrome-2 (SARS-CoV-2). SARS-CoV-2, using its Spike protein, interacts with angiotensin converting enzyme-II (ACE2) protein expressed in human kidneys. Upon internalization, host cells may go through pyroptosis, a process characterized by membranous pore formation, cytokine storm and cell death. We report light microscopy (LM), immunofluorescence microscopy (IF), and electron microscopy (EM) findings in renal biopsies of patients with COVID-19 to further understand the pathological process.

Case Description: 10 patients were biopsied, age range 25-63 years. 7 were confirmed by polymerase chain reaction (PCR) via nasopharyngeal swab. 3 patients were suspected, but PCR-negative. Common comorbidities include hypertension, hyperlipidemia, and obesity. Patients had AKI with elevated creatinine, range 1.2 to 13.48 mg/dL. Kidney ultrasound showed enlargement and increased echogenicity. Biopsies were performed 9 to 71 days from symptom onset of such as fever, cough, and diarrhea. Tissue was fixed in formalin and processed for LM. Fresh frozen tissue was utilized for IF. Tissue was fixed in paraformaldehyde and processed for EM. All had acute tubular injury and viral particles on EM (Figure). Patients received supportive care. None required ventilation, but 4 required hemodialysis. Survival rate is 100% (8-12 weeks).

Discussion: Renal biopsies were evaluated in 7 confirmed and 3 suspected COVID-19 patients. Although PCR is the gold standard, it is known to have a 15% false negative rate. This may be due to low viral loads and antibody testing may be warranted in suspected PCR-negative patients. Coronavirus particles are reported to measure 50-200 nm, and SARS-CoV-2 50-140 nm. Viral particles were seen in all 10 patients. The particles are contained in vesicles or sacs, and can be found in podocytes, endothelial, and tubular epithelial cells. This may contribute to intrinsic injury resulting in AKI seen in patients.

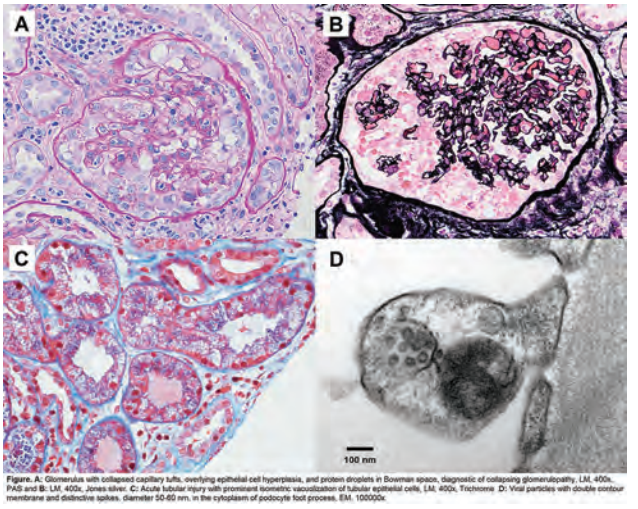

Figure. A: Glomerulus with collapsed capillary tufts, overlying epithelial cell hyperplasia, and protein droplets in Bowman space, diagnostic of collapsing glomerulopathy, LM, 400x, PAS and B: LM, 400x, Jones silver. C: Acute tubular injury with prominent isometric vacuolization of tubular epithelial cells, LM, 400x, Trichrome. D: Viral particles with double contour membrane and distinctive spikes, diameter 50-80 nm, in the cytoplasm of podocyte foot process, EM, 100000x.

PO0830

AKI in the Setting of COVID-19: Histopathologic and Ultrastructural Findings in Postmortem Kidney Biopsy

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Background: COVID-19 has been associated with a very high risk of AKI. The pathophysiology of the AKI is unclear with conflicting reports regarding the presence of direct infection of the kidney with SARS-CoV2.

Methods: Postmortem kidney biopsy was performed in adult patients with confirmed COVID-19 and stage 2 /3 AKI. Biopsies were examined using light and electron microscopy. Immunohistochemistry and RNA in situ hybridization were performed for SARS-CoV2.

Results: 12 patients (83% male) with mean age of 70±13 years underwent biopsy. Mean baseline and peak creatinine were 1.0 and 5.3 mg/dL, respectively. Renal replacement therapy was required in 8 (67%) patients (Table 1). All 12 patients had a pathologic diagnosis of acute tubular injury with focal acute tubular necrosis (Table 2). There was no glomerulitis, vasculitis, or thrombotic microangiopathy. There were no characteristic viral particles on electron microscopy and there was no evidence of SARS-CoV-2 on Immunohistochemistry or in situ RNA hybridization.

Conclusions: AKI in patients with COVID-19 infection was associated with acute tubular injury and focal epithelial necrosis in all patients. There was no evidence of direct viral infection. It appears unlikely that SARS-CoV-2 causes renal injury by direct infection.

Table 1. Clinical characteristics of the study population

Patient Number	Age (Y)	Sex	Race	BMI(kg/m2)	Prior Kidney disease	Hypertension	Diabetes	Cardiovascular disease	Creatinine, mg/dL			Urine			peak Cx (U/L)	Vancomycin trough>20 (ug/ml)	IV Contrast	Bacteremia/Fungemia	vasopressor	Mechanical ventilation	RRT	COVID treatment*	Time to biopsy (hr)
									Baseline	Admission	Peak	Proteinuria mg/dl	RBC ≥ 5/hpf	WBCs 5/hpf									
1	58	M	H	29.7	N	N	N	N	1.1	5.5	8.9	100	Y	Y	135	Y	Y	N	Y	Y	Y	2	20
2	92	F	H	30	N	Y	N	N	0.7	5	5.01	30	N	N	250	Y	N	N	Y	Y	N	1	70
3	78	M	B	25	N	Y	Y	Y		2.6	6.15	100	Y	N	3745	Y	N	N	Y	Y	Y	1	2.5
4	49	M	H	28.4	N	N	N	N	0.5	0.51	2.64	30	Y	N		Y	N	Y	Y	Y	N	2	17
5	77	M	H	32.8	N	N	N	N	0.6	0.76	5.7	30	N	Y	420	Y	N	N	Y	Y	Y	2	2
6	72	M	H	28.5	N	Y	Y	Y	1.07	2	5.6	30	N	N	2900	Y	N	Y	Y	Y	Y	1	1.5
7	81	M	W	22.1	Y	Y	Y	Y	2.5	2.61	5.4	30	N	N	153	Y	N	N	Y	Y	Y	1	19
8	76	M	W	24.4	N	Y	N	N	1.1	1.6	4.2	100	Y	N	576	N	N	N	Y	Y	Y	2	15
9	56	M	H	28.3	N	Y	N	N	0.9	0.77	3.6	30	Y	N	508	N	N	Y	Y	Y	Y	2	19
10	76	F	W	23	N	Y	N	N	1	2.35	2.35				148	N	N		N	N	N		24
11	74	M	B	38	N	Y	N	N	1	1.6	2.7	30	Y	N	890	N	Y	N	Y	Y	N	2	12
12	54	M	B	44.4	N	Y	Y	N		2.2	11	30	N	N	4170	Y	Y	N	Y	Y	Y	2	18

* Race, B: Black, H: Hispanic, W: White. BMI: body mass index. RBC: red blood cell. WBC: white blood cell. CK: creatine kinase. RRT: renal replacement therapy. *COVID treatment, 1=hydroxychloroquine+IV steroid±azithromycin, 2=Tocilizumab+ hydroxychloroquine+IV steroid±azithromycin. Empty cell: no data available

Table 2. Summary of histopathologic findings

Patient Number	% Tubules involved by ATN	Level of autolysis	Other findings	Glomeruli (total / globally sclerosed)	Glomerular pathology	IFTA %	AAS
1	<5	Mild	Rare muddy casts	19/1	None	10	Moderate
2	30	Moderate	Dialysis	30/0	None	10	Mild
3	30	Mild	None	39/8	None	15	Moderate
4	50	None	Focal THP in interstitium	22/2	Mild hypoperfusion	20	Severe
5	10	Moderate	Rare muddy casts	30/0	None	5	None
6	50	None	Mild AIN, focal THP in interstitium	17/2	Mild ME	10	Severe
7	50	Moderate	Focal brown pigment – neg Fe stain	16/4	Early nodular GS	25	Severe
8	10	Moderate	Focal brown pigment – neg Fe stain	38/8	None	15	Severe
9	30	Moderate	None	33/3	None	10	Moderate
10	<5	Mild	Rare tubules with PRG	33/1	None	5	Moderate
11	<5	Moderate	None	18/0	GH, mild ME	5	Moderate
12	10	Moderate	Muddy casts	39/8	None	15	Moderate

* ATN: Acute tubular necrosis; THP: Tamm-Horsfall protein; AIN: Acute interstitial nephritis; Fe: iron; PRG: Protein reabsorption granules; ME: Mesangial expansion; GS: glomerulosclerosis; GH: Glomerular hypertrophy; IFTA: interstitial fibrosis and tubular atrophy; AAS: Arterial and arteriolar sclerosis

PO0831

Serum Induces Major Transcriptional and Epigenetic Changes at COVID-19-Associated Gene Loci in Primary Renal Epithelial Cells

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Background: Tubular epithelial cells express high levels of COVID-19 entry receptors ACE2 and the accessory protease TMPRSS2. High systemic levels of IL-6 and IL-8 may contribute to the "cytokine storm" associated with poor outcome with COVID-19 infection. We sought to understand the regulation of these key genes in a 3D microphysiological system (MPS) containing primary human tubular epithelial cells treated with human serum, a surrogate for a disease-state ultrafiltrate.

Methods: Primary human tubular epithelial cells cultured in the 3D MPS were exposed to 0.5 and 2% serum for 48 hours and their transcriptional responses were evaluated by RNA-seq. Observed changes in transcription of secreted proteins were validated by ELISA on MPS effluents. We also orthogonally validated our MPS findings against gene expression and chromatin accessibility (ATAC-seq) data generated from intact human renal cortex and primary tubular epithelial cells cultured in 2D in the presence of 10% serum.

Results: Serum exposure of tubular MPS elicited 535 up and 285 downregulated genes with upregulation of pro-inflammatory and chemotactic cytokines *IL6* and *IL8* consistently seen across multiple donors. This was associated with increased IL6 and HAVCR1 (KIM-1) protein secretion in MPS effluents. Tubular epithelial cells cultured in 2D with 10% serum expressed higher levels of *HAVCR1* (up 4.5x), *LCN2* (*NGAL,* up 6x), *IL6* (up 11.2x) and *CXCL8* (*IL8,* up 7.6x) compared to renal cortex. In contrast, *ACE2* (down 8.6x) and *TMPRSS2* (down 4.4x) were significantly downregulated. Analysis of open chromatin regions revealed a stress response signature at these gene loci, indicating active regulation in response to injury.

Conclusions: Proteinuria is common in COVID-19 infected patients and we studied serum-exposure, as a model of glomerular dysfunction and subsequent proximal tubule responses in our kidney MPS. Serum induces the expression and secretion of IL6 and IL8, suggesting a localized, pro-inflammatory tubule response. Our epigenetic analysis revealed that COVID-19 associated genes have a stress response signature with implications for inter-individual variability in expression. Our kidney MPS model and data represent a powerful system for studying the complex effects that COVID-19 infection exerts on the kidney.

Funding: Other NIH Support - NCATS

PO0832

Kidney Injury Molecule 1 Is a Receptor for SARS-CoV-2

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Background: Acute kidney injury (AKI) is a common feature of Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. **K**idney **I**njury **M**olecule-**1** (**KIM-1**) has been reported to be a receptor for Hepatitis A virus. KIM-1 is a scavenger receptor in kidney epithelial cells. We hypothesized that KIM-1 is a receptor for SARS-CoV-2 and may play an important role in COVID-19-associated AKI.

Methods: Liposomal nanoparticles displaying the SARS-CoV-2 spike protein trimer (S1 and S2) on their surface (virosomes) were generated. We evaluated spike protein and virosome uptake by human KIM-1 expressing kidney epithelial cells and human kidney tubuloids, 3D structures of kidney epithelial cells. KIM-1-mediated uptake was compared to uptake by ACE2, a well-known receptor for SARS-CoV-2. Our recently discovered specific KIM-1 uptake inhibitor, JB-1 was tested for its ability to block virosomes uptake by KIM-1 expressing cells. KIM-1 expression was augmented in the tubuloids by infection with adenovirus vector carrying human KIM-1 cDNA to examine if the virosome uptake was enhanced. Protein-protein interaction characteristics between purified SARS-CoV-2 spike protein and S1 binding domain and purified KIM-1 were determined using microscale thermopheresis.

Results: KIM-1 expression on kidney epithelial cells markedly enhanced virosome uptake, despite no change in ACE2 expression. This KIM-1 specific uptake was inhibited by JB-1. Human kidney tubuloids also endocytosed virosomes, and tubuloids with enhanced KIM-1 expression secondary to infection of KIM-1-adenovirus had increased uptake of virosomes. Using microscale thermopheresis the Kd for interaction between KIM-1 and SARS-CoV-2 spike protein and the receptor binding domain were 56.2+/-28.8 nM and 9.95+/-3.10 nM respectively.

Conclusions: KIM-1 is a receptor for SARS-CoV-2. KIM-1 specific uptake of the SARS-CoV-2- virosomes suggests that KIM-1 confers efficient SARS-CoV-2 binding in kidney epithelial cells when these cells are expressing KIM-1. The KIM-1 dependent virosome uptake by 3D tubuloids indicates that this can be a valuable human cell model for studying SARS-CoV-2 interactions and testing for inhibitors. KIM-1 inhibitors, such as JB-1, can be potential therapeutics SARS-CoV-2 for COVID-19. Kidney tubular intraluminal and systemic circulating levels of KIM-1 ectodomain may be protective by acting as decoy receptor for the virus.

Funding: NIDDK Support

PO0833

Morphological Evidence Suggests That Kidney Injury Molecule 1 May Serve as a Proximal Tubule Receptor for SARS-CoV-2

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Background: Kidney injury molecule-1 (KIM-1), a type-1 transmembrane glycoprotein, has been well studied as a specific injury marker for proximal tubules (PT). KIM-1 functions as a receptor for apoptotic fragments through a phagocytic process. KIM-1 (also called TIM-1) serves as a receptor for hepatitis A virus and Ebola virus, and possibly for severe respiratory syndrome-coronavirus (SARS-CoV-1). During the pandemic spread of coronavirus disease 2019 (COVID-19), many patients have suffered from acute kidney injury (AKI) as well as lung damage, Viral upkake has been attributed to interactions with ACE2, a receptor for the virus. The goal of this study was to investigate whether there is kidney histological data that KIM-1 may also serve as a receptor for SARS-CoV-2 to infect the PT.

Methods: Two patients (one adult and one child) who died of COVID19 and 10 patients with AKI but no COVID19 (control group) were included in the study. All kidney tissue sections were stained for KIM-1 (monoclonal AKG7 antibody) and scored from 0 to 3+. Electron microscopy was conducted using kidney tissue of the COVID19+ patients.

Results: Both COVID19+ patients had normal pre-mortem levels of serum creatinine (sCr) (adult 0.63 and child 0.17 mg/dl), whereas the control cases all had elevated sCr (1.9 to 10.7 mg/dl). Control renal biopsies revealed positive KIM-1 staining ranging from 1+ to 3+ along the surface of PT in a patchy pattern involving 20 to 80% of the cortex; no cytoplasmic granular materials were identified. By contrast, the KIM-1 staining in COVID19+ kidneys revealed spotty granular staining in the cytoplasm and diffuse surface 2+ to 3+ staining in most PTs, while glomeruli stained negatively for KIM-1 as internal negative controls. In the two COVID19+ patients, SARS-CoV-2 particles showed spiking-crown appearances with sizes ranging from 70 to 110 nm in the PT cytoplasm by ultrastructural studies.

Conclusions: Our initial evidence suggests there is an atypical staining pattern of KIM-1 in the PT of COVID19+ patients, raising a possibility that KIM-1 may serve as a receptor for SARS-CoV-2. KIM-1 may also serve to internalize the virus into the PT. In addition the two COVID+ patients had normal sCr levels but positive KIM-1 staining, indicating that sCr underestimates renal injury caused by SAR-CoV-2 infection.

PO0834

Kidney and Lung ACE2 Expression After an ACE Inhibitor or an Angiotensin II Receptor Blocker: Implications for COVID-19

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Background: There have been concerns that ACE inhibitors and Ang II receptor blockers may cause an increase in full length (FL) membrane bound ACE2, the main receptor for SARs-CoV-2, that could enhance the risk and worsen the clinical course of COVID -19. Information on the impact of ACE deficiency and AT1 blockade on ACE2 expression at target sites is required to understand this issue.

Methods: Kidneys from two genetic models of kidney ACE ablation and mice treated with captopril or telmisartan were used to examine ACE2 in isolated kidney and lung membranes.

Results: In global ACE KO mice, ACE2 protein abundance in kidney membranes was reduced to 42 % of wild type, $p < 0.05$. In ACE 8/8 mice that over-express cardiac ACE protein but has no kidney ACE expression, ACE2 protein in kidney membranes was

also decreased (38 % of the WT, p<0.01). In kidney membranes from mice that received captopril or telmisartan for 2 weeks there was a reduction in ACE2 protein to the level of 37%, p<0.01 and 76%, p <0.05 of that of vehicle control mice, respectively. In lung membranes the expression of ACE2 was very low and not detected by western blotting but no significant differences in terms of ACE2 activity could be detected in mice treated with captopril (118% of control) or telmisartan (93% of control).

Conclusions: Genetic kidney ACE deficiency, suppressed ACE enzyme activity by Captopril or blockade of the AT1 receptor with telmisartan are all associated with a decrease in ACE2 expression in kidney membranes. These findings altogether suggest that ACE2 protein abundance at two potential target sites for SARS-CoV-2 infection is decreased or unaffected by RAS blockers. Since these medications do not increase ACE2 expression in lung or kidney epithelia, we conclude that they likely would not pose a risk for increased susceptibility to COVID -19.

Funding: NIDDK Support

PO0835

Noninvasive Mapping of the Cellular Response to COVID-19 via Urine Single-Cell RNA Sequencing (scRNAseq)

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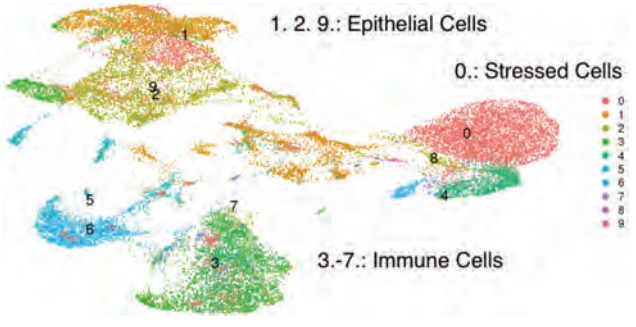
Background: COVID-19 is associated with a high incidence of AKI. Mapping the transcriptional profiles of kidney and urinary track derived single cell populations can establish a framework to assess renal molecular response to COVID-19 and emerging treatment strategies.

Methods: Patients throughout the COVID-19 disease course were recruited to the study. A modification of our protocol (Arazi et al. Nat Immunol) allowed for immediate isolation of urinary cell pellets followed by 10X Genomics Chromium based scRNAseq.

Results: Urine scRNAseq data sets were generated from 13 COVID patients: age 50+/-17; 7 males; 7 African Americans; urine sampling 11 days post SARS-CoV-2 diagnosis (IQR 5-29) with 8 in AKI at time of sampling. 25,954 single cell profiles passed QC with a median of 433 cells per sample [IQR 271 to 718]). Cellular clusters were annotated to immune (9780 cells, Fig: cluster 3.-7.), renal epithelial (4364, cluster 1.) and bladder cells (4151, cluster 2.). The SARS-CoV2 receptor ACE2 was found in epithelial cells and co-expressed with CTPSL. The COVID-19 therapeutic target IL-6 was robustly detected in both myeloid and epithelial cells with co-expression networks linking IL6 expression in proximal tubular epithelial cells to HMGB1, VEGF and HIF signaling and to viral response networks in myeloid cells.

Conclusions: COVID-19 patients urine cells contain a spectrum of epithelial and immune cells expressing viral receptors of SARS-CoV-2 and therapeutic targets of emerging COVID-19 therapies offering a window to monitor renal cellular responses in COVID-19 trials.

Funding: NIDDK Support



Cell clusters from urinary pellets

PO0836

Stimulus and Cell-Specific Responses to Volume Depletion, Ischemia, and COVID-19

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Background: A stimulus-response map of the injured kidney might reflect a common stereotyped "final common pathway" or alternatively, a set of "stimulus-specific", "cell-specific", and "time-specific" read outs.

Methods: We expressed uracil phosphoribosyl transferase (Uprt) in specific segments of the kidney (Rosa-*Uprt$^{fl/+}$;Hoxb7Cre* and Rosa-*Uprt$^{fl/+}$;Atpase6v1b1Cre*) and identified nascent RNA by 4-thiouracil pulse labeling after initiating two clinically relevant stimuli. Thio-RNA was isolated from intact kidneys with thio-biotin beads. We examined human biopsies with RNAScope to confirm patterns of gene expression.

Results: Hierarchical clustering of z-score transformed normalized counts (padj<0.05 and $\log_2$ fold changes ≥1) demonstrated that 3180 genes distinguished volume depletion from arterial ischemia in Hoxb7Cre purified genes and 1405 genes in AtpaseCre purified genes, respectively. The vast majority of these stimulus specific genes (96% ischemia and 83% volume depletion) constituted cell specific responses as well (exclusive to Hoxb7Cre or AtpaseCre purified RNA). Pathway analyses demonstrated immune regulation, complement and the coagulation pathways in ischemic disease, whereas volume depletion activated inhibitors of inflammatory pathways and metabolic Foxo signaling, clock genes, and lipid metabolism. Timed evaluation demonstrated distinct early and late responses. To confirm the unique responses to clinical injury, we examined the most prominent mouse genes responding to ischemia, *LCN2* (NGAL) and *HAVCR1* (KIM1) in human ATN kidneys (associated with NSAIA (1), hypotension (1), DGF (1), nephrectomy (2), COVID-19 (8), unknown etiology (1)), together with segment specific anchor genes (*LRP2*, *AQP2*). *LCN2* and *HAVCR1* expression was cell specific (*HAVCR1*: proximal tubule, *LCN2* : Loop of Henle and Collecting Ducts > Proximal Tubules) in the majority of biopsies. *LCN2* and *HAVCR1* overlapped in the proximal tubule in a minority of severely affected kidneys.

Conclusions: KDIGO criteria for AKI imply that any elevation of serum creatinine marks injury to the nephron. Yet, without resorting to destructive methods of dissection or cell isolation, we identify snapshots of genes induced by different stimuli, expressed by different cells, specific in timing, constituting different sets of unrelated molecular responses.

Funding: NIDDK Support

PO0837

AKI and Collapsing Glomerulopathy Associated with COVID-19 and APOL1 High-Risk Genotype

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Background: Acute kidney injury (AKI), with or without proteinuria, has been described in patients with Coronavirus disease 2019 (COVID-19). Kidney involvement in COVID-19 has been reported to be of greater severity in African Americans (AA). Herein, we report genetic, histopathological and molecular findings in 6 AA patients with COVID-19 presenting with AKI and *de novo* nephrotic-range proteinuria.

Methods: Percutaneous kidney biopsies were performed in 6 patients with COVID-19 with respiratory manifestations and proteinuric AKI. Peripheral blood was obtained for apolipoprotein L1 (APOL1) risk allele assessment. Kidney tissue was also examined by *in situ* hybridization (ISH) for viral detection and by NanoString for COVID-19 associated genes and genes related to tubular injury.

Results: Six AA patients with COVID-19 (4 men, 2 women), mean age 55 years (37-65) were included in the series. At biopsy day, the mean serum creatinine was 6.5 mg/dL (2.9 – 11.4) and the mean urine protein-to-creatinine ratio was 11.5 g (3.6 – 25.0). Kidney biopsy specimen showed collapsing glomerulopathy, extensive foot process effacement, microcystic tubular dilation and focal or diffuse acute tubular injury. Three patients had reticular endothelial aggregates. No viral particles were identified. ISH and NanoString showed absence of SARS-CoV-2 RNA. NanoString analysis showed changes in genes related to acute tubular injury and an increase in chemokine gene expression. All 6 patients tested positive for 2 APOL1 risk alleles. Two patients died, 1 remained dialysis dependent, 2 partially recovered after transient need for dialysis and 1 partially recovered without needing dialysis.

Conclusions: Collapsing glomerulopathy in AA patients with COVID-19 was associated with high risk variants of APOL1. Direct viral infection in the kidneys was not observed, suggesting a possible "two-hit" phenomenon of genetic predisposition and cytokine-mediated host response to infection. Given the resemblance with HIV-associated nephropathy, we propose the term COVID-19-associated nephropathy (COVAN) to this new entity.

PO0838

COVID-19-Associated Kidney Injury: A Case Series of Kidney Biopsy Findings

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Background: Acute kidney injury (AKI) has been recognized as a common complication of severe COVID-19 in hospitalized patients. Proteinuria and microscopic hematuria have also been observed. While a recent autopsy series of patients who died with severe COVID-19 in China found acute tubular necrosis (ATN) in the kidney, few case reports of collapsing glomerulopathy in COVID-19 have also been reported

Methods: To better understand the clinical and histopathologic findings, we looked at 10 kidney biopsy cases in patients with COVID-19 along with clinical features of AKI with or without proteinuria or hematuria in our institution. We described their clinical features, pathologic findings and outcomes.

Results: The mean age of the patients who underwent kidney biopsy was 65 years. Five patients were African American, three patients were Hispanic, and two were Caucasian. Nine patients had varying degree of proteinuria. Eight patients had severe

AKI necessitating renal replacement therapy. On kidney biopsy, all patients had varying degree of ATN, with one patient having associated widespread myoglobin casts. In addition, two patients had findings of thrombotic microangiopathy (TMA), one patient had pauci-immune crescentic glomerulonephritis and another patient had global as well as segmental glomerulosclerosis with features of healed collapsing glomerulopathy. Interestingly, all patients had negative immunohistochemistry staining for SARS-CoV-2 on their kidney biopsy material.

Conclusions: This biopsy series reveals ATN as the most common kidney biopsy finding with AKI in COVID-19 infection with no evidence of significant viral presence in the kidney tissue

Case #	1	2	3	4	5	6	7	8	9	10
Age (years)	77	60	62	69	76	45	69	64	59	69
Gender	F	M	M	M	F	F	F	M	M	F
Race	AA	H	H	H	C	AA	C	AA	AA	AA
DMII/HTN present	HTN	DMII, HTN	DMII	HTN	DMII/HTN	HTN	None	None	HTN	HTN
Admission Scr. (mg/dl)	8.1	0.8	1.2	0.9	1.0	7.4	0.7	7.8	4.5	1.9
Proteinuria (grams/day)	1.5	4.7	NA (urine dipstick-300 mg/dl)	2.4	0.9	5.7	1.4	5.0	2.8	7.6
Hematuria (Yes/No)	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
Pertinent Serologies	None	CK>90,000 High LDH Low platelets	IgG lambda band(weak)	None	None	High LDH, low haptoglobin	High LDH, low haptoglobin	+ MPO titer	Serum Kappa/Lambda ratio-10.69	None
Vasopressor use at time of AKI	No	Yes	Yes	Yes	No	No	Yes	No	No	No
Peak Scr. (mg/dl)	8.3	13.1	6.3	5.8	4.4	8.4	4.3	7.8	6.0	2.0
Potential precipitants of AKI	None	Hypotension	Hypotension	Hypotension+ vancomycin	Vancomycin+ piperacillin/tazobactam	Gemcitabine	Hypotension	None	Hypertensive Emergency	Vancomycin + piperacillin/tazobactam.
Kidney size (cm) (right/left)	13/11.8	15/13.7	12.2/14.7	NA	15/14.6 cm	9.8/10.3	9.6/9.3	11/11.3	8.7/8.7 cm	11.3/11.4
Kidney biopsy diagnosis	ATN, features of healed collapse	ATN+ myoglobin casts	ATN	ATN+ chronic sclerosis	ATN+ early diabetic changes	ATN +TMA	TMA+ cortical necrosis	Crescentic GN, ATN	ATN+ chronic sclerosis	ATN+ chronic sclerosis

PO0839

Kidney Pathology Findings in Patients Dying with COVID-19

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Background: The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to coronavirus disease 2019 (COVID-19) has predominantly resulted in a profound hypoxic respiratory disease with a significant subset of patients demonstrating abnormalities in renal function. Acute kidney injury (AKI) in these patients is an independent risk factor for mortality; however, the mechanism for injury is unknown and our understanding of the pathologic findings is limited.

Methods: Kidney tissue from nine patients who died with COVID-19 was obtained at autopsy and evaluated by light, immunofluorescence, and electron microscopy. RNAScope technology was used to perform RNA in situ hybridization (RNA ISH) with probes to the SARS-CoV-2 virus (sense) and for human gene *ACE2*.

Results: The cohort was comprised of 6 men and 3 women, 78% black, median age of 65 years (37 - 78) and median body mass index 29 (26 – 48) kg/m^2, of which 6 (67%) had hypertension and 4 (44%) had diabetes. AKI was present in 7 of 9 (78%), 5 (55%) of them needed dialysis. One patient had creatine kinase about 5000 U/L suggestive of rhabdomyolysis. All but one expired while on mechanical ventilation. The predominant morphologic finding on postmortem biopsy was acute tubular injury. Three cases (33%) demonstrated endocapillary platelet aggregates with one demonstrating fibrin tactoids and loss of endothelial fenestrations by EM, consistent with early TMA; however, no overt thrombotic microangiopathy was present. Immunofluorescence in one case demonstrated mesangial C3 staining without deposits by EM. Background mild-to-moderate arterionephrosclerosis was present in 6 of 9 (67%) cases. In one patient with AKI at time of death, RNA-ISH detected SARS-CoV-2 in tubular epithelial cells which also express *ACE2*, the receptor for coronavirus cell entry.

Conclusions: Among a cohort of 9 patients dying with COVID-19, postmortem evaluation of kidney samples predominantly revealed ATI without overt evidence of hypercoaguloability, complement dysregulation, or immune complex deposition. While the mechanism for AKI in most cases is not immediately apparent, this series suggests, but does not prove, direct renal infection with SARS-CoV-2 as the presence of viral RNA does not prove active viral infection.

PO0840

Renal Histopathological Post-Mortem Findings of 17 Patients with COVID-19 in New York City

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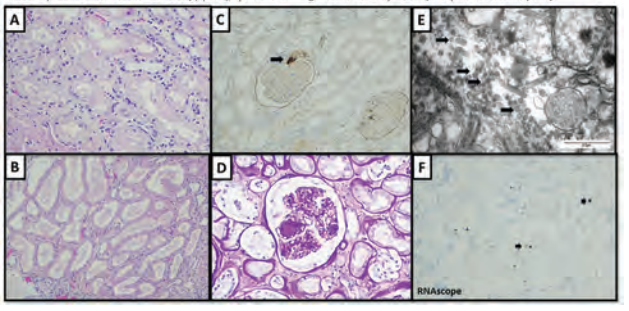
Background: While acute kidney injury (AKI) is a common and serious complication of patients with COVID-19, the mechanisms are unclear. Histopathologic reports of kidney tissue in COVID-19 are limited.

Methods: This was a retrospective case series of autopsy cases with confirmed SAR-CoV-2 infection performed at the Mount Sinai Hospital in patients who died between 3/21/2020 to 4/23/2020. Patients who had a kidney transplant, were on dialysis, if severe autolysis was present, or had no clinical data were excluded. To identify SARS-CoV-2, sections were examined by Transmission Electron Microscopy (TEM) and stained by In Situ Hybridization (RNAscope) in kidney sections.

Results: 32 patients had autopsies done, of which 17 patients fulfilled our inclusion criteria. The median age was 64 (interquartile range (IQR) 50, 79), 70% were male, 18% were black, 42% had diabetes and 59% had hypertension. Of the 17 patients, clinical evidence of AKI was present in 12 (71%) patients; 4/12 (33%) had Stage 1 AKI, 6/12 (50%) had Stage 2 AKI, and 2/12 (17%) had stage 3 AKI. Median peak creatinine was 0.96 mg/dL IQR 0.92-1.23 in those without AKI and 2.98 mg/dL IQR 2.11 – 5.99 in those with AKI. 3 patients had urine studies performed, only one of them had AKI and had hematuria, proteinuria, and leukocyturia. On histopathology, 9/17(53%) had acute tubular injury (ATI) only (Fig 1A & B) and 1/17 (5%) had TMA and ATI (Fig 1C). ATI was present in 4/5 (80%) of patients without AKI. There was no TMA found in patients without AKI. Glomerular pathology included nodular sclerosis in diabetic nephropathy (Fig 1D) and glomerulosclerosis secondary to ischemic hypertension. Virus was found in 4 samples (Fig 1E & F).

Conclusions: There is direct involvement of kidney by SARS-CoV-2 supported by identification of viral particles by TEM, and by ISH RNAscope. The most common histopathologic finding in patients that died with COVID-19 was ATI, which was also present in patients who did not have AKI by serum creatinine criteria.

Figure 1: Representative histopathologic findings of A) Vacuolization (isometric) of proximal tubules (H&E x200), B) Proximal tubules show diffuse attenuation of epithelial cells consistent with acute tubular injury (H&E x100), C) Mesangial sclerosis in a case of diabetic nephropathy (PASx200), D Platelets aggregates in the hilum of one glomerulus highlighted by CD61 immunoperoxidase (x100), E) Viral particles in proximal tubules by Transmission Electron Microscopy (x25k), F) Positive staining of SARS-CoV-2 by RNAscope in proximal tubules (x100)



PO0841

COVID-19-Associated Nephropathy (COVAN): An Emerging Entity of Severe Viral Podocyte Injury and Collapsing Glomerulopathy in Kidney Biopsies

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Background: COVID19 caused by novel Coronavirus SARS-COV-2 initially presenting primarily as a respiratory illness, is now known to affect several organ systems as part of multiorgan failure including acute kidny injury (AKI), some cases also manifesting nephrotic range proteinuria or syndrome.

Methods: 10 renal biopsies from 6 institutions (1 transplant) performed in April-May 2020 were processed for light microscopy, immunostaining (IS) and electron microscopy (EM) for clinco-pathologic analysis.

Results: The 10 patients ranged from 25-73 years (Mean 43), male:female 5:5, 8 African American, 1 Hispanic, 1 Asian Indian, having pre-existing co-morbidities of hypertension (7), Diabetes mellitus (5), obesity (9), presenting with AKI (10), nephrotic syndrome (9), proteinuria ranging from 1.5-25g/24hrs, lung symptoms or pneumonia (7), fever (5). SARS-COV-2 RT-PCR positive (7), IgG antibody positive (2), both negative (1). All kidney biopsies showed widespread acute tubular injury with focal necrosis, 9 with typical features of segmental/global collapsing glomerulopathy in 10-53% of glomeruli, global glomerulosclerosis (0-35%), focal tubular microcystic changes (8), patchy (7) or diffuse (2) active tubulointerstitial inflammation and scarring (10-40%), focal & diffuse peritubular capillary inflammation, moderate vascular sclerosis and

diabetic kidney disease in 2. No immune deposits were localized by IS. By EM, varied glomerular capillary wall wrinkling and collapse with segmental or global loss of patency (7), total foot process effacement (7), with hyperplastic and vacuolated epithelial cells having protein droplets are noted. The endothelial cells are variably swollen, with tubuloreticular inclusions in 2. Viral particles are identified within cells of glomeruli and tubulointerstitium, scattered or in clustesr in the cytoplasm and endoplasmic reticulum vesicles, confirmed by IS.

Conclusions: The constellation of typical glomerular collapsing features with tubulointerstitial findings and localization of virus by EM, suggests a distinct viral associated nephropathy, reminicent of HIV associated nephropathy. A role for viral cytopathic effect, cytokines and underlying APOL1 gene variants could be considered.

PO0842

COVID-19 Renal Pathology Protocols and Pathology Practice in Latin America: Analysis from GlomCon Latin America Working Group (LGlomCon)

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Background: A significant fraction of patients with COVID-19 display renal involvement (60%); however, the histological findings and pathology practice in Latin America (LA) have not been reported. The aim is to know how COVID-19 pandemic has affected the protocols for renal pathology and the main pathology findings in the kidney.

Methods: An online survey with 75 questions in 6 sections, directed to pathologists, nephrologists and other specialists from 16 Spanish speaking LA countries treating COVID patients with kidney involvement. We are analyzing the impact of COVID-19 in renal pathology and pathology practice in LA.

Results: From 430 responses, 360 (84%) were considered for analysis. Only13 participants from 16 countries were renal pathologists but the rest of responders also contributed with the pathology section. Only 10% is performing renal biopsies (RBx) of COVID-19 patients. Acute kidney injury (AKI) (85%) was the most frequent indication for RBx, hematuria-proteinuria (42%), nephrotic syndrome (28%) and subnephrotic proteinuria (21%). Combination of AKI and other syndrome was seen. Handling fresh tissue for immunofluorescence (IF) is a regular practice in the centers that perform IF (66%). No ultrastructural examination in 90% due to the lack of EM equipment. Postmortem studies only in 3% of the centers. Autopsy and biopsies shiwed thrombotic microangiopathy (TMA), with acute tubular injury (ATI). Pathology redeployment to clinical areas, ICU and inpatient care is seen in 12%. Only 70% of those received guidance or updating clinical courses.

Conclusions: The survey has highlighted the deep shortage of renal pathologists and the lack of equipment (EM) compromising the best practice of renal pathology in LA. Protocols for tissue handling for COVID have not been established in any center, adding a burden to the practice. Most frequent indication for renal biopsy is AKI while the presence of TMA and ATI is found in autopsy and renal samples. Collapsing glomerulopathy (CG) has a high prevalence in hispanics and has been described in COVID patients, however CG was not seen. Outbreaks had forzed pathology redeployment to clinical care without proper preparation.

PO0843

Oxidative Stress, the Final Common Pathway in Lung-Kidney Pathophysiological Cross-Talk in an Experimental Model of COVID-19: Clinical Implications

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Background: AKI occurs frequently in patients with COVID-19 disease early in the course, in temporal association with respiratory failure and is associated with a poor prognosis. AKI is primarily seen in Covid-19 patients with respiratory failure, with 90% of patients on mechanical ventilation developing AKI compared to 22% of non-ventilated patients. To develop experimental models investigating pathophysiological mechanism of Lung- kidney inetarctions is an essential part of understanding the mechanisms of organs cross talk, i.e., the complex biological communication and feedback between distant organs mediated via cellular and molecular pathways.

Methods: In a novel experimental model similar to human COVID-19, ARDS followed by AKI developed by single injection of a Toxoid.(TOX). Two days post injection lungs and kidney were analyzed for antioxidant enzyme activities including superoxide dismutase, glutathione peroxidase, catalase and oxidative stress. Lungs wet/dry weight ratios were measured to evaluate edema. After sacrificing the animals, kidney and the lung were removed for histology.

Results: At 2 days post-TOX injection there was acute lung injury with cytotoxin influx, lung edema, neutrophil infiltration, hypoxemia and pulmonary artery thrombosis. In the kidney there was acute tubular necrosis with inflammatory infiltration. Oxidative stress was increased in the lung and the kidney. Antioxidant enzymes activities of SOD and GSHPx were decreased in the lung and the kidney.

Conclusions: In this experimental model mimicking COVID-19 organ failure, AKI and ARDS in rats correlates with a decrease in antioxidant and increase in oxidative stress in the lung & the kidney. This suggest the role of antioxidant as the potential adjunct therapeutic agents in COVID-19 related organ failure.

PO0844

Renal Pathology of 34 Consecutive COVID Autopsies: A Single-Institution Experience

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Background: Patients infected with the novel coronavirus 2019 (COVID19) have a wide spectrum of symptoms ranging from asymptomatic carriers to multisystem organ failure and death. While 20-40% of critically ill patients develop acute kidney injury (AKI) during the course of the disease, only few are biopsied. The most severely affected patients, frequently with multiple co-morbidities, provide insight into renal disease at autopsy.

Methods: 30 of 34 autopsies performed on COVID patients had kidneys available for routine evaluation. Clinicopathologic features are presented.

Results: The 34 patients range in age from 30-100 years (mean 68.5), 24 males and 10 females, 13 Caucasian, 10 Hispanic, 5 African American, 3 Indian, 3 Asian. All cases were positive by RT PCR nasal swab for SARS-CoV-2 except 3 (presumed false negative). All had on average 3.4 comorbidities (range: 0-7, hypertension (HTN), diabetes (DM), obesity, COPD, asthma, stroke, dementia, cancer), frequently HTN (20) and DM (20), 11 required intubation. 18 patients had AKI (53%), 2 previously ESRD, and 5 required renal replacement therapy. Presenting Cr ranged from 0.7-9.6 mg/dl (mean 1.7). Renal pathology included diabetic nephropathy (14, 47%), with tubulointerstitial scarring ranging from <25% (60%), 25-50% (23%), to >50% (17%), and moderate (40%) or severe (40%) chronic vascular sclerosis. Other findings: obesity related glomerulopathy (2), atheroemboli (1), bilateral infarction (1), papillary necrosis (2), and thrombotic microangiopathy (2). No collapsing glomerulopathy was seen. Tubular autolysis prevents complete assessment of ATN. Platelet thrombi were seen by CD61 staining in 43% of cases to involve >20% of glomeruli and peritubular capillaries. C5b-9 staining was strong, 2-3+ arteriolar in 67% and glomeruli in 20%, suggesting localized complement activation. By electron microscopy, viral particles were identified within cells of glomeruli and tubulo-interstitium.

Conclusions: Pathology in autopsy kidneys from 30 patients with COVID display pre-existing chronic disease correlating with co-morbidities, presenting with AKI or ESRD (59%). Despite varied tissue autolysis and the absence of significant proteinuria, the majority of AKI is presumed to be acute tubular injury due to ischemia and other causes. The viral particles in the renal glomerular and tubular cells may play a role in renal cytopathic injury.

PO0845

RAAS Inhibition, Mortality, and Severity in COVID-19 Patients: A Systematic Review and Meta-Analysis

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Background: The effect of angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) on outcome and severity in COVID-19 patients has been postulated.

Methods: We performed a systematic review in different databases to identify studies and research work that assessed the association of ACEi/ARBs on the severity of illness and mortality in COVID-19 subjects. Inclusion criteria for our meta-analysis were all studies that included human subjects with COVID-19 infection, reported mortality and severity of the disease, and described ACEi/ARB treatment. The data collected were the name of the first author, journal title, the country of the study, sample size, relative risk and confidence intervals for association of ACEi/ARB treatment and mortality and severity. We used the random-effects model for the meta-analysis and the funnel plot analysis to assess potential publication bias.

Results: Out of 4,702 records reviewed in different databases, 11 papers were included in our meta-analysis. Altogether, 8,643 patients were included in the final analysis. Random effects model (REM) for the relationship between ACEi/ARB and survival showed that ACEi/ARB does not affect survival (relative risk [RR]=0.81, confidence interval ranges [CIR] from 0.53 to 1.23). There was no evidence of heterogeneity with I-squared =25.5% and p<0.235. By applying Egger's test, there was no evidence of small studies effect with P=0.64. REM for the relationship between ACEi/ARB and disease severity showed that ACEi/ARB are not related to disease severity (RR=0.90, CIR from 0.70 to 1.15). There was evidence of heterogeneity with I-squared =56.2% and p=0.01. By applying Egger's test, there was no evidence of small studies effect with P=0.93.

Conclusions: Based on the results of this meta-analysis, ACEi/ARB are not associated with increased mortality or severity in COVID-19 subjects.

PO0846

The Use of ACE Inhibitors and ARBs in Patients Admitted for COVID-19

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Background: Angiotensin converting enzyme (ACE 2) receptor has been implicated as an entry point for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) causing pandemic coronavirus disease 2019 (COVID-19). Experts have postulated the potential benefits of using ACEI/ARB to reduce the severity of acute lung injury and as the treatment of hypertension in COVID-19. However, there is limited data in showing the renal outcomes after the use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in COVID-19 patients.

Methods: This is a retrospective, single center study of 300 patients diagnosed with COVID-19 confirmed by real-time reverse transcription polymerase chain reaction. Four groups were divided based on ACEI/ARB exposure. Group 1 (n=51 patients; 17%) were initiated on ACEIs/ARBs during hospitalization, group 2 (n=58 patients; 19%) were on ACEIs/ARBS at home and discontinued, group 3 (n=76 patients; 25%) were on ACES/ARBS at home and continued during hospitalization and group 4 (n=116 patients; 38%) were never treated with ACEIs/ARBS. The primary end points including the incidence of AKI using KDIGO definition, hyperkalemia, the necessity of dialysis and the secondary end points being the length of total hospital stays, the recovery rate, mortality rate were compared between group 1,2,3 with 4 using adjusted odd ratios (ORs).

Results: In group 1, the use of ACEI/ARB has 4 times higher risk of developing AKI than the control group 4 (P= 0.001, 95% CI of 1.70-9.59). and is 4.6 times for stage 2 or above AKI (P= 0.001; 95% CI of 1.8-11.5). OR for hyperkalemia is 5.7 (P= 0.001, 95% CI of 2.09-15.5) and for hemodialysis is 3.7 (P= 0.02, 95% CI of 1.2-11.2). Their mortality rate is increased 2.9 times (P=0.026, 95% CI of 1.23-7.44). In group 2, the incidence of AKI is 7.5 times higher (P= <0.001, 95% CI of 3.3-17) and 3.5 times (P=0.001, 95% CI of 1.6-7.7) for stage 2 above AKI. OR for the initiation of hemodialysis and the mortality rate are not statistically significant after adjusted with variables. In group 3, no statistically significant data were found.

Conclusions: Our findings suggest that the initiation of ACEI/ARB in COVID 19 patients have increased risk of AKI, hyperkalemia, necessity of dialysis and mortality rate.

PO0847

Prospective Feasibility Study with the Use of Losartan in COVID-19

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Background: The risks of administering Angiotensin II Receptor Blockers for hypertension in hospitalized patients infected with SARS-CoV-2 remains debated. To date, there are no prospective studies evaluating outcomes with the use of ARBs in patients with hypertension and COVID 19.

Methods: We conducted a single-center prospective feasibility study to ascertain the safety and efficacy of losartan in patients with COVID-19 and HTN. Inclusion criteria are patients with age ≥ 18yr, PCR confirmed SARS-CoV-2, BP>130/80, and required FiO2 ≥ 0.25 to maintain SpO2 > 92%. These patients were started and titrated on losartan 25mg daily to reach BP goal of <130/80. The vital signs, FiO2 requirements, LFTs, inflammatory markers, serum creatinine and K+ were monitored until discharge, with weekly evaluation of symptoms post-discharge.

Results: 250 patients were screened from April 22 to May 18, 2020, and 16 patients enrolled. Average time to enrollment was 5.5 days, with varying degrees of acuity. 6 patients were removed from the study (see Table 1). Eight patients completed the minimum 7 days of losartan while in the hospital 6/8 patients demonstrated no deterioration of SaO2/FiO2 ratio, SaO2/FiO2 compared on day 1 (201.1 ± 108.1) and day 7 (252.3 ± 148.4), and 2/8 patients improved to room air on day 7. Among all patients, inflammatory markers were not significantly changed from admission to peak values (Table 1).

Conclusions: This study has demonstrated that patients admitted with COVID 19 and hypertension who completed 7 days of Losartan showed no significant deterioration in oxygenation/worsening of inflammatory markers, thereby providing the rationale for a RCT with the use of losartan versus nonRAAS blockade in COVID-19.

Medications and Treatments		
Average Duration Losartan, days	7.0 ± 6.6	
Average Daily Losartan dose in mg	30. 2 ± 17.4	
Average Total Losartan dose in mg	233.3 ± 223.5	
Blood pressure	Average Daily SBP, mm Hg	Average Daily DBP, mm Hg
	130 ± 13	73 ± 6
Liver Function	Average Daily ALT, IU/L	Average Daily AST, IU/L
	44.0 ± 38.9	33.0 ± 21.0
Serum Creatinine, mg/dL	On admission	Peak
	0.93 ± 0.47	1.03 ± 0.53
Ferritin, ng/mL	On admission	Peak
	1060 ± 858	1813 ± 1162
T-test	1.81; 95% CI, -120 to 1624; P 0.087	
LDH, IU/L	On admission	Peak
	372 ± 167	472 ± 206
T-test	1.38; 95% CI, -51 to 251; P 0.182	
D-Dimer, ng/mL	On admission	Peak
	645.3 ± 760.4	3211.8 ± 4464.2
T-test	1.96; 95% CI, -294 to 5410; P 0.074	
CRP, mg/dL	On admission	Peak
	14.0 ± 12.5	20.7 ± 13.5
T-test	1.00; 95% CI, -5.5 to 15.9; P 0.325	
Patient Outcomes		
AKI	0 (0.0%)	
Hyperkalemia	1 (6.3%)	
Hypotension	7 (43.8%)	
Days of Hypotension while on Losartan,%	7% ± 10.0%	
Transaminitis	2 (12.5%)	
ICU Admission	5 (31.3%)	
Invasive mechanical ventilation	4 (25%)	
Remains in Hospital	4 (25.0%)	
Discharged	11 (68.8%)	
Deceased	1 (6.3%)	
Average Length of Stay (days)	14.7 ± 7.8	
Removed from Study	6/16 (37.5%)	
Reason for Removal		
Hypotension	3/6 (50.0%)	
Elevated Creatinine	1/6 (16.7%)[a]	
Hyperkalemia	1/6 (16.7%)	
Respiratory Failure Requiring Intubation	1/6 (16.7%)[b]	

a. Patient not started on Losartan
b. Had elevated creatinine, but did not meet study criteria for AKI

Table 1. Clinical characteristics of patients (N16)

PO0848

Renin-Angiotensin-Aldosterone System Blocking Drugs in Patients with SARS-CoV-2: Systematic Review and Meta-Analysis

Chang Chu,[1,3] Shufei Zeng,[1,3] Ahmed A. Hasan,[2,3] Carl-Friedrich Hocher,[3] Bernhard K. Krämer,[3] Berthold Hocher.[3] *[1]Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Department of Nutritional Toxicology, Institute of Nutritional Science, University of Potsdam, Potsdam, Germany; [3]Fifth Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany.*

Background: COVID-19 patients requiring treatment with blockers of the renin-angiotensin-aldosterone system (RAAS) are at highest risk of developing pneumonia and dying. ACE2 is the functional receptor for SARS-CoV-2. Animal studies suggest that RAAS blocking agents might increase the expression of ACE2 and hence potentially increase the risk of SARS-Cov-2 infection.

Methods: We conducted a systematic review and meta-analysis of published studies on the association of RASS blocking agents with lung disease related outcomes.

Results: The effect of ACE inhibitor treatment on the incidence of pneumonia in non-COVID-19 patients was analyzed in 25 studies (330,780 patients). ACE inhibitor use was associated with a 27% reduction of pneumonia risk (OR: 0.73, p<0.001). Pneumonia related death cases in ACE inhibitor treated non-COVID-19 patients were reduced by 27% (OR: 0.73, p=0.004). ARB treatment was analyzed in 10 studies (275,621 non-COVID-19 patients). The risk of pneumonia was not different between patients who did or did not use ARBs. Pooled result from 13 studies (27,704 COVID-19 patients) showed that COVID-19 related severe adverse clinical outcomes were not different between patients who did or did not use RAAS blocking agents (OR: 0.87, p=0.28). All-cause mortality risk in COVID-19 patients was reduced by 27% (p=0.04).

Conclusions: Given the weak evidence coming from animal studies and the clear beneficial data of ACE inhibition in non-COVID-19 patients and the limited but promising data in COVID-19 patients, the use of RAAS blocking agents in patients with SARS-CoV-2 infection is justified. Further clinical studies analysing ARBs and ACE inhibitors separately in COVID-19 patients are needed.

PO0849

Association of Prehospital RAAS Inhibitor Use with AKI and Death in a Cohort of Hospitalized COVID-19-Infected Patients

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Background: The relationship of RAAS inhibitors (RAASi) and their purported role in increasing COVID-19 viral attachment and worse outcomes is controversial. In this study we examined the association of RAASi use with Acute Kidney Injury (AKI) and in-hospital death.

Methods: We assembled a cohort of all patients admitted to the 3 main Montefiore hospitals and diagnosed with COVID-19. RAASi use was defined by a prescription within 365 days prior to hospitalization. The association of RAASi use with COVID associated AKI incidence and mortality was evaluated using logistic regression models. Propensity score matching was then used to derive the odds ratio (OR) of AKI and death in those using RAASi compared with controls.

Results: Of 3345 hospitalized patients, 9.3% were prescribed a RAASi prior to hospitalization. Those prescribed RAASi were older (71.9 vs 63.6 years, p<0.001), more commonly Black or Hispanic (RAASi users 41.3% Black and 41.0% Hispanic vs non-RAASi 35.4% Black and 36.9% Hispanic) and had higher Charlson co-morbidity scores (median 4 (IQR 3-7) for RAASi users vs 2(1-3) for non-RAASi users). In unadjusted analysis, RAASi use was associated with a higher OR for AKI (OR 1.32(95% CI 1.04-1.68)) and a higher OR for death (OR 1.53 (95% CI 1.18-1.98). Multivariate adjustment for age, demographics, and clinical comorbidity attenuated associations of AKI and death towards the null (AKI: OR 1.00 (95% CI 0.76-1.31); Death: OR 0.92 (95% CI 0.68-1.24)). Similarly, in propensity score analysis there was no association between RAASi use and either AKI (OR 0.96 (95%CI 0.88-1.04)) or death (OR: 0.96 (95%CI 0.89-1.05).

Conclusions: RAASi use prior to hospitalization was not associated with AKI or in-hospital mortality in a cohort of patients hospitalized with COVID-19.

	Hospitalized COVID+ Group N=3345	Yes to RAASi use N=310 (9.3%)-	No to RAASI use N=3035 (90.7%)	P value
Age	64.4(16.4)	71.9(11.9)	63.6(16.6)	<0.001
Age Decile				
<30	113(3.4)	1(0.3)	112(3.7)	
31-40	189(5.6)	2(0.6)	187(6.2)	
41-50	311(9.3)	9(2.9)	302(10.0)	<0.001
51-60	553(16.5)	24(7.7)	529(17.4)	
61-70	779(23.3)	91(29.3)	91(29.4)	
71-80	771(23.0)	100(32.3)	100(32.3)	
>80	629(18.8)	83(26.8)	83(13.2)	
Sex				
Female	1569(46.9)	147(47.4)	1422(46.8)	0.8
Male	1776(53.1)	163(52.6)	1613(53.2)	
Race				
White	275(8.2)	28(9.0)	247(8.1)	
Black	1201(35.9)	127(41.0)	1074(35.4)	<0.001
Hispanic	1247(37.3)	128(41.3)	1119(36.9)	
Other	622(18.6)	27(8.7)	595(19.6)	
Diabetes				
Yes [n(%)]	906(27.1)	185(59.7)	721(23.8)	<0.001
CKD				
Yes [n(%)]	310(9.3)	112(27.4)	198(6.7)	<0.001
Charlson with age				
Median (IQR)	2(1-3)	4(3-7)	2(1-3)	<0.001
Nursing Home	548(16.4)	74(23.9)	474(15.6)	<0.001
BMI				
<30	1797(57.1)	185(59.9)	1612(56.8)	
30-35	725(23.0)	57(18.4)	668(23.5)	0.1
>35	626(19.9)	67(21.7)	559(19.7)	
Heart Failure				
Yes [n(%)]	129(3.9)	72(23.3)	57(1.9)	<0.001
Proteinuria (n=1837)				
<30	14(0.8)	0	14(0.8)	
30-500	1761(95.9)	171(9.7)	1590(95.8)	0.5
>500	62(3.4)	6(3.4)	56(3.4)	
Office Visit within previous one year	310(9.3)	294(12.0)	16(1.8)	<0.001
Outcomes				
AKI				
Yes [n(%)]	1903(56.9)	195(62.9)	115(37.1)	0.02
RRT				
Yes [n(%)]	164(4.9)	7(2.3)	157(5.2)	0.02
Mechanical Ventilation				
Yes [n(%)]	624(18.6)	48(15.5)	576(19.0)	0.1
Death				
Yes [n(%)]	775(23.2)	95(30.6)	680(22.4)	0.001

PO0850

Outcomes Associated with the Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hospitalized Patients with SARS-CoV-2 Infection

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Background: SARS-CoV-2 uses the angiotensin converting enzyme (ACE) receptor for cell entry leading to COVID-19. The use of ACE Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) in hypertensive COVID-19 patients remains unclear. Since hypertension is a major comorbidity in COVID19, evaluating the efficacy versus adverse outcomes with the use of ACEI or ARB in patients with COVID-19 is essential.

Methods: In this retrospective single-center study, we analyzed electronic medical record data on 300 patients admitted with COVID-19 disease. Data collection included comorbidities, medications, vital signs, and laboratory values (on admission and during hospitalization). Outcomes included inflammatory burden (calculated using composite scores for multiple markers of inflammation), AKI, admission to the intensive care unit (ICU), need for mechanical ventilation, and mortality. For multivariate analyses, generalized linear model (continuous outcomes) and logistic regression (dichotomous outcomes) were used.

Results: Of the 300 patients, 80 patients (26.7%) had history of ACEI or ARB use prior to admission, with 61.3% (49/80) of these patients continuing the medications during hospitalization. Outpatient users of ACEI or ARB had a higher burden of comorbid disease and increased rates of admission and in-hospital AKI in the descriptive analysis, but not on multivariate analysis (after adjusting for multiple covariates). Continuation of ACEI or ARB inpatient was associated with lower peak C-reactive protein (CRP) levels, peak inflammation score, ICU admission and mortality in the univariate analysis. On multivariate analysis, continuation of these agents during hospitalization predicted lower ICU admissions (OR=0.25, 0.08-0.81, p=0.02), peak CRP (-6.9 ± 3.1 mg/dl, p=0.03) and peak inflammatory score (-2.3 ± 1.1, p=0.04) as compared to their discontinuation.

Conclusions: In hospitalized patients with COVID-19, the use of ACEI or ARBs as an outpatient was not associated with adverse outcomes despite greater comorbid illness in users. The continued use of these medications during hospitalization was also not associated with adverse events, rather it predicted fewer ICU admissions and decreased inflammatory burden.

Funding: NIDDK Support, Veterans Affairs Support

PO0851

Glomerular Diseases and Immunosuppression Practices in Latin America During the COVID-19 Pandemic: Analysis from GlomCon Latin America Working Group (LGlomCon)

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Background: As COVID-19 spreads across the world, nephrologists are facing difficult decisions regarding the management of active glomerular diseases (GD). We aimed to report how COVID-19 pandemic may have changed the use of immunotherapies among nephrologists In Latin America (LA) for the treatment of glomerulopathies.

Methods: Descriptive analysis extracted from an online survey carried out among nephrologists, renal pathologists and other health workers treating kidney diseases between May 20-27, 2020 from sixteen Spanish speaking LA countries divided into 6 categories. We present the results for the GD and immunosuppression category.

Results: 430 responses were obtained of which 360 (84%) were considered for analysis. The participants were mainly nephrologists 276 (86%), renal pathologists 13 (4%) and physicians in training 11 (3%). 213 (59%) of the respondents treat patients with GD. For patients at risk but without COVID-19 infection, the induction immunosuppression for GD treatment was not changed by 54.1% of the respondents while 24.2% gave only a fraction of it and 21.7% deferred the induction treatment. For maintenance immunosuppression, the same regimen was maintained by 74.2% of the respondents, 24.3% decreased it and 1.5% suspended it completely. In case of relapse or flare, 53.6% used standard increase of immunosuppression, 39.7% increased it but at lower levels than usual and 6.7% continued the maintenance regimen. For patients already on immunosuppression diagnosed with COVID-19 infection, 42% would decrease immunosuppressive regimens for mild disease, 62.3% in case of moderate disease and 70.8% would consider completely discontinuing immunosuppression in case of severe disease.

Conclusions: Over 40% of the respondents in LA are already prescribing lower than recommended doses of immunosuppression for induction, relapses or flares as a preventive strategy in the context of COVID-19 pandemic. How this change in practice would affect the renal outcomes remains to be seen. The experience in the treatment of GD in patients with concurrent COVID-19 infection remains limited.

PO0852

Ramipril Decreases Lung and Kidney Angiotensin Converting Enzyme 2 (ACE2) in Diabetic Mice: Lessons for COVID-19 Infection

Ander Vergara,[1,2] Conxita Jacobs Cachá,[2] Pamela Domínguez Báez,[2] Mireia Molina Van den Bosch,[2] Anna Giralt-López,[2] Clara García-Carro,[1,2] Daniel Serón,[1,2] Maria Jose Soler.[1,2] Nephrology Research Group *[1]Hospital Vall d'Hebron, Barcelona, Spain; [2]Vall d'Hebron Institut de Recerca, Barcelona, Spain.*

Background: ACE2 is a component of the renin-angiotensin system(RAS) that mainly degrades angiotensin II to angiotensin(1-7). It is expressed in renal tubular cells. Lung type 2 alveolar cells also express ACE2 where it acts as a receptor for SARS-CoV-2, which is responsible for the current coronavirus disease 2019(COVID-19) pandemic. A controversy raised regarding the use of RAS blockers in COVID-19 patients despite its demonstrated efficacy in cardiovascular disease. We studied the effect of ramipril on ACE2 expression in experimental diabetes.

Methods: 12 weeks old diabetic db/db mice were given ramipril(8 mg/Kg/day) or vehicle during 8 weeks. db/m mice were used as controls. ACE2 expression and enzymatic activity were studied in kidney, heart and lung.

Results: In non-treated db/db, ACE2 mRNA expression was increased in kidney($p<0.0001$) and ramipril treatment reversed this effect. In heart, ACE2 expression decreased in db/db when compared to db/m($p=0.028$) and ramipril had no effect. We found no differences in lung. ACE2 enzymatic activity was increased 23% in kidney and 22% in lung of db/db mice when compared to db/m. Ramipril treatment decreased ACE2 activity 25% in the lung and 13% in the kidney when compared to untreated db/db. In the heart, ACE2 activity tended to decrease in db/db mice when compared to db/m, and increased with ramipril, but did not exceed the cardiac ACE2 activity of the db/m.

Conclusions: ACE2 is increased in the kidney and in the lung, and decreased in the heart of diabetic mice. Ramipril treatment restores ACE2. Our results suggest that diabetes and hypertension may *per se* be risk factors for COVID-19 and not the treatment with ACE inhibitors, which may exert a protective effect on COVID-19 infection.

Funding: Government Support - Non-U.S.

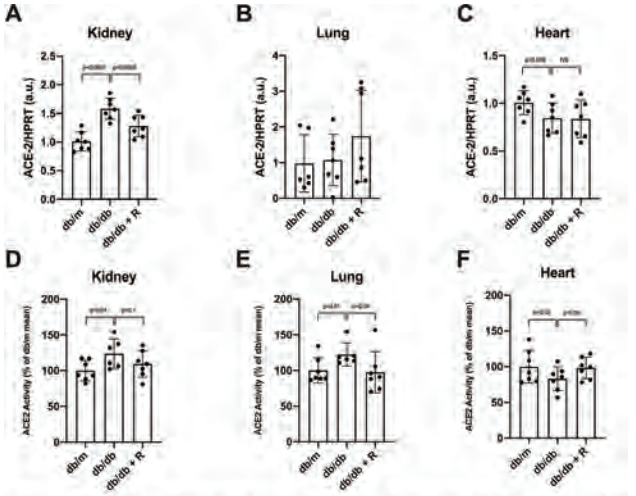

Figure 1. **ACE2 gene expression and activity in kidney (A and D), lung (B and E) and heart (C and F) of db/m, db/db and db/db treated with ramipril.**

PO0853

Caring for Patients with Kidney Disease in the COVID-19 Era: The Kaiser Permanente Northern California Experience

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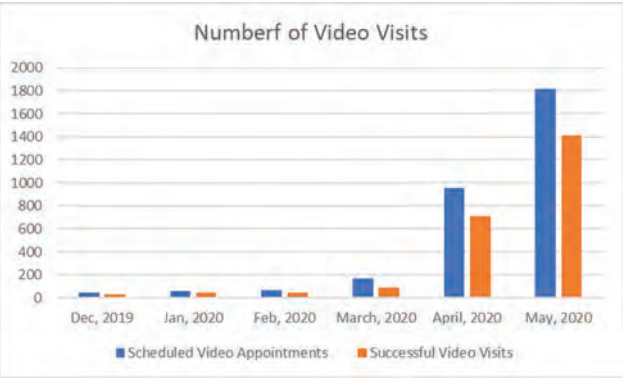
Background: The COVID-19 pandemic has presented health care system in the United States with unprecedented challenges. Kaiser Permanente Northern California is an integrated health care system with 4.5 million members, who are cared for by The Permanente Medical Group (TPMG), a multiple specialty medical group of 10,000 physicians. Utilizing coordinated care, sophisticated Electric Medical Record system. KPNC Nephrology service line has developed several strategies to mitigate the effect of COVID-19, including rapidly increased video visit appointments for members with CKD.

Methods: After the "Shelter in place" order in March 2020, KP nephrologists started weekly virtual townhall meetings to coordinate care among 85 nephrologists in 19 hospitals covering patients with chronic kidney disease, receiving dialysis, and post kidney transplant. TPMG nephrologists have developed guidelines on: 1. Tier testing for Person Under Investigation (PUI) members; 2. Management of patients with Glomerulonephritis; 3. Post-kidney transplant care; 4. Expand advance care planning; 5. Converting direct patient visits to video visits; 6. Coordinating care with contracted dialysis providers for members on outpatient dialysis.

Results: The video visits have increased 780% from March to April and 1968% from March to May of 2020 (Figure). The top three diagnosis for video visits were: CKD3, CKD4, and post kidney transplant. Since April 8, 2020, average 0.038% of Dialysis patients were tested positive for COVID-19 and average 1.6% are PUI.

Conclusions: As an integrated health care system, KPNC has developed a systematic, collaborative and rapid crisis management of patients with CKD in COVID era. Further studies are needed to evaluate the long-term outcomes of these approaches.



PO0854

Benefits of Telephonic Case Management: Increased Home Dialysis and Decreased Hospitalizations

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Background: Home dialysis has been noted to improve quality of life in patients receiving dialysis. Patients at risk for COVID-19 include those on dialysis. The pandemic has resulted in additional focus on social distancing and home dialysis offers this distinct advantage compared to in center hemodialysis. The ASN also similarly has supported advancing education around home dialysis, and COVID is being noted as a true catalyst to home dialysis care. Our study on a commerical poppulation analyzed cost of care with regards to home versus in center dialysis.

Methods: The KRS Case Management program identified and educated commerical patients with this case management benefit regarding the options for home versus in center hemodialysis. Patients were enrolled in the program and educated on the benefits of home dialysis, the benefits of permanent access, and the benefits of transplantation. Cost of care analysis was conduted using claims paid until February 2020, and variables studied included in-patient cost, skilled nursing facility cost, professional cost for dialysis service, facility cost for dialysis service, non dialysis outpatient cost and professional cost for physician visits. Patients were educated telephonically of the benefits of home dialysis and permanent access placment, and demographics including age and gender were also calculated.

Results: A total of 6692 members were analyzed. Of these patients 1793 members were attributed to home based dialysis. It as noted that when adjusting for per diseased member per month, there was a 62% decrease in cost of care for in-patient hospitalizations in the home dialysis group. In addition, there was a striking reduction of 247% in skilled nursing facility costs for the home dialysis group as well. After adjusting for all variables, there as a 5% cost savings in the home dialysis group as compared to in-center.

Conclusions: There are cost of care benefits to home dialysis. Further studies are needed to help identify barriers to home dialysis, and given the advent of COVID-19, it is important to consider home dialysis for all patients more now than ever before.

PO0855

Bridging Office-Based Care with the Virtual Practice Care Model: Evolving Care for CKD Patients in the COVID-19 Pandemic—and Beyond

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Background: Since the outbreak of the coronavirus epidemic, the "virtual" telemedicine has become a critical substitute for patient-provider interactions. However, virtual encounters often face challenges in care for high-risk patients such as chronic kidney disease (CKD) patients. In this study, we explore the patient's satisfaction and practical effects of a newly established telemedicine program in CKD patients' care during the pandemic.

Methods: We established an online CKD patient care program, including triage strategy, medical care delivery, and psychological support, based on a smartphone application. A total of 278 CKD patients were invited, at least 3 months before the pandemic or during the pandemic. A pilot survey interrogating medical and psychological

conditions was conducted. The feedback to the program and the psychological assessment repeated after one month.

Results: Totally, 181 patients showed active responses to the program, with 289 person-time medical consultations occurred during the study. The virtual care program provided a rapid triage, with 17% patients provided a timely referral to in-patient medical encounters. Nearly all patients (97.4%) believed the program was helpful. The number of symptoms (OR 1.309, 95%CI 1.113-1.541; *P*=0.001) and being enrolled during pandemic (OR 3.939, 95% CI 1.174-13.221; *P*=0.026) were associated with high stress. After the follow-up, the high-stress CKD group at baseline showed a significant decrease in avoidance score (6.9±4.7 vs. 9.8±1.9, *P*=0.015).

Conclusions: During the pandemic, we established an online telemedicine care program for CKD patients that provides a rapid triage function, effective CKD disease management, and essential psychological support.

PO0856

How the COVID-19 Pandemic Sparked Change: What Will Be the "New Normal" in Physician Practices and Patient Care?

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Background: The COVID-19 pandemic and resulting social distancing and stay-at-home orders significantly impacted physician practices across the board. The objective of this study was to evaluate the COVID-19 impacts and responses across different specialists as they unfolded and to understand how the model of patient care delivery will change moving forward.

Methods: Survey data was collected weekly or bi-weekly between March 20th and May 8th, to provide rapid responses on the quickly evolving COVID-19 outbreak. Approximately 50 nephrologists participated in each each wave, along with 200 neurologists, dermatologists, rheumatologists and gastroenterologists.

Results: The impact of the COVID-19 outbreak on physician practices was swift and monumental, as of early April office visits were down more than 70% across specialties. As of early May, nephrologists remained one of the hardest hit groups and continued to report 85% fewer patients compared to a typical, pre-COVID week. Nephrology was somewhat buffered from overall declines due to their dialysis patient responsibilities. Not only did these significant drops in patient office visits impact patient access to medical care, physician practices also suffered drastic financial impacts. More than half of the specialists reported a "substantial" impact on the financial health of their practice by early May. Practices responded swiftly with telemedicine adoption, and by early April more than 90% of most specialties had adopted some telemedicine capabilities. By the final wave, 78% reported that the COVID-19 experience will have a lasting impact on how their practice operates from the way physicians interact and see patients to long-term staffing structure and variations in the way they interact with the pharmaceutical industry.

Conclusions: The delivery of patient care, which has remained largely unchanged for decades and relied primarily upon direct, in-person care, has had to evolve to meet the demands of a world in pandemic. As a result, significant changes have occurred with the adoption of telemedicine, and given physicians and patients a new way to interact. Additionally, as practices try to rebuild from significant lost revenues, staffing structures and typical in-office activities, such as meeting with pharmaceutical representatives, along with conference attendance, will likely never return to their pre-pandemic levels.

PO0857

Resource Utilization and Provision of In-Hospital Dialysis in an Academic Hospital in New Orleans During the COVID-19 Pandemic

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Background: COVID-19 has caused an ominous healthcare toll in the United States. New Orleans rated among the top affected cities. Acute kidney injury (AKI) requiring renal replacement therapy (RRT) affected 16% of COVID-19-related hospitalizations, resulting in an exponential upsurge in resource utilization related to RRT. We report our single center experience providing metrics of overall utilization and workforce expansion.

Methods: We conducted a prospective collection of data of daily census of hospitalized patients with COVID-19 and AKI or ESKD for 7 weeks (3/8-4/30, 2020) quantifying usage of RRT equipment and allocation of personnel. Two independent electronic health record databases were simultaneously used to track the data.

Results: Within 1 month, in-hospital COVID-19 census peaked at 377 patients, with 97 (26%) of them receiving RRT at peak day. Starting from a mean of 65 patients on RRT per day in pre-COVID-19 era, the estimated RRT growth peaked at 49%. Four out of 10 newly purchased Fresenius K2 SLED machines (FKs) were utilized by week 5 (after delivery, assembly and negative culture). Starting from an average 80% usage of baseline capacity (31 of 38 FKs), usage of 42 K2s at peak revealed 35% growth. Four new reverse osmosis devices were obtained (growth: 25 to 29, 16%) by week 5. For CVVHDF, 4 PrismaFlex machines (PFs) were rented and 10 new PrisMax were bought. Starting from an average 33% usage of baseline capacity (2 of 6 FKs), use of 6 PFs at peak meant 400% growth. Up to 30 nurses were trained virtually on RRT. Eight agency nurses and 6 perfusionists were recruited, to increase the operator number from 21 to 35 (67% growth). Five of 21 (24%) RRT nurses were out of work at peak due to COVID19+ status. One attending physician, 1 nurse practitioner and 2 subspecialty residents were added to the inpatient service, increasing the number of providers from 9 to 13 (44% growth).

Conclusions: The pandemic of COVID-19 resulted in substantial increase in in-hospital RRT demand and resource utilization. Our experience may provide other centers a guide to optimize preparedness in the event of facing a "second wave" of COVID-19 in the near future. Delay in implementation has to be accounted for during strategic planning.

PO0858

Telemedicine for Nephrology Outpatient Care in a Large Integrated Health System During the COVID-19 Pandemic

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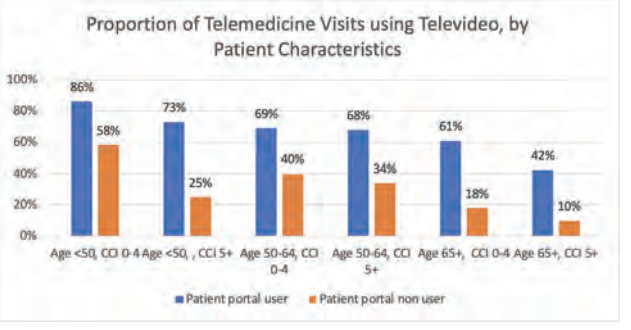
Background: The COVID-19 pandemic has necessitated increased use of telemedicine for outpatient care. Understanding factors impacting access to telemedicine is important to optimize care delivery during the pandemic.

Methods: We examined trends in telemedicine use during the COVID-19 pandemic using data from Geisinger, a large, integrated, predominantly rural health system in central and northeast Pennsylvania. We also examined the association between patient characteristics (age, sex, patient portal status, Charlson Comorbidity Index [CCI]) and use of televideo nephrology visits.

Results: From 3/15/20-5/29/20, nephrology was the top adult specialty using telemedicine at Geisinger in terms of proportion of office visits using telemedicine (televideo or telephone) with 1911 (94% of all outpatient visits). The proportion of nephrology visits using telemedicine increased rapidly from <1% pre-COVID-19 crisis to 21% (week of 3/15/20) to consistently ≥95% each week from (3/22/20-5/29/20). Visit completion rate during this time was 84% with 8% same-day cancellations and 8% no-shows/left prior to being seen. The majority of nephrology clinic patients were ≥65 years old (63%), had severe CCI score 5+ (70%), and had active patient portal status (65%). The proportion of telemedicine visits using televideo was 42% overall with large differences by age, CCI score, and patient portal status **(Figure)**. For example, the proportion of telemedicine visits using televideo was as low as 10% (65+ year old patients, CCI 5+, non-user of patient portal) and as high as 86% (<50 year old patients, CCI score 0-4, active patient portal users).

Conclusions: Telemedicine may serve an important role in providing nephrology care to elderly patients with many comorbidities who are particularly susceptible to ill effects from COVID-19. Patient portal users were much more likely to use televideo for telemedicine visits. Further investigation into the digital divide (e.g. broadband internet access) is needed to optimize care delivery during the COVID-19 crisis.



PO0859

Telemedicine Heightens Healthcare Disparities in Nephrology Ambulatory Care After COVID-19

Florence Lima, Jay Christian, Clay Larkin, Yahya R. Ahmad, Katherine M. Donaldson, Ashami Athukorala, Hana Kebede, Madison Ginn, Madhumathi Rao. *University of Kentucky Medical Center, Lexington, KY.*

Background: The COVID-19 pandemic paused in- person clinic visits and introduced telehealth (TH) creating a paradigm shift in ambulatory practice. TH remains out of reach for many patients, highlighting healthcare (HC) disparities.

Methods: We studied Nephrology ambulatory clinic schedules during the transition to TH (April 1 to May 15 2020) at the University of Kentucky (UK), Lexington KY. We estimated the proportion of patients who could perform TH visits, trends over time, compared TH use in Nephrology vs other clinics (cardiology, pulmonology, Infectious disease, women's health), evaluated causes for non-use, and studied the geographic variation of TH use/non-use across the regions served by the hospital.

Results: TH was successfully adopted by 43.5% of the clinic population, without significant change across weeks (wk) 1 to 5. Wk 6 increased when reimbursement was allowed for telephone visits (p<0.01) (Figure 1). The % of patients unable to do TH dipped from 72% in wk 1 and remained steady at ~56.5% thereafter. Lack of internet access and/or smart device was the most frequent reason. The Nephrology clinic trend did not differ from other clinics. By spatial analysis, TH non-use rates clustered in geographic areas of Eastern and Southern KY with the lowest socioeconomic indices (Figure 2).

Conclusions: The Nephrology clinic at UK, serves the Eastern half of KY, that includes poorer and largely rural regions. While TH provides a remarkably useful tool to reach patients, over 50% did not benefit, and use-rates reached saturation rapidly. TH further highlights HC disparities and the need to mitigate them.

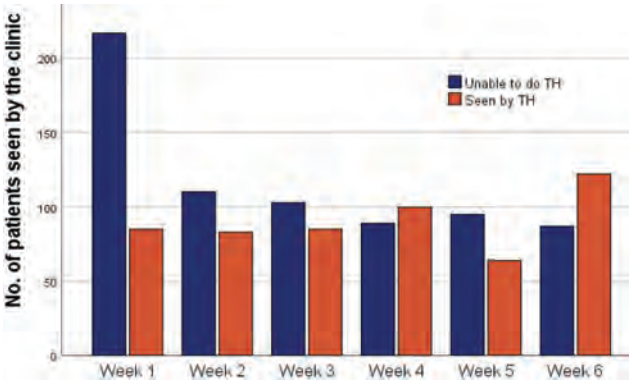


Figure 1: TH trend by week

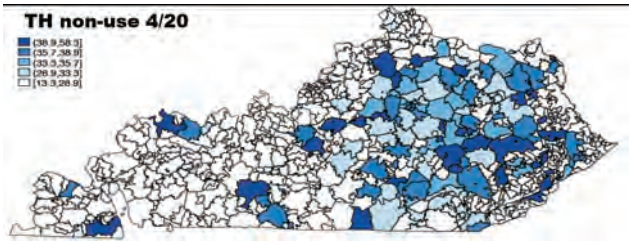


Figure 2: Distribution of TH non-use by zip-code

PO0860

Urgent Training with the Tablo Hemodialysis System in Response to COVID-19

Michael A. Aragon, Michelle L. Gilliland, Marc Maynard. *Outset Medical, Inc., San Jose, CA.*

Background: During the COVID-19 pandemic, many facilities experienced dialysis resource shortages of specialized dialysis staff, sterile dialysate, dialysis systems, and treatment locations. The Tablo® Hemodialysis System was deployed in numerous hospitals to help meet the increased need for dialysis delivery. Tablo is an all-in-one, easy-to-learn system indicated for clinic, hospital and home settings. Features include integrated water purification, on demand dialysate production, simplified user interface and two-way wireless connectivity. Tablo's clinical versatility and simplicity allow for broad prescribing and treatment location options. The objective is to report on Tablo training effectiveness during urgent deployment to facilities amidst the COVID-19 pandemic.

Methods: Standard training with Tablo (< 4 hours) was performed during the peak COVID months of March through May at 51 facilities. Information regarding nursing experience and current role was recorded. Nursing staff trained on Tablo in May completed an electronic survey post-training. Based on a Likert scale ranging from Strongly Agree to Strongly Disagree, respondents rated their satisfaction with training, system ease of use, and confidence performing dialysis independently post training.

Results: Of 926 clinicians trained, 854 were registered nurses (RNs). 136 RNs completed the survey and were representative of the entire group (49% vs 47% ICU, 35% vs 34% HD, 11% vs 16% Non ICU/Non HD). Responses of Strongly Agree or Agree are presented in Table 1 by experience and current role.

Conclusions: Nurses of varied experience and areas of focus trained on Tablo during the pandemic reported: high levels of satisfaction with training, the device was easy to use, and confidence in providing treatment to patients. The Tablo Hemodialysis System can allow training of existing staff to efficiently expand a facility's renal replacement capabilities.

Funding: Commercial Support - Outset Medical, Inc.

Table 1 - Tablo Training Survey Responses

RN	EXP	I am Satisfied with Tablo Training	I Found Tablo Easy to Learn and Use	I am confident Treating with Tablo Independently
HD	≤ 5yrs	100% (8/8)	100% (8/8)	100% (8/8)
	> 5yrs	100% (39/39)	97.4% (38/39)	82.1% (32/39)
ICU	≤ 5yrs	100% (24/24)	95.8% (23/24)	75% (18/24)
	> 5yrs	93% (40/43)	93% (40/43)	76.7% (33/43)
Neither	≤ 5yrs	100% (7/7)	100% (7/7)	100% (7/7)

PO0861

Use of Tablo Hemodialysis Systems to Extend Dialytic Capabilities for the COVID-19-Associated Surge of AKI

David S. Goldfarb,[1,3] Jessica M. Yan,[3] Matthew A. Gross,[3] Clay A. Block.[2] *[1]NYU Langone Health, New York, NY; [2]Dartmouth College Geisel School of Medicine, Hanover, NH; [3]VA New York Harbor Healthcare System, New York, NY, NY.*

Background: The COVID-19 pandemic was associated with a greater incidence of AKI than expected. At the NY Harbor VA we faced an overwhelming number of AKI patients who were critically ill with multi-organ failure. We needed to invoke new mechanisms of providing kidney replacement therapy (KRT).

Methods: We obtained 3 Tablo systems in late March, 2019. The machines have self-contained reverse osmosis capabilities and so do not require other equipment to operate. They can make dialysate from concentrate and tap water and so do not require special plumbing adaptation. Their self-contained step-by-step procedures are relatively simple to follow and allow rapid training of previously unskilled personnel. Tablo generates 300 ml dialysate per minute, and blood flow was increased to up to 400 ml/min as tolerated.

Results: Training was completed by 2 nephrologists and 2 RNs without previous dialysis experience. We used the Tablo Hemodialysis System to provide KRT to critically ill patients. In the first week we demonstrated that water cultures and endotoxin testing were negative, and that AAMI water tests were acceptable. We used the machines to provide KRT for ICU patients with double-lumen dialysis catheters. In addition we used the machines on hospital wards where KRT had not been provided before because of a lack of the plumbing needs of conventional HD machines. We provided multiple treatments 3-6 times per week for 15 AKI patients, mean age 65 years. The mean of the best urea reduction ratio achieved in the first 1-4 treatments, if available, was 41% (often limited by hypotension and fulfillment of ultrafiltration, UF, needs). Most treatments were successful and were slowed for hypotension or tachycardia. Some were aborted because of water pressure alarms if sediment filters needed replacement, or lines clotted due to hypercoagulability associated with COVID-19. Personnel availability dictated that most treatments were 3-4 hours (and up to 8h), and generally achieved UF goals. Later HD nurses cannulated arteriovenous fistulas in ESKD patients and left treatment to non-HD nurses to complete.

Conclusions: By incorporating a user-friendly platform and an accelerated training program including nephrologists and RNs without previous dialysis experience, we were able to nearly *double* our capacity to deliver KRT during the surge.

Funding: Veterans Affairs Support

PO0862

The Introduction of Quanta SC+ to Critical Care for Haemodialysis During the COVID-19 Pandemic

Ian Rechner,[1] Ria D. Mcmullen,[1] Angela M. Clarke,[2] Bernice G. Boore,[2] Emma C. Vaux.[2] *[1]Royal Berkshire NHS Foundation Trust, Reading, United Kingdom; [2]Berkshire Kidney Unit, Royal Berkshire NHS Foundation Trust, Reading, United Kingdom.*

Background: Of 800 patients treated annually in 19 ICU beds (catchment 500,000) 120 require renal replacement therapy (RRT) delivered by Baxter Prismaflex® (continuous veno-veno haemodiafiltration (CVVHDF)). With the onset of the COVID19 pandemic significant increased incidence of acute kidney injury (AKI) requiring RRT & existing intermittent haemodialysis (IHD) patients contracting COVID19 requiring ICU support raised concerns regarding RRT ICU capacity. Additionally a worrying national shortage of CVVHF/HDF consumables & new machines to deliver this requirement; all critical drivers to seek local solutions for RRT provision beyond usual capability

Methods: A kidney unit neighbour described their successful experience trialling SC+ in home IHD patients. Translation of SC+ from home use to safe IHD treatment in ICU was quickly apparent alongside ease of supporting technical infrastructure set up & minimal training requirements. Immediate availability & fiscal acceptability of purchasing 4 Quanta SC+ and 2 supporting RO machines were critical determinants in making IHD a realistic & sustainable solution to desperate RRT shortages. Provision of expert technical support and clinical nurse specialist facilitation expedited training of ICU workforce & enabled swift implementation

Results: 27 ICU nurses were trained in 3 weeks (23 in 14 days). Between 22/4/20 & 17/5/20 8 patients (range 37-63 yrs, median 53.5; 7/8 known IHD, 1/8 AKI; 7/8 COVID19 positive) received 20 treatments (1-5/patient) using SC+ in ICU. An agreed ICU IHD protocol was co-designed gaining consensus in an unfamiliar territory of provision of IHD in ICU & differing clinical perspectives in IHD prescription in a critical care setting

Conclusions: At a time of unprecedented national shortage of dialysis machines & increased RRT need associated with COVID19, Quanta provided an effective solution for safe provision of IHD in ICU. Ease of use with training delivered in <6 hours enabled ICU nurses to effectively treat patients independent of dialysis nurses allowing continuity of the chronic HD programme. Learnings identified the importance of training, enabling rapid growth of a critical mass of expertise & confidence. Critical elements included mastering unfamiliar technique, establishing infrastructure, procurement & team communication enabled by online & face-to-face troubleshooting support

Funding: Commercial Support - Quanta Dialysis Technologies

PO0863

Design of PREVENT: A Phase 2 Study of the Effect of RBT-9 on Progression of COVID-19 Infection in High-Risk Individuals, Including Those with Advanced CKD

Stacey Ruiz,[1] Philip T. Lavin,[5] Donald J. Keyser,[1] Alvaro F. Guillem,[1] Richard A. Zager,[2,3] Bhupinder Singh.[4,1] *[1]Renibus Therapeutics, Southlake, TX; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]University of Washington Department of Medicine, Seattle, WA; [4]University of California Irvine, University of California Irvine, Irvine, CA, US, Department of Medicine, Irvine, CA; [5]Boston Biostatistics Research Foundation, Framingham, MA.*

Background: Coronavirus 2019 (COVID-19) has infected millions of people worldwide, with the US reporting the most deaths. Many individuals are at high risk of disease progression, which may result in multi-organ failure and death. Risk factors include advanced age, cardiovascular disease (CVD), and chronic kidney disease (CKD). In addition, more than 40% of hospitalized patients develop acute kidney injury (AKI), with 20% of those requiring dialysis. Several therapeutic agents are in development, but patients with advanced CKD or those requiring immunosuppressive therapy are frequently excluded from participation in clinical trials. RBT-9, a proprietary formulation of stannous protoporphyrin, has organ protective effects, as demonstrated in animal models of kidney, liver, and lung injury. RBT-9 also has antiviral effects, as demonstrated in several enveloped viruses, including influenza, HCV, dengue, and yellow fever. A Phase 2, randomized, placebo-controlled study was designed to evaluate the effect of RBT-9 on progression of COVID-19 infection in high-risk individuals.

Methods: This study will enroll up to 252 subjects with documented SARS-CoV-2 infection who are at risk of progression based on age (≥70 years) or comorbidities, including CKD (all stages, not on dialysis), CVD, chronic lung disease, diabetes mellitus, obesity, and mild hypoxemia. Subjects will be randomized 2:1 to receive a single dose of RBT-9 or placebo and will be followed for 56 days.

Results: Study Objectives The primary objective is to evaluate the effect of RBT-9 versus placebo on clinical status measured using the 8-point World Health Organization (WHO) Ordinal Clinical Scale at Day 28. Secondary objectives include time to first occurrence of death from any cause or new/worsened organ dysfunction, survival, AKI incidence, new or worsening heart failure, hospitalization status and duration, ICU status, days on ventilator, vasopressor utilization or ventricular arrythmias.

Conclusions: The organ protective and antiviral effects of RBT-9 warrant conduct of this clinical study, which is aimed at preventing progression to severe COVID-19 and organ failure. The first patient is expected to be enrolled in June 2020.

Funding: Commercial Support - Renibus Therapeutics

PO0864

The COVID-19 Infodemic

Tejas Desai,[1] Arvind Conjeevaram.[2] *[1]NOD Analytics, Harrisburg, NC; [2]The Bangalore Hospital, Bangalore, India.*

Background: In Situation Report #13 by the World Health Organization and 39 days before declaring COVID-19 a pandemic, the WHO declared a "COVID-19 infodemic". The volume of coronavirus tweets was far too great for one to find accurate or reliable information. Healthcare workers were flooded with "noise" which drowned the "signal" of valuable COVID-19 information. To combat the infodemic, physicians created healthcare-specific micro-communities to share scientific information with other providers.

Methods: We analyzed the content of six physician-created communities and categorized each message in one of five domains (Symptoms, Diagnostics, Therapeutics, Prevention, Pathophysiology). We programmed 1) an application programming interface to download tweets and their metadata in JavaScript Object Notation beginning 11 March and 2) a reading algorithm using visual basic application in Excel to categorize the content. We superimposed the publication date of each tweet into a timeline of pandemic events. Finally, TD created a free repository of the dataset in the #NephTwitter Archives (https://bit.ly/2M6HJQ2) to help healthcare workers find quality information when treating patients.

Results: From 11 March to 27 April, 45% of the 19270 tweets in the dataset were categorized (signal). Tweets about Therapeutics (34%) and Prevention (32%) were the most prevalent. Tweets about Therapeutics spiked six times; the first coming 4 days after the WHO declared COVID-19 a pandemic. The largest spike came on day 8: 5 days after the US President suggested hydroxychloroquine as a potential treatment. Tweets about antimalarial therapy comprised 15% of tweets in this category. Tweets about Prevention spiked five times; the largest coming 21 days after the pandemic declaration when 1 million global cases were reported. Protective equipment comprised 13% of tweets in this category. There were 2210 searches performed of the signal tweets in the #NephTwitter Archives. Evidence-based tweets comprised 1 in every 8 tweets in the categorized corpus. That ratio was better for tweets about antimalarials (1 in 3) and vaccines (2 in 3), the same for protective equipment, and worse for mechanical ventilation (1 in 31).

Conclusions: Algorithmic coding can 1) mitigate the COVID-19 infodemic and 2) identify & elevate illuminating evidence-based tweets. Both outcomes help healthcare workers find higher-quality information to combat the pandemic.

PO0865

The Impact of the COVID-19 Pandemic on the Mental Health of Health Workers Treating Patients with Kidney Diseases in Latin America (LA): Analysis from GlomCon Latin America Working Group (LGlomCon)

Sonia Rodriguez Ramirez,[1] Franco H. Cabeza Rivera,[2] Julio A. Gutierrez-Prieto,[3] Javier Soto-Vargas,[4] Blanca Martinez-Chagolla,[5] Denisse Arellano-Mendez,[6] Diana Aguirre,[7] Desiree Garcia Anton,[2] Carmen Avila-Casado.[1] GlomCon Latin America Working Group (LGlomCon) *[1]University Health Network, Toronto, ON, Canada; [2]University of Mississippi Medical Center, Jackson, MS; [3]Hospital Central del Estado de Chihuahua, Chihuahua, Mexico; [4]Hospital General Regional 46, Guadalajara, Mexico; [5]Hospital General "Dr. Miguel Silva", Morelia, Mexico; [6]Unidad Medica de Atencion Ambulatoria 254, Morelia, Mexico; [7]Hospital General de Mexicali, Mexicali, Mexico.*

Background: The rapid spread of the COVID-19 pandemic into LA countries where health systems were already facing major limitations might further challenge their physician's emotional and mental wellbeing. We aimed to describe the perception of health workers managing kidney diseases in the context of the COVID-19 pandemic.

Methods: Descriptive analysis extracted from an online survey carried out among nephrologists, renal pathologists, and other health workers treating kidney diseases between May 20-27, 2020 from sixteen Spanish speaking Latin American countries divided into 6 categories. We present the results for the mental health category.

Results: 430 responses were obtained of which 360 (84%) were considered for analysis. The participants were mainly nephrologists 276 (86%), renal pathologists 13 (4%), and physicians in training 11 (3%). Ages ranged between 30-49 years old in 271 (75%), mostly working on tertiary centers 258 (71%). 329 (90%) participated in inpatient care. 277 (86%) considered that the COVID-19 pandemic has impacted their mental health. Prevailing symptoms were anxiety, insomnia, and depression, with 75.2%, 42.5%, and 18.2%, respectively. Physical or verbal violence from the community was reported by 18 (5%) of the participants because they were seen as a source of viral transmission. 179 (55%) considered personal protective equipment (PPE) was sufficiently provided and 275 (79%) had to invest up to 20% of their income to obtain PPE. In addition, 144 (44%) of the respondents reported a shortage of COVID-19 tests and only 99 (30%) felt their hospital was well equipped to care for COVID-19 patients. 126 (39%) of the health workers responded that they received adequate training, while 105 (32%) endorsed they did not feel prepared in the management of patients with COVID-19.

Conclusions: This survey reveals the considerable impact that the COVID-19 pandemic is generating among physicians treating patients with kidney diseases in LA. Possible aggravating factors also found in our survey included lack of testing, PPE availability, and overall hospital preparedness.

Funding: Private Foundation Support

PO0866

Developing a COVID-19 Screening Program for an Emergency-Only Dialysis Cohort Within a Large Public Safety-Net Hospital

Ravi D. Bhatia,[1,2] Lauren Kasper,[1,2] Sarah A. Johnson.[1,2] *[1]Emory University School of Medicine, Atlanta, GA; [2]Grady Health System, Atlanta, GA.*

Background: As the prevalence of coronavirus disease 2019 (COVID-19) worsens, one patient population that warrants further inquiry are those receiving emergency-only hemodialysis (EoHD). This cohort specifically at Grady Health System (GHS) in Atlanta, consisting largely of undocumented immigrants, receives 1-3 times weekly hemodialysis (HD) via emergency departments due to legislative restrictions on Medicaid funding. GHS has one of the largest populations of EoHD patients in the nation. The cohort of 91 patients is 89% Hispanic with a mean age of 51. The majority of patients, 69%, reside in Fulton or DeKalb counties, the intended service region for GHS. The remaining patients reside in more distant counties, potentially increasing risk of transmission to a larger area. Prior to our screening program, 6 patients in the cohort had positive diagnostic tests and 4 of these patients required hospitalization (67%). Notably, 3 out of those 4 patients were admitted due to hypertensive emergency with pulmonary edema, so symptomatic COVID disease is debatable. Due to the frequency of hospital visits and requirement of isolation HD treatments if COVID+, a screening of the cohort was conducted. Our aim was to establish a baseline prevalence rate to direct an ongoing screening program in this vulnerable population.

Methods: Over 5 days, we conducted 84 COVID PCR screening tests via nasopharyngeal swab. One patient was excluded due to missed sessions. Patients were asked about symptoms prior to swabs. Swabs were obtained by a single operator in a consistent fashion. Data was collected and stratified by patient demographics.

Results: A total of 84 patients were screened for COVID. Notably, 3 asymptomatic patients had positive results, a rate of 3.6%, and 6 patients had positive diagnostic tests prior to screening, resulting in a rate of 9.9% positive COVID tests. 6 patients were DeKalb/Fulton residents (67%).

Conclusions: The risk of COVID-19 in EoHD patients is an issue that will require a coordinated effort to prevent the spread of disease. A collaboration between nephrology and infectious diseases has led to the implementation of a bimonthly screening program. Future directions include antibody screens and contact-tracing to understand more fully the spread of disease as well as elucidating the asymptomatic positive rate vs. actual disease prevalence.

PO0867

SARS CoV-2 Continuous Quality Improvement Program: Initiation of a Standardized Protocol for AKI Prevention

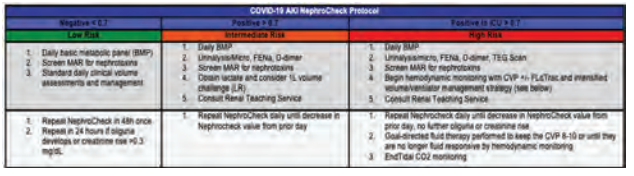
Adam Dossaji, Asad H. Khan, Spencer Hodgins, Daniel L. Landry, Daniel Engelman, Jonathan Slater, Bill Mcgee, Michael J. Germain. *Baystate Medical Center, Springfield, MA*.

Background: During the initial phase of the SARS CoV-2 pandemic our institution had high rates of acute kidney injury (AKI) requiring renal replacement therapy (RRT). Nephrocheck (NC), a renal biomarker, indicating renal stress was the basis of a continuous quality improvement (CQI) program to identify patients at risk for AKI & RRT.

Methods: Patients admitted from 4/17-5/15/2020 were all tested for SARS CoV-2. All positive patients ≥ 18 years old & with a creatinine <2.0 mg were tested with NC. Values ≥ 0.7 led to nephrology consults & utilization of a renal-protective strategy including monitoring volume status, scrutinizing nephrotoxic medications & urine studies. A "Plan-Do-Study-Act" approach was used to increase utilization of NC and the resulting protocol for positive results. Intervention was biphasic with a follow up maintenance phase, each lasting 10 days. Phase 1 was adding NC to the SARS CoV2 admission order set & Phase 2 was educating hospitalist providers about using and interpreting NC to increase appropriate nephrology consults. Education was reinforced with protocol cards & reminders via encrypted text services. Additionally, intervention team members reviewed charts daily & reminded providers in real time.

Results: In Phase 1, 58% of the SARS CoV-2 positive patients had a NC but only 48% of NC positive patients had a renal consult. In Phase 2, 79% of SARS CoV-2 positive patients had a NC with 80% of positive patients getting a renal consult. In the maintenance phase, 67% of SARS CoV-2 positive patients had NC with 59% of NC positive patients getting a renal consult.

Conclusions: During our CQI project, efforts to mitigate severe AKI by using a biomarker-based alert for nephrology consultation saw the number of SARS CoV2 positive patients screened with NC & the number of positive NC patients seen by nephrologists rise significantly. Barriers to implementation included the weekly turn-over of house staff & a reliable alert system to ensure adequate screening. The multidisciplinary team reviewing charts and reminding hospitalists of the protocol also helped significantly but was difficult to sustain.



COVID-19 AKI NephroCheck Protocol

Negative < 0.7	Positive > 0.7	Positive in ICU > 0.7
Low Risk	Intermediate Risk	High Risk
1. Daily basic metabolic panel (BMP) 2. Screen MAR for nephrotoxins 3. Standard daily clinical volume assessments and management	1. Daily BMP 2. Urinalysis/Micro, FENa, D-dimer 3. Screen MAR for nephrotoxins 4. Obtain lactate and consider 1L volume challenge (LR) 5. Consult Renal Teaching Service	1. Daily BMP 2. Urinalysis/micro, FENa, D-dimer, TEG Scan 3. Screen MAR for nephrotoxins 4. Begin hemodynamic monitoring with CVP +/- FLoTrac and intensified volume/ventilator management strategy (see below) 5. Consult Renal Teaching Service
1. Repeat NephroCheck in 48h once 2. Repeat in 24 hours if oliguria develops or creatinine rise >0.3 mg/dL	1. Repeat NephroCheck daily until decrease in Nephrocheck value from prior day	1. Repeat Nephrocheck daily until decrease in NephroCheck value from prior day, no further oliguria or creatinine rise 2. Goal-directed fluid therapy performed to keep the CVP 8-10 or until they are no longer fluid responsive by hemodynamic monitoring 3. EndTidal CO2 monitoring

PO0868

Renal Critical Care Project Management of COVID-19 Pandemic Surge

Richard L. Barnett, Steven Fishbane, Mark A. Finger. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

Background: The COVID-19 surge for the NY area severely stretched hospitall resources as critical care areas expanded 2-3 fold. In addition to well chronicled ventilator management of respiratory failure, 37% sustained some degree of AKI with many requiring continuous renal replacement therapy (CRRT). The challenge of providing optimal renal critical care given unprecedented demand was met with a defined project plan which required close integration of physician, nursing, pharmacy and materials management resources over multiple hospital sites

Methods: The Renal Critical Care Project Management Team (T) initially met on 3/11 and identified likely shortfalls in the quantity of Baxter Prisma machines for Long Island Jewish and contiguous Cohen Children's Hospital (LIJ 7), Southside Hospital(SSH 3) and NorthShore University Hospital (NSUH 18). 10 PrisMax and an additional 5 Prismaflex were delivered to NSUH and redeployed as required. Alternative CRRT fluid supplies were defined as T precluded acute PD. Spot shortages of machines, fluids and filter sets by 3/26 finalized the creation of multisite T with project manager selected from Central Procurement. Detailed communication plan kept all components and sites informed of daily changes.

Results: During the Pandemic Peak 4/3-5/1 T met daily. From 445-845 am Director of Renal Critical Care examined the electronic records from 74-92 COVID+ patients receiving CRRT, HD OR deemed likely to require RRT in the near future, and reviewed with each renal provider. At 9am T examined supplies of machines, fluids and filter sets, requiring daily shift of resources among each site 4/3-4/24. Machines were redeployed SSH(6), LIJ(13) and NSUH(24) with 36 peak total daily usage. Each patient averaged 13 five L/bags fluid daily which could be reduced by SCUF or other methods. Pre COVID filter life of 22 hours declined by half in these hypercoagulable patients only partially offset by step wise anticoagulation strategy. Fluid supplies during these 3 weeks averaged 1-2 days with low 0.25 on 4/22. A SLED program was initiated 4/21. FIVE day fluid and filter supplies were delivered 4/24.

Conclusions: The magnitude of the COVID-19 surge required tight project management to ensure adequate renal critical care. The ability to shift resources among multiple sites using CRRT was a major key to success. This integrated approach may have application for future pandemic surges.

PO0869

Electrolyte Abnormalities in Hospitalized Patients with COVID-19

Diane Liu,[1] Molly Fisher,[2] Abby M. Basalely,[1] Neelja D. Kumar,[2] Jyotsana Thakkar,[2] Ladan Golestaneh,[2] Kimberly J. Reidy,[1] Wei Chen.[2] *[1]Children's Hospital at Montefiore, Bronx, NY; [2]Montefiore Medical Center, Bronx, NY.*

Background: Electrolyte abnormalities have been observed in hospitalized patients with COVID-19. Whether the prevalence of electrolyte disturbances differ between hospitalized patients with and without COVID-19 is unknown.

Methods: We performed a retrospective observational study of adult patients hospitalized in a large tertiary healthcare system in the Bronx between March 11-April 26, 2020. We compared the prevalence of the disturbances in sodium, potassium, calcium and magnesium between patients with and without COVID-19 using Chi-square. Electrolyte disturbances were defined as the following: hypernatremia (>145 mEq/L), hyponatremia (<135 mEq/L), hyperkalemia (>5 mmol/L), hypokalemia (<3.5 mmol/L), hypermagnesemia (>2.5 mEq/L), hypomagnesemia (<1.5 mEq/L), hypocalcemia (<8.5 mg/dL) and hypoalbuminemia (<3.5 g/dL).

Results: Of 4579 patients, 51.8% were male. Median age was 65 years, IQR (52-76). 3313 (72.3%) were positive for the COVID-19. Hypernatremia, hyponatremia, hyperkalemia, hypermagnesemia, hypocalcemia, and hypoalbuminemia were significantly more common in hospitalized patients with COVID-19 (p<0.0001).

Conclusions: Dysnatremias, hyperkalemia, and hypermagnesemia were more common in patients with COVID-19. Hypocalcemia was more common in patients with COVID-19 but this may be due to a higher prevalence of hypoalbuminemia. Further studies are needed looking at adjusted models to describe the association between electrolyte abnormalities and clinical outcomes.

Funding: NIDDK Support

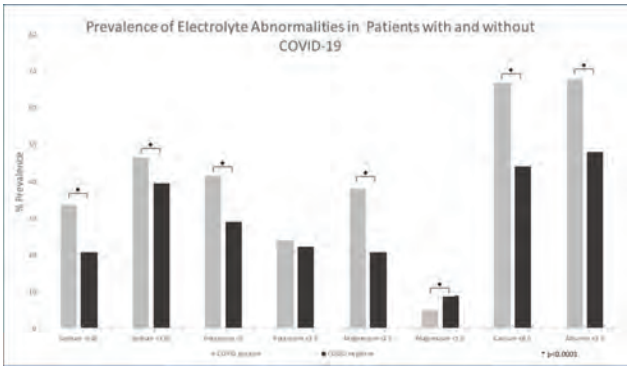


Figure 1. Prevalence of Electrolyte Abnormalities in Patients with and without COVID-19

PO0870

Quality Improvement Project: Examining Urine Sediment and Microscopic Findings in COVID-19 AKI Patients

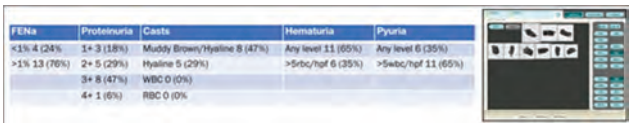
Abdulhadi T. Gelaidan, Ajai S. Rajabalan, Janice P. Lea, Jose E. Navarrete, Jason Cobb. *Emory University School of Medicine, Atlanta, GA.*

Background: The examination of the urine microscopy manually is common in the work-up of AKI. SARS-CoV-2 has been detected in urine samples of infected patients. There have been safety concerns about the handling of urine samples in patient under investigation and COVID-19 confirmed cases. Limitations in personal protective equipment have provided challenges. There has been limited reports of urine microscopic findings during the COVID-19 pandemic. We developed a QI project examining the urine sediment of COVID-19 AKI patients from digital pictures provided by the IRIS IQ200 Microscopy System.

Methods: This QI project took place at Emory University Hospital Midtown. We retrospectively evaluated baseline characteristics, labs, and urine volume. The urinalysis and urine sediment were evaluated for each patient by digital images produced by the IRIS IQ200 Microscopy System.

Results: A total of 17 African American patients with a mean age of 71±12.5 years (range, 55 to 98); 64.7 % were female. Comorbidities included hypertension (94.1%), diabetes (58.8%), CAD (11.9%) and CKD (52.9%). Average serum creatinine was 3.1 mg/dL. 8 patients (47%) were oliguric; 4 patients had FENa < 1%. 8 patients (47%) had 2+ proteinuria. 9 patients (52.9%) had a positive leukocyte esterase and all were nitrate negative. 8 patients (47%) had ATN with visible muddy brown casts. 6 patients (35%) had ≥ 5 rbc/hpf and 11 patients (65%) had ≥ 5 wbc/hpf. 8 patients (47%) had shock requiring vasopressor support, 8 patients (47%) required dialysis and 13 patients (76.5%) required mechanical ventilation.

Conclusions: Urinalysis and urine microscopy are important in evaluation of AKI, and there is a paucity of data about findings in COVID-19 AKI patients. Without conclusive evidence of the infective potential of urine samples, it is much needed at this time to device a safe alternative to manual urine microscopic examination. Almost half of our patients had ATN and we were able to arrive at the diagnosis using digital images from this automated urine microscopy system. Use of such technology will help nephrologists safely examine urine sediments and minimize exposure to COVID-19.



FENa	Proteinuria	Casts	Hematuria	Pyuria
<1% 4 (24%	1+ 3 (18%)	Muddy Brown/Hyaline 8 (47%)	Any level 11 (65%)	Any level 6 (35%)
>1% 13 (76%)	2+ 5 (29%)	Hyaline 5 (29%)	>5rbc/hpf 6 (35%)	>5wbc/hpf 11 (65%)
	3+ 8 (47%)	WBC 0 (0%)		
	4+ 1 (6%)	RBC 0 (0%		

PO0871

Clinical Relevance of AKI Trial Data for Severe COVID-19 Patients

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Background: Coronavirus disease 19 (COVID-19), caused by SARS-CoV-2 was declared a pandemic in March 2020 and remains without any approved treatments. After entering the cells, the virus begins to replicate and viral antigen is presented to antigen presenting cells (APCs), the cells that stimulate the body's normal anti-viral immune response. In severe cases however, this immune reaction becomes dysregulated as evidence by high levels of certain cytokines and chemokines in the blood, a reaction known as cytokine storm. This results in a systemic uncontrolled inflammatory state that triggers a violent attack by the immune system to the body, causes acute respiratory distress syndrome (ARDS) and multiple organ failure, leading to death.

Methods: Mesenchymal stromal cells (MSCs) are a unique source of secreted factors that modulate an inflammatory response and enhance the repair of injured tissue. MSCs have been extensively studied in ARDS and other acute organ injuries. Sentien has created a novel delivery approach to enable sustained exposure to MSCs and their secreted factors, overcoming limits of cell transplantation/infusion while preserving their broad acting and dynamically responsive properties. Our lead product, SBI-101, contains allogeneic human MSCs inoculated into a hollow-fiber hemofilter, which enables communication with patient blood via the semi-permeable membrane, while maintaining MSC viability. Through this interplay, SBI-101 aims to restore balance to the immune system by reprogramming the molecular and cellular components of blood in patients with severe inflammation and organ injury.

Results: Sentien's Phase I/II clinical study of SBI-101 in critically ill patients with Dialysis-Requiring Acute Kidney Injury (AKI-D) has produced data to support the therapeutic hypothesis of SBI-101. Consistent with MSC biology, inflammatory markers, such TNFa and IFNg, were shown to be modulated, suggestive of a shift from a pro- to an anti- inflammatory state in treated patients.

Conclusions: Data obtained in our AKI-D trial showed modulation of many biological molecules and immune populations that may be correlated with severe COVID-19 immunopathology. Here we make the case, using our existing AKI-D trial data, that SBI-101 may be of therapeutic benefit to severe cases of COVID-19.

PO0872

Point-of-Care Ultrasound Findings in Patients with COVID-19 and AKI

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Background: More than one third of patients presenting with COVID-19 in the United States develop acute kidney injury (AKI) and many require dialysis. AKI portends a poor prognosis particularly if dialysis is required. Point-of-care ultrasound (POCUS) is a valuable tool for the evaluation of AKI particularly for assessment of volume status. Here we describe clinical and ultrasonographic characteristics of COVID-19 patients with AKI.

Methods: This cohort includes prospectively enrolled adult patients with confirmed COVID-19 who developed AKI as part of their hospital encounter in April and May of 2020. Ultrasounds were performed using a published 12-point lung and limited 5-view cardiac protocol. The diagnosis of AKI was determined by a nephrologist. The institutional review board at the University of Pennsylvania approved this study.

Results: 33 patients were included. 79% were African-American. 56% were female. Median age was 65 and average BMI 30±9. 29% had CKD, 47% had diabetes, 68% had hypertension and 24% had heart failure. 12 experienced stage 1 AKI, 4 had stage 2 AKI, 17 had stage 3 AKI, and 10 required dialysis. 16 patients (52%) had a diagnosis of acute tubular injury. 18 (53%) had significant proteinuria, 24 (71%) had hematuria, and 20 (59%) had pyuria. 73% required ICU admission, 15 were discharged and 5 died. 25 of 33 had a left ventricular ejection fraction (EF) assessment, 22 had an EF >55%, 4 had an EF 30-55% and 1 had an EF <30%. 23 had an assessment of their inferior vena cava (IVC). 8 had a normal IVC, while 6 had a full, non-collapsing IVC and 9 had a flat IVC. 5 had pericardial effusion. 2 had right-ventricular dysfunction. The lung US assessments included an average of 10 of the 12 specified zones, favoring the anterior zones. An average of 3.8 zones per scan showed scattered b-lines, 3.1 zones showed confluent b-lines and 1.0 zone showed consolidations. 3 patients had pleural effusion.

Conclusions: Our study describes cardiac and lung US findings in patients who experience AKI during their COVID-19 course. Most patients had multifocal b-line findings. Most had normal ejection fractions but there was wide variation in IVC distension. More studies are needed to determine if ultrasound can guide fluid management or identify reversible causes of AKI.

PO0873

Constitutive Activation of Hedgehog Signaling Disrupts Nephrogenic and Stromal Differentiation

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Background: Nephron progenitors (NPs) and stromal cells differentiate from a common *Osr1+* progenitor. While maldifferentiation of nephrogenic and stromal tissue is a hallmark feature of renal dysplasia, signaling mechanisms regulating the genesis of stroma relative to NPs are largely undefined. We have shown that increased Hedgehog (Hh) signaling in murine *Osr1+* cells *in vivo* causes urinary tract obstruction through abnormal stromal cell localization (Sheybani-Deloui et al., 2018). Here, we investigated mechanisms that function downstream of Hh to control NP and stromal cell differentiation using human induced pluripotent stem cell (hiPSC) kidney organoids and genetic mouse models.

Methods: Agonists of the Hh receptor, SMO, were added to hiPSCs differentiated into kidney organoids at the stage of cell aggregation. Mature organoids were analyzed by histology, light sheet fluorescence microscopy, and RNA microarray. Processes downstream of Hh signaling were investigated in mouse kidneys with deficiency of *Ptch1* specific to FOXD1(+) stromal cells (*FoxD1Cre;Ptch1*$^{loxP/-}$) using histology, RNAseq, and scRNAseq.

Results: Stimulation of Hh activity in kidney organoids with SAG (120 nM) or Purmorphamine (10 μM) resulted in a 26% increase in surface area compared to controls. Volumetric analysis using light sheet fluorescent imaging of WT1+ nephrogenic structures and CDH1+ tubular structures in SAG-treated organoids demonstrated an 88% (n=3, $p<0.01$) and 67% (n=3, $p<0.05$) reduction, respectively. In contrast, the mass of non-epithelial cells was increased by 79% (n=2, $p<0.05$). RNA microarray analysis of SAG-treated organoids (n=3) revealed elevated expression of medullary stromal markers *TnC* (2.60 fold-change [FC], $p<0.01$) and *Pdgfrb* (1.60 FC, $p<0.01$), and decreased expression of nephron markers *Nphs1* (0.23 FC, $p<0.01$), *Slc3a1* (0.32 FC, $p<0.01$), and *Slc12a1* (0.08 FC, $p<0.001$). Mice with constitutive Hh activity in FOXD1+ stromal cells showed a 41% reduction in nephrons at E18.5 (n=4, $p<0.05$) and a 19.5% decrease in nephron intermediate structures at E15.5 (n=4, $p<0.01$). In contrast, RNAseq of E13.5 mutant kidney tissue demonstrated increased expression of medullary stroma genes *TnC* and *Pdgfrb*.

Conclusions: Increased Hh signaling in human and mouse increases differentiation of stroma compared to NPs, providing new insights into mechanisms that may underlie kidney dysplasia.

Funding: Government Support - Non-U.S.

PO0874

Caspase Inhibition in a Mouse Model of Prenatal Ureteropelvic Obstruction Rescues Normal Ureter Development

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Background: The most common cause of congenital obstructive nephropathy is ureteropelvic junction obstruction (UPJO). We previously described a unique mouse model of *in utero* UPJOs through urothelial knockout of Exoc5, a central subunit of the exocyst trafficking complex. In this neonatal-lethal model, UPJO formation is preceded by urothelial cell death in the ureter between E16.5 and E17.5. Here, we investigated if normal ureter development could be restored in this mouse model by blocking cell death pathways, and conversely, if we could induce UPJOs by simply activating urothelial cell death during ureter development.

Methods: We utilized the Cre-lox system to achieve either targeted gene knockout or activation during mouse embryonic development. For inhibition of cell death pathways in Exoc5$^{FL/FL}$;Ksp-Cre ureters, we performed IP injections of caspase inhibitors into pregnant mice at gestational day E16.5. Also, diphtheria toxin A (DTA) mice crossed with Ksp-Cre^{ERT2} mice were used to investigate the effect of inducing urothelial cell death with tamoxifen administration at E16.5.

Results: Morphologically, dying Exoc5-KO urothelial cells appeared more necrotic than apoptotic, and they were negative for cleaved PARP and active caspase-3. However, a single IP injection of pan-caspase inhibitor z-VAD-FMK at E16.5 rescued ureter development in all Exoc5$^{FL/FL}$;Ksp-Cre mice analyzed. At E18.5, all z-VAD-FMK treated embryos displayed patent ureters with no hydronephrosis (n=9 from multiple litters). If followed past birth, z-VAD-FMK treated Exoc5$^{FL/FL}$;Ksp-Cre mice survived to adulthood. Interestingly, caspase-1 inhibitor Ac-YVAD-cmk also rescued ureter development when injected at E16.5, supporting the hypothesis that a non-apoptotic pathway is responsible for urothelial cell death in this mouse model. Conversely, DTA-induced urothelial cell death in E16.5 ureters showed evidence of UPJO formation by E18.5.

Conclusions: Based on these findings, we have shown that urothelial cell death is a critical event leading to UPJO pathogenesis and lethality in our mouse model. The data suggest inflammasome-associated caspase-1 may play a role in activating cell death in urothelial cells with disrupted exocyst trafficking.

Funding: NIDDK Support

PO0875

Exocyst Inactivation in Urothelial Cells Disrupts Autophagy and Upregulates the Fibroblast Growth Factor-Inducible 14 (Fn14) Receptor

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Background: Despite their prevalence, the etiology of congenital ureter obstructions in infants is poorly understood, with little evidence identifying genetic or environmental causes. We previously reported a unique mouse model of *in utero* ureteropelvic junction obstruction (UPJO) in which ureter urothelial cells with deleted Exoc5 gene failed to differentiate into a stratified epithelium and underwent cell death. This resulted in bilateral UPJOs, hydronephrosis, and neonatal lethality. Here, we investigated the urothelial cells prior to cell death to identify the disrupted cell processes necessary for urothelial differentiation and ureter development.

Methods: Gene expression profiling was performed on E16.5 ureters of $Exoc5^{FL/FL}$;Ksp-Cre mice and control littermates, with validation using real time qPCR and immunohistochemistry. Follow up investigations utilized an *ex vivo* ureter explant organ culture model, where mouse embryonic ureters were isolated at E15.5 and maintained in culture for 72 hours. Additionally, we used primary human urothelial cells (pHUCs) and immortalized SV-HUC1 cells for advanced studies on exocyst regulation of autophagy, which was measured through immunoblotting and immunostaining of p62, LC3I/II, and autophagy-related genes (ATGs).

Results: Analysis of gene profiling data from E16.5 $Exoc5^{FL/FL}$;Ksp-Cre ureters revealed that metabolic pathways were significantly downregulated and NF-kB signaling was significantly upregulated, indicating cell stress. The highest upregulated gene was Fn14 (>30-fold), a member of the TNF receptor subfamily that binds the ligand TWEAK. Fn14 is upregulated in damaged tissues and can activate non-canonical NF-kB signaling and cell death via multiple pathways. Using ureter explants and cell line models, we found exocyst is critical for urothelial autophagy, which when disrupted, led to a high Fn14 increase and cell death.

Conclusions: From our data, we propose that autophagy is necessary for urothelial differentiation during ureter development, and irregular autophagy may trigger urothelial cell death through Fn14 signaling. This disruption of autophagy during a critical stage in ureter development may contribute to UPJOs in humans.

Funding: NIDDK Support

PO0876

Transcription Factor 21 Regulates Nephron Progenitor Cells Self-Renewal/Induction and Podocyte Development

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Background: Most forms of CAKUT arise from mutations in genes of kidney development. We previously showed that Transcription Factor 21 (Tcf21) regulates branching morphogenesis by downregulating GDNF. We now aim to study Tcf21 in nephron progenitor cells (NPC). During nephrogenesis, WNT9b signals to NPC through the canonical Wnt/β-catenin pathway, which promotes both self-renewal at a state of low β-catenin level, and induction at a state of high β-catenin. Following induction, β-catenin level must decrease for MET to progress. Additionally, optimal intensity of β-catenin is essential for NPC differentiation to podocytes. Hence, discrete levels of β-catenin promote disparate cell fates. It remains unclear however what drives this change and direct NPC to exit/maintain self-renewal.

Methods: Kidneys from $Six2CreTcf21^{f/f}$ mice were extracted for qPCR and immunohistochemistry. MK3 cells were used to study Tcf21 signaling. Recombinant Tcf21 was used for over-expression.

Results: $Six2CreTcf21^{f/f}$ kidneys show marked decrease in Cited1 expression from E12.5 through P0 compared to control, while still expressing normal levels of Six2, indicating decreased self-renewing NPC population. $Six2CreTcf21^{f/f}$ kidneys also demonstrated low Lef1 expression suggesting decreased NPC epithelialization. However, Wnt4, a marker of the pretubular aggregate, was persistently elevated in the developing nephrons of $Six2CreTcf21^{f/f}$. This state of $Cited1^{low}Wnt4^{high}Lef1^{low}$ in the mutants suggests arrested MET and persistently elevated β-catenin levels in the differentiating progenitors. In uninduced mesenchymal cell culture (MK3), over-expression of wild-type Tcf21 led to enhancement of genes that mark renewing NPC: Cited1, Tafa5, and Pla2g7, while over-expression of mutated-Tcf21 abrogated that enhancement, again supporting Tcf21 involvement in NPC dynamics. As to podocyte differentiation, lineage tracing of Tcf21Cre showed its expression in a subset of NPC in the cap-mesenchyme and then in developing and mature podocytes. At P0, $Six2CreTcf21^{f/f}$ kidneys showed very low podocin expression. This suggests that Tcf21 is required for NPC differentiation to podocytes.

Conclusions: Together, these data suggest that Tcf21 modulates Wnt/β-catenin signal intensity spatially and temporally to direct NPC toward self-renewal or differentiation.

Funding: NIDDK Support, Private Foundation Support

PO0877

A Novel ADPKD Model Using Kidney Organoids Derived from Disease-Specific Human Induced Pluripotent Stem Cells

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most prevalent hereditary diseases, accounting for up to 10% of end-stage kidney disease worldwide. Although many disease models have been proposed for ADPKD, the pre-symptomatic pathology of the human disease remains unknown and no definitive therapies are currently available. To elucidate the mechanisms of early cytogenesis, robust and genetically relevant human models are needed.

Methods: Using a stepwise differentiation protocol that we have recently reported (Tsujimoto H. et al., 2020), we generated kidney organoids from two kinds of disease-specific human induced pluripotent stem cells (hiPSCs), *PKD1* gene-edited hiPSCs and ADPKD patient-derived hiPSCs. We applied chemical treatment to reproduce cystic phenotypes within kidney organoids, quantitatively analyzed macroscopic cystic lesions, and performed immunofluorescence analyses. ADPKD patient-derived kidney organoids were further utilized to examine the effects of known inhibitors of cystogenesis.

Results: Although wild-type organoids developed cystic lesions under forskolin, *PKD1*-mutant organoids exhibited significantly larger cystic areas depending on the *PKD1* genotype. Importantly, ADPKD patient-derived kidney organoids as well as gene-edited heterozygous *PKD1*-mutant ones also recapitulated cystogenesis *in vitro*. Immunofluorescence analyses confirmed that the cyst epithelia predominantly originate from LTL-positive cells. Furthermore, inhibitor experiments suggested the predictive validity of patient-derived kidney organoids as a disease model.

Conclusions: We established a novel model for ADPKD using kidney organoids differentiated from gene-edited *PKD1*-mutant and ADPKD patient-derived hiPSCs. Further, we demonstrated the possibility of ADPKD kidney organoids serving as drug screening platforms. This newly developed model will contribute to identifying novel therapeutic targets, extending the field of ADPKD research.

Funding: Government Support - Non-U.S.

PO0878

Kidney Organoids Represent a Novel Platform to Study Adaptive and Innate Immunity

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Background: Human kidney organoids have been utilized as a model to study genetic kidney diseases and kidney development. Innate or adaptive immune responses in organoids are currently poorly defined. Kidney transplant rejection and activation of complement pathways are two common renal immune phenomena. SARS-CoV-2 virus, the pathogen of the recent pandemic, leads to complement pathway activation in human kidneys and can infect kidney organoids. Here, we investigated (i) the alloimmunogenicity of kidney organoids in a humanized mice model, and (ii) the responses to exogenous complement C5a and spike protein (S1) of SARS-CoV-2 in kidney organoids.

Methods: Kidney organoids were generated from human embryonic stem cells using protocols developed in our laboratory, and transplanted under the kidney capsule in humanized (BLT) mice. Immunophenotype, mixed lymphocyte reaction, and intracellular cytokine staining were analyzed from grafts and mouse splenocytes collected after 30 days of transplantation. In other experiments organoids were treated with S1 protein and human recombinant C5a for 24 hours or 3 days respectively, followed by qPCR and immunofluorescence analysis.

Results: Transplanted organoids were extensively infiltrated by lymphocytes. Graft $CD8^+$ T cells demonstrated a switch from naïve to memory T cells. Splenocytes isolated from transplanted BLT mice showed increased IFN-γ and TNF-α. Splenocytes proliferated after exposure to 2D kidney organoids (MLR) for 72 hours ex vivo, and organoids were markedly injured as reflected by DNA damage (γ-H2AX) and cleaved caspase 3. Reflecting innate responses, robust interstitial fibrosis was found in non-transplanted organoids after direct activation of C5aR by exogenous C5a. We confirmed ACE2 expression on proximal tubules and parietal epithelium of glomeruli, consistent with human autopsy results. Non-transplanted organoids treated with S1 protein showed transcriptionally upregulated C5a1 receptors.

Conclusions: Our results indicate the alloimmunogenicity of kidney organoids and the deleterious effects of C5a in kidney organoids. Human kidney organoids represent a novel platform to study renal immunology including adaptive and innate immunity and the inflammatory responses to coronavirus disease (COVID-19).

Funding: NIDDK Support, Other NIH Support - NCAT

PO0879

Kidney Organoids Derived from a Pediatric Patient with Type 1 Diabetes and Steroid-Dependent Nephrotic Syndrome Show Losses of Podocyte Podocalyxin and Increased Proximal Tubule Injury

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Background: Whole exome sequencing of a pediatric patient, who at age 3 developed Type 1 diabetes mellitus and steroid-dependent nephrotic syndrome, revealed a de novo heterozygous mutation of the *GREM1* gene. Gremlin is a BMP antagonist crucial for kidney development and also implicated later in life in diabetic kidney disease. Specifically, gremlin has been associated with kidney inflammation, Notch activation and fibrosis, and proposed to be a mediator of diabetic nephropathy and other progressive kidney diseases. 3D kidney organoids differentiated from induced pluripotent stem cells (hiPSCs) provide a platform technology to explore the effects of genetic changes on pathobiology of human tissue.

Methods: An induced pluripotent stem cell (iPSC) line was created from the patient. Organoids were generated from iPSCs by modifications of our laboratory's prior published techniques without use of undefined matrices. Structures of kidney organoids were imaged by immunostaining for LTL, CDH1, GATA3, PODXL, NPHS1, NPHS2, and CD31. Organoids were also stained for gremlin, SGLT2, and KIM-1 to investigate phenotypes.

Results: A de novo heterozygous mutation of the *GREM1* gene was identified. The *GREM1* mutation specifically eliminates one of the three known *GREM1* splicing isoforms while leaving the other two intact. When compared to organoids generated from embryonic stem cells or BJFF iPSCs the patient-derived organoids had several kidney disease phenotypes including decreased expression of podocalyxin, aberrant expression of SGLT2, and pronounced expression of KIM-1, an indicator of proximal tubule injury. The phenotypes could be rescued by treatment of the kidney organoids with recombinant GREM1 protein, altering the balance of long and short forms of gremlin.

Conclusions: Organoids derived from a patient with a *GREM1* heterozygous mutation demonstrated decreased podocalyxin, aberrant SGLT2 staining, and increased proximal tubule injury. Better understanding of the relative roles for *GREM1* isoforms could lead to better understanding of diabetic progressive kidney disease and organoids can be used to find potential therapies.

Funding: NIDDK Support, Other NIH Support - NCATS, T32

PO0880

CD133^{+} Progenitor Cells in Proximal Tubules Are Most Likely the First Responding Cells to Acute Tubular Injury in Human Kidneys

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Background: Proximal tubules (PT) are mainly used for the reabsorption of electrolytes and fluid. Recent studies reveal CD133+ progenitor cells scattered along the PT, and CD133 wrapped in extracellular vesicles (EV) of urine can be used as an injury biomarker. The main goal of the study was to investigate how CD133+ progenitor cells are distributed along the convulated PT and whether CD133+ progenitor cells are related to initial repairing of PT.

Methods: Ten early metanephrons, 10 control adult renal sections and 40 renal biopsies with various degrees of acute tubular injury (ATI) were stained CD133 for highlighting progenitor cells of PT, followed by special Periodic Acid Schiff (PAS) staining for identifying brush borders. The dual stains sections fo evaluate surface CD133 expression and PAS positive brush borders were evaluated by light microscopy.

Results: CD133 staining was positive in the renal S shape body, parietal epithelium of primordial glomeruli, distal tubules and focally positive in PT of early metanephros. The control adult nephron revealed single CD133+ progenitor cells at the U turn niches of convoluted PT, which were stained negatively for PAS, indicating that CD133+ progenitor cells may watch turning segments (convoluted loops) of PT and do not have reabsorption capacity. At the early stage of ATI, there were side-by-side and nearby dual or triple CD133+ cells in each cross section of PT, which were negative for PAS staining as well. Surface CD133+ micro-granules of proximal tubules were identified in the early injured PT.

Conclusions: Our data indicate that CD133 in parietal epithelium and renal tubules are most likely derived from the condensing mesenchymal cells/S-shaped body after the induction of ureteric bud in the metanephros. There are two types of cells in proximal tubules – classic PT cells with brush borders for reabsorption and scattered CD133+ progenitor cells that are lack of brush borders and may serve as " injury watchdog" at each turning segment of convoluted PT. During early ATI, dual or triple CD133+ cells were present, implying that CD133+ progenitor cells may represent the first responding cells to acute tubular injury for tubular repairing. CD133+ micro-particles were present at the surface of injured PT imply that CD133+ progenitor cells may pass the CD133+ EV to signal surrounding cells for the injury insult.

PO0881

Renal Endothelial Cells After Injury Were Dominantly Regenerated by an Adult Renal Endothelial Cell Pool

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Background: Previously we demonstrated that endothelial repair in murine kidneys exclusively depends on local renal mechanisms. This is related to the question whether a renal non-endothelial (precursor) cell pool/niche exists parallel to local endothelial cell proliferation.

Methods: Inducible Cdh5(PAC)-ERT2 tdTomato (tdT) reporter mice were used to assess the proportion of renal endothelial cells regenerating exclusively from labelled endothelial cells, which persisted after selective endothelial cell injury (ECI) in individualized animals. ECI was induced by renal arterial perfusion of the left kidney with ConcanavalinA (ConA)/anti-ConA. The recombination efficiency of tamoxifen-induced mice was determined 24h prior to ECI by flow cytometric analysis. 24h after ECI, a biopsy of the previously damaged kidney was taken to determine the degree of endothelial damage. One week after ECI the mice were sacrificed and all kidneys were examined by flow cytometry (CD105+CD31+CD45-) and histology (CD31+ERG+ cell/glomeruli). Sham operated mice (SHAM) and the intact contralateral kidney (CL) served as controls.

Results: More than 85% of all renal endothelial cells expressed tdT in 19 of 27 induced mice, which were selected for further experiments. The mean labelling efficiency with tdT was 94.1% of all endothelial cells. Seven mice served as sham. 24h after ECI (n=12), and a 28.6±9% reduction of glomerular ERG+ endothelial cells (8.7±1.1 cells) vs. sham control mice (13.5±0.9 cells) was observed ($p<0.02$). Seven days after ECI, the number of ERG+ glomerular cells was not significantly different compared to the non-damaged kidney or sham (d7 ECI:12.4±1.9 cells vs CL:13.1±0.8 cells; SHAM:13.5±0.9 cells) demonstrating complete repair. Hereby, the proportion of tdT positive cells did not significantly differ between any of the groups, neither at different time points (24h: 92.8%; d7 ECI: 91.2%) nor between sham and injured kidneys one week following ECI (ECI: 91.2%; CL: 93.6%; SHAM 94.2%).

Conclusions: In individualized inducible Cdh5(PAC)-ERT2 tdT reporter mice, the percentage of tdTomato positive versus total endothelial cells does not change during/after endothelial regeneration. This experimental study suggests that the renal endothelium regenerates from an existing intrarenal endothelial cell pool and not from a non-endothelial precursor cell pool.

PO0882

Single-Cell RNA Sequencing Reveals Subpopulation of PDGFRβ^{β} Pericytes as Fibroblast Precursor in Interstitial Kidney Fibrosis, and Smad Anchor for Receptor Activation Overexpression Modifies Their Fates

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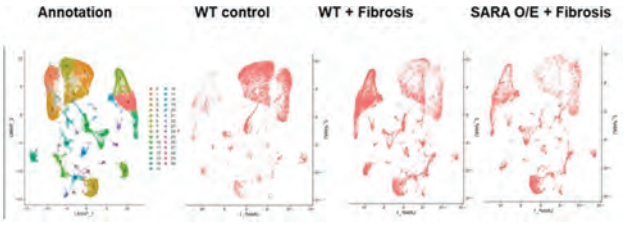
Background: In last several ASN meetings, we showed that SARA plays a critical role for fibroblast precursor activation, and that overexpressing SARA in PDGFRβ^{+} pericytes prevents chemically-induced kidney fibrosis in interstitium. Here, we present our findings from single cell RNAseq analyses of PDGFRβ^{+} pericytes with or without fibrosis.

Methods: PDGFRβ-Cre; Z/EG; SARA^{Tg} or ^{WT} mice that express GFP and SARA (in SARA^{Tg} line) only in PDGFRβ^{+} cells were given aristolochic acid (AA, 10 mg/kg, i.p., 3x week for 3 weeks). After 3 more weeks, kidneys were harvested and digested with Liberase/DNAse I. GFP^{+} cells were flow sorted and subjected to scRNAseq. 2-3 samples from a group (WT or SARA^{Tg,} and AA or control) were analyzed altogether by Seurat clustering, and subsequent inter-cluster analyses.

Results: Unsupervised analyses with Surat identified 30 clusters. Clusters characterized with differential expression of Apoe1 and C1a1 were dominant in cells isolated from healthy WT kidney, whereas clusters differentially expressing Kap and Cd74 became dominant in WT kidney treated with AA. This shift was abrogated in cells isolated from fibrotic SARA^{Tg} kidney. RNA velocity analyses to reveal specific clusters that transition to fibroblasts are being analyzed.

Conclusions: These results implicate a sub-population of PDGFRβ^{+} pericytes are progenitors for fibroblasts in fibrosing kidney and genes identified that are differentially expressed could have therapeutic implication in treating kidney fibrosis.

Funding: NIDDK Support



PO0883

Successful Introduction of Renovascular Units into the Mammalian Kidney

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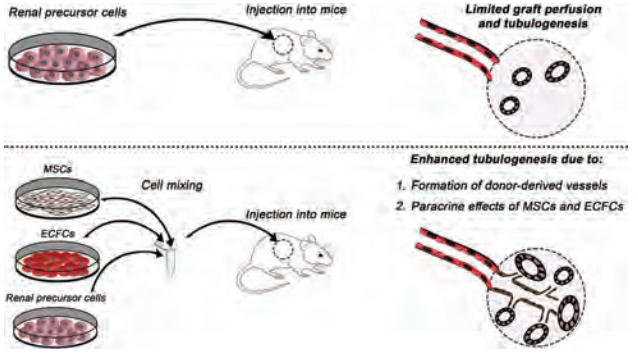
Background: Various cell-based therapies, aimed at replenishing renal parenchyma, have been proposed as means to treat chronic kidney disease (CKD). However, a key limitation to the applicability of these strategies is the failure of in-vivo administered cell types to develop donor-derived vessels, resulting in poor graft survival. Similarly, such strategies do not address renal hypoxia, a key factor in CKD progression. We hypothesized that administering self-organizing human renal tubule-forming cells (RTFCs) derived from adult and fetal kidneys, previously shown to exert a functional effect in CKD mice, alongside mesenchymal stromal cells (MSCs) and endothelial colony-forming cells (ECFCs), would result in generation of both vessels and tubules with potential interaction.

Methods: NOD-SCID mice were injected with either RTFCs or a mix of RTFCs, MSCs and ECFCs in Matrigel into the sub-cutis (SC), under the renal capsule or into the renal parenchyma. The resulting grafts were analyzed after 2 weeks.

Results: While RTFC-derived grafts harbored few host-derived vessels, injection of MSC, ECFCs and RTFCs into the SC, sub-renal capsular space, or renal parenchyma, resulted in robust formation of donor-derived reno-vascular units. These consisted of both well-developed renal tubules tubular epithelia of different nephron segments, and human vascular networks, which connect to host vasculature. The latter demonstrated the presence of both $CD31^+$ endothelium and αSMA^+ pericytes, originating from administered ECFCs and MSCs, respectively. Notably, MSC/ECFC-derived vessels augmented *in-vivo* tubulogenesis by RTFCs while *in vitro* co-culture experiments showed MSC/ECFCs to induce self-renewal and mesenchymal-epithelial transition-associated genes in RTFCs, disclosing paracrine effects.

Conclusions: Combined cell therapy of vessel-forming cells and RTFCs aimed at enhancing tubulogenesis and potentially alleviating renal hypoxia may serve as the basis for new renal regenerative therapies.



PO0884

Elastin-Microfibril Axis Proteins Form Transient 3D Structures During Murine Nephrogenesis

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Background: Dynamic changes in the composition and structure of the extracellular matrix (ECM) are understudied but critical during renal development. Our recent proteomic study indicated proteins in the *elastin-microfibril* axis were upregulated with development; however, structural changes during maturation are unclear.

Methods: Kidneys were decellularized, stained for *elastin-microfibril* axis protein (EMILIN1), FREM2, and proteoglycans (WGA), imaged using confocal microscopy, and rendered in 3D using FIJI. For comparison, E18.5 cryosections were stained for additional members of the e*lastin-microfibril* axis (COL26A1, FBN2).

Results: At perinatal timepoints, *elastin-microfibril* axis proteins were organized in the interstitium surrounding developing tubular and glomerular elements, including vertical fibers connecting to the capsule and medullary ray sheath fibers. Patterning was lost in the adult (Fig. 1). Different *elastin-microfibril* axis proteins displayed similar staining patterns perinatally (Fig. 2).

Conclusions: The 3D corticomedullary junction structures for *elastin-microfibril* axis proteins at the perinatal timepoint were consistent with the proteomic trends. We hypothesize the structures are important for nephrogenesis through mechanical support and growth factor modulation.

Funding: Other NIH Support - National Institutes of Health [DP2 AT009833 to S.C.]

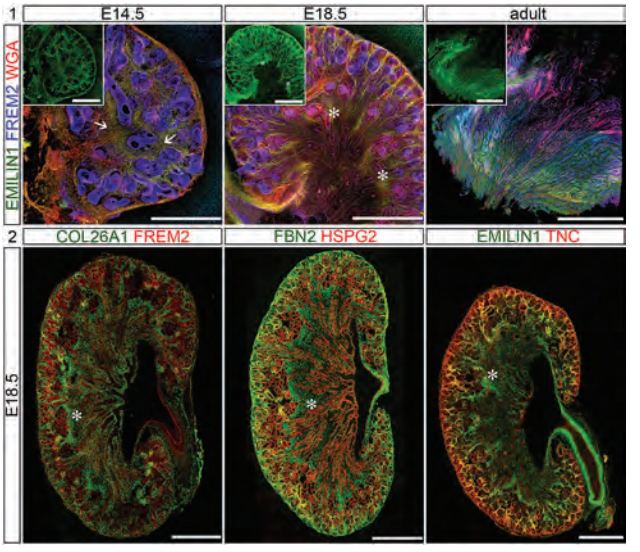

Figure 1 (top): 3D visualization of EMILIN1 showed medullary ray sheath fibers transiently formed at E18.5. EMILIN1 was localized to the corticomedullary junction (green, white arrow) fibers surrounding tubules at E14.5 that grouped into medullary ray sheath fibers (*) at E18.5 but regressed in the adult murine kidney. Insets are visualization of the EMILIN1 channel. scale bar=500 μm**Figure 2 (bottom): *Elastin-microfibril* axis proteins displayed similar staining patterns at E18.5.** *Elastin-microfibril* axis proteins (green) were co-stained for ECM (red). medullary ray sheath fibers (*), scale bar=500 μm

PO0885

Development of Noninvasive Clinically Applicable In Vivo Tracking of Extracellular Vesicles Using Magnetic Resonance Imaging (MRI)

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Background: Extracellular vesicles (EVs) derived from amniotic fluid stem cells (AFSC) hold great potential for the treatment of chronic kidney diseases (CKD). We have already shown that AFSC-EVs are renoprotective in a mouse model of CKD, Alport syndrome. However, there is an important unmet need for real-time *in vivo* monitoring of these therapeutic EVs after they are injected into a subject to understand their safety, targeting, and effectiveness. While current optical imaging solutions like bioluminescence and fluorescence are useful for EV tracking studies in animal models, there is limited utility in clinical applications. Here we present a novel *in vivo* tracking solution for our therapeutic EVs in Alport mice, utilizing clinically applicable MRI technology.

Methods: To generate trackable EVs, AFSC were labeled with a novel magnetic agent (VSCM). EVs secreted by the labeled AFSC were isolated by ultracentrifugation. The viability and morphology of labeled-cells were evaluated, and the *in vitro* MR properties of EVs were analyzed by magnetometer. Purity, potency and identity of labeled EV was compared to non-labeled EVs. *In vivo* biodistribution of labeled EVs was evaluated in WT and Alport mice by MRI at 10 min and 3 hr post injection, and retro-orbital and intra-cardiac routes of delivery were compared.

Results: The magnetic label did not affect the physiological characteristics of the cells and did not change identity, purity and potency (therapeutic effect in vivo) of EVs. MRI phantom studies confirmed the in *vitro/ex vivo* detectability of labeled-EVs. Importantly, as expected MRI studies showed that EV homing to the kidney injected intra-cardiacally into Alport mice was more efficient vs the retro-orbital route, and Prussian blue staining of sections confirmed EV homing to the kidney.

Conclusions: We have developed a clinically applicable novel magnetic nanoparticle agent that can be used to label and track the biodistribution of EVs in the kidney and other organs using non-invasive, safe, and effective MRI technology that's widely available. This technology is highly adaptable and can be deployed in both preclinical and clinical settings.

Funding: Private Foundation Support

PO0886

Obesity Blunts the Reparative Function of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Ischemic Murine Kidneys

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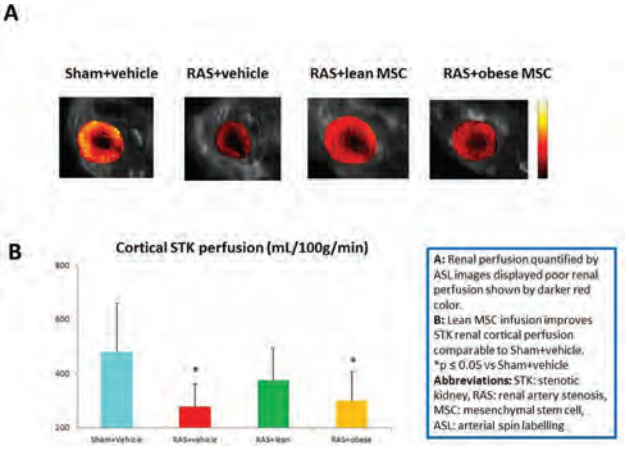
Background: Obesity is a health burden that can affect cellular processes. Mesenchymal stromal/stem cells (MSC) ameliorate renal injury in several diseases. Obesity impairs MSC function *in vitro*, but its effect on *in vivo* reparative function of human MSC remains unknown.

Methods: MSC were harvested from non-obese ('lean') (body mass index [BMI] <30 kg/m^2) and obese (BMI≥30) human subjects during kidney donation or bariatric surgery, respectively. To test their function *in vivo*, MSC (5x10^5/200 μL) or vehicle were injected into 129S1 mice 2 weeks after renal artery stenosis (RAS) or sham surgery (n=6-8/group). Two weeks later, mice underwent magnetic resonance imaging to assess renal perfusion and oxygenation, and kidneys then harvested.

Results: A similar number of lean and obese human MSC engrafted in stenotic mouse kidneys. Vehicle-treated RAS mice had reduced cortical and medullary perfusion. Lean (but not obese) MSC normalized cortical perfusion (p=0.2 vs sham+vehicle) (Figure A&B), whereas both effectively mitigated renal hypoxia. Serum creatinine and blood pressure were elevated in all RAS mice, and lowered only by lean MSC (p=0.4 vs sham+vehicle). Both alleviated renal fibrosis in RAS, but lean more effectively than obese MSC (p=0.02). Tubular and glomerular injury was improved similarly by both.

Conclusions: Lean MSC are superior to obese MSC in repairing ischemic kidney injury and blood pressure in murine RAS, implying dysfunction of the endogenous MSC repair system in obese patients. This should also be considered during autologous cell-based approaches.

Funding: NIDDK Support



PO0887

Single-Cell Transcriptional and Chromatin Accessibility Profiling Redefines Cellular Heterogeneity in the Adult Human Proximal Tubules

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Background: Single nucleus RNA sequencing (snRNA-seq) has improved our understanding of cell-specific genes and pathways, however, relatively less is known about how chromatin accessibility contributes to cell identity. We hypothesized that an integrated analysis by snRNA and ATAC sequencing (snATAC-seq) would enhance our ability to detect unique cell types and states in the kidney, uncovering previously unrecognized cellular heterogeneity.

Methods: We performed snRNA-seq and snATAC-seq on 5 healthy adult kidney samples (3M and 2F, mean age = 55.8y, mean sCr = 1.07 mg/dl). Nuclear preparations were processed using 10x Genomics 5' v2 (snRNA) and Single Cell ATAC (snATAC) Chromium kits, sequenced and counted with Cell Ranger. Seurat was used to integrate snRNA and snATAC datasets with label transfer. Chromatin interactions were predicted with Cicero and pseudotemporal ordering was performed with Monocle.

Results: We analyzed a total of 52,097 nuclei by snRNA-seq (n=19,985) and snATAC-seq (n=32,112), identifying 214,890 accessible chromatin regions that confer kidney cell type identity. This multi-modal analysis highlighted a unique subpopulation of proximal tubule (PT) cells characterized by increased chromatin accessibility in *VCAM1* and a pro-inflammatory gene expression signature. Immunofluorescence studies showed that these cells are present in a scattered distribution in the kidney cortex. Transcription factor motif analysis implicated NFkB signaling in the transition between healthy PT and the *VCAM1*-positive subpopulation. We identified candidate regulatory regions that are predicted to interact with the *VCAM1* promoter via cis-coaccessibility networks. Inter-species snRNA-seq data integration suggests this subpopulation exists in the post-IRI mouse kidney and bulk RNA-seq deconvolution implicates a potential role in CKD and kidney aging.

Conclusions: Our multi-omics approach improves the ability to detect unique cell states within the kidney and reveals a previously unrecognized subpopulation of proximal tubule cells with a pro-inflammatory signature.

Funding: NIDDK Support

PO0888

Vegfr3 Is Expressed in Fenestrated Microvascular Beds of the Kidney and Is Required for Glomerular Development

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Background: Chronic Kidney Disease is associated with pathological changes to the kidney vasculature which contribute to disease progression. Despite the recognized importance of vascular dysfunction in kidney disease, the mechanisms by which these changes occur are poorly understood, limiting therapeutic design. Dysregulation of Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), known for its role in lymphangiogenesis, is causally linked to the development of kidney diseases, including renal fibrosis and cystogenesis. How VEGFR3 signaling influences kidney disease progression and the specific vascular beds involved remains unclear.

Methods: We performed a detailed expression analysis of *Vegfr3* in the kidney using a *Vegfr3-YFP* reporter mouse line. We generated a new transgenic mouse model to investigate the role of *Vegfr3* in the kidney vasculature (*Vegfr3^{flox}*). Conditional and cell-specific excision of the floxed allele was performed using the *Rosa-rtTA-TetOCre, Cdh5-Cre/ERT2, and PDPN-GFPCre* driver strains to evaluate global, pan-endothelial, and lymphatic endothelial cell deletion of *Vegfr3* respectively. Mice underwent a detailed phenotypic evaluation and kidney sections were processed for histology.

Results: *Vegfr3* undergoes dynamic expression through development in several fenestrated blood microvascular beds of the kidney including the peritubular capillaries, the ascending vasa recta, and the glomerular capillaries. Constitutive deletion of *Vegfr3* results in early embryonic lethality while induced deletion at later embryonic stages results in lymphatic pathologies including chylous ascites, blood-filled lymphatic vessels, and reduced viability. Both global and endothelial-cell specific deletion of *Vegfr3* at embryonic day 11.5 resulted in marked disruption of glomerular development with cavernous capillary malformations. Immunofluorescence and electron microscopy revealed endothelial cell lined structures surrounded by immature podocytes with disrupted basement membrane development.

Conclusions: VEGFR3, while typically associated with lymphatic vessels, is expressed in fenestrated microvascular beds of the kidney and is required for glomerular development. These findings have important implications for the development of therapeutics targeting this pathway for the treatment of kidney disease.

Funding: NIDDK Support, Private Foundation Support

PO0889

Malnutrition During Pregnancy Impairs Nephrogenesis by Interrupting Methionine Metabolism

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Background: Poor nutritional status during pregnancy has long term effects on kidney health by impairing nephron endowment in an unknown mechanism. Nephron progenitor cells are dependent on constant nutrient supply for maintaining high metabolic activity. We aimed to study the effect of malnutrition during pregnancy on the metabolic profile of nephron progenitor cells.

Methods: Six2 Cre$^{tg/+}$ males were mated with wild type females. Pregnant mice were fed with 70% of the daily chaw intake in individual cages. Six2$^+$ NPC's cells were FACS sorted and the metabolites were extracted and measured using mass spectrometry. For kidney organ cultures, kidneys were dissected and immediately incubated in well plates containing media either with or without L-methionine. By the end of the incubation period, the kidneys were fixed and whole-mount immunostained for Six2 and cytokeratin (ureteric bud marker). The nephron number was measured by acid maceration.

Results: The metabolomic analysis showed significant impairment in methionine metabolism in E15.5 NPCs. Methionine deprivation in organ culture reduced nephron progenitors' density in metanephric mesenchyme of cultured embryonic kidneys. The effect was reversible by supplementation of the media without L-methionine, with metabolites that promote methionine recycling. Supplementation of methionine-enriched drinking water to caloric restricted pregnant mice prevented the reduction in nephron number in offspring.

Conclusions: Impairment of methionine metabolism plays a major role in mediating the effect of caloric restriction on kidney development. Replenishing methionine may revert the effect of malnutrition on the future risk of developing chronic kidney disease in offspring.

PO0890

Generation of Branching Ureteric Bud Organoids from Human Pluripotent Stem Cells

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Background: Directed differentiation of human pluripotent stem cells (hPSCs) to kidney organoids has been well established; however, the generation of hPSC-derived ureteric bud (UB), which undergoes branching morphogenesis to generate collecting duct (CD) epithelia, has remained a significant challenge. Here we describe a highly efficient method for deriving UB/CD organoids from hPSCs, which form unprecedented branching structures. This method provides a new platform for studying human CD development, physiology, and disease modeling. Moreover, this will provide the opportunity to markedly enhance existing kidney organoids by providing a collecting system and importantly, introducing an iterative branching component that is essential to driving metanephric kidney development.

Methods: First, we modified existing methods to efficiently direct hPSCs into anterior intermediate mesoderm cells in monolayer format. From that point, we optimized a process of 3-D development that included forced aggregation followed by spontaneous budding and then branching of the UB epithelia.

Results: We generated GATA3/PAX2 AIM with >80% efficiency within 5 days of induction, which was then aggregated into 3-D spheres. Over the subsequent days, the cells underwent a spontaneous process of organization and maturation that parallels normal development of the embryonic nephric duct (ND). Nearly synchronously, each aggregate then formed a single epithelial outgrowth that exhibited expression of UB markers PAX2, GATA3, RET, SOX9 and CALB1. Next, we embedded the UB-like buds into a hydrogel matrix, and they underwent a complex branching morphogenetic program driven by growth factor signals. At later stages, we identified culture conditions to stimulate differentiation of the ureteric epithelia into CD principal cells, identified by expression of AQP2 and SCNN1A/B. Additionally, GATA3+ UB progenitor cells were maintained and expanded over several passages in our 3-D culture system.

Conclusions: We have developed a novel strategy to generate branching UB tissues from hPSCs, which are also competent to differentiate into CD epithelia. Efforts are ongoing to investigate the functional and physiologic properties of these tissues, as well as to model genetic diseases that impact morphologic development of the collecting system.

Funding: NIDDK Support, Other NIH Support - NCATS

PO0891

Modeling Damage-Associated Molecular Pattern Injury and Fibrosis Using Human Kidney Organoids

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Background: Recent developments in generating human kidney organoids *in vitro*, have provided an invaluable tool to study human renal diseases, injury, and screening new therapeutics. In order to study acute kidney injury (AKI) we have developed a human kidney organoid model of injury with the damage associated molecular pattern molecule (DAMP), hemin, which is released during hemolysis, often occurring after ischemia/reperfusion and rhabdomyolysis. To spatially and temporally characterize tubule injury in the hemin AKI model, we generated transgenic iPSC lines that carry an early apoptosis biosensor, CytochromeC-GFP. Healthy cells within organoids will localize CytochromeC to the mitochondria but, upon injury, will diffuse into the cytoplasm before activating the apoptotic pathway. This approach provides a real-time readout of injury progression in the kidney organoids.

Methods: Kidney organoids at day 14 of culture were treated for 48 hours with varying concentrations of hemin to determine the optimal dose for measurable injury at day 26. CytochromeC-GFP iPSC lines were generated using AAVS1 Safe Harbor targeting approach. CytochromeC-GFP response in the organoid was validated using menadione (mitochondrial toxin) and tested with hemin to determine the extent of injury. To test efficacy of new therapeutic compounds, hemin injured organoids were treated with varying concentrations of 4-(phenylthio)butanoic acid (PTBA) analogs for 10 days and analyzed to determine changes in fibrotic, and oxidative stress markers.

Results: We show injury in the organoids with optimal hemin dose leading to a reproducible increase in fibrotic, and oxidative stress response. CyochromeC-GFP biosensor iPSC lines allowed us to monitor organoids under hemin insult. Organoids treated with nephrotoxin or hemin exhibit cytoplasmic GFP signal in the injured cells and morphological changes of the mitochondria. Hemin injured organoids treated with PTBA analogs showed a reduction in fibrotic markers at day 26 suggesting a reduction in fibrotic scar tissue development.

Conclusions: We have developed a reliable injury model using hemin, and together with CytochromeC-GFP as a biosensor, these tools can be exploited to test nephrotoxicity, study acute kidney injury, and new therapeutic compounds in a human based *in vitro* model.

Funding: Other NIH Support - R01 DK069403, Private Foundation Support

PO0892

Delaying Nephrogenesis In Vitro Results in Enhanced Proximal Tubule Alignment and Maturity in Kidney Organoids

Jessica M. Vanslambrouck,[1] Ker sin Tan,[1] Sean Wilson,[1] Sara E. Howden,[1,2] Kynan T. Lawlor,[1] Michelle Scurr,[1] Melissa H. Little.[1,2] Kidney Development, Disease and Regeneration *[1]Murdoch Children's Research Institute, Parkville, VIC, Australia; [2]The University of Melbourne, Department of Paediatrics, Parkville, VIC, Australia.*

Background: Stem cell-derived organoids represent a promising model for complex organs such as the kidney, with studies of disease, physiology and drug interactions relying mostly on simplistic cell cultures or animals that do not completely recapitulate the complex human environment. However, kidney organoids are still less mature than the *in vivo* organ, a limitation arguably most apparent in the proximal tubule (PT) compartment. The critical role of the PT in performing the bulk of solute reabsorption makes it a key requirement for drug screening and bioengineering. By inhibiting promiscuous epithelialisation, we report the development of PT-enhanced kidney organoids with improved PT alignment, maturity, functionality and suitability for therapeutic applications.

Methods: Standard and fluorescent reporter iPSC lines were subjected to prolonged monolayer differentiations, with 4 - 5 day initial CHIR exposure durations (modified from: Howden *et al*, *EMBO Rep*, 2019; Vanslambrouck *et al.* JASN, 2019) and precisely-timed modifications to signalling pathways such as canonical WNT, BMP and NOTCH. Organoids were generated as previously published (Takasato *et al*, *Nat Protoc*, 2016) and analysed using confocal immunofluorescence, live imaging of fluorescent reporters, transcriptional profiling (single cell RNAseq) and functional transport assays.

Results: PT-enriched organoid could be generated in a highly reproducible manner from multiple cell lines. Proximal tubules showed mature protein and gene expression, as well as transport capacity in multiple assays. Nephron spatial arrangement/directionality, as well as shifts in proximo-distal nephron patterning, were influenced by these modified conditions.

Conclusions: Here, we describe PT-enhanced kidney organoids with improved PT maturity and functionality, with this approach providing a more stringent control over the spatial arrangement of nephrons. Such findings have significant implications for downstream applications including drug screening, toxicology assays and bioengineering of functional replacement cells or tissues.

Funding: NIDDK Support, Government Support - Non-U.S.

PO0893

Glomerular Endothelial Glycocalyx Damage Occurs in Human Diabetic Nephropathy and Could Be Prevented by Early Mineralocorticoid Receptor Inhibition

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Background: The glomerular endothelial glycocalyx (GEnGlx) forms the first part of the filtration barrier. In rodent models, damage to the GEnGlx occurs early in the pathogenesis of diabetic nephropathy (DN). Until now no techniques have been available to quantify GEnGlx damage in human disease. Mineralocorticoid receptor (MR) antagonists slow disease progression, but side effects limit their clinical use. We aimed to develop a method to study GEnGlx changes in human disease and investigate whether MR inhibition could preserve the GEnGlx in a rat DN model.

Methods: Human renal biopsies from patients with DN and thin basement membrane disease (TBMD) were analysed using our novel peak-to-peak confocal imaging method (UEA-I lectin) to assess GEnGlx depth. Male Wistar rats injected with streptozotocin (50mg/kg I.P.) were used to study if spironolactone (50mg/kg daily S.C.), an MR inhibitor, could preserve the GEnGlx and limit the development of DN. Our glomerular permeability assay was used to directly measure the albumin permeability (Ps'alb), in isolation from haemodynamic changes. Peak-to-peak (WGA lectin) was validated against electron microscopy GEnGlx depth measurements. MMP2 activity was quantified using a specific activity assay and ELISAs were used to measure urine albumin levels.

Results: In human DN, GEnGlx depth was reduced compared to patients with TBMD (p=0.013). Diabetic rats developed albuminuria and the Ps'alb increased 1.6-fold (p<0.001). Again, GEnGlx depth was reduced in DN compared to controls (p<0.001). Plasma and urinary active MMP2 were increased (p=0.017 and p<0.001). MR blockade preserved the GEnGlx, restored Ps'alb to control values and prevented albuminuria progression. Reduced urinary active MMP2 (p=0.012) and glomerular *Mmp2* mRNA expression (p=0.002) were seen following MR blockade in DN. GEnGlx enzymatic degradation, with hyaluronidase, reversed the effect of MR blockade in DN confirming the importance of GEnGlx preservation in this model.

Conclusions: MR blockade in DN preserves the GEnGlx, reduces Ps'alb and retards the development of albuminuria. Alternative approaches to block MR-induced GEnGlx damage represent a novel potential therapeutic strategy, to reproduce the benefit of MR antagonists without adverse side effects.

PO0894

Targeting αvβ8 Integrin Improves Renal Function Through Local Inhibition of TGF-β Activation

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Background: TGFβ signalling plays a central role in the development and progression of renal interstitial fibrosis in chronic kidney disease (CKD), which predicts time to dialysis. Systemic blockade of TGFβ has shown serious adverse effects (progression of premalignant lesions) and limited efficacy at doses that were safe for patients, highlighting the need for a targeted inhibition of TGFβ in the kidney. αvβ integrins have a unique ability to activate latent TGFβ through the binding of latency-associated peptide (LAP) to release active TGFβ and therefore can modulate fibrotic processes. Consequently, they have emerged as promising therapeutic targets.

Methods: We generated MEDI8367, an antibody that specifically binds human integrin β8 and works allosterically reducing its affinity for the LAP domain, hence preventing β8-mediated TGFβ activation but not its cell adhesion function. We confirmed its neutralising activity using a reporter cell *in vitro* assay that detects TGFβ bioactivity.

Results: To assess its therapeutic effect ITGB8 humanized mice were subjected to unilateral ureteral obstruction to induce fibrosis. Obstructed kidneys showed strong up-regulation of integrin β8 in the tubular compartment and MEDI8367 significantly improved fibrosis without affecting integrin β8 expression. This was accompanied by inhibition of TGFβ activation, which mimicked the effect of a pan-TGFβ neutralizing antibody, suggesting that MEDI8367 reduces renal fibrosis by blocking local TGFβ activation. We next tested the effect of targeting integrin β8 in a mouse model of diabetic nephropathy, the db/db-uninephrectomy model. Mice underwent uni-nephrectomy at 8 weeks of age and were randomized to receive either an anti integrin β6/β8 or an anti integrin β6 antibody at 12 weeks of age for 3 weeks. Blocking integrin β6 did not affect albuminuria in these mice while blocking integrins β6/β8 stopped the progression of albuminuria in all the mice tested (n=9). These data suggest that it is the blockade of integrin β8 that has a beneficial effect on albuminuria.

Conclusions: We conclude that targeting integrin β8 in CKD ameliorates kidney dysfunction and reduces fibrosis, an effect that is mediated by inhibition of local TGFβ activation.

PO0895

Integrated Single Nucleus RNA and ATAC-Seq Implicate Cis-Regulatory Chromatin Interactions That Promote Gluconeogenesis in the Human Diabetic Proximal Tubule

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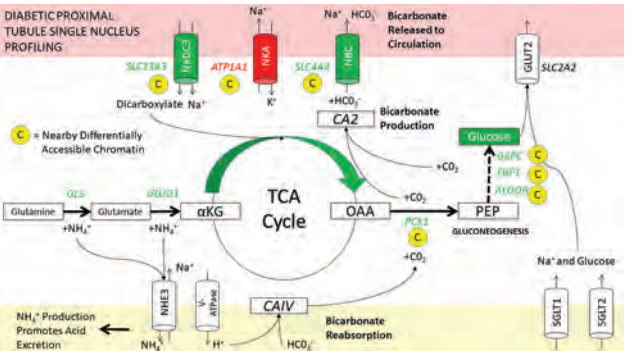
Background: Type 2 diabetes is characterized by impaired glucose metabolism, but relatively little is known about cell-specific changes in the kidney. We hypothesized that single nucleus ATAC (snATAC) and RNA (snRNA) sequencing of kidney tissue from patients with early diabetes would reveal cis-regulatory chromatin interactions that promote expression of genes that lead to glucose intolerance.

Methods: We analyzed five kidney samples from patients with early diabetes and five healthy controls. Diabetic patients had elevated A1c and two of five had proteinuria. Serum creatinine (mean = 1.01 mg/dl) was not different between groups. Nuclear preparations were processed with 10x Genomics 5' v2 or Single Cell ATAC kits, sequenced and counted with Cell Ranger. Analysis was performed with Seurat. snATAC peaks were called with MACS2 using SnapATAC. Chromatin interactions were predicted with Cicero.

Results: A total of 80,576 nuclei were analyzed by snATAC (n=46,564) or snRNA (n=34,012) sequencing and included all cell types. In the diabetic proximal tubule, we observed increased expression of gluconeogenic genes *PCK1*, *ALDOB*, *FBP1*, and *G6PC* and the sodium bicarbonate exchanger, *SLC4A4* (Figure 1; green=upregulated, red=downregulated). Increased expression of *GLS* and *GLUD1* implicate glutamine as a gluconeogenic substrate. Transcriptional changes were accompanied by cell-specific differential chromatin accessibility in regulatory regions that were linked to their respective promoters via predicted chromatin interactions. Differentially accessible regions in the proximal tubule were enriched for NFkB binding motifs, suggesting it may regulate chromatin accessibility in diabetes.

Conclusions: This is the first single cell multi-omic analysis of early human diabetic kidney injury. Our analysis reveals that early diabetes induces changes in chromatin accessibility that promote gluconeogenesis and ammoniagenesis in the proximal tubule, and suggests utility for single cell multi-omic analyses.



PO0896

Mapping the Response of Murine Diabetic Nephropathy to Therapy at Single-Cell Resolution

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Background: Diabetic Kidney Disease (DKD) is the major cause of kidney failure in the USA. Angiotensin blockers (ACEi/ARBs) and SGLT2 inhibitors (Canagliflozin) are only two approved therapies demonstrated to slow the progression of DKD.

Methods: We treated 40 diabetic db/db hypertensive (reninAAV) mice either with ACE inhibitor (lisinopril), an SGLT2 inhibitor (JNJ-39933673), a PPARg agonist (Rosiglitazone), or vehicle control (n=10/group). Each group received either 2 days or 2 weeks of treatment. We measured BP, glucose and UACR and collected kidneys for snRNA-seq.

Results: Drug treatment at 2d and 2 wks significantly reduced BP (lisinopril), glucose (Rosi and JNJ'3673), and Uacr (lisinopril, Rosi and JNJ'3673) from baseline demonstrating that either BP or glucose control independently impact Uacr in this model. We generated 1,324,051 single nucleus transcriptomes, detecting 2,028 unique genes/cell on average. Unbiased clustering identified 19 cell clusters representing all major cell types, including rare ones such as the JGA (3,614 cells), podocytes (8,851 cells) and macula densa (MD, 4,239 cells), with differential expression of hundreds of genes across all clusters. These expression changes included JGA renin expression which was strongly downregulated by exogenous renin in ReninAAV db/db mice compared to WT. SGLT2 expression was restricted to the S1 segment of the PT, and SGLT2 inhibition acutely downregulated S1 glucose transporter Slc2a5 (Glut5) perhaps reflecting compensation. Sglt1 expression was strongly downregulated in db/db reninAAV MD, and Sglt2 inhibition partially restored this expression. MD Sglt1 has been shown to act as a glucose sensor and, inhibit tubuloglomerular feedback, so increased expression would increase GFR.

Conclusions: This is the first comprehensive single cell transcriptional atlas of the effects of diabetic nephropathy treatments in a mouse model. Drug specific and overlapping gene expression patterns were identified and should help elucidate cell-specific mechanisms of therapeutic benefit.

Funding: Commercial Support - Janssen Research & Development

PO0897

The β_2-Adrenergic Receptor Agonist Formoterol Restores Mitochondrial Dynamics and Energy Production in the Diabetic Renal Proximal Tubule

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Background: While diabetic kidney disease (DKD) is the leading cause of end stage renal disease, the early pathophysiology of this disease remains poorly understood. In type 2 diabetes mitochondrial dysfunction and changes in energy metabolism occurs in proximal tubules. We examined the effects of formoterol, a β_2-adrenergic receptor (AR) agonist previously demonstrated to induce mitochondrial biogenesis and promote recovery from acute kidney injury, on renal mitochondrial homeostasis and energy production in diabetic db/db mice and in renal proximal tubule cells (RPTC) treated with high glucose.

Methods: RPTC from rabbits were isolated using the iron oxide perfusion method and grown in 0 glucose, 17mM glucose or 17mM mannitol as an osmotic control for 96 hr. ATP, uncoupled oxygen consumption rate (OCR) and mitochondrial dynamics and energetics proteins were measured. Db/db and nondiabetic db/m control mice were treated with either vehicle or formoterol (1mg/kg, i.p.) daily for three weeks beginning at 10 weeks of age. At 13 weeks, kidneys were harvested and changes in mitochondrial proteins were measured.

Results: RPTC treated with glucose for 96 hr exhibited a decrease in ATP, uncoupled OCR and the mitochondrial fusion protein Mfn1. In contrast, the fission protein pDrp1 and electron transport chain (ETC) complexes I-V increased. Treatment with formoterol (30nM) restored ATP, Mfn1, pDrp1 and ETC complex proteins to control levels. Similarly, vehicle treated db/db mice exhibited increases in ETC protein complexes I, II, III and V, and pDrp1 in renal cortex. Diabetic mice showed a decrease in Mfn1 in renal cortex. Formoterol restored complexes I, II, III and V, pDrp1 and Mfn1 to control levels in db/db mice. ATP was decreased in db/db mice and was restored to control levels with formoterol treatment.

Conclusions: Together, these in vivo and in vitro results suggest that increased glucose alters mitochondria dynamics (increase fission/decrease fusion) and decreases ATP in spite of increased ETC proteins. Formoterol reverses these glucose-induced effects and may be used as a potential therapy to prevent early disease progression of DKD.

Funding: NIDDK Support, Veterans Affairs Support

PO0898

UCP2 Activates Autophagy to Protect Against Albuminuria and Podocyte Injury in Diabetes

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Background: Podocytes injury and albuminuria are leading features of glomerular damage in diabetic kidney disease. Autophagy plays an important role in maintaining podocyte homeostasis. However, the underlying mechanism remains unknown. In this study, we reported a critical role of mitochondrial uncoupling protein 2 (UCP2) in maintaining autophagic activity and protecting podocyte from hyperglycemia-induced injury.

Methods: First, to elucidate the role of UCP2 in podocyte homeostasis and injury in vivo, we generated conditional knockout mice in which UCP2 is specifically ablated in podocytes by using Cre–LoxP recombination system. Second, autophagosome was detected by transmission electron microscopy. Dual-fluorescence lentiviral mRFP-GFP-LC3 was transfected into podocyte to detect the autophagic flux. Autophagy marker, LC3II, p62 and Beclin1, were tested by quantitative real-time PCR and western blot. At last, AMPK activator and mTORC1 inhibitor were used to identify the signaling pathway UCP2-mediated to regulate autophagy.

Results: UCP2 was upregulated synchronously with autophagy marker during glomerular development. Loss of UCP2 in podocytes led to a decrease of autophagic activity and an increase of podocyte injury. Podocyte-specific knockout of UCP2 aggravated age-related proteinuria and increased podocyte susceptibility to hyperglycemia in streptozotocin (STZ) -induced DKD mice. UCP2 promotes podocyte autophagy through activation of AMPK/mTOR signaling pathway.

Conclusions: Our findings demonstrates a critical protective role of UCP2 in podocyte survival via maintaining autophagic activity through AMPK/mTOR signaling pathway.

Funding: Government Support - Non-U.S.

PO0899

Darunavir Protects Mice with Type 1 Diabetes Against Kidney Injury

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Background: Despite the success of antiretroviral therapy (ART) in improving mortality, HIV-positive persons still have increased risk of death and kidney disease and diabetes mellitus are important contributors to this excess mortality. Data from our laboratory demonstrate that the HIV protease inhibitor darunavir (DRV) prevents kidney disease in HIV-transgenic mice via mechanisms independent of HIV protease. Since diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) in the general population and HIV infection predisposes persons with diabetes to more rapid progression of CKD, we studied the efficacy of DRV in a non-HIV animal model of DKD.

Methods: eNOS-/- 9 week-old C57BL/6 mice underwent induction of diabetes by administration of 5 daily 50mg/kg doses of streptozotocin (STZ) injection. Blood glucose was measured before and after DRV treatment. 14 weeks after STZ induction, mice were treated with either DRV (100mg/kg) or control by daily oral gavage for 4 weeks. Albumin-to-creatinine ratio (ACR) assay, immunocytochemistry, western blotting and real-Time PCR were performed with routine protocols. Mouse blood pressure (BP) was measured with CODA mouse tail-cuff system.

Results: STZ induced severe sustained hyperglycemia in eNOS-/- mice, which resulted in marked increase urine ACR. DRV-treated mice had a 60% decrease in UACR compared to control-treated mice but blood glucose levels did not change. DRV also reduced renal fibrosis as detected by tubulointerstitial type 1 collagen and fibronectin and prevented loss of synaptopodin expression in podocytes. Since the renin-angiotensin system (RAS) is an important contributor to DKD pathogenesis, we studied whether DRV affected expression of RAS genes. Unexpectedly, DRV increased renin expression and ACE expression in kidneys of diabetic eNOS -/- mice to levels similar to non-diabetic mice. DRV also increased endothelial CD31 and VEGFR2 expression in glomeruli, but did not change renal VEGF expression in diabetic eNOS-/- mice. Surprisingly, DRV treatment reduced mean BP in diabetic eNOS-/- mice.

Conclusions: These data demonstrate that DRV protects mice against type I diabetic renal injury. Further studies are needed to determine whether changes to renal gene expression are due to direct effects of DRV or secondary to reduced renal injury, resulting in normalization of gene expression suppression and BP.

Funding: NIDDK Support

PO0900

Proteasome Mediated NF-E2 Degradation Occurs Upstream of JNK Activation-Mediated CTGF Expression in Renal Tubules and Diabetic Kidneys

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Background: TGF-β is a critical mediator of diabetes-induced renal fibrosis. We recently demonstrated that TGF-b and diabetes (Type 1 and type 2) decreased NF-E2 expression and promoted pro-fibrotic signaling in renal cells and kidneys. P38 MAPK and ERK MAPK pathways contributed to proteasome activation and NF-E2 degradation. As JNK pathway is known to induce CTGF expression, current studies examined the contribution of JNK pathway in mediating NF-E2 degradation in TGF-β treated renal tubule cells.

Methods: HK-11 cells were pre-treated with/without JNK inhibitor SP600125, p38 inhibitor SB203580, or p38 and MEK/ERK inhibitor PD98059, or proteasome inhibitor MG132, for an hour prior to treatment with TGF-b for 24 h. Cell lysates were immunoblotted with appropriate antibodies. Kidney homogenates from FVB and OVE26 diabetic mice treated with 10 μg/Kg MG132 daily for 3 mo starting at 3 mo of age when OVE26 mice already displayed significant albuminuria.were immunoblotted with appropriate antibodies. MG132 were injected intraperitoneally at a dose of 10 μg/kg daily for 3 mo starting at 3 mo of age when OVE26 mice already displayed significant albuminuria.

Results: Inhibition of p38 MAPK partially preserved NF-E2 expression but induced CTGF expression, as p38 blockade induced ERK phosphorylation. Blockade of both p38/ERK, prevented NF-E2 degradation and inhibited CTGF expression. Blockade of JNK pathway, inhibited CTGF expression without preserving NF-E2 expression. Interestingly, proteasome inhibition in renal cells and OVE26 mice preserved NF-E2 expression and inhibited JNK activation and CTGF expression suggesting JNK activation occurs downstream of proteasome activation.

Conclusions: Our studies have demonstrated that p38 and ERK MAPK pathways promote proteasome activation and NF-E2 degradation while proteasome activation promotes JNK activation and CTGF expression in renal cells and diabetic kidneys. We have recently demonstrated that NF-E2 over-expression inhibited CTGF expression however; future studies will examine effects of NF-E2 over-expression on TGF-b-induced and diabetes-induced JNK activation in renal cells.

PO0901

Single-Cell Immune Landscape of Mouse Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is historically been considered as a non-inflammatory glomerular disease that is induced by metabolic and haemodynamic derangement. Increasing evidence suggests that renal inflammation contributes to the pathogenesis and progression of DKD. However, specific characteristics of dysregulated immune cells under diabetic conditions are poorly understood. We hypothesized that single cell RNA-seq could provide insight into the cellular mechanisms of diabetic nephropathy.

Methods: We collected kidney samples from control(n=9) and OVE26 (n=9) mice at 16 weeks. CD45+ innate immune cells were harvested by flow cytometry cell sorting and processed using 10x Genomics Chromium platform.

Results: 18000 immune cells (avg=1400 unique genes detected/cel) from control and diabetic mice were included in the integrated analysis. 17 immune cell clusters were identified and included all major immune cell types, with differential expression of hundreds of genes across all clusters. Increased expression of inflammatory cytokines was detected in particular immune cell clusters. Resident macrophages which took the majority of macrophage subtypes in the kidney are decreased after injury. Trem2high, IFN signature high, Stmn1high macrophage, and Chemokinehigh dendritic cells, which exhibited inflammatory response activation and strong ability of proliferation was observed with higher infiltration in diabetes. By Macspectrum analysis, we found a spectrum of diabetic macrophage activation states with greater complexity than traditional M1/M2 definitions. We generated a detailed diabetic immune cell intercellular communication map between macrophage, NK cell, T cell and Neutrophil. We observed restricted expression for kidney risk inflammatory signature (KRIS) in specific cell types, with macrophage showing the highest enrichment suggesting multiple unique functionalities may contribute to dysfunctional kidney physiology in diabetes.

Conclusions: This is the first comprehensive immune single cell landscape of a mouse model of DN. We demonstrate that (1) activated macrophage subtype recruitment, (2) spectrum of macrophage activation; (3) detailed diabetic immune cell intercellular communication, (3) Macrophage-specific expression of KRIS that associated with progression of ESRD in T1DM and T2DM patients.

Funding: NIDDK Support

PO0902

Rab27b Repression by Foxo1 Leads to Decreased Exosome Production in Diabetic Kidneys

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Background: Diabetic kidney disease (DKD) is associated with changes in exosomes. However, it is unclear whether the production or secretion of exosomes is affected in DKD. This study aims to investigate whether and how the secretion of exosomes is affected in DKD using in vivo and in vitro diabetic models.

Methods: In vivo, exosomes were isolated from kidney cortical tissues of Akita and streptozotocin-induced diabetic mice for analysis. In vitro, mouse kidney proximal tubular BUMPT cells were incubated with high glucose (30mM, HG) or mannitol (control) for 8 days to collect exosomes in culture medium. Exosomes were examined by electron microscopy (EM), nanoparticle tracking analysis (NTA), and immunoblotting. Knockdown and overexpression were used to study the roles of Rab27b and Foxo1 on exosome secretion.

Results: In vivo, diabetic mice had a reduced number of exosomes in renal cortical tissues compared with non-diabetic mice. In vitro, HG treatment led to a significant decrease in exosome secretion in BUMPT cells, which was associated with the specific downregulation of Rab27b, a key GTPase for exosome secretion. Overexpression of Rab27b restored exosome secretion in HG-treated cells, suggesting a role of Rab27b downregulation in decreased exosome secretion in DKD. For the mechanism of Rab27b downregulation, bioinformatic analysis predicted Foxo1-binding sites at Rab27b gene promoter. We demonstrated the phosphorylation of Foxo1 in HG-treated cells, accompanied by less Foxo1 accumulation in the nucleus. Overexpression of Foxo1 increased Rab27b expression, whereas Knockdown of Foxo1 had opposite effects. Moreover, expression of non-phosphorylatable (constitutively active) Foxo1 led to the upregulation of Rab27b and increases in exosome secretion in HG treated cells.

Conclusions: In diabetic kidney cells and tissues, Foxo1 is phosphorylated and inactivated, leading to decreases in Rab27b expression and consequential secretion of exosomes.

Funding: NIDDK Support

PO0903

Disruption of Long Non-Coding RNA MIAT Induces Mitotic Catastrophe of Podocyte in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is becoming the principal inducement of end-stage renal disease (ESRD) worldwide. Importantly, mitotic catastrophe (MC) is characterized as impeded mitosis-linked cell death, which plays an essential role in expediting podocyte loss and detaching from glomerular basement membrane (GBM). The concrete mechanism of MC in podocyte injury and proteinuria, however, remains inadequately elucidated. In the current study, we demonstrated the biological function and underlying mechanism of a long noncoding RNA myocardial infarction-associated transcript (Lnc MIAT) in podocytes MC.

Methods: The role of MIAT was investigated by resorting to cultured podocytes, CRISPR/Cas9 MIAT knockout mice and human samples. Immunofluorescence, western bolt, Transwell assay, TEM and histology staining including PAS and Masson staining were performed to assess the lesion of podocytes. RNA-FISH, RIP and luciferase reporter assays were utilized for mechanistic study of the interaction between MIAT, miR-130b and Sox4 further. Moreover, apoptosis and cell cycle of podocytes were detected by flow cytometry and the expression of G_2/M transition-related proteins ($p21^{cip1/waf1}$, cyclin B and cdc2).

Results: MIAT is noticeably upregulated in HG-stimulated podocytes, STZ-induced mice and serum of DN patients, accompanied by higher creatinine production and significantly lower eGFRs values in clinical. And MIAT contributes to the proliferation, apoptosis, migration and G_2/M arrest of podocytes, while depletion of MIAT significantly meliorates podocytes injury and albuminuria by restoring slit diaphragms (SD) integrity, attenuating foot processes effacement (FPE) and suppressing cyclin B/cdc2-mediated G_2/M arrest. Mechanistic investigation reveals that MIAT not only elevates Sox4 protein expression and subsequently manipulates the ubiquitination and acetylation of p53, thereby stifling downstream factors cyclin B/cdc2 via enhancing $p21^{cip1/waf1}$ activity, but also participates in crosstalk with Sox4 mRNA through competition for miR-130b binding.

Conclusions: Our findings provide plausible insight in the interplay between LncRNA MIAT, miR-130b and Sox4 which consequently lead to podocyte mitotic dysfunction involved in the progression of DN, indicating MIAT may act as a promising biomarker and therapeutic target for DN patients.

Funding: Government Support - Non-U.S.

PO0904

The Decrease in Renal Cystathionine β-Synthase/Hydrogen Sulfide Was Involved in the Pathogenesis of Diabetic Nephropathy

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Background: Hydrogen sulfide (H_2S) and its producing enzymes are associated with human diseases including coronary heart disease, Alzheimer's disease, diabetic retinopathy and obstructive kidney disease, etc.

Methods: In order to determine their roles in pathogenesis of diabetic nephropathy, we examined plasma H_2S levels in diabetic nephropathy patients and mice, renal H_2S production & H_2S producing enzymes in the mouse model, and the effects of glucose on H_2S producing enzymes, mainly Cystathionine β-synthase(CBS), in cultured mouse proximal convoluted tubule cells (mPTC).

Results: Plasma H_2S levels were decreased in patients (17.8±0.5 vs 24.8±0.8 umol/l, $p<0.05$, n=18/group) and mice(18.7±1.6 vs 40.7±1.8 umol/l,$p<0.05$,n=6/group). The renal H_2S production in mice was decreased (vs 52.1±2.9 vs 81.5±5.8 umol/l, $p<0.01$) along with the reduction of renal protein expression of CBS (52.1±13.4,% of control). A similar protein decrease of CBS(52.5±12.2, $p<0.01$) was found in cultured mPTC sitimulating by high glucose (25mmol/l D-glucose), but not CSE or MST. CBS protein expression was correlated negatively with glucose concentration (0,5,10,15,20,25,mM) ($p<0.01$). The significant decrease of CBS by glucose occurred at 1, 2, 24 and 48 hrs. Ubiquitination of CBS was increased remarkably (588.7± 140, $p<0.05$) within 1 hr of high glucose stimulation. CBS immunostaining became less strong with high glucose at the time points of 1hr & 2hr while the co-staining of CBS and LAMP2, a lysosome marker, reached the maximum at 30 min. The decrease of CBS mRNA expression was also found at points of 6 hr, 12hr. High glucose increased nitrotyrosine(NT) (170.6±22.9, $p<0.05$) in mPTC, which was restored by GYY4137, a slow-releasing H_2S donor. The expression of NT was increased by inhibition of CBS protein with its siRNA but was reversed by GYY4137 in normal glucose medium. Furthermore, in diabetic nephropathy mice, the urine albumin(58.6±6.6 vs 117.6±8.6 ug/d, $p<0.01$),mesangial matrix proliferation and glomerular basement membrane thickening were ameliorated by exogenous supplement GYY4137 at 20mg/kg for 8 weeks.

Conclusions: These findings suggest that high glucose may decrease renal CBS protein by increasing its ubiquitination / degradation and inhibiting its mRNA, eventually induce proximal tubular cell injury due to loss of protective mechanism of H_2S.

Funding: Government Support - Non-U.S.

PO0905

Lysophospholipids Predict Fast Decliners with Diabetic Kidney Disease

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Background: In type 2 diabetes, lipid metabolism disorder is frequently complicated due to insufficient insulin secretion and cytokines by visceral fat and regarded as one of the most important risk factors for renal dysfunction. However, specific lipid metabolites that have critical effects on renal dysfunction are not fully understood.

Methods: We performed the metabolomic analysis for patients with diabetic kidney disease (DKD) to identify novel metabolites related to renal prognosis. Plasma and urine biosamples in stage G3 DKD patients (n=135) are collected, and the whole metabolites of them were quantified by capillary electrophoresis mass spectrometry (CE-MS). Significantly fluctuating metabolites in patients with rapidly impaired renal function within 3 years (called "fast decliners"; about 10% in total) were statistically extracted. We also validated the metabolomic candidates with animal DKD model of SDT-fatty rats, or *in vitro* study using renal proximal tubular cells (HK-2).

Results: In the clinical metabolomic analysis of the biosamples, over 250 metabolites, including lipids, glycates, and amino acids were identified by CE-MS. Among them, specific urinary lysophospholipids (named as $LPLs_X$) in the fast decliners of DKD were significantly increased. The $LPLs_X$ were moderately correlated with eGFR decline after 3 years (r=0.42, $p<0.01$). In animal experiments, the level of $LPLs_X$ was also increased in both the urine and the kidney in the subnephrectomized SDT-fatty rats, while we did not see these damages in normal SD rats. *In vitro* experiments: the exposure of $LPLs_X$ to HK-2 induced apoptosis within 24 h and upregulated pro-apoptotic gene expressions. More physiological changes were investigated in refence to transcriptomic analysis, and we could find that $LPLs_X$ also deranged the lipid metabolism, estimated by intracellular lipid droplet accumulation, and increased the level of mitochondrial reactive oxygen species.

Conclusions: $LPLs_X$ predict "fast decliners" in DKD patients or DKD rats and may have crucial roles in renal tubular damage and dyslipidemia. Our findings provide new insights into the pathophysiological understanding of the relationship between lipid metabolism disorder and DKD progression.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

PO0906

Podocyte-Specific Induction of KLF6 Attenuates Diabetic Kidney Disease in Mice

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Background: Krüppel-Like Factor 6 (KLF6), a zinc finger transcription factor, is a key regulator of cytochrome c oxidase assembly in the podocytes. Podocyte-specific *Klf6* knockdown increases the susceptibility to streptozotocin (STZ) induced-diabetic kidney disease (DKD). However, salutary effects of podocyte-specific *KLF6* induction in DKD remain to be explored.

Methods: Podocyte-specific inducible human KLF6 (*hKLF6*) was generated in mice using the "Tet-on" system, by breeding *NPHS2-rtTA* mice with newly generated *TRE-hKLF6* to generate *hKLF6^{PODTA}* mice. *TRE-KLF6* transgene were generated using the (TetO)7/CMV regulatory element driving the full-length human *KLF6* coding sequence (CCDS 7060.1). Transgene was purified from plasmid vector sequences and microinjected into the pronucleus of *FVB/N* single-celled embryos. Founder mice were selected based on the level of *hKLF6* induction after doxycycline (DOX) treatment. STZ + Unilateral nephrectomy (STZ-UNX) was utilized to induce DKD in mice. First, DOX diet was administered at 8 weeks of age in all mice. UNX or Sham was performed at 10 weeks of age followed by low-dose STZ or vehicle (VEH) treatment respectively, at 12 weeks for 5 consecutive days. DOX-STZ-UNX treated *NPHS2-rtTA,* DOX-VEH-Sham treated *NPHS2-rtTA* and *hKLF6^{PODTA}* mice served as controls. All mice were euthanized at 20 weeks of age and assessed for functional and histological changes in the kidney.

Results: DOX-STZ-UNX treated *hKLF6^{PODTA}* mice exhibited significantly lower albuminuria, focal and global glomerulosclerosis, mesangial expansion, and improved mice survival as compared to age and gender-matched DOX-STZ-UNX treated *NPHS2-rtTA* mice. DOX-STZ-UNX treated *hKLF6^{PODTA}* mice also exhibited less tubulointerstitial fibrosis and inflammation (pathology scoring) as compared to age- and gender-matched DOX-STZ-UNX treated *NPHS2-rtTA* mice.

Conclusions: These data suggest that podocyte-specific induction of human *KLF6* attenuates podocyte injury and DKD, and improves overall survival in mice.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

PO0907

nPOD-Kidney, a New Tool for Investigating Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is a common complication of diabetes, yet it remains poorly understood. The network for Pancreatic Organ donors with Diabetes - Kidney (nPOD-K) project was initiated to assess the feasibility of evaluating human kidneys from organ donors with long-standing diabetes (>8 years), with the long-term goal of improving our understanding of DKD pathogenesis.

Methods: Formalin-fixed paraffin-embedded sections from nPOD-K were stained for specific renal cell and disease markers by multiplex immunofluorescence, followed by periodic acid-Schiff (PAS) staining. Whole sections were imaged using an Axioscan Z1 scanner (20X objective) and quantitative image analyses were performed using Visiopharm software

Results: Tissue integrity and histological stage were independently assessed by two renal pathologists. The majority of cases presented a moderate or severe diagnosis, and 20% of the cohort displayed no overt sign of kidney disease despite long-standing diabetes. Algorithms for automatic segmentation of kidney compartments (e.g. glomeruli, tubules) in the PAS layer were then developed using deep convolution neural network DeepLabV3+. We achieved a DICE coefficient of 0.95 for glomeruli and 0.89 for tubules. Quantification of renal markers was performed using machine learning classification methods. In accordance with published studies, our quantitation demonstrated loss of podocyte marker WT1, endothelial marker CD31, and tubular marker *Lotus tetragonolobus* lectin correlating with the progression of DKD, concomitantly with increased tubular atrophy and expression of fibrotic markers.

Conclusions: In conclusion, kidneys obtained from organ donors are viable and display all expected features of human DKD at the level of light microscopy. This cohort provides a unique opportunity to better understand DKD pathophysiology through analysis of large, CKD stage-specific regions. Similar to the results from the nPOD pancreas cohort, all histological stages of disease can be detected in affected kidneys, providing a pseudo-timeline of the evolution of DKD and supporting the potential to identify novel therapeutic targets.

Funding: Commercial Support - Novo Nordisk, Inc.

PO0908

Nerve Growth Factor Protects Podocyte Apoptosis by Regulating Sirt1 Expression

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Background: Podocyte injury contributes to the progression of diabetic kidney disease (DKD). In the previous studies, we demonstrate that expression of Cdk5/p35 play an important role in the diabetic kidney and associated with the progression of DKD in human. As know, podocyte can secret NGF and Sirt1 is one substrate of CDK5, so the objective of this article is to investigate the mechanism of NGF protecting podocyte apoptosis by regulating Sirt1 expression and to provid a new biological target for clinical treatment.

Methods: The immortalized mouse podocyte was cultured in vitro, then were transfected with control siRNA or siNGF vector to detect protein level of Sirt1 and apoptosis associated protein Cleaved caspase3 through western blot. In addition, podoctyes were also given different concentration of NGF to detect the expression of Sirt1 and Cleaved caspase 3 in order to find the relationship of NGF and Sirt1, and the role of NGF on podocytes.

Results: To understand the role of NGF on podocyte, we stimulated immortalized mouse podocytes with NGF in different concentration, the protein level of Sirt1 was positive associated with NGF expression. 2. Podocytes were transfected with control siRNA or siNGF vector by using ViaFect™ Kit, the effect of siNGF was verified by western blot. knockdown of NGF decreased the expression of Sirt1 and Cleaved caspase. 3. When gave NGF stimulation, the protein lelvel of Cleaved caspase3 was deceaed.

Conclusions: NGF plays a key role in protection podocyte by regulating the expression of Sirt1, NGF/SIRT1 axis may be a new biological target for preventing podocyte injury.

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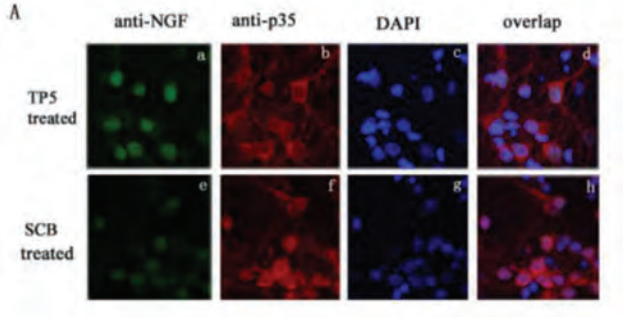

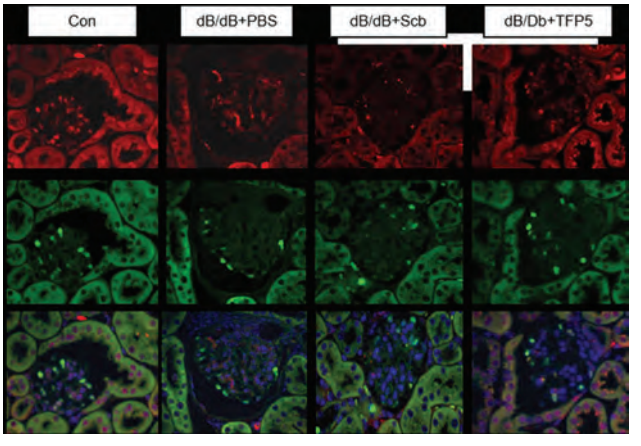

PO0909

Integrin aVb8/TGF-b Activation in Kidney Is Associated with Renal Function Deterioration and Can Be Monitored in Urine

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Background: Integrin-TGFb activation plays a central role in fibrosis. The specificity of TGFb activation is regulated by the expression of integrin isoforms in tissues. We set out to study molecular signatures associated with various aetiologies in CKD, the specific integrins that modulate TGFb activation and fibrotic initiation in the kidney and the potential for non-invasive monitoring of renal TGFb activation.

Methods: Kidney biopsies were obtained from CKD cohorts of diverse aetiologies and living donor (LD) controls. Gene profiling data (Microarray) were obtained from glomeruli and tubulointerstitium. Renal integrin expression was evaluated and the correlation with TGFb activation as well as eGFR was assessed.

Results: In the Gene Set Variation analysis (GSVA), fibrosis signatures including collagen signature increased with CKD severity compared to LD. This was more prominent in diabetic nephropathy (DN) in both glomeruli (N=12, p=1.09e-04) and tubulointerstitium (N=17, 2.31e-04). Further analysis showed that renal integrin b8 (ITGB8) was enriched and elevated at CKD stage 2, maintained at the similar level at

stage 3 and 4. ITGB8 was higher in DN tubolointerstitium (FC=1.23, p=5.56e-04, N=17) vs LD. Consistent with this, immune-histochemistry showed that ITGB8 protein was increased in tubular tissues in kidney biopsies from DN patients and co-localized with areas of fibrosis. Moreover, TGFb activation signature of 30 genes was significantly correlated with ITGB8 expression (R=0.58, p=2.39e-16, N=169) and inversely correlated with eGFR (p<0.01). Active TGFb was detectable in urine by a Simoa immunoassay. The active TGFb/creatinine ratio was increased by 4.4 fold (p=0.0003) in CKD subjects (median: 7.5 ug/g, N=20) compared to non-CKD controls (1.4 ug/g, N=20). The level of active TGFb in urine can potentially identify patients at risk for fibrosis and progression of renal dysfunction.

Conclusions: In conclusion, fibrosis is associated with CKD severity, most prominent in DN. Integrin b8 is enriched in DN and correlates with TGFb activation. The fibrosis status may be monitored via measuring active TGFb in urine.

Funding: Commercial Support - AstraZeneca

PO0910

Omentin 1 and Histone 1 Variants as Remote Candidate Prognostic Biomarkers of CKD Among People with Type 1 Diabetes Mellitus (T1DM)

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Background: It has been difficult to identify biomarkers that antedate the development of CKD. In a previous study we identified omentin-1 and histone H1 (HISTH1) variants as candidate surrogate prognostic biomarkers associated with future CKD development in T1DM Diabetes Control and Complications Trial (DCCT) study participants. Work presented here extends these findings into the follow-up samples from the Epidemiology of Diabetes Interventions and Complications (EDIC) study.

Methods: Paired-serum samples from 23 controls (defined as participants with stable renal function) and 23 cases (defined as participants who went on to develop CKD stage 3 (GFR<60ml/min/1.73m2) were examined prior to and following the development of CKD. HISTH1 variant proteins were quantified using a parallel reaction monitoring (PRM) LCMS method to quantify HISTH1-variant specific peptides unique to H1.1, H1.2, H1.3, and H1.4. Omentin-1 was quantified using a commercial ELISA kit for omentin-1 (BioVendor; Asheville, NC). Protein abundance data were analyzed using Kruskal-Wallis rank sum tests with an unadjusted p-value 0.05 considered significant.

Results: HISTH1 peptides did not differentiate (p>0.05) DCCT cases and controls. HISTH1.3 was significantly increased in EDIC cases over controls. A multivariate logistic regression analyses of histone peptides identified HISTH1.4 as best able classify case or control DCCT-to-EDIC progression (p<0.05). Omentin-1 quantification confirmed discovery findings (DCC control >case, fold-change 1.2, p<0.05). Additionally, in cases, omentin-1 increased significantly (p<0.0001) from the DCCT to the EDIC (1.4) whereas it did not (p=0.06) in controls (fold-change 1.1).

Conclusions: Plasma HISTH1 variants levels did not predict future CKD3 status but did predict DCCT versus EDIC cohorts. Increased plasma omentin-1 levels in DCCT cohort were associated with stable renal function but in EDIC cohort were associated with CKD stage 3. These data suggest a role for omentin-1 or pathways regulating omentin-1 expression are associated with progression of kidney function loss in T1DM.

Funding: NIDDK Support, Veterans Affairs Support

PO0911

Investigations on Urinary Exosomal MiRNA Biomarkers That Reflect Pathologic Features of Patients with Diabetic Kidney Diseases

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Background: Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease worldwide. Although histological severity of DKD is a well-established predictor of adverse renal outcomes, investigations on the identification of non-invasive biomarkers that can reflect intrarenal status are scarce. The aim of this study was to discover urinary exosomal miRNA biomarkers of DKD and to examine their associations with the degree of various pathologic injury scores.

Methods: We collected and analyzed urinary samples obtained from 95 patients with biopsy-proven DKD and 32 healthy controls. The candidate microRNAs of DKD were selected based on the analysis of GEO dataset (GPL22945 and GPL24120) and public microRNA databases (miRTarBase, TargetScan, microRNA). Urinary exosomes were extracted by column-based isolation kit, and the levels of selected candidate microRNAs were measured by quantitative real-time polymerase chain reaction.

Results: Mean estimated glomerular filtration rate and urinary protein-to-creatinine ratio of enrolled DKD patients were 46.0 mL/min/1.73 m^2 and 6.8 g/g creatinine, respectively. Upon the analysis of public dataset, we identified 11 candidate microRNAs for DKD, whose expression in urinary exosomes were all significantly higher in patients with DKD compared to controls. In particular, urinary exosomal miR-30a-5p and miR-335-3p levels showed positive correlation with the degree of interstitial inflammation and arterial hyalinosis, respectively. There was no significant association between the remaining microRNAs and the degree of glomerular injury, tubulointerstitial fibrosis, or arteriosclerosis. Finally, we found significant correlation between urinary protein-to-creatinine ratio and the levels of urinary exosomal miR-98-5p.

Conclusions: Urinary exosomal microRNAs could reflect the degree of intrarenal pathologic status in patients with diabetic kidney disease.

PO0912

Urine Biomarkers of Tubulointerstitial Injury in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is a serious complication of diabetes. Chronic damage to the tubulointerstitium often predicts loss of kidney function, but kidney biopsies are seldom obtained during the routine clinical care of patients with presumed DKD. This study was done to identify non-invasive urine biomarkers that reflect kidney histology in DKD.

Methods: Urine and serum were collected from 34 diabetic patients at the time of kidney biopsy, and from 30 healthy volunteers who served as controls. Biopsies were read by a nephropathologist. The severity of interstitial fibrosis/tubular atrophy (IFTA) was reported semi-quantitatively using Tervaert's Score. Epidermal growth factor (EGF), NGAL, and complement component C5a were measured in urine and serum by ELISA. Analyte levels were compared between patients and controls and correlated to histologic lesions using ANOVA, the Wilcoxon test, linear regression, and logistic model fitting.

Results: Compared to controls, urine (u)C5a and uNGAL levels were about 359 and 20-fold higher, and uEGF levels were 4-fold lower in the DKD cohort (all p<0.0001). Serum and urine C5a and EGF were not correlated, but there was a modest correlation between serum and urine NGAL (r2 0.41, p 0.0024). uEGF was negatively correlated with IFTA (r2 0.41, p < 0.0001) while uC5a, uNGAL, and serum (s)NGAL were positively correlated (r2 0.21, p=0.009; r2 0.17, p=0.02; r2 0.46, p=0.0007). Receiver operating characteristic (ROC) curves were modeled to determine the best combination of biomarkers to distinguish between mild, moderate, and severe IFTA in DKD. The model with a combination of uEGF+sNGAL yielded an area under the ROC curve (AUC) of 1.00 to differentiate mild from moderate IFTA, an AUC of 0.86 to differentiate mild from severe IFTA. The model with uEGF+uNGAL+uC5a gave an AUC of 0.94 to differentiate moderate from severe IFTA. These composite biomarkers outperformed serum creatinine (AUC 0.9 mild-moderate; AUC 0.82 mild-severe; AUC 0.74 moderate-severe) and proteinuria (AUC 0.76 mild-moderate; AUC 0.67 mild-severe; AUC 0.60 moderate-severe).

Conclusions: Urine EGF, C5a and serum and urine NGAL reflect chronic tubulointerstitial damage in patients with DKD. These biomarkers may be useful for monitoring the effectiveness of treatment to slow progression of DKD.

PO0913

Renoprotective Effect of a GLP-1 Receptor Agonist, Liraglutide, in an Early Phase of Diabetic Kidney Disease in Spontaneously Diabetic Tori Fatty Rats

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Background: Early intervention is extremely needed for preventing the progression of diabetic kidney disease (DKD) to end stage renal disease. The aim of this study is to investigate the renoprotective effect of GLP-1 receptor agonist, liraglutide, in early phase of DKD and to determine the mechanisms underlying its effects using an animal model of type 2 diabetes with various metabolic disorders.

Methods: Male spontaneously diabetic torii (SDT) fatty rats (n = 30) at 8 weeks of age were randomly assigned to three groups; the liraglutidegroup (n = 11) was subcutaneous injected liraglutide. Another treatment group(n = 6) was subcutaneous administered insulin against hyperglycemia and was given hydralazine against hypertension for matching both levels of blood glucose and blood pressure with the liraglutidegroup. A control group (n = 13) was injected only a vehicle. Urinary tubular marker, L-type fatty acid-binding protein (L-FABP), was measured to evaluate the effect of liraglutide against tubulointerstitial damage.

Results: Control group of SDT fatty rats exhibited hyperglycemia, obesity, hypertension, glomerular sclerosis and tubulointerstitial injury with high levels of urinary albumin and L-FABP, whereas treatment with liraglutide reduced body weight, food intake, both blood glucose and blood pressure levels, as well as, amelioration of renal pathological findings with lower levels of both urinary albumin and L-FABP. Liraglutide increased in expressions of both phosphorylated (p)-eNOS and p-AMPK in glomeruli. It also down-regulated renal expression of p-mTOR, and up-regulated renal expressions of LC-3 II, suggesting activation of autophagy. However, these effects were not brought

by the treatments of both insulin and hydralazine, despite comparable levels of both hyperglycemia and hypertension to those of liraglutide.

Conclusions: Liraglutide may exert a renoprotective effect via prevention of glomerular endothelial dysfunction and acceleration of autophagy in the early phase of DKD, independently of both blood glucose and blood pressure levels. Furthermore, urinary L-FABP may be a useful marker reflecting the therapeutic efficacy of liraglutide.

PO0914

PLVAP as a Novel Marker for Endothelial Injury in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is associated with endothelial cell dysfunction and progressive loss of kidney function. The plasmalemma vesicle associated protein (PLVAP) has been found to be necessary for the formation of endothelial diaphragms in fenestrae, caveolae, and transendothelial channels. In the adult kidney, glomerular endothelial cells lack diaphragms in the fenestrae. Previous studies reported glomerular expression of PLVAP in transplant glomerulopathy, in mesangioproliferative glomerulonephritis model and in mice developing renal thrombotic microangiopathy as a consequence of defective Gsα/cAMP signaling in renin cells. Therefore, we investigated whether PLVAP expression in glomerular capillaries is induced in different models of DN.

Methods: To induce a model of type 1 diabetes, one dose of streptozotocin (STZ, 180 mg/kg) was administered by intraperitoneal injection in 6-8 weeks old mice. 16-week-old black and tan brachyuric (BTBR) ob/ob mice, with spontaneous mutation in the leptin gene were used as a model of type 2 diabetes. Immunohistochemical staining and analysis was performed to examine the expression of PLVAP. We co-stained the Intercellular Adhesion Molecule 2 (ICAM2) as a marker for endothelial cells.

Results: Glomerular hypertrophy was found in STZ mice and BTBR ob/ob mice, which was interpreted as evidence for successful induction of DN (STZ: 2750 μm^2, control: 2527 μm^2; BTBR ob/ob: 4471 μm^2, control: 2295 μm^2). Using immunohistochemical analysis, the BTBR ob/ob mice and the STZ mice revealed induced PLVAP expression in their glomeruli, as compared with non-diabetic controls ($p<0.05$ respectively). ICAM2 expression in glomeruli of STZ mice tended to be lower than in control mice, but the difference was not statistically significant. In BTBR ob/ob mice, the expression of ICAM2 was significantly decreased compared to control mice ($p<0.05$).

Conclusions: Our results indicate that the glomerular expression of PLVAP is induced in diabetic nephropathy. The protein PLVAP represents a potential novel marker for endothelial injury in diabetic nephropathy.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0915

MTORC1/STAT1 Signaling Stimulates CFB Expression and Alternative Complement Pathway Activation to Induce Podocyte Dysfunction and Diabetic Kidney Disease

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Background: Alternative complement pathway activation has been reported in diabetic kidney disease (DKD). However, the role and mechanisms for regulating alternative complement pathway activation in podocyte dysfunction and DKD are not understood.

Methods: STZ-induced DKD mice, db/db mice, Podocyte-specific TSC1 deletion mice were used.

Results: The analysis of GSE30528 data and the immunohistochemical staining results showed that mTORC1 signaling, STAT1, complement factor B (CFB) and complement alternative pathway were activated in podocytes from patients and animal models with DKD. Knocking down CFB remarkably alleviated podocyte loss, glomerular basement membrane thickening, mesangial expansion, and proteinuria in DKD mice. In addition, ablation of Tsc1 in podocytes led to mTORC1 and STAT1 signaling activation, CFB induction, and alternative complement pathway activation in the glomeruli. In cultured podocytes, high glucose culture could activate mTORC1 signaling, stimulate STAT1 phosphorylation and upregulate CFB expression. Blockade of mTORC1 or STAT1 signaling could abolish high glucose upregulated CFB expression in podocytes.

Conclusions: This study uncovers that mTORC1/STAT1 activation in podocytes may promote DKD progression through activating complement alternative pathway.

Funding: Government Support - Non-U.S.

PO0916

Loss of Nrf2 Exacerbates Diabetic Kidney Disease in Akita Mice

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Background: Diabetic kidney disease (DKD) is a devastating microvascular complication with considerable mortality in patients with diabetes mellitus. Excessive reactive oxygen species and inflammation have been identified as major components in the progression of this microvascular complication. Transcription factor Nrf2 (NF-E2-related factor-2), which plays essential roles in protection against oxidative/xenobiotic stresses, is known to alleviate inflammation and oxidative tissue damage. We hypothesized that keeping Nrf2 activated is beneficial for the treatment of DKD.

Methods: To clarify roles Nrf2 plays in the pathogenesis of DKD, we generated *Nrf2*-knockout Akita mice (Akita::Nrf2$^{-/-}$) by crossing *Ins2*$^{Akita/+}$ (Akita) mice (C57BL/6J) with *Nrf2* knockout (Nrf2$^{-/-}$) mice (C57BL/6J). Phenotypic parameters of male mice were measured, and samples were harvested from the mice at 4 months.

Results: We found that Akita::Nrf2$^{-/-}$ mice displayed more pronounced hyperglycemia and diabetes symptoms than Akita mice did. While expression of Nrf2-tageted genes *Nqo1* and *Hmox1* was induced in Akita mouse kidneys; the expression was significantly reduced in kidneys of Akita::Nrf2$^{-/-}$ mice. Histologically, Akita mice showed modest mesangial expansion, but Akita::Nrf2$^{-/-}$ mouse glomeruli showed marked distended capillary loops suggesting enhanced mesangiolysis. Akita::Nrf2$^{-/-}$ mice exhibited dilated distal tubules mainly within cortex, which might be associated with osmotic polyuria and oxidative stress-mediated injury; this notion was supported by increased tubular staining of oxidative stress marker 8-OHdG. Nrf2-deficiency in Akita mice contributed to the decrease of glutathione (GSH), which was assessed by *in situ* matrix-assisted laser-desorption/ionization mass-spectrometry imaging (MALDI-MSI) and lowered expression of GSH-synthesis related genes. Kidneys of Akita::Nrf2$^{-/-}$ mice suffered from severe inflammation, which was evidenced by increased infiltrated monocytes/macrophages and elevated pro-inflammatory cytokine expression. Interstitial fibrosis was developed in the Akita::Nrf2$^{-/-}$ mouse kidneys along with increased expression of fibrogenic genes.

Conclusions: These results demonstrate that Nrf2-deficiency exacerbated inflammatory response, oxidative stress and interstitial fibrosis in the Akita mouse kidneys, indicating that Nrf2 plays important roles in the protection of DKD kidneys.

Funding: Government Support - Non-U.S.

PO0917

The Novel Soluble Guanylyl Cyclase (sGC) Activator Runcaciguat Improves Cardiorenal Morbidity in a Diabetic Rat Model of CKD

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Background: Patients with chronic kidney disease (CKD) and Type-2-Diabetes (T2D) have a high risk of kidney failure and cardiovascular events. CKD and T2D are associated with oxidative stress impairing NO/sGC signaling thus driving CKD progression. Runcaciguat is a novel potent and selective, sGC activator able to restore sGC signaling by activating the oxidized and heme-free sGC. Here we investigated the therapeutic potential of Runcaciguat in a rat model of T2D associated CKD.

Methods: Cardiorenal morbidity was studied in diabetic and proteinuric rats. Rats (ZDF/Crl-Lebr-fa/fa, 22 weeks old male, n=20/group) were treated orally for up to 42 weeks with Runcaciguat (3 mg/kg) or placebo. Key outcome parameters included mortality, blood pressure, proteinuria, kidney histology, biomarkers of kidney and heart damages, and gene expression.

Results: Proteinuria steadily increased over time in the placebo arm (uPCR (g/mmol) 0.9±0.1 @ baseline, 1.8±0.1 @12 wk, 5.9±0.7 @42 wk)) and was significantly reduced in the Runcaciguat arm (0.8±0.1 @ 12 wk, 3.0±0.5 @ 42 wk). Improved proteinuria was paralleled by significantly improved glomerular filtration rates @ 42 wk (55±5 ml/min vs. 36±9 in the placebo arm). Histological examination of kidney revealed that Runcaciguat strongly reduced tubular dilation, glomerulopathy and accumulation of protein cylinders. Runcaciguat significantly improved left ventricular heart weight as well as several kidney and heart injury markers in urine and in plasma.

Conclusions: The novel sGC activator Runcaciguat improved kidney and heart function and structure in a preclinical diabetic and hypertensive rat model and may become an effective treatment option for diabetic and chronic kidney disease patients.

Funding: Private Foundation Support

PO0918

RNA-Binding Proteins Tristetraprolin and Human Antigen R Are Novel Modulators of Podocyte Injury in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the most common complications of diabetes and the most common cause of end-stage renal disease, with no definitive therapy yet available to halt its progression. As key RNA-binding proteins (RBP) that play a pivotal role in epigenetic regulation, Tristetraprolin (TTP) and human antigen R (HuR) competitively bind to mRNAs of myriad cytokines, exert opposite effects on RNA stability, and dictate overall inflammatory states. However, the roles of these RBP in diabetes-related glomerulopathy is poorly understood. Herein, we investigated whether and how TTP and HuR are involved in the posttranscriptional regulation of podocytopathic molecules and inflammatory cytokines in DKD.

Methods: Kidney tissues were procured from diabetic patients and from db/db mice. Quantitative RT-PCR was performed to measure mRNA expression levels of *IL-17* and *claudin-1*. Lentivirus vector transduction was employed to overexpress or silence target proteins. RNA immunoprecipitation (RIP) and co-immunoprecipitation assays were used to identify RNA-protein and protein-protein interactions.

Results: In DKD patients and db/db mice, TTP expression was significantly decreased and HuR expression was increased in glomerular podocytes, concurrent with podocyte injury, histological signs of DKD, and augmented glomerular expression of interleukin (IL)-17 and claudin-1, which are targets of TTP and HuR, as evidenced by RNA

immunoprecipitation. In cultured podocytes, exposure to high ambient glucose amplified HuR expression and repressed TTP expression, upregulated IL-17 and claudin-1, and promoted podocyte injury. Thus, TTP hypoactivity or HuR hyperactivity is sufficient and essential to diabetic podocytopathy. Moreover, in silico analysis revealed that several kinases govern phosphorylation and activation of TTP and HuR, and glycogen synthase kinase (GSK)-3β activated both TTP and HuR, which harbor putative GSK-3β consensus phosphorylation motifs.

Conclusions: TTP and HuR are dysregulated in DKD via a GSK3b-mediated mechanism and play crucial roles in podocyte injury via posttranscriptional regulation of diverse molecules implicated in inflammation and podocytopathy. Our findings provide novel insights into the mechanism of and identify therapeutic targets for diabetic kidney disease.

Funding: Government Support - Non-U.S.

PO0919

Nogo-B and Soluble Nogo-B Modulate VEGFA/VEGFR2 Signalling in Glomerular Endothelial Cells

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Background: Nogo-B is an endoplasmic reticulum protein present either as a full-length or circulating soluble isoform (sNogo-B) corresponding to the first ~200aa of the N-terminus. Nogo-B is expressed in the vasculature and in glomerular endothelial cells (GECs) and downregulated in diabetic glomeruli. Overexpression of sNogo-B ameliorates diabetic glomerulopathy, but the biological mechanisms are unknown. We hypothesise that, in GECs, Nogo-B and/or sNogo-B modulate VEGFA/VEGFR2 signalling and vascular remodelling.

Methods: Nogo-B deficient human GECs were generated with CRISPR/CAS9 technology. VEGFA signalling was studied in differentiated, serum starved (5 h, FBS 2%) GECs exposed to VEGFA (50 ng/ml) for 5, 10 and 15 min. VEGFR2 phosphorylation (Tyr1175) was assessed with western immunoblotting. Experiments were conducted in GECs transfected with adenoviral vector expressing sNogo-B or control vector. To investigate the role of Nogo-B on GECs survival, Caspase-3/7 activity was utilised as marker of apoptosis in WT and Nogo-B deficient GECs after 5 h incubation in 2% FBS. *In vivo* Matrigel-angiogenesis assay in wild-type (WT) and Nogo-A/B deficient mice were conducted in parallel.

Results: When compared to WT GECs, Nogo-B deficient cells appeared more elongated with a peripheral distribution of F-actin but maintained expression of endothelial markers such as eNOS and CD31. Phosphorylated VEGFR2/total VEGFR2 ratio was similar in baseline condition in WT and Nogo-B deficient GECs. VEGFA-mediated VEGFR2 phosphorylation (15 min) was observed in WT GECs but not in Nogo-B deficient GECs ($p<0.01$). In the presence of sNogo-B, there was significant reduction in VEGFA-mediated VEGFR2 phosphorylation in WT GECs ($p<0.05$). There was no significant effect of sNogo-B on VEGFR2 phosphorylation in Nogo-B deficient GECs. Apoptosis was higher in Nogo-B deficient GECs when compared to WT ones ($p<0.04$). Preliminary work in *in vivo* Matrigel angiogenesis showed that Nogo-B deficient ECs were unable to form vascular structure when compared to wild-type cells ($P<0.05$). Presence of sNogo-B blunted the angiogenesis in WT mice.

Conclusions: Nogo-B is required for VEGFA-mediated VEGFR2 phosphorylation and for vascular remodelling (angiogenesis). Overexpression of sNogo-B blunts VEGFA-mediated VEGFR2 phosphorylation. sNogo-B could represent a tool to modulate VEGFA signalling in diseases.

PO0920

Cytosine Methylation Changes in Early Diabetic Kidney Disease (DKD) in a Pima Indian Cohort

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Background: Pima Indians of Arizona have an extremely high prevalence of type 2 diabetes and DKD. Genetically related Pima Indians living in Mexico, whose lifestyle remains traditional, have a much lower prevalence of these morbidities. The differences in lifestyle indicate that environmental factors play an important role in disease origins and suggest involvement of epigenetic programming. We analyzed cytosine methylation (5mC) changes in Pima Indians from Arizona.

Methods: 327 Pima Indians (205 women, 122 men) were selected from a longitudinal cohort, all had an eGFR greater than 60ml/min and ACR <300mg/g at baseline. DNA methylation from peripheral blood leukocytes was analyzed on an Illumina Infinium HumanMethylation 450 Beadchip. Preprocessing and Quality Control were performed using Minfi Package, normalization was performed using BMIQ. Methylation changes were expressed transformed to M values. Covariates included age, sex, duration of diabetes, mean blood pressure, HbA1c, genotype, batch, cell count and conversion efficiency. P-values were corrected for multiple comparisons.

Results: Mean age was 42.4±11.9 years, diabetes duration 7.8±7.5 years, HbA1c 8.8±2.4%, GFR 107±16 ml/min and median albuminuria was 20.2[48.2]mg/g. Subjects were followed for a median of 10 years (range 3-17 years) and had a mean GFR decline of 2.0±2.8 ml/min/year. Ranked regression, adjusted for key variables, identified 20 probes that passed the corrected significance threshold for kidney function decline. Most significant probes were enriched on gene regulatory regions such as promoters and enhancers. The top identified probe was cg05711886 around the Maternally expressed gene 3 (MEG3)on chromosome 14, ($p=2.66E-10$). MEG3 is a non-coding RNA previously associated with diabetic microvascular complications. Other probes included cg11306628 ($p=1.62E-5$) in Platelet Derived Growth Factor Alpha (PDGFA) on chromosome 7, a known type 2 diabetes risk gene, as well as cg06392169 ($p=3.14E-5$) in Interferon Related Factor 4 (IRF4) on chromosome 6 and cg12577105 ($p=4.11E-5$) in Corticotrophin Releasing Hormone Receptor 1 (CRHR1) on chromosome 17 involved in the HPA axis.

Conclusions: We identified cytosine methylation changes that correlated with early kidney function decline in Pima Indians with type 2 diabetes.

PO0921

Pathogenic Impact of Altered Leptin in Diabetes Induced by Genetic Deletion of the Canonical Transient Receptor Potential Channel 1 (TRPC1): Role of Insulin, Body Weights, Calcium-Sensing Receptor, and Intracellular Calcium

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Background: We recently reported diabetic phenotypes in TRPC1 mutatioon. The role of the elevated serum leptin & reduced adiponectin is unclear. Like CaSR, TRPC1 participates in cell Ca homeostasis & its deficiency impairs Ca entry & induces hyperparathyroidism (JCI Apr 2020). We tested if by raising serum Ca by 4-5 mg%, we would raise cell Ca in adipocytes to lower lepin & elevate adiponectin, based on published in vitro data.

Methods: In age- & sex-matched TRPC1 +/+, +/- & -/- mice, we did metabolic studies, IP glucose toleranace tests, & measured serum cytokines & PTH by ELISA. At 10 m, we injected IP Ca to cause hypercalcemia (~15 mg%) to raise cell Ca enough to lower PTH, & by inference, similar rises in adipocytes & beta cells to alter leptin & insulin. At 16 m, we injected calcimimetic (Parsabiv) IP x 2 wks to evaluate if glucose tolerance is improved by chronically raising cell Ca.

Results: Serum leptin increase in -/- mice vs +/+ by 17% at 4.5 m, 75% ($p<0.05$) at 6.5 m, & 130% ($p<0.001$) at 9.5 m. It is directly related to body weight (BW) at 4.5 mon regardless of genotypes or gender ($N=80$; $p<0.05$). The relationship holds true at 17 m ($p<0.05$ for +/+ & $p<0.05$ for -/-). High fat diet x 3 m stimulates leptin 3 to 5 fold for all 3 genotypes, but linkage to BW holds. Serum leptin after fast ($r=0.93$) & 30 min post IP glucose ($r=0.75$) are highly correlated with simultaneous insulin. Leptin rose from 6.6 to 10.6 ng/ml 2 h after IP glucose ($p<0.01$). With induced hypercalcemia, PTH, elevated in null (288 vs 119 pg/ml), fell 75% (vs. 48% in +/+), but the elevated leptin (15.1 vs. 6.6 ng/ml) did not fall; insulin, similar between +/+ & -/-, fell comparably in both genotypes. GTT did not improve in +/+ or -/- mice after 2 wk of calcimimetics.

Conclusions: 1. Leptin is upregulated by anabolism, high fat diet, weight gain, & correlated with body weight & insulin in normal & TRPC1 null mice. 2. It is however increased in TRPC1 deficiency, uncorrected by raising intracellular Ca by hypercalcemia (sufficient to inhibit PTH by 50 to 75%) 3. Like insulin-resistant diabetes in mice with leptin receptor deficiency, we postulate the lack of TRPC1 impairs leptin signaling in neurons inhibiting hyperphagia. The elevated leptin reflects inadequate compensation to combat obesity.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support, Clinical Revenue Support

PO0922

The Significance of Renal TSPAN9 Overexpression in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. We performed proteomic analysis in isolated human glomeruli (DN vs. normal control) and RNAseq in glomeruli from a murine model of DN (db/db/eNOS$^{-/-}$) vs. nondiabetic controls (eNOS$^{-/-}$). We identified differentially expressed molecules with potential impact in DN, including tetraspanin 9 (TSPAN9), which mediates transduction signaling and regulates cell development, growth and motility. We investigated the potential contribution of TSPAN9 in DN.

Methods: Human kidney biopsies from DN (class II, III and IV, total n=30) were studied, and compared to control (non-cancer regions of human nephrectomy (Nx), n=10). TSPAN9 immunostaining was assessed and correlated with morphologic lesions and clinical data. Human mesangial cells (HMC) were cultured in normal glucose, mannitol or high glucose medium. TSPAN9 expression in HMC was determined by qPCR, western blot and immunofluorescence. HMC viability and migration were assessed by MTT assay and transwell experiments. Collagen IV protein in the cellular supernatant was detected by ELISA. Apoptosis regulating molecules Bax and BCL-2 were assessed by qPCR and western blot.

Results: TSPAN9 was expressed weakly in normal human kidney control, in glomerular mesangial areas and luminal side of tubules. Immunostaining intensity was gradually increased in class II, III and IV DN. TSPAN9 translocated from the luminal to apical side in tubular epithelial cells, and extended to more extracellular expression in mesangial areas. In DN samples, glomerular TSPAN-9 expression correlated with extent of glomerulosclerosis, hyalinosis, mesangial expansion and proteinuria, while tubular

TSPAN-9 correlated with extent of interstitial fibrosis, proteinuria and serum creatinine. In vitro, TSPAN9 in HMC was significantly upregulated by mannitol and high glucose, accompanied by decreased cell viability, migration and increased apoptosis.

Conclusions: DN was associated with increased TSPAN9 overexpression and translocation in mesangial and tubular epithelial cells, respectively, and was associated with worse renal function and more severe structural injury.

Funding: NIDDK Support

PO0923

Loxl4 Deacetylates OPA1 to Regulate Mitochondrial Dynamics During Diabetes

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Background: Mitochondrial morphology is regulated by the balance between two counteracting mitochondrial processes of fusion and fission. There is significant evidence suggesting a stringent association between morphology and bioenergetics of mitochondria. Morphological alterations in mitochondria are linked to several pathological disorders, including diabetic kidney disease. The consequences of high glucose-induced acetylation of mitochondrial proteins on the organelle morphology and function remain largely unexplored.

Methods: Here, we examined the kidneys of mice with streptozotocin-induced diabetes and primary tubular epithelial cells exposed to high glucose.

Results: Using high-resolution mass spectrometry, we identified 152 hyperacetylated and 19 hypoacetylated proteins in the mitochondria from kidney tubule of diabetic mice compared with control mice. OPA1, a mitochondrial fusion protein was hyperacetylated at lysine 228, 792 and 847 residuals under high glucose-induced pathological stress and this posttranslational modification increased mitochondrial fragmentation. Overexpression of a deacetylation-mimetic version of OPA1 recovered the mitochondrial functions of OPA1-null cells, thus demonstrating the functional significance of K228/792/847 acetylation in regulating OPA1 activity. The newly discovered deacetylase lysyl oxidase like 4 (Loxl4) interacts with OPA1 in mitochondria. Overexpression of Loxl4 prevents high glucose-induced acetylation, preserved mitochondrial networking and protected the high glucose-induced decrease of oxygen consumption rate.

Conclusions: In summary, these data indicated that hyperacetylation of OPA1 regulates mitochondrial fusion and fission under diabetes conditions. Loxl4 promotes mitochondrial function by regulating mitochondrial dynamics by targeting OPA1.

Funding: Government Support - Non-U.S.

PO0924

Discovery of a Small-Molecule Drug for Treating Diabetic Kidney Disease

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Background: Diabetic Kidney Disease (DKD) is the leading cause of chronic kidney disease and one of the fastest growing epidemics worldwide. Podocyte injury is a hallmark of DKD. As such, preventing podocyte injury is necessary for effectively treating DKD. Our prior studies demonstrated that the accumulation of lipid droplets (LDs) in podocytes is associated with increased susceptibility to apoptosis in the context of DKD. Conversely, reducing LD accumulation in podocytes prevented renal disease in a mouse model of DKD (BTBR ob/ob). Thus, compounds that reduce LD accumulation may protect podocytes from injury and prevent the progression of DKD. The goal of this study is to identify compounds that reduce LD accumulation *in vivo* and lead to the identification of therapeutic candidates for DKD.

Methods: Advances in high throughput synthetic chemistry have enabled the design of combinatorial libraries for efficient screening and identification of novel bioactive compounds. The approach is particularly powerful when combined with a phenotypic screening assay that recapitulates disease biology. We have developed a high content screening assay to quantify LD accumulation in human podocytes in response to stress stimuli. The assay is highly suitable for screening with a Z factor consistently > 0.5.

Results: We performed a pilot screen using 100 compound mixtures, each containing thousands of compounds, obtained from the Torrey Pines Institute for Molecular Studies (TPIMS). We identified one compound mixture (2275) that consistently reduces LD accumulation in a dose-dependent manner. 2275 significantly reduces LD accumulation induced by TNF, a pro-inflammatory cytokine associated with DKD, and induced by sera from patients with DKD. The TPIMS hit deconvolution method will be used to identify the active compound(s) within the 2275 mixture.

Conclusions: We identified compounds that significantly reduce LD accumulation in cultured human podocytes in response to stress stimuli, including sera from DKD patients. Further studies to deconvolve and validate those compounds, and test them in an animal model of DKD, are underway.

PO0925

Altered Protein Translation in the Kidney Precedes the Development of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the most serious complications of diabetes. Diabetes is characterized by a variety of physiologic derangements and maladaptive pathways that contribute to cell stress and the development of DKD. There is mounting evidence in a variety of disease models demonstrating that altered protein translation, a fundamental step in gene expression, is important in both responding and contributing to cell stress. The hypothesis of this study is that altered protein translation precedes the development of overt DKD. It was the aim of this study to undertake a detailed examination of protein translation in the kidney early in the course of diabetes.

Methods: Ribosome footprint profiling (Ribo-seq) was employed to unbiasedly examine translational processes in the kidney at nucleotide level resolution across the whole genome during the develpment of diabetes in db/db mice. RNA-seq was done in parallel to examine transcriptional pathways of translation and augment findings from the translatome.

Results: Ribo-seq in 12 week-old db/db mice and age-matched, background C57BL/6J control mice (BC) demonstrated a marked (50%) global increase in translation in kidneys from db/db mice as compared to BC mice. This findings of increased translation was further supported by polyribosomal profiling and pathway analysis of RNA-seq done in parallel. Increase of global translation was also observed as the vintage of diabetes increased from 9 weeks to 12 weeks in db/db mice. Increased translation in the kidney of important pathgenic mediators were observed in pathways that contribute to alterations in cell cycling (p21), fibrogenesis (fibronectin), inflammation (osteopontin), glucose transport (SGLT2), and oxidative stress (NOX4). Although overall transcription and translation of p53 was not observed early in diabetes, translation of ΔNp53 (Δ40p53), a stress-induced, translationally-regulated isoform of p53 important for development of the diabetic phenotype was found to be increased by Ribo-seq. These findings underscore the importance of examining the translatome in the kidney as a missing omics layer in DKD.

Conclusions: Generalized protein translation is increased in the kidney early in the course of DKD. Pharmacological manipulation of translation may represent a novel therapeutic approach to the development and progression of DKD.

Funding: NIDDK Support

PO0926

Esculin Restores Kidneys Mitochondrial Function in the Early Stage of Experimental Diabetic Nephropathy

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Background: Diabetes mellitus (DM) is a chronic disease which progresses with many complications such as diabetic nephropathy (DN). Mitochondria are the main producer of reactive oxygen species (ROS) in a hyperglycemic condition, consuming oxygen without providing ATP to the cell. In turn, ROS act as a trigger to activation of inflammatory processes. Coumarin derivatives, as esculin, reduced oxidative damage seen in intestinal inflammation, arthritis and cognitive impairment related to diabetes. The aim of this study was to evaluate the effects of esculin on mitochondrial function and on the kidneys cortex in the DN development in rats.

Methods: DM was induced in 7-week-old male Wistar rats, using a single dose of streptozocin (60 mg/kg; i.v) and confirmed with blood glucose ≥ 200mg/dL. The animals received daily doses of esculin (50 mg/kg, p.o.) or its vehicle, during 8 weeks. After this period they were euthanized under anesthesia and the kidneys cortex were collected for histology and mitochondria isolation, to be analyzed by high resolution respirometry. Statistical analysis was performed in GraphPad Prism 6. The results are described as mean ± SEM, significance defined for $p < 0.05$.

Results: Esculin reduced 24 hs proteinuria in DM rats. The histological analysis of kidneys cortex showed the presence of intense inflammatory lymphomononuclear infiltrate, mild fibrosis and interstitial atrophy characterized by collagen IV deposition in diabetic animals, that were not observed in any of those treated with esculin. In addition, esculin restored mitochondrial function in the kidneys cortex of diabetic rats as analyzed by glycolysis (3.08 ± 0.17 *vs* 2.39 ± 0.08; $p < 0.05$) and β-oxidation substrates (4.75 ± 0.08 *vs* 3.68 ± 0.20; $p < 0.05$).

Conclusions: Esculin restored mitochondrial function in DM rats and probably through ROS control, reduced the kidney lesions. We suggest the use of esculin as an adjuvant therapy to control the development of DN.

Funding: Government Support - Non-U.S.

PO0927

Selonsertib Reduces TNFα-Induced Markers of Injury and Inflammation in an Organ-on-a-Chip Model of Proximal Tubular Injury

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Background: Increased Circulating levels of TNF Superfamily Receptors 1 and 2 (TNFRSF1A and TNFRSF1B) in patients are associated with rapid declines in eGFR and proposed as biomarkers of DKD progression. In a phase 2 DKD trial which evaluated

safety and efficacy of the ASK1 inhibitor Selonsertib (SEL), higher serum sTNFR1 levels associated with progression to End Stage Renal Disease (ESRD). In vitro, mono-culture studies have demonstrated that ASK1 signaling is required for TNFα induced apoptosis in kidney and other organ systems. Current studies with a microfluidic organ-on-a-chip system to investigate the effects of TNFα in a kidney co-culture system and determine effect of SEL treatment on kidney proximal tubular injury.

Methods: After populating cells in a co-culture, microfluidic device (Emulate Bio) containing either Lonza RPTEC (top channel) or kidney microvascular endothelial cells (bottom channel), TNFa (2ng/ml) was added at Day 0 along with SEL (10μM) to inlet flow of each channel. After 7 days, RNA was isolated from each channel and gene expression analyzed by qPCR. Outlet supernatant from each channel was analyzed for kidney injury and inflammation markers on Mesoscale Discovery device (MSD). Data shown as fold-of-change or mean ± standard error of the mean (s.e.m.)

Results: TNFα significantly increased expression of both TNFRSF1A and1B in the RPTEC channel (1.4 and 2.6-fold, respectively vs. control), and SEL decreased TNFRSF1A expression by 108% (p=0.0058) and lowered TNFRSF1B expression by 64% (p=0.1549). SEL decreased TNFα-induced expression of IP-10 (6.4 vs. 37.3-fold, p=0.0083) and IL-18 expression (0.67-fold vs 1.6-fold, p<0.0001) in proximal tubules. Osteoactivin and Clusterin, biomarkers used to assess proximal tubule injury were significantly increased in RPTEC supernatant following TNFα stimulation channel (2.1 and 3.7-fold, respectively, p<0.0001 for each). SEL significantly reduced levels of osteoactivin (139.6 ± 33.74 vs 778.2 ± 44.24 pg/ml, p<0.0001) and clusterin (28.9 ± 1.8 vs. 108.5 ± 1.7 ng/ml, p<0.0001).

Conclusions: In a microfluidic, RPTEC/Endothelial co-culture model, treatment with the ASK1 inhibitor Selonsertib reduced several markers of kidney injury. Efficacy to reduce inflammatory gene expression and biomarkers of proximal tubular damage indicate SEL treatment may have potential to impact DKD progression.

Funding: Commercial Support - Gilead Sciences

PO0928

The Usefulness of Antisense Oligonucleotide Modified with Serinol Nucleic Acid for Kidney Disease

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Background: The use of nucleic acid drugs such as antisense oligonucleotides (ASOs) and siRNA has received a lot of attentions as next-generation drugs. However, the nucleic acid drugs for kidney diseases have not been put to practical use. Recently, we have newly developed the serinol nucleic acid (SNA) modified ASO which had strong nuclease resistance. In this study, we investigated the *in vivo* efficacy of SNA-modified ASO in mouse kidney.

Methods: Various types of PS-modified gapmer ASOs with or without SNA targeting both human and murine SGLT2 (sodium glucose cotransporter 2) were tested in the immortalized human proximal tubule epithelial cell (HK-2), and subcutaneously administered into mice. Urinary and blood glucose levels, renal function, liver function and renal SGLT2 expression were analyzed.

Results: First, we confirmed that SGLT2 ASO had enough inhibitory effects of SGLT2 expression in HK-2 cells. Next, we synthesized various types of SNA gapmer SGLT2-ASOs (SGLT2-SNA-ASO). Subcutaneous administration of SGLT2-SNA-ASO significantly suppressed renal SGLT2 mRNA and protein expressions and increased urine glucose in dose dependent manner. Those inhibitory effects of SGLT2-SNA-ASO were high and long-lasting compared with ASOs without SNA (SGLT2-ASO). No apparent kidney disfunction was observed. Mild and similar liver damages were found in both SGLT2-ASO and SGLT2-SNA-ASO groups. After subcutaneous administration of Cy5-labeled SGLT2-SNA-ASO, we observed the SGLT2-SNA-ASO accumulation in kidney, especially in renal proximal tubules, by in vivo imaging system (IVIS) and fluorescent microscope.

Conclusions: Systemic administration of SGLT2-ASO modified with novel artificial nucleic acid SNA well suppressed renal SGLT2 expression and induced urinary sugar excretion. These results indicated that ASOs modified with SNA might be applied to the development of neucleic acid drugs.

PO0929

Empagliflozin Inhibits Basal and IL1-β-Mediated CCL2 and Endothelin1 Expression in Human Proximal Tubular Cells

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Background: SGLT2 inhibitiors (SGLT2i) slow the progression of type II diabetic kidney disease, however, evidence for underlying molecular mechanisms is scarce. As reno-protection is observed promptly after starting SGLT2i, we aimed at investigating pathways involved in early disease pathogenesis.

Methods: human proximal tubular cell (HPTC) culture (HK-2 and RPTEC), microarray hybridization, real-time PCR, ELISA.

Results: Microarray hybridization identified 1263 genes that presented a uniform expression pattern 24h after ligand stimulation: IL1-β-mediated up- and Empagliflozin (Empa) mediated down-regulation in two HPTC lines (n=2, each). Functional annotation of these genes using DAVID enrichment analysis identified 33 pathway clusters. Based on their established involvement in early pathogenesis of diabetic kidney disease, 2 genes of interest, namely CCL2 and endothelin1, that were represented in the two top ranked clusters, have been selected for verification on the mRNA level: Basal CCL2 mRNA expression was upregulated by IL1-β (10 ng/ml) (15-fold, p<0,01 and 19-fold, p<0,01) but downregulated by Empa (500nM) (0,6-fold, p<0,01 and 0,5-fold, p<0,001) as early as 1h and at least for 24h after ligand stimulation in HK-2 and RPTEC cells, respectively. Coadministration of Empa inhibited IL1-β-mediated CCL2 mRNA expression after 1h (0,2-fold, p<0,01 and 0,2-fold, p<0,01) and 24h (0,2-fold, p<0,001 and 0,6-fold, p<0,01) in HK-2 and RPTEC cells, respectively. Basal endothelin1 mRNA expression was upregulated by IL1-β (3-fold, p<0,001 and 8-fold, p<0,001) but downregulated by Empa (0,3-fold and 0,2-fold, p<0,001 each) as early as 1h and at least for 24h after ligand stimulation in HK-2 and RPTEC cells, respectively. Coadministration of Empa inhibited IL1-β-mediated endothelin1 mRNA expression after 1h (0,2-fold and 0,2-fold, p<0,001 each) and 24h (0,1-fold, p<0,001 and 0,7-fold, ns.) in HK-2 and RPTEC cells, respectively. In HK-2 cells, Empa inhibited both IL1-β-induced CCL2 (0,24-fold, p<0,001) and basal endothelin1 (0,4-fold, p<0,001) protein expression.

Conclusions: By demonstrating an inhibitory effect of Empa on basal and IL1-β-mediated CCL2 and endothelin1 expression in two independent HPTCs, we present novel evidence for early non-hemodynamic, nephro-protective effects of SGLT2i.

PO0930

Comparison of the Effect of Calorie-Matched High Saturated Fat and High Unsaturated Fat Diets on Lysosomal Renal Injury in Non-Obese, Streptozotocin-Injected CD-1 Mice

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Background: Type 2 diabetes mellitus often causes renal injury characterized by autophagic vacuoles. Although many studies with comparisons of high fat versus a normal balanced diet have been reported in diabetic models, there are few studies that equalized calorie intake and body weights. We reported that a high fat diet induced renal injury with impaired lysosome-mediated autophagic degradation in streptozotocin (STZ) injected mice (ASN Kidney Week 2019). However, the effect of fat type, saturated- or unsaturated-fat, was not determined. In the current study, an AIN93M diet (CONT group) was compared to energy-matched lard derived high saturated fat (LARD group) and soybean oil derived high unsaturated fat (SOY OIL group) diets to compare their effects on biochemical markers and renal morphology with lysosome-associated membrane protein 1 (LAMP1) expression.

Methods: Male CD1 mice were randomly divided into three pair-fed groups with 380 kilocalorie/100g energy from 7 to 20 weeks of age. CONT group: AIN93M diet with 62% (w/w) cornstarch, 10% sucrose, 4% soybean oil and 5% cellulose; LARD group: Diet with 31% cornstarch, no sucrose, 22% lard oil and 28% cellulose; SOY OIL group: Diet identical to the LARD diet, except that soybean oil replaced lard oil. At 17 and 18 weeks of age, STZ (100mg/kg body wt) was injected. At 20 weeks of age, blood was taken for measurements of insulin, triglyceride, total cholesterol, ALT, AST, creatinine and SUN. Kidneys were prepared for H&E staining and immunohistochemical staining to detect LAMP1.

Results: Final body weight, total intake of water, food and energy were not different between all groups. No statistical differences in all blood biochemical markers were detected as well. In kidneys, the number of LAMP1-positive renal tubular lipid vacuoles was higher in LARD compared with SOY OIL and CONT groups, whereas no difference was shown between SOY OIL and CONT groups.

Conclusions: The results suggest that high intake of saturated-fat may aggravate lysosomal renal injury in a non-obese, streptozotocin-induced diabetes mellitus model.

Funding: Government Support - Non-U.S.

PO0931

Overexpression of ACE in Macrophages Accelerates Diabetic Kidney Disease

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Background: We previously reported that renal tubular angiotensin-converting enzyme (ACE) is mainly involved in the pathological progression in diabetic kidney disease (DKD). Although ACE in macrophages has been shown to be important in controlling inflammation, the expression and function of ACE in macrophages in DKD are still unknown.

Methods: Diabetes was induced by five consecutive daily intraperitoneal injections of streptozotocin (55 mg/kg) using C57Bl6/J male mice. Primary peritoneal macrophages

were harvested after intraperitoneal injection with 2 mL of 4% thioglycolate solution into mice. Mouse-ACE overexpressing plasmid was electroporated into Raw 264.7 to evaluate cytokine release and migration ability. ACE 10/10 mice was deficient of ACE in the whole body but overexpressed only in monocytes/macrophages. We induced diabetes in ACE 10/10 and wild-type mice and analyzed albuminuria or pathological changes of kidney after six months of diabetes.

Results: ACE mRNA was increased in peripheral blood monocytes and peritoneal macrophages from diabetic mice. LPS-induced release of IL-6 and nitric oxide was increased in macrophages overexpressing ACE. The migration ability of macrophages overexpressing ACE was higher than that of control vector-expressing cells. In diabetic ACE 10/10 mice, glomerular hypertrophy and glomerular hyperfiltration were not evident as in diabetic wild-type mice. Although ACE 10/10 mice lacks ACE in vascular endothelial cells and tubular cells, mesangial expansion and interstitial fibrosis in the kidney, and albuminuria from diabetic ACE 10/10 mice were similar to those from diabetic wild-type mice.

Conclusions: In diabetes, the expression of ACE in macrophage is enhanced. As a result, dysregulation of macrophage function occurred, and it may be involved in the development of diabetic kidney disease.

PO0932

Transgenic Mechano-Growth Factor Overexpression in Mice Induces Glomerular PKCα and Type I Collagen with Glomerulosclerosis

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Background: Mechano-Growth Factor (MGF), a normally expressed component of several positive feedback loops in the renal glomerular mesangial cells (MC), was implicated by us in the control of glomerulosclerosis. Transgenic mice overexpressing MGF (LK440-mMGF) were produced to determine the role of MGF in glomerulosclerosis (GS).

Methods: Our previous studies demonstrated that MGF was induced in the glomeruli of diabetic mice with subsequent induction of several factors responsible for diabetic GS. In the current study, immunohistochemistry using specific antibodies was performed to compare the expression of select glomerular proteins involved in GS, in MGF–overexpressing transgenic mice (MGF Tg) vs. non-transgenic control mice (NT). DAB staining with 0-4^{+} scoring in glomeruli was performed, and $p < 0.05$ between groups was considered significant. PAS staining was performed to assess development of overall GS. The effects of transgenic MGF overexpression on mouse body weights and kidney weights was also assessed.

Results: A 2.5-fold higher expression of MGF was found in glomeruli of MGF Tg as compared to NT mice. This resulted in 2.1-fold increased expression of active PKC α, a potential mediator of the 2.2-fold increased GLUT1 expression observed. These changes appeared to drive the 2.2-fold increased Collagen Type I (Col-I) in glomeruli. All these prosclerotic factors likely contributed to the resultant GS, evidenced by 2.2-fold increased PAS positive material in MGF Tg glomeruli. All the above results were found to be significant with a P value <0.0001. Adult body weight in MGF Tg tended to be 8% higher in both males and females (NS). Mean kidney weights were 14% larger in MGF Tg vs same gender NT mice (NS).

Conclusions: 1. MGF Tg displayed increased glomerular PKC α activation, Col-I protein, and PAS-positive extracellular matrix similar to diabetic GS with increased MGF. 2. Future studies of glomerular MGF inhibition in diabetic mice may help define the potential value of this maneuver in blocking GS.

Funding: Private Foundation Support

PO0933

Severe Diabetic Glomerulosclerosis by Chronic Hypoxic Housing of db/db Mice: The Role of Mesangiolysis and Podocyte Injury

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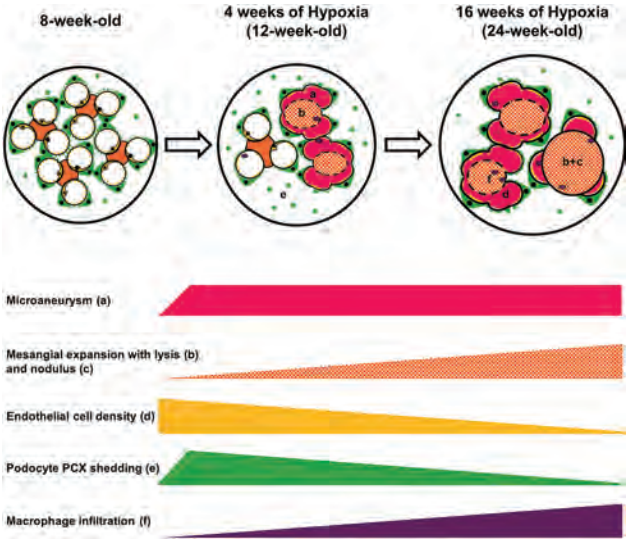
Background: Chronic hypoxia may play a pivotal role in the development of diabetic nephropathy (DN). However, the precise mechanisms underlying progressive hypoxia-induced glomerular injury remain unclear.

Methods: We housed db/db mice in a hypoxia chamber (12% O_2) for up to 16 weeks beginning at 8 weeks of age. Various urine, serum and kidney abnormalities and glomerular mRNA expression were compared with those in age-matched db/db mice housed under normoxia.

Results: Levels of urinary albumin and podocalyxin (PCX) were significantly higher in hypoxic mice early during hypoxia. Ultracentrifugation of urine samples revealed that podocytes in the hypoxic mice shed PCX-positive microparticles into the urine. After 16 weeks of hypoxia, the mice also had higher hematocrits with lower serum glucose and various degrees of mesangiolytic glomerulosclerosis with microaneurysms and the infrequent occurrence of nodular lesions. Immunohistologically, hypoxic mice showed significantly decreased endothelial cell densities early during hypoxia and decreased podocyte densities later. In both hypoxic and normoxic mice, glomerular macrophage and transforming growth factor-β1 (TGF-β1) staining significantly increased with aging, without changes in vascular endothelial growth factor or endothelial nitric oxide synthase (eNOS). Glomerular mRNA expression of monocyte chemoattractant protein-1, eNOS, and TGF-β1 was significantly enhanced in the hypoxic mice.

Conclusions: These results indicate that chronic hypoxia induces advanced glomerulosclerosis with accelerated albuminuria triggered by mesangiolysis and podocyte injury in a murine model of DN.

Funding: Commercial Support - Daiwa Securities Health Foundation, Government Support - Non-U.S.



Summary of the glomerular changes in db/db mice exposed to chronic hypoxia.

PO0934

Overexpression of Nrf2 Increases Sglt2 Gene Expression and Exacerbates Dysglycemia and Nephropathy Progression in Diabetic Transgenic Mice

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Background: Nuclear factor erythroid-2 related factor 2 (Nrf2), a transcription factor abundantly expressed in renal proximal tubule cells (RPTCs), possesses cytoprotective effects. However, clinical trial with Nrf2 activator (bardoxolone methyl) in T2D patients increased mortality, heart failure rates, heightened hypertension and albuminuria without favorable effect on end-stage kidney disease (ESKD), though the underlying mechanism(s) remain unknown. We reported previously that Nrf2 deficiency ameliorates hyperglycemia and kidney injury in diabetic Akita (T1D) mice, and we identified putative NRF2-binding sites in the promoter of SGLT2. We here hypothesized that overexpression of Nrf2 may upregulate Sglt2 expression and contribute to nephropathy progression in diabetes.

Methods: We generated Akita Nrf2$^{-/-}$/Nrf2^{RPTC}-Tg mice by cross-breeding Akita Nrf2 knockout mice (Akita Nrf2$^{-/-}$) with Nrf2 transgenic mice (Nrf2^{RPTC}-Tg) overexpressing Nrf2 in RPTCs, studying them until age 20 weeks. Immortalized human RPTC (HK2) stably transfected with plasmid containing *SGLT2* gene promoter were also used.

Results: Akita Nrf2$^{-/-}$/Nrf2^{RPTC} Tg mice had increased blood glucose, glomerular filtration rate, urinary albumin-creatinine ratio, tubulointerstitial fibrosis and *Sglt2* expression as compared to their Akita Nrf2$^{-/-}$ littermates. *In vitro*, addition of oltipraz (a Nrf2 activator) or transfection of *NRF2* cDNA increased *SGLT2* mRNA expression and promoter activity in HK2; these effects were blocked by small interference (si) RNA of *NRF2*. Deletion of NRF2-*responsive elements (*NRF2-*REs)* in the *SGLT2* promoter abolished the stimulatory effect of oltipraz on *SGLT2* promoter activity. NRF2 bound to NRF2-*RE*s of *SGLT2* promoter was seen on gel mobility shift and chromatin immunoprecipitation assays.

Conclusions: Our results identify a novel mechanism by which NRF2 mediates hyperglycemia (oxidative stress)-stimulation of SGLT2 expression and exacerbates dysglycemia and kidney injury in diabetes.

Funding: Government Support - Non-U.S.

PO0935

Durable Euglycemia by Intraperitoneal Administration of Allogeneic Neo-Islets, 3D Organoids of Pancreatic Islet and Mesenchymal Stem Cells, Effectively Reduces Diabetic Nephropathy in Immune-Component Non-Obese Diabetic Mice

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Background: We demonstrated that the i.p. administration of allogeneic "Neo-Islets" (NIs), 3-D organoids of culture expanded Pancreatic Islet (PI) and Mesenchymal Stem Cells (MSC), induces permanent euglycemia without the need for anti-rejection drugs in NOD mice with auto-immune Type I Diabetes mellitus (T1DM). The NIs engraft in the omentum and physiologically deliver insulin and other islet hormones into the hepatic portal system, while providing auto- and allo-immune isolation, up regulate T-regs, stimulate angiogenesis, prevent apoptosis and inflammation. As a significant percentage of patients with T1DM develop diabetic nephropathy (DNP) and other end organ damage, we tested whether the induction of stable euglycemia in NOD mice would prevent or ameliorate DNP.

Methods: Three Groups of adult mice (n=7 each; ~25 g b.wt.; age 12 weeks) were examined: (1) Non-diabetic, age and sex matched C57/Bl6 mice; (2) Vehicle treated NOD mice with fully developed auto-immune T1DM; (3) NI treated NOD mice with normal blood glucose levels. Animals were followed for 21 weeks post treatment (blood glucose levels, body weights, blood pressures, proteinuria, renal function).

Results: At the termination of the study, kidneys from all groups were examined for glomerulosclerosis and interstitial fibrosis (Trichrome staining). The vehicle treated NOD mice (Group 2) had blood glucose levels of 400-600 mg/dL, lost weight, had systolic hypertension and showed extensive interstitial fibrosis, glomerulosclerosis, proteinuria, hypertension and elevated SCr and BUN levels, while NI treated, euglycemic NOD mice (Group 3) showed significantly lower degrees of glomerulosclerosis, interstitial fibrosis, proteinuria, hypertension and better preserved renal function. All tested variables remained normal in non-diabetic Group 1 control mice.

Conclusions: The presented data demonstrate that NI therapy-induced normalization of glycemia significantly improves the manifestations of DNP without fully correcting them when compared to non-diabetic controls. Modifications in NI treatment protocols are expected to further improve the development of DNP, which, if successful, would further strengthen the translational relevance of this novel therapy. (No U of Utah resources used.)

Funding: Commercial Support - SymbioCellTech, LLC

PO0936

IL-17A Deficiency Attenuates Autophagosome Formation in Streptozotocin-Induced Rat Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the most important medical complications in diabetes mellitus. Autophagy is an important mediator of pathological responses and plays critical roles in inflammation during the progression of diabetic nephropathy. The Th-17 effector cytokine interleukin (IL)-17A can favorably modulate inflammatory disorders including DN. In this study, we examined whether IL-17A deficiency affects the autophagy process in streptozotocin (STZ)-induced DN in kidney.

Methods: The autophagic response for IL-17A in the nephrotoxicity of STZ was evaluated by observing STZ-induced functional and histological renal injury in *IL-17a*$^{-/-}$mice.

Results: IL-17A KO STZ-treated mice were developed more severe nephropathy, exhibiting increased albuminuria, glomerular damage and renal interstitial fibrosis at 12 weeks. IL-17A deficiency also increase the up-regulation of proinflammatory cytokine and fibrotic genes expression after STZ treatment. Meanwhile, autophagy-associated proteins were induced in STZ wild type mice however, IL-17A KO STZ-treated mice displayed a significant decrease in these protein expression. Especially, LC3 and ATG7, which play crucial role for autophagosome formation, is notably decreased in IL-17A KO STZ-treated mice compared with their wild type counterparts.

Conclusions: These results suggested that autophagy is closely related to the increased cellular stress due to IL-17A deficiency. Our study demonstrate an important role of IL17A for autophagosome formation during the progression of DN and provide a potential therapeutic target for DN

Funding: Clinical Revenue Support, Government Support - Non-U.S.

PO0937

NQO1 Deficiency Aggravates Renal Fibrosis Downregulating Through PI3-Complex Formation in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of cause leading to end-stage renal failure and the main pathological feature is renal fibrosis. An autophagy is a vital for cellular remodeling and intracellular homeostatsis and negatively regulate and limit renal fibrosis. NAD(P)H: quinone oxidoreductase 1 (NQO1) modulates the ratios of reduced/oxidaized nicotinamide nucleotide pools acting cytoprotective function. In this study, we examined the relationship between NQO1 and autophagy, and furthermore renal fibrosis alteration in NQO1$^{-/-}$ streptozotocin (STZ)-induced DN.

Methods: STZ (50 mg/kg) was injected to C57BL/6 (Wile type) and NQO1$^{-/-}$ mice to induce DN. After 12 weeks of STZ injection, renal pathology and the markers of autophagy and fibrosis were examined. To confirm the effects of NQO1 genes in DN progression *in vitro*, autophagy proteins and pro-fibrotic markers were assessed in silencing or overexpression of NQO1 on human proximal tubular cells (HK2) and human renal mesangial cells (HRMC).

Results: The STZ administration induced phenotypes of hyperglycemia and aggravated renal fibrosis in NQO1-/- mice. Futhermore, NQO1 deficiency reduced the autophagy down-regulating hVps34 and ATG14L of PI3-complex and induced pro-fibrotic genes including TGF-β1, Smad3, and MMP9, *in vitro* and *in vivo*. The fluorescence intensity of both hVps34 and ATG14L was reduced in siNQO1. However, NQO1-overexpression increased the expression of hVps35 and ATG14L but, reduced the expression of TGF-β1, Smad3 and MMP9.

Conclusions: NQO1 deficiency aggravated renal fibrosis mediating autophagy induction and phagophore formation. This results suggested that NQO1 may have a potential role for DN amelioration.

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PO0938

Cell Sex and Sex Hormones Modulate Glucose and Glutamine Kidney Metabolism: Implications for Diabetic Kidney Disease

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Background: Male sex predisposes to diabetic kidney disease (DKD). We uncovered androgen-induced perturbations in kidney metabolic proteins that may drive faster DKD progression in men. Our goal is to characterize cell sex- and sex hormone-specific alterations in the kidney cell metabolism.

Methods: Human primary proximal tubule epithelial cells (PTEC) from 3 male and 3 female donors were stimulated with control, dihydrotestosterone (DHT), or estradiol (EST). We assessed glycolysis (extracellular acidification rate, ECAR) and oxygen consumption rate (OCR) in a Seahorse analyzer. We also studied sex differences in 16-week-old diabetic Akita mice.

Results: Male PTEC showed significantly higher ECAR, OCR, superoxide levels and apoptosis, compared to female PTEC ($p<0.05$). Higher OCR in male PTEC was further enhanced in the presence of glutamine as a unique susbstrate. In male PTEC, ECAR was increased by DHT, whereas OCR was increased by DHT and EST. Further, glucose levels in the media were reduced by DHT. DHT-induced metabolic changes were prevented by androgen receptor (AR) inhibitors. ATP, superoxide and apoptosis were increased by DHT, especially in male PTEC. Under hyperglycemia (25mM glucose), male cells showed a more rapid decline in OCR, and DHT increased superoxide and ATP levels. Transcriptional regulator analysis predicted that PTBP1, MCM4, and KDM5D (Y-linked) regulate proteins increased by DHT. Targets of PTBP1 and MCM4 include enzymes involved in glucose and glutamine metabolism (TKT, GLUD1). *In vivo*, diabetes increased kidney gene expression of *Tkt, Glud1,* and glutamine transporter *Slc38a3* in males, but not females.

Conclusions: PTEC metabolism is influenced by cell sex and sex hormones. Male PTEC show higher glycolysis, oxygen consumption, and respiratory capacity than female PTEC, and a higher propensity to oxidize glutamine in the mitochondria. Importantly, glutamine plays a key role as anaplerotic substrate for the TCA cycle in diabetes. Our *in vivo* data support the link between male sex and regulation of glutamine metabolism, and suggests that kidney utilization of glutamine in DKD is sex-specific. By understanding and monitoring how these metabolic changes occur in male and female patients, our findings may contribute to a more personalized management of DKD.

PO0939

Effects of Dapagliflozin-Induced Glucosuria on Urinary Tract Infection Susceptibility

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Background: Individuals with diabetes mellitus (DM) have a higher risk for urinary tract infection (UTI). The infection is more likely to cause acute kidney injury leading to an increased risk for chronic and end-stage kidney disease. Glucosuria is one of the proposed mechanisms by which people with DM have increased UTI risk, but this association is understudied and uncertain. In order to study the relationship between glucosuria and UTI susceptibly *in vivo*, mice were treated with an SGLT-2 inhibitor Dapagliflozin (Dapa) and subjected to experimental UTI.

Methods: Non-diabetic C57BL/6 female mice were treated via oral gavage with vehicle or Dapa at 0.1, 1, or 10 mg/kg/dose. One group received a 2-dose regimen: 6 hours before and 3 hours post infection. Another group was treated daily for 7 days. Mice were transurethrally infected with uropathogenic *E. coli* (UPEC). 24 hours post infection (hpi) bacterial burden was enumerated in the urine and bladder. Serum glucose, urine glucose, and urinary output was monitored over the course of treatment.

Results: Compared to controls, Dapa-treated mice developed glucosuria while maintaining normoglycemia and comparable weights. After UTI with the 2-dose regimen, control and Dapa-treated mice had comparable bladder and urine UPEC titers. Mice treated over a longer time course had no significant differences in CFUs in the bladder and urine at 24 hpi – suggesting that glucosuria may not be a primary UTI risk factor. Urine output was increased in mice treated with Dapa which could impact infection susceptibility.

Conclusions: These data suggest that there is no direct relationship between glucosuria, SGLT2 inhibitors, and UTI susceptibility. Also, glucosuria alone doesn't explain the increase in DM-associated UTI risk. More studies are needed to understand the mechanisms that increase UTI susceptibility in individuals with DM.

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PO0940

Systemic Therapies Targeted to Ischemia in a Model of Diabetic AKI

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Background: In acute kidney injury (AKI) and chronic kidney disease (CKD), ischemia in the kidney results in inflammation and tissue damage. The initial response to injury is the infiltration of reactive macrophages into the kidney with subsequent pro-inflammatory cytokine expression. Upon systemic administration, hydroxyl dendrimers selectively target reactive macrophages in the ischemic kidney with renal clearance maximizing kidney exposure.

Methods: Diabetes was induced in Wistar rats by administration of streptozotocin (70 mg/kg) as a single intraperitoneal (IP) injection. Rats with a blood glucose of >16.7 mM were allocated to 4 groups (G1-4; n=3/group). After 6 weeks, ischemia reperfusion injury (IRI) was conducted with 60 min ischemia(I)/6 hr reperfusion (R) (G2), or 45 min I/24 hr R (G3 & G4). A sham surgery was performed as a control (G1). Hydroxyl dendrimer labeled with Cy5 (D-Cy5) was administered IP 1 hr after IRI in G1, G2 and G3 and 12 hr after IRI in G4. Renal function was assessed by clinical chemistry, glomerular filtration rate (GFR), and kidney injury biomarkers. Rats were euthanized 6 (G2) or 24 hr (G1, G3, G4) after surgery. Kidneys were evaluated for tubular damage and tubular epithelial cell necrosis and stained by DAPI and anti-CD68 antibody (macrophage).

Results: Glucose levels increased to ~30 mM prior to IRI. GFR was significantly reduced from 1.8 mL/min (sham) to <0.1 mL/min in IRI rats. Serum creatinine and blood urea nitrogen were significantly elevated in IRI groups (G4>G3>G2). The degree of kidney damage increased with the longer reperfusion time prior to sacrifice (G4, G3 > G2). In all IRI groups, renal tubular necrosis was moderate to severe and proximal tubule damage was severe. Maximal uptake of the D-Cy5 was observed in renal tubules in reactive macrophages in G2.

Conclusions: A diabetic model of AKI was successfully established to evaluate targeting of hydroxyl dendrimers to reactive macrophages. Prolonged ischemia followed by rapid reperfusion increased reactive macrophages and subsequent uptake of hydroxyl dendrimers. Given the high incidence of diabetic nephropathy and higher risk for AKI in these patients, these results provided a model and treatment strategy to evaluate targeted therapies with hydroxyl dendrimer drug conjugates to treat AKI and CKD.

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PO0941

Novel Analysis Approach for Intravital Single Nephron GFR Measurement in Mice

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Background: Intravital microscopy in animals is an emerging technique with advanced applications in kidney research. Particularly, the measurement of single nephron (SN) GFR in mice comprises a method to assess a key parameter of kidney disease. Filtration in single glomeruli is measured by two-photon microsopy in a time series after intravenous injection of a freely filtered fluorescent dye. From the intraglomerular capillaries to the connected proximal tubulus (PT) the glomerular filtration is observed and the intratubular dye intensity shift is measured. However, existing methods for the analysis of the image data in rats (Kang et al. 2006) had limited robustness in mice, due to smaller size, higher tubular curvature and therefore smaller acquisition distances.

Methods: By continuous, rather than punctual measurement of signal intensity along the PT in the time series we extended the published workflow. To further increase reliability and objectivity, we replaced the inaccurate estimation of the tubular volume by additional modelling in a 3D dataset. After normalizing the shift of the intensity position along the PT over time against the exact tubular volume, the filtrated volume per second is calculated by linear regression.

Results: With the method published by Kang the results were highly variable in our hands. After repeated analysis of image material (10 glomeruli in 5 animals, analyzed 5 times by one person), the GFR varied by a mean relative SD of 41%. By reducing overall user interaction with our method, this SD could be decreased to 14%. When applying the analysis to image data acquired in healthy and diabetic C57BL/6J mice, we detected a 4-fold increase in SN GFR in diabetic mice. Administration of the ACE inhibitor enalapril for three days ameliorated this effect in diabetic mice by 50%.

Conclusions: To increase the reliabilty of SN GFR measurements by intravital microscopy in mice, we extended an existing workflow by continuous measurement, 3D-modelling and sophisticated data analysis while reducing manual interaction. Application to microscopy data acquired in diabetic and healthy mice prove the general applicability and high reliability of this novel analysis approach. The clinical relevance is apparant in the context of monitoring disease progression as well as effects of medical intervention.

PO0942

A Hyaluronan Synthesis Inhibitor Delays the Progression of Diabetic Kidney Disease in a Mouse Experimental Model

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Background: There is a paucity of options to treat Diabetic Kidney Disease (DKD) in the clinical practice. Hyalinosis is an important morphological feature of DKD. However, the role of hyaluronan (HA) in the development and progression of DKD as well as the precise mechanisms and consequences of HA involvement in this pathology are still to be clarified.

Methods: In this study, we assayed the effects of hyaluronan synthesis inhibitor 4-Methylumbelliferone (4-MU) on the development of DKD. As a model, we used the diabetic and moderately hypertensive endothelial nitric oxide synthase/leptin receptor deficient (eNOS$^-$ C57BLKS/J^{db}) double mutant mice.

Results: At 9 weeks old, the diabetic model mice were separated into two similar groups regarding sex, body weight, non-fasting plasma glucose concentrations, and consanguinity; then, experimental animals were fed *ad libitum* identical artificial diets formulated by Envigo-Teklad, containing or not 5% of 4-MU sodium salt for 9 weeks. Our measures of daily food consumption show that treated animals had a dose of 270±50mg per day of 4-MU (about 6.2g/Kg body weight/day). At the end of the experimental period, we found that 4-MU-treated diabetic animals: **1)** kept their average GFR, while a significant reduction of GFR was observed in diabetic controls (P=0.042, n=9/8 per group); **2)** kept the average urine ACR and plasma cystatin-c values significantly lower than controls (P=0.049 (n=12 per group) and P=0.043 (n=11/10 per group) respectively); **3)** had lower average kidney weight (P=0.041, n=6), and 36% less hyaluronans in kidneys (P=0.095; Effect size=1.32, n=5); and **4)** 4-MU treated animals kept their body weight (final weight/maximum weight relationship) much higher than diabetic controls (P=0.002, n=16/15 per group) as well as their median survival was 6.4 weeks longer (P=0.048, n=6/5 per group). Moreover, after the treatment, an independent histopathology study showed a significant lower glomerular injury score in kidneys of 4-MU-fed animals (P=0.039, n=5/7 per group).

Conclusions: These results showed that the hyaluronan synthesis inhibitor 4-MU effectively slowed the progression of DKD. 4-MU provides a potential new therapeutic approach to treat DKD.

Funding: Private Foundation Support

PO0943

Therapeutic Benefit of CCR2 Antagonism in a Model of Diabetic Nephropathy Suggests a Mechanism of Action Distinct from Nrf2 Activation

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Background: Diabetic nephropathy (DN) affects nearly half of the patients with type 2 diabetes and is characterized by albuminuria and/or a relentless decline in renal function that may lead to ESRD. We have recently shown that a CCR2 antagonist improved renal structure and reduced proteinuria in the db/db murine model of DN, as well as in the Adriamycin and 5/6 nephrectomy models of CKD. To understand the mechanism we compared CCX872, a small molecule antagonist of CCR2, with Bardoxolone methyl, an investigational drug targeting Nrf2 pathway in the db/db murine model of DN.

Methods: The [KS1] CCR2 specific inhibitor CCX872 and Nrf2 activator Bardoxolone methyl were formulated in 1 % HPMC and dosed for 2 weeks. Proteinuria (urinary albumin excretion rate- UAER) and glomerular filtration rate (GFR) were assessed by measuring murine albumin ELISA and FITC-insulin, respectively. The kidneys were disrupted non-enzymatically, and preparations enriched in glomerular cells were obtained by filtration. Activated parietal epithelial cells (PECs) were analyzed in these preparations by flow cytometry.

Results: UAER was rapidly and significantly reduced after treatment with CCX872: 59% (p=0.004) and 76% (p<0.0001), versus vehicle by week 1 and 2 respectively. In contrast, Bardoxolone did not improve UAER. The db/db mice had kidney hyperfiltration, which measured 943 µl/min at 8 weeks. Bardoxolone reduced hyperfiltration in db/db mice by 36% versus vehicle at week 2, while CCX872 had no effect on GFR. Furthermore, CCX872 significantly reduced the number of CD44 positive activated PECs in the glomerular cell preparations(p=0.04), while Bardoxolone had no effect on the number of these cells.

Conclusions: Treatment with CCR2 antagonist provides rapid renal protection in the db/db mice, as measured by improved UAER. The reduction in UAER was associated with reduction of activated PECs, which are known to contribute to kidney disease. Although Bardoxolone was able to improve GFP, it did not improve UAER or reduce the number of activated PECs. Thus, CCR2 blockade and Nrf2 activation appear to afford renal protection by different mechanisms in the db/db model of DN.

PO0944

Can Nrf2 Inducers Cause Renal Proximal Tubule Epithelial Cell De-Differentiation?

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Background: Nrf2 is a transcription factor serving as a master regulator of cytoprotective responses and Nrf2-inducing agents have been shown to attenuate renal injury in animal models of kidney disease. However, use of these agents in the clinical setting are limited and defining/comparing mechanisms of action of different agents remains to be defined. Previous lab studies showed two Nrf2 inducers (Protandim [nutritional supplement] and DMF [Dimethyl fumarate]) caused differing effects on proximal tubule cell shape, actin and tubulin cytoskeleton, junction proteins, and extracellular matrix (ECM) secretion. Some of these responses were similar to tubule cell changes during epithelial to mesenchymal transition (EMT) and diabetes. This study tested the hypothesis that the combined effect of high glucose and DMF or Protandim may cause tubule cell de-differentiation.

Methods: Human proximal tubule cells (HK-11 cells) were cultured in high glucose (HG; 25mM) or normal glucose concentrations (NG; 5mM) for 24h, followed by additional treatment with 5μg/ml Protandim or 10μM DMF for another 24h. To test markers of EMT and cytoskeleton, cells were immuno-stained for vimentin and fibronectin, and actin filaments stained with FITC-phalloidin. Cell extracts were immunoblotted for E-cadherin and vimentin.

Results: Protandim and DMF increased vimentin filaments by image analysis of immunostained cells, and HG+DMF conditions led to a further increase. Treatment with Protandim following culture in both HG and NG caused collapse of actin filaments (as previously observed) and vimentin encapsulated and co-localized with the collapsed actin. The cell-cell junction protein E-cadherin was downregulated by DMF and culture in HG prior to DMF was not additive to this effect. Protandim did not alter E-Cadherin expression. Extracellularly deposited fibronectin increased with HG and this effect was augmented by additional treatment with DMF.

Conclusions: Protandim and DMF distinctively regulate the cell cytoskeleton. Increased vimentin filament formation with Protandim may be a compensatory mechanism due to collapse of actin filaments. DMF decreases E-Cadherin and increases vimentin and ECM deposition, suggestive of tubule cell de-differentiation. The disparate effects of these two Nrf2 inducers may lead to varying outcomes if used for treatment of diabetic or other types of kidney disease.

Funding: NIDDK Support

PO0945

Beneficial Effect of Chloroquine and Amodiaquine on Diabetic Tubulopathy by Attenuating Mitochondrial Nox4 and Endoplasmic Reticulum Stress

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Background: Oxidative stress induced by chronic hyperglycemia is recognized as a significant mechanistic contributor to the development of diabetic kidney disease (DKD). Nonphagocytic nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4) is a major source of reactive oxygen species (ROS) in many cell types and in the kidney tissue of diabetic animals. We designed this study to explore the therapeutic potential of chloroquine and amodiaquine for inhibiting mitochondrial Nox4 and diabetic tubular injury.

Methods: Human renal proximal tubular epithelial cells (hRPTCs) were cultured in high-glucose media (30 mM D-glucose), and diabetes was induced with streptozotocin (STZ, 50 mg/kg i.p. for 5 days) in male C57/BL6J mice. Chloroquine and amodiaquine were administered to the mice via intraperitoneal injection for 14 weeks.

Results: Chloroquine and amodiaquine inhibited mitochondrial Nox4 and increased mitochondrial mass in hRPTCs under high-glucose conditions. Reduced mitochondrial ROS production after treatment with the drugs resulted in decreased endoplasmic reticulum (ER) stress, suppressed inflammatory protein expression and reduced cell apoptosis in hRPTCs under high-glucose conditions. Notably, chloroquine and amodiaquine treatment diminished Nox4 activation and ER stress in the kidneys of STZ-induced diabetic mice. In addition, we observed attenuated inflammatory protein expression and albuminuria in STZ-induced diabetic mice after chloroquine and amodiaquine treatment.

Conclusions: We substantiated the protective actions of chloroquine and amodiaquine in diabetic tubulopathy associated with reduced mitochondrial Nox4 activation and ER stress alleviation. Further studies exploring the roles of mitochondrial Nox4 in the pathogenesis of DKD could suggest new therapeutic targets for patients with DKD.

Funding: Government Support - Non-U.S.

PO0946

In Vitro Evaluation of [^{18}F]Canagliflozin, a Potential PET Tracer for Imaging Tissue Distribution of the SGLT2 Inhibitor Canagliflozin in Type 2 Diabetes Patients In Vivo

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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are guideline recommended for prevention of kidney and cardiovascular outcomes in patients with diabetic kidney disease. But not all patients benefit from these agents, possibly due to differences in SGLT2 inhibitor tissue distribution. Imaging studies can assist to quantify *in vivo* tissue drug distribution and SGLT2 density in patients in order to unravel the underlying determinants of this response variability. The objective of this study was firstly to synthesize [^{18}F]canagliflozin ([^{18}F]CANA) for human use, and secondly, to confirm its affinity for SGLT2.

Methods: [^{18}F]CANA was synthesized by GMP compliant automated substitution of a boronic ester precursor with [^{18}F]fluoride. Its *in vitro* binding with SGLT2 was tested by incubating human kidney slices with [^{18}F]CANA alone or together with canagliflozin or glucose and analyzing them with autoradiography. [^{18}F]CANA binding sites were compared with SGLT2 distribution using immunohistochemistry on consecutive slices.

Results: [^{18}F]CANA radiochemical yield was 2.0% ± 1.9% within 80 min, molar activity 5-20 GBq/μmol and radiochemical purity >99%. Autoradiography shows [^{18}F] CANA binding in kidney slices with a significant reduction in binding in presence of canagliflozin and a clear trend in reduced binding in presence of glucose (Fig 1A and B). The pattern of [^{18}F]CANA binding on autoradiography corresponds with the distribution of SGLT2 in the apical membrane of proximal tubules as shown with immunohistochemistry (Fig 1C).

Conclusions: We showed the successful automated synthesis of the SGLT2 inhibitor [^{18}F]CANA and its specificity to the SGLT2. Given its unchanged structure compared to the marketed compound, canagliflozin tissue distribution and SGLT2 density can now be studied *in vivo* in human as determinants of between-patient response variability.

Funding: Private Foundation Support, Government Support - Non-U.S.

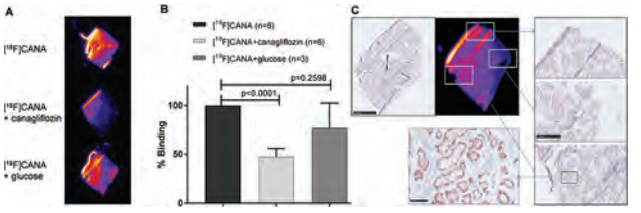

Figure 1. A and B: [^{18}F]CANA binding in kidney sections with autoradiography. C: [^{18}F]CANA binding using autoradiography compared with SGLT2 distribution using immunohistochemistry.

PO0947

Exploring New Targets of Diabetic Nephropathy by Bioinformatics Analysis

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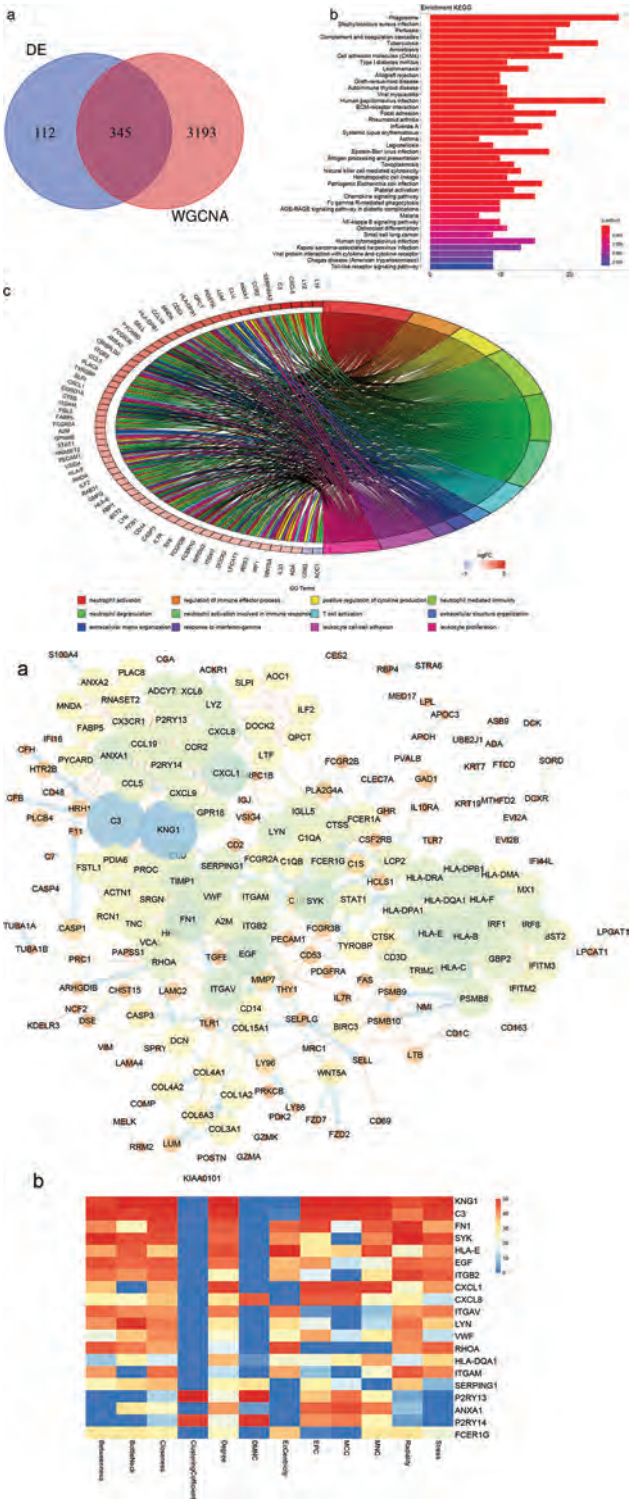
Background: The pathogenesis of diabetic nephropathy has not been fully understood and the public platform contains mass data for bioinformatics analysis.

Methods: Difference analysis and weighted gene coexpression network analysis were carried out on GSE30529 to obtain target genes and perform functional enrichment analysis. Non-coding RNA analysis was studied to understand the potential mechanism of differential expression of target genes. Using STRING database to build protein-protein interaction network. Nephroseq v5 database can access gene expression characteristics and clinical characteristics.

Results: From the GSE30529, 345 genes were identified through bioinformatics analysis. GO annotations of them included neutrophil activation, regulation of immune effector process and positive regulation of cytokine production. KEGG pathways included phagosome, complement and coagulation cascades and cell adhesion molecules. From miRNA profile, miR-1237-3p/SH2B3, miR-1238-5p/ZNF652 and miR-766-3p/TGFBI axis may be involved in diabetic nephropathy. C3 is located at the center of PPI network. Correlation analysis with GFR showed *SYK, CXCL1, LYN, VWF, ANXA1, C3, HLA-E, RHOA, SERPING1, EGF and KNG1* may be related to diabetic nephropathy.

Conclusions: C3 may serve as a therapeutic target for diabetic nephropathy



PO0948

Apolipoprotein C3 Inhibition Reduces Diabetic Kidney Disease and Atherosclerosis in a Mouse Model

Cheng-Chieh Hsu,[1] Farah Kramer,[1] Charles E. Alpers,[1] Rosanne M. Crooke,[2] Jenny E. Kanter.[1] *[1]University of Washington School of Medicine, Seattle, WA; [2]Ionis Pharmaceuticals Inc, Carlsbad, CA.*

Background: Diabetes increases the risk of cardiovascular disease and kidney disease. Importantly, the majority of the excess cardiovascular risk in people with diabetes is observed in those who also have kidney disease. Apolipoprotein C3 (APOC3) is a small lipoprotein that is elevated by insulin-insufficiency and regulates plasma triglyceride levels.

Methods: To test if APOC3, and the dyslipidemia it represents, play a role in diabetic kidney disease (DKD) we treated BTBR wildtype (WT) and leptin-deficient (OB; diabetic) mice with an antisense oligonucleotide (ASO) to APOC3 or a control ASO (cASO), all in the setting of human-like dyslipidemia (accomplished by administration of an LDLR ASO).

Results: APOC3 ASO treatment reduced triglycerides, triglyceride-rich lipoproteins, and prevented diabetes-accelerated atherosclerosis in the brachiocephalic artery and the aorta (aortic lesion was 9.3 ± 1.5 mm^2 lesion in cASO-treated OB mice compared to 4.7 ± 0.93 mm^2 in APOC3 ASO-treated OB mice, $p<0.001$, n=7-10). Intriguingly, APOC3-ASO treatment reduced diabetes-associated urinary albumin excretion but had no effect on non-diabetic mice (WT mice: 108 ± 24.0 mg urinary albumin/day, OB cASO mice: 1076 ± 219 mg/day and OB mice with APOC3 ASO: 435 ± 63 mg/day, $p<0.001$, n=7-14). Diabetes resulted in a dramatic increase in glomerular neutral lipid and APOC3-accumulation, which was attenuated by APOC3 ASO-treatment. Diabetes led to a doubling of glomerular volume (45126 ± 1908 μm^3 glomerular volume in OB mice vs. 21775 ± 1041μm^3 in WT mice, $p<0.001$, n=7-14), increased glomerular PAS-staining indicative of mesangial expansion (2494 ± 332 μm^2 PAS-positive matrix in OB mice and 822 ± 40 μm^2 in WT mice, $p<0.001$; or from 21% in WT to 28% in diabetes, $p<0.01$), and a significant loss of podocytes (80 ± 8 podocytes/10^6 μm^3 glomerular volume in OB mice and 230 podocytes/10^6 μm^3 glomerular volume in WT mice, $p<0.001$), all of which were in part reversed by APOC3 inhibition (glomerular volume in OB mice treated with APOC3 ASO 36331 ± 2240 μm^3, $p<0.05$; PAS area 1761 ± 131 μm^2, $p<0.01$; and podocyte density 114 ± 9 podocytes/10^6 μm^3 glomerular volume, $p=0.07$, all compared to OB mice treated with cASO).

Conclusions: Together, this suggests that targeting APOC3 and diabetic dyslipidemia might be beneficial for both diabetes-accelerated atherosclerosis and DKD.

Funding: NIDDK Support

PO0949

Shen-Qi-Yan-Shen Formula Attenuates Diabetic Renal Lipid Deposition by Down-Regulating Proteoglycan Expression

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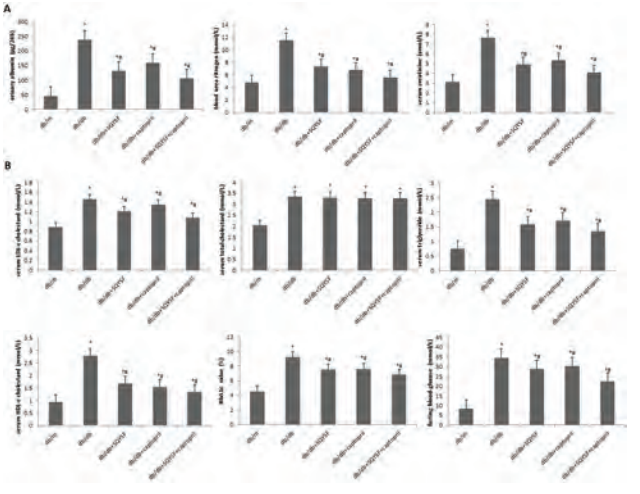
Background: Renal lipid deposition is a crucial factor in the pathophysiology of diabetic nephropathy (DN). Proteoglycan (PG) is an important component of the extracellular matrix. Shen-Qi-Yan-Shen Formula (SQYSF) is a clinical empirical formula in treating DN. In this study, db/db mice are used to explore the potential mechanism of SQYSF by down-regulating PG expression.

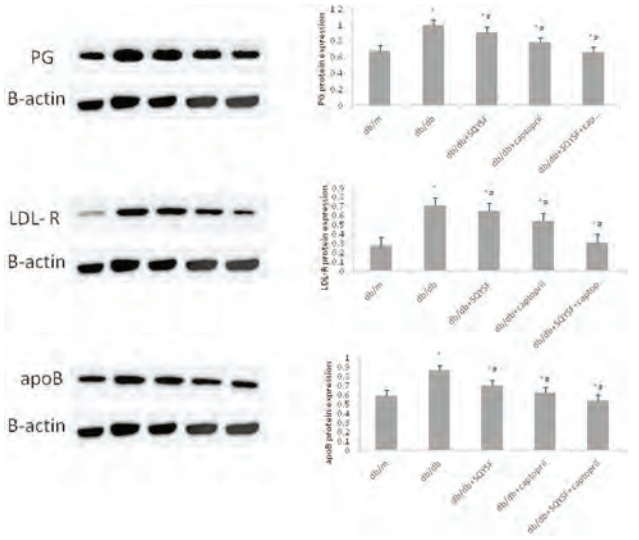
Methods: We divide the mice into db/m normal control group, db/db model group, SQYSF treated group, captopril treated group, and SQYSF + captopril treated group. The groups of mice are given continuous administration of saline, SQYSF, captopril or SQYSF + captopril for 12 weeks, respectively.

Results: We have revealed that treating db/db mice with SQYSF protects them against renal injury. Our finding is supported by lower blood urea nitrogen and serum creatinine and less urinary albumin in the treated mice compared with the saline-treated db/db controls. Mice treated with SQYSF have significantly reduced protein levels of fasting blood glucose (FBG), HbA1c, TG, LDL-c and HDL-c. SQYSF markedly down-regulates protein expression of proteoglycan (PG), apoB and LDL- receptor in the db/db mice. In addition, captopril exhibits a partial inhibitory effect on PG and other proteins, which can be enhanced by SQYSF.

Conclusions: SQYSF may protect db/db mice by relieving lipid deposition through the down-regulation of PG. These encouraging results corroborate SQYSF's potential of becoming a novel therapeutic strategy for diabetic nephropathy.

Funding: Government Support - Non-U.S.





PO0950

Circulating MicroRNAs Associated with Hyperglycemia and Their Effects on Renal Function Decline in Type 2 Diabetes: Global miRNome Analysis

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Background: It has been reported that microRNAs (miRNAs) play an important role in the pathogenesis of diabetic complications. We aimed to search for circulating miRNAs that were associated with hyperglycemia in type 2 diabetes (T2D) and examine their effects on renal function decline.

Methods: Using the next-generation sequencing-based HTG EdgeSeq miRNA platform, a total of 2,083 miRNAs were measured in baseline plasma specimens obtained from 73 subjects with T2D and normal renal function (discovery panel), and 136 subjects with T2D and impaired renal function (replication panel). Subjects in both panels were followed for 6-12 years to determine eGFR decline.

Results: We identified 11 candidate miRNAs that were strongly associated with elevated levels of glycated hemoglobin (HbA1c) in both screening and replication panels. Using bioinformatics analyses, we found that the candidate miRNAs targeted proteins of 6 pathways (the Ras signaling pathway, Signaling pathways regulating pluripotency of stem cells, the MAPK pathway, Glutamatergic synapse, the Rap 1 signaling pathway, and the AMPK signaling pathway). Importantly, 4 of these 11 miRNAs were significantly associated with risk of renal function decline.

Conclusions: There were few previous reports about the association between circulating miRNAs, hyperglycemia, and diabetic kidney disease in T2D. The present study comprehensively examined and identified hyperglycemia-regulated miRNAs in human samples. Our findings are novel in that circulating miRNAs regulated by hyperglycemia are associated with risk of eGFR decline in T2D.

Funding: Other NIH Support - National Institutes of Health (DK041526-23), Commercial Support - Novo Nordisk Foundation (NNF14OC0013659)

PO0951

Longitudinal Changes in Plasma Biomarkers and Diabetic Kidney Disease Progression in VA NEPHRON-D

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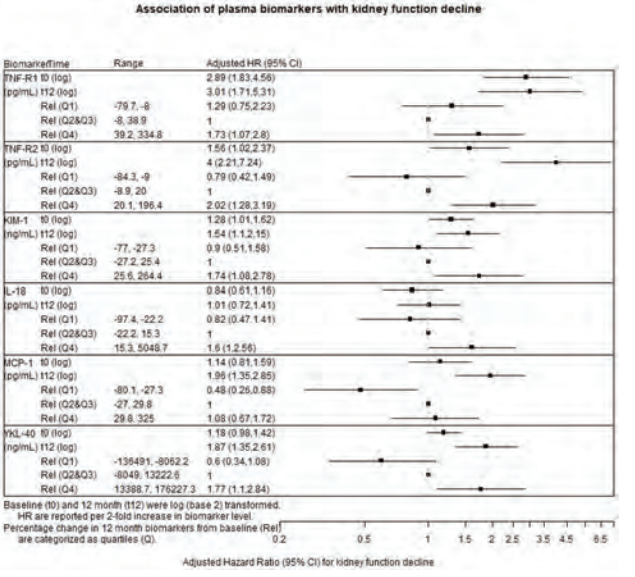
Background: Pathways of inflammation are central to the pathogenesis of diabetic kidney disease (DKD). We previously reported in VA NEPHRON-D that higher baseline levels of soluble tumor necrosis factor receptors 1 and 2 [sTNFR1, sTNFR2] and kidney injury molecule-1 [KIM-1] were associated with DKD progression. Whether longitudinal changes in these and other promising biomarkers are also associated with subsequent kidney function decline is unclear.

Methods: We measured 6 plasma biomarkers (sTNFR1, sTNFR2, KIM-1, interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1], chitinase-3-like protein-1 [YKL-40]) at baseline and 12 mths. Using Cox models, we studied associations of each biomarker (at baseline, at 12 mths, and relative change from baseline to 12 mths) with kidney function decline (first occurrence of eGFR decrease ≥30 ml/min/1.73 m^2 or >50% if randomization eGFR ≥60 and <60, respectively, or ESRD), adjusting for biomarker, sex, race, treatment arm, BMI, HgbA1c, eGFR, UACR at baseline and age, systolic BP, eGFR, UACR at 12 mths. We excluded events before 12 mths (n=5).

Results: Of 754 VA NEPHRON-D participants with baseline and 12-mth plasma samples, mean eGFR=57 ml/min/1.73 m^2 and median UACR=0.8 g/g. Over a median follow-up of 2.5 yrs, 118 (16%) had kidney function decline. Compared to quartiles 2&3, the highest quartile of delta sTNFR1, sTNFR2, KIM-1, and YKL-40 had 1.7 to 2.0-fold greater risks and the lowest quartile of delta MCP-1 had 52% lower risk of kidney function decline. Higher baseline and 12-mth biomarker levels were also associated with DKD progression [**Figure**].

Conclusions: Repeated measures of several plasma biomarkers in patients with DKD provided additional prognostic information even after adjusting for baseline biomarker levels, clinical variables, and time-updated eGFR and UACR.

Funding: NIDDK Support, Veterans Affairs Support



PO0952

A Polyubiquitinated Form of PTEN Predicts Declining Kidney Function and ESKD in Type 2 Diabetes

Helen C. Looker,[1] Chunru Lin,[2] Viji Nair,[3] Matthias Kretzler,[3] Michael Mauer,[4] Behzad Najafian,[5] Robert G. Nelson.[1] [1]*National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ;* [2]*University of Texas MD Anderson Cancer Center, Houston, TX;* [3]*University of Michigan, Ann Arbor, MI;* [4]*University of Minnesota, Minneapolis, MN;* [5]*University of Washington, Seattle, WA.*

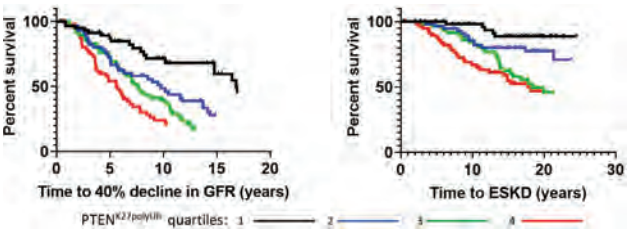
Background: Fibrosis is a major driver of chronic kidney disease and epithelial-mesenchymal transformation (EMT) may contribute to its development. A polyubiquitinated form of phosphatase and tensin homolog (PTEN ^{K27polyUb}) promotes EMT *in vitro* and may be a useful biomarker of progressive kidney fibrosis.

Methods: PTEN^{K27polyUb} was measured in 234 serum samples from American Indians (80 men, 154 women) with early diabetic kidney disease (DKD). Quartiles of serum PTEN^{K27polyUb} were assessed as risk factors for DKD progression (≥40% loss of GFR) or onset of end-stage kidney disease (ESKD) using Cox proportional hazards models adjusted for age, sex, diabetes duration, HbA1c, blood pressure, measured GFR and albuminuria.

Results: Baseline, mean age was 42.8 years (SD 10.5), diabetes duration 11.5 years (7.1), mean arterial pressure 90.5 mmHg (9.5), HbA1c 9.3% (2.4), GFR 151 ml/min (45) and median albumin:creatinine ratio 38 mg/g (interquartile range 14-217). 168 subjects had a ≥40% loss of GFR and 74 (64 with prior ≥40% GFR loss) developed ESKD during median follow-up of 6.3 and 15.8 years, respectively. In univariate analysis, serum PTEN^{K27polyUb} was associated with risk of ≥40% GFR decline and of ESKD (Figure). After adjustment for clinical covariates higher PTEN^{K27polyUb} was associated with greater risk of ≥40% GFR decline [Hazard ratio (HR) for the 4th vs. 1st quartile = 3.67, 95% CI 1.98-6.78, p<0.001] and with ESKD [HR quartile 4 vs. 1 = 5.00, 95% CI 1.77-14.11, p=0.002]. Adding serum PTEN^{K27polyUb} increased the model c-statistics from 0.696 to 0.725 for DKD progression and from 0.738 to 0.766 for ESKD.

Conclusions: Higher serum PTEN^{K27polyUb} is associated with increased risk for GFR decline and ESKD in type 2 diabetes and improves prediction over standard clinical measures.

Funding: NIDDK Support



Survival plots for kidney outcomes by quartile of serum PTEN^{K27polyUb}

PO0953

Renal, Cardiovascular (CV), and Safety Outcomes of Canagliflozin (CANA) According to Baseline Albuminuria: A CREDENCE Secondary Analysis

George L. Bakris,[1] Meg J. Jardine,[2,3] Zien Zhou,[2,4] Hiddo J. L Heerspink,[2,5] Qiang Li,[2] Rajiv Agarwal,[6] David M. Charytan,[7,8] Richard Oh,[9] Carol A. Pollock,[10] David C. Wheeler,[1,11] Dick de Zeeuw,[5] Hong Zhang,[12] Bernard Zinman,[13] Kenneth W. Mahaffey,[14] Vlado Perkovic.[1,15] *[1]Department of Medicine, University of Chicago Medicine, Chicago, IL; [2]The George Institute for Global Health, Sydney, NSW, Australia; [3]Concord Repatriation General Hospital, Sydney, NSW, Australia; [4]Department of Radiology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [5]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [6]Indiana University School of Medicine and VA Medical Center, Indianapolis, IN; [7]Nephrology Division, NYU School of Medicine and NYU Langone Medical Center, New York, NY; [8]Baim Institute for Clinical Research, Boston, MA; [9]Janssen Research & Development, LLC, Raritan, NJ; [10]Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal North Shore Hospital, St Leonards, NSW, Australia; [11]Department of Renal Medicine, UCL Medical School, London, United Kingdom; [12]Renal Division of Peking University First Hospital, Beijing, China; [13]Lunenfeld-Tanenbaum Research Institute, Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada; [14]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA; [15]The Royal North Shore Hospital, Sydney, NSW, Australia.*

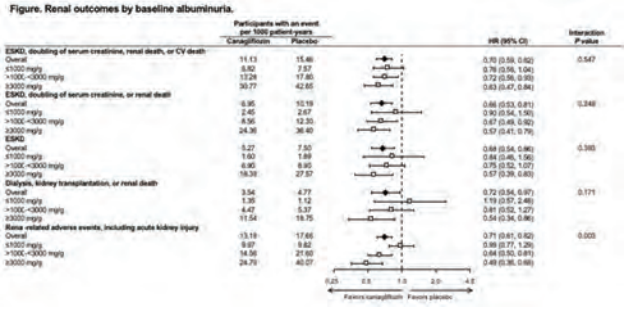
Background: Albuminuria is a risk factor for kidney disease progression and CV disease. We examined the relative and absolute effects of CANA by baseline albuminuria among CREDENCE participants.

Methods: CREDENCE was a double-blind, randomized study of 4401 participants with eGFR 30-<90mL/min/1.73m^2 and uACR >300-5000mg/g who demonstrated that CANA significantly reduced renal and CV outcomes, including the primary composite of end-stage kidney disease, doubling serum creatinine, or renal or CV death. We analyzed the effect of CANA on renal, CV, and safety outcomes by baseline uACR.

Results: At baseline, 2348 (53.4%), 1547 (35.2%), and 506 (11.5%) participants had uACR ≤1000, >1000-<3000, ≥3000mg/g. Higher uACR was associated with higher event rates (Figure). CANA reduced renal and CV endpoints, with no statistical variation by uACR (all p heterogeneity >0.17). CANA led to a greater absolute reduction in renal events in those with higher uACR (number needed to treat to prevent 1 episode of the primary composite: 22 and 8 for uACR >1000-<3000 and ≥3000mg/g). Rates of renal-related adverse events were lower with CANA, and the relative reduction was greater with higher uACR (p heterogeneity=0.003). CANA had no significant effect on acute kidney injury, volume depletion, hyperkalemia, urinary tract infections or hypoglycemia, with no differences by uACR (all p heterogeneity >0.12).

Conclusions: CANA safely reduces renal and CV events in people with type 2 diabetes and substantial albuminuria, with the greatest absolute renal benefit in those with uACR of 3000-5000mg/g.

Funding: Commercial Support - Janssen Scientific Affairs, LLC



PO0954

Lower Cardiorenal Risk with SGLT2 Inhibitor vs. DPP4 Inhibitor in Type 2 Diabetes Patients Without Established Cardiovascular and Renal Diseases

Kåre I. Birkeland,[1] Johan Bodegard,[2] Amitava Banerjee,[8] Dae Jung Kim,[6] Jan W. Eriksson,[3] Marcus Thuresson,[7] Suguru Okami,[5] Kyoung Hwa Ha,[6] Nils Kossack,[10] Jil Billy Mamza,[5] Ruiqi Zhang,[5] Toshitaka Yajima,[5] Issei Komuro,[9] Takashi Kadowaki.[4] *[1]Oslo Universitetssykehus, Oslo, Norway; [2]AstraZeneca PLC, Luton, United Kingdom; [3]Uppsala Universitet, Uppsala, Sweden; [4]Toranomon Byoin, Minato-ku, Japan; [5]AstraZeneca PLC, Luton, United Kingdom; [6]Ajou University School of Medicine and Graduate School of Medicine, Suwon, Gyeonggi-do, Republic of Korea; [7]Statisticon, Uppsala, Sweden; [8]University College London, London, United Kingdom; [9]The University of Tokyo Graduate School of Medicine Faculty of Medicine, Tokyo, Japan; [10]Wissenschaftliches Institut fur Gesundheitsökonomie und Gesundheitssystemforschung, Berlin, Germany.*

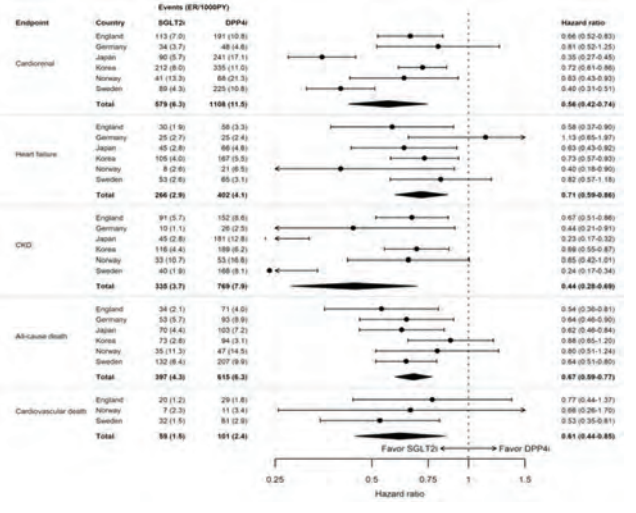
Background: Cardiorenal disease, defined by chronic kidney disease (CKD) or heart failure (HF), is a frequent disease manifestation associated with serious risks in T2D patients. We compared new use of sodium-glucose cotransporter-2 inhibitor (SGLT2i) vs. dipeptidyl peptidase 4 inhibitor (DPP4i) and the risk of cardiorenal disease in T2D patients without history of established cardiovascular and renal disease, defined as CVRD-free.

Methods: In this observational cohort study, patients were identified in health care databases in England, Germany, Japan, Norway, Sweden, and South Korea between the years 2012 and 2018. New users of SGLT2i were propensity score matched 1:1 with users of DPP4i. Unadjusted Cox regressions were used to estimate hazard ratios (HRs) for outcomes; cardiorenal disease, HF, CKD, stroke, myocardial infarction (MI) cardiovascular (CV) - and all-cause death (ACD).

Results: Baseline characteristics were well balanced between the treatment groups (n=105,130 in each group) with mean follow up of 1.5 years and 315,015 patient-years. The distribution of follow-up time for SGLT2i and DPP4i types was, dominated by dapagliflozin (91.7%) and sitagliptin/linagliptin (55.0%). SGLT2i was associated with lower risk of cardiorenal disease, HF, CKD, CV- and all-cause death, HR (95% CI) 0.56 (0.42-0.74), 0.71 (0.59-0.86), 0.44 (0.28-0.69), 0.67 (0.59-0.77) and 0.61 (0.44-0.85) respectively. No differences for stroke (0.87 [0.69-1.09]) and MI (0.94 [0.80-1.11]).

Conclusions: In this large multinational observational study of CVRD-free T2D patients, the unique preventive effects of SGLT2is on cardiorenal disease reported from clinical trials are confirmed in a real-world setting.

Funding: Commercial Support - AstraZeneca



PO0955

In Patients with Biopsy-Proven Diabetic Nephropathy, 38% Have a Second Significant Diagnosis

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Background: AIM: determine the renal biopsy (Bx) incidence of a second kidney disease (2nd DX) in patients (Pts) with diabetic nephropathy (DN) Bx'ed for various clinical indications.

Methods: Of 45,422 non-transplant cases received from 2001-2014 (2222 nephrologists, 39 states), 7,746 Pts with DN were found. 1,749 cases were excluded for insufficient data. 1,398 cases with FSGS were excluded (separate study). 4,599 cases were analyzed (age range: 8 - >89 years; males 53.5%). Bx indication: acute kidney injury (AKI), acute nephritic syndrome (ANS), rapidly progressive renal failure (RPRF), hematuria (Heme), suspect a non-DN renal disease (Non-DN), sudden increase in

proteinuria (Prot) or chronic kidney disease (CKD). We recorded a specific rule out (r/o) diagnosis if one was given. BX DN Grade: I EM changes; II Mesangial increase; III Nodular Sclerosis; IV >50% Global Sclerosis.

Results: A 2nd DX was found in 1750 (38%) cases. Overall, there were 40 2nd DXs: ATI 41%, acute interstitial nephritis 14%, infection-related glomerulopathy (GN) 7%, etc. There were multiple unexpected 2nd DXs: fibrillary GN, amyloid, dense deposit disease, among others. The highest odds ratio (OR) of a 2nd DX was in Pts with AKI at 3.25 whereas CKD had an OR of 0.03 (Table). Age correlated with a 2nd DX ($p<0.001$) with the Bx incidence ranging from 29% in Pts <30 to 56% for those ≥ 80. In 1,589 cases, a specific DX was to be ruled out. A 2nd Dx was found in 48% of Bx's with a r/o Dx versus 33% when no r/o Dx was given (OR=1.83, CI (1.62, 2.08), $p<0.001$). Lesser grades of DN significantly correlated with a 2nd DX; I - 75%, II - 64%, III - 38%, IV - 20% ($p<0.001$).

Conclusions: In Bx proven DN, a significant 2nd DX was found in 38%, with AKI and ANS most likely to yield a 2nd DX. Age and a r/o DX can further differentiate patient groups most likely to have a 2nd DX. Given the worldwide toll of diabetes, the finding of a potentially treatable 2nd DX in diabetics already at high-risk of end stage kidney disease should provide significant savings in morbidity, mortality and health care expense.

Table: Clinical indication: Odds Ratio of a 2nd DX

Clinical	OR of a 2nd Dx	95% CI	p-value
AKI	3.25	(2.91, 3.63)	<0.001
ANS	2.32	(1.59, 3.37)	<0.001
RPRF	1.43	(0.93, 2.20)	0.099
Heme	0.71	(0.54, 0.93)	0.012
Non-DN	0.64	(0.45, 0.90)	0.01
Prot	0.36	(0.32, 0.40)	<0.001
CKD	0.03	(0.01, 0.08)	<0.001

PO0956

A Clinical and Pathological Study on Association of 4-Hydroxynonenal with Diabetic Kidney Disease

Zhimei Peng, Fanna Liu. *First Affliated Hospital of Jinan University, Guang Zhou City, China*.

Background: To explore the potential correlation between plasma 4-HNE level ,tubulointerstitial 4-HNE deposition and DKD renal tubular atrophy during disease progression.

Methods: 59 patients with clinical diagnosis of DKD and 11 normal control were collected in the First Affiliated Hospital of Jinan University from Dec 2018 to Dec 2019. The 59 patients were divided into CKD Phase 1-3, 4-5 according to the estimate glomerular filtration rate(eGFR). Oxidative stress indicators 4-HNE, superoxide dismutase (SOD) were measured in DKD patients.34 cases of diabetic nephropathy(DN) diagnosed by biopsy in the hospital were divided into 3 groups(CKD 1-2,3,4-5). Biopsy cases were subjected to 4-HNE immunohistochemical staining. Univariate and multivariate logistic regression analysis was performed to identify independent risk factors of DKD incidence, and establishment of DKD eGFR multiple linear regression model was made.

Results: Compared with the normal group, oxidative stress index 4-HNE gradually increased in CKD phase 1-3, 4-5 groups, but SOD gradually decreased ($P<0.05$). Logistic regression analysis found that plasma 4-HNE is an independent risk factor for DKD. ($P=0.008$; OR=1.003,95%CI 1.001~1.006) Pearson correlation analysis showed that plasma 4-HNE levels were positively correlated with systolic blood pressure, mean arterial pressure, urea nitrogen, cystatin C and creatinine, and negatively correlated with hemoglobin and eGFR. The eGFR multiple linear regression model showed that eGFR is independently negatively correlated with tubulointerstitial 4-HNE expression (ß=-0.50,$P<0.001$), urea, history of hypertension, renal tubular atrophy, and independently positively correlated with hemoglobin($R^2=0.84$,$P<0.001$). Variance analysis revealed that there was a statistically significant difference between tubulointerstitial 4-HNE staining scores with the degree of renal tubular atrophy and interstitial infiltrates. ($P< 0.05$)

Conclusions: In the progression of DKD, tubular atrophy, anemia, hypertension were associated with oxidative stress, based on serum and staining of 4-HNE. Staining of 4-HNE can be used as a predictor of renal dysfunction, which may be related to tubular atrophy and interstitial infiltrates. 4-HNE is an independent risk factor for progression of DKD.

Funding: Clinical Revenue Support

PO0957

Association of Renal Pathological Lesions and Renal Prognosis in Patients with Diabetic Nephropathy and Effect Modification by Proteinuria

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Background: There are few detailed studies on renal pathological findings in diabetic nephropathy (DN) with low urinary protein (UP). We examined whether the association of renal histology with renal prognosis was modified by UP levels in DN diagnosed by renal biopsy.

Methods: The total of 396 participants diagnosed with DN by renal biopsy were divided into 2 groups by the level of UP; ≥0.5 g/day (high-UP group, n = 197) or <0.5 g/day (low-UP group, n = 199). The association of glomerular lesion (GL) and interstitial/tubular lesion (IFTA) with incidence of end-stage kidney disease (ESKD) was examined using Cox proportional hazard model with the adjustment for confounding factors in each proteinuria group.

Results: Compared to high-UP group, low-UP group had a higher eGFR (median [interquartile range (IQR)]: 66 [48, 89] mL/min/1.73m^2 vs 49 [31, 70], $p<0.001$), lower systolic blood pressure (128 [112, 140] mmHg vs 140 [126, 154], $p<0.001$), lower prevalence of severe GL (6.1% vs 56.8%, $p<0.001$) and IFTA (12.2% vs 61.3%, $p<0.001$). During a median [IQR] observation period of 8.3 [3.9, 17.6] years, 14 and 78 patients reached ESKD in low-UP and high-UP groups, respectively. Cox hazard model adjusted for confounding factors showed that both GL and IFTA were significantly associated with renal prognosis in the high-UP group, whereas only IFTA showed significant association in the low-UP group. The association of IFTA with renal prognosis was consistent (p for interaction = 0.45), but that of GL was significantly different between the two groups (p for interaction <0.01).

Conclusions: IFTA is consistently associated with renal prognosis regardless of UP levels, but GL is associated with renal prognosis only in patients with overt UP.

PO0958

Comprehensive Ultrastructural Analysis Strongly Predicts Kidney Function Decline in the Multicenter TRIDENT Cohort

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Background: While diabetic kidney disease (DKD) is responsible for more than half of all chronic and end stage kidney disease (ESKD), the association of light (LM) and electron microscopical (EM) structural changes with clinical parameters and prognosis in late stage DKD is not completely determined.

Methods: TRIDENT (Transformative Research in Diabetic Nephropathy) is a multi-center observational cohort aimed to identify changes associated with kidney function decline in an unbiased manner. Sixty-two patients diagnosed with biopsy-confirmed DKD were enrolled. Digital scans of biopsy slides and EM were scored for twelve LM and eight EM parameters. Demographic and clinical features of the patients were recorded at enrollment and patients were followed-up every six months.

Results: The median estimated glomerular filtration rate (eGFR) was 28.91(20.87) ml/min/1.73m^2 and the urine protein to creatinine ratio (UPCR) at enrollment was 4.64(7.25) mg/mg. During a mean follow-up time of 10.6 months, the median change in eGFR was -25.8(58) % and median fold change in UPCR was 1.29(2.15) and 17 patients progressed to ESKD. Multiple linear regression analysis revealed that interstitial fibrosis independently associated with eGFR at enrollment. Glomerular lesions including global glomerulosclerosis and mesangiolysis were associated with eGFR decline. Foot process effacement significantly associated with UPCR at enrollment and mesangial hyalinosis predicted UPCR fold change. Unbiased clustering analysis identified three disease subgroups of which cluster 2(N=11) showed more pronounced damage by LM and EM parameters and had the fastest eGFR decline, while cluster 1(N=25) had the slowest eGFR decline and the least severe structural lesions. Cox regression analysis showed that the subjects in cluster 2 had the highest risk to reach ESKD (HR=14.8, 95%CI; 1.76-123.73, P=0.01).

Conclusions: This study confirms association of structural and clinical parameters even in late stage DKD. Furthermore, it highlights specific ultrastructural features that can strongly predict kidney function decline.

PO0959

The Association Between Kidney Biopsy Findings in Diabetic Patients and Renal Replacement Therapy Initiation

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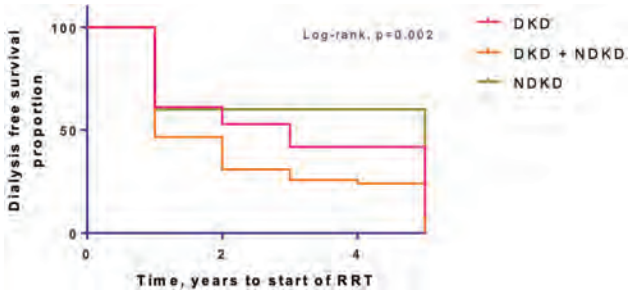
Background: Diabetic Kidney Disease (DKD) is the leading cause of Chronic Kidney Disease (CKD) worldwide. Nevertheless, about a third of type 2 diabetic patients with kidney involvement have Non-Diabetic Kidney Disease (NDKD). The distinction between DKD and NDKD can only be done accurately with kidney biopsy. There is lack of evidence in regards to the association between NDKD and CKD progression. The objective of the study was to evaluate the association of DKD, NDKD or both with Renal Replacement Therapy (RRT) initiation.

Methods: This is a retrospective study of patients with T2DM who underwent a kidney biopsy between 2006 and 2019 at the Department of Nephrology at the National Institute of Cardiology in Mexico City. The included patients were followed for five years or until start of RRT. According to presence of diabetic nephropathy and non-diabetic glomerular disease, three groups were identified: group 1: patients with DKD, group 2: patients with NDKD and group 3: patients with combined DKD and NDKD.

Results: A total of 141 DM patients were included, the mean age was age 52.4 ± 12.2 years and 48.2%. The main indication for kidney biopsy was nephrotic proteinuria in 46 patients (32.6%), rapidly impaired kidney function in 23 patients (16.3%), nephrotic syndrome in 24 patients (17%) and suspicion of others glomerulopathies in 4 patients (2.8%). Based on kidney biopsy findings, 53 (39.1%) had DKD, 13 (9.2%) had NDKD and 75 (53.5%) had both DKD and NDKD. One hundred and four (74%) patients required RRT in the follow-up, 36 in DKD group, 10 in the NDKD group and 58 in the group with both DKD and NDKD. Patients with highest degree of fibrosis (grade 2 and 3 vs 1) (n =93) had a higher risk of starting RRT (RR 9.53, CI 95% 1.77- 51.3, p=0.009). Kidney survival was poorer in the DKD and NDKD group (p = 0.002) (**Figure 1**).

Conclusions: Kidney biopsies is this population could be of use in order to risk stratify this population. Subjects with the combination of DKD and NDKD have the worst renal prognosis.



PO0960

The Aging Kidney: Renal Parenchymal Volumes from MRI, a Comparison Between Type 2 Diabetes and Non-Type 2 Diabetes in 37,450 UK Biobank Participants

Lars Johansson,[1] Taro Langner,[3] Paul Hockings,[1] Lisa Jarl,[1] Lukas Maldonis,[1] Tove Fall,[2] Håkan Ahlström,[3,1] Joel Kullberg.[3,1] *[1]Antaros Medical, Mölndal, Sweden; [2]Uppsala universitetet Institutionen for medicinsk biokemi och mikrobiologi, Uppsala, Sweden; [3]Uppsala University, Department of Surgical Sciences, Radiology, Uppsala, Sweden.*

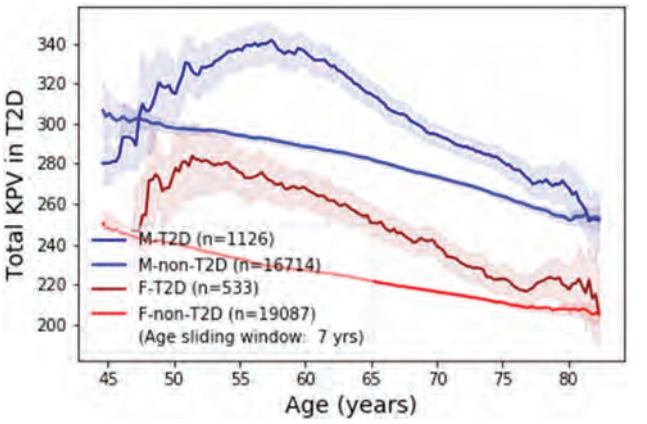
Background: It is well known that Type 2 Diabetes (T2D) early on is associated with increased kidney volumes but also can cause Diabetic Nephropathy. UK Biobank (UKB) is a large-scale cross-sectional study aiming to examine 100,000 subjects aged 44 to 82 years using Magnetic Resonance Imaging (MRI). Resulting images allow measurements of Kidney Parenchyma Volume (KPV). The purpose of this study was therefore to quantify KPV and investigate the association with age in T2D and non-T2D subjects.

Methods: An automated deep learning-based method for direct KPV segmentations and measurements was developed and validated and applied to UKB MRI in 37,450 subjects. KPV was analyzed as a function of diagnosed T2D (defined as diagnosis of diabetes after 40 y/o), sex and age. Furthermore, correction for lean tissue volumes assessed by MRI was performed in all subjects.

Results: KPVs from 37,450 subjects (47.6% males) as a function of T2D, sex and age are shown in Fig1. In non-T2D a steady decline in KPV is seen in both males and females. KPV is significantly larger in T2D subjects (1126 males, 530 females), over 50 years of age compared to non-T2D. This is followed by a faster KPV decline in T2D compared to non-T2D subjects. Adjusting for lean tissue volumes from MRI did not change the difference in decline rates between T2D and non-T2D subjects.

Conclusions: T2D subjects have a larger KPV than non-T2D in middle aged subjects but show a faster KPV decline, independent of lean tissue volume differences. The faster decline in T2D can potentially be explained by increased hyperfiltration and oxidative stress in T2D.

Funding: Private Foundation Support, Government Support - Non-U.S.



Total KPV as a function of T2D, sex and age. Mean values and 95% confidence intervals are shown from a sliding window of 7 years.

PO0961

Assessment of Histopathological Prognosticators in Diabetic Nephropathy: Single-Center Experience

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Background: Diabetic nephropathy (DN) is the leading cause of end stage kidney disease worldwide. Identification of clinical, laboratory and histopathological predictors of kidney failure in DN may improve outcomes.

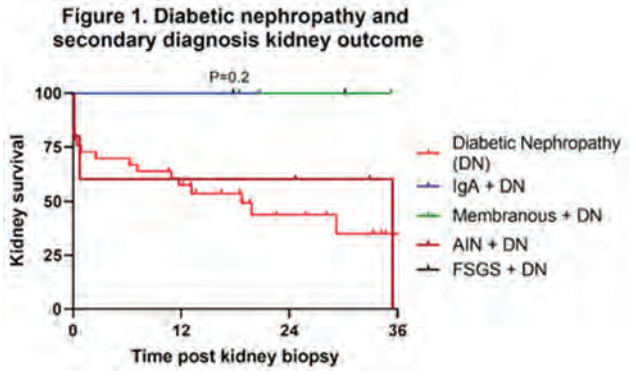
Methods: We identified 45 kidney biopsies between 2017 to 2018 that were diagnosed with DN. Clinical, laboratory and histopathological variables were analyzed to prognosticate 1-year kidney failure.

Results: Sixteen of 45 patients with DN had kidney failure within 12 months of kidney biopsy while 29 patients did not. All patients who developed kidney failure had diabetic retinopathy as shown in table 1. Laboratory findings such a serum creatinine (597umol/L vs. 205umol/L, P<0.0001) and presence of hematuria (88% vs. 45%, P=0.01) prognosticated kidney outcome, while neither proteinuria or Hemoglobin A1C did. IFTA score (2.4 vs. 1.8, P=0.02) and global glomerular sclerosis (52% vs. 32%, P=0.002) were the only histological findings that prognosticate kidney failure. Patients who have a second kidney diagnosis in addition to DN such as IgA, FSGS and MN had favorable outcomes compared to DN and AIN or DN only [figure 1].

Conclusions: We identified serum creatinine, hematuria, IFTA and glomerular sclerosis as prognosticators of kidney failure at 1-year following DN diagnosis. Identification of patients at risk of kidney failure help individualize therapy and hence improve kidney outcomes.

Table 1. Predictors of kidney failure in diabetic nephropathy

Variable	Kidney failure (n=16)	No kidney failure (n=29)	P value
Clinical Findings			
Age at biopsy	50±14	50±11	0.9
Female gender	3 (13%)	3 (10%)	0.7
Duration of diabetes mellitus (years)	13±7	13±9	0.9
Diabetic Retinopathy at biopsy	13/13 (100%)	13/18 (72%)	0.06
Indication of biopsy			
Proteinuria	7 (44%)	17 (59%)	0.4
Worsening CKD/AKI	5 (31%)	8 (28%)	0.9
Laboratory Finding			
Hemoglobin A1C at biopsy	7.4±1.6	7.6±2.2	0.7
Creatinine at biopsy	597±382	205±107	<0.0001
Urine protein/creatinine ratio at biopsy (mmol/g)	948±509	670±393	0.07
Hematuria at biopsy	14 (88%)	13 (45%)	0.01
Biopsy finding			
Interstitial fibrosis and tubular atrophy score (IFTA, 0-3)	2.4±0.8	1.8±1.0	0.02
Glomeruli with global sclerosis (%)	52±20	32±22	0.002
Nodular hyalinosis	11 (69%)	17 (59%)	0.5
Arteriosclerosis	16 (100%)	26 (90%)	0.5
Immunofluorescent deposition	13 (81%)	18 (62%)	0.3
Second diagnosis in addition to diabetic nephropathy	3 (19%)	11 (38%)	0.3
Focal Segmental glomerular sclerosis	0	3 (10%)	0.5
IgA nephropathy	0	1 (3%)	1
Acute interstitial nephritis (AIN)	2 (13%)	3 (10%)	0.3



PO0962

Phosphorylated Akt (pAkt) and Myostatin: The Yin and Yang of the Control of Muscle Protein Metabolism in Patients with Diabetic Kidney Disease

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Background: Muscle wasting is common in patients with diabetic kidney disease (DKD). Both uremia and diabetes cause inflammation and insulin resistance in skeletal muscle, thus promoting wasting. However, the muscle response in DKD is not known yet. Our aim was to evaluate the intracellular signals controlling protein synthesis and degradation in muscle of patients with DKD. We studied intracellular pAkt (a downward effector of the insulin signal), myostatin (MSTN), p38MAPK, MURF and Atrogin in skeletal muscle of patients with diabetic CKD (DCKD) (n=17, age 69 years±7, eGFR 9 ± 3 ml/min/1.73m^2) as compared to non diabetic CKD (NDCKD) (n=32, age 67 years±11, eGFR 7.5 ± 2 ml/min/1.73m^2) and controls (C) (n=24, age 67 years±11, eGFR 77 ± 13 ml/min/1.73m^2).

Methods: Rectus abdominis muscle biopsies were obtained during the insertion of peritoneal dialysis catheters and during elective surgery for abdominal wall hernias (C). Protein expression (pAkt, MSTN, p38MAPK) was evaluated by immunohistochemistry and western blot, mRNA expression (MSTN, Murf, Atrogin) by rt-PCR.

Results: The expression of pAkt was significantly more downregulated in DCKD as compared to NDCKD and C (P <0.05). MSTN expression was significantly lower in C as compared to DCKD and NDCKD (P<0.05). MSTN mRNA was similary upregulated in DCKD and in NDCKD with respectively a 21- and a 18- fold increase compared to controls. Atrogin and Murf mRNA were both upregulated in DCKD and in NDCKD; in DCKD Murf mRNA presented a 18- and atrogin mRNA a 16- fold increase compared to controls while in NDCKD we found respectively a 12- and a 9- fold increase.

Conclusions: With respect to non DKD, intracellular insulin signaling is particularly blunted in muscle of patients with DKD, while myostatin is similarly overexpressed. In diabetes, the abnormal pAkt levels in conjuction with myostatin overexpression are likely to orchestrate the wasting syndrome.

PO0963

Incident CKD in Diabetes, Hypertension, and Prediabetes

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Background: Hypertension (HTN), diabetes mellitus (DM), and prediabetes (PDM) are major risk factors for chronic kidney disease (CKD), yet community-level longitudinal studies of CKD incidence are lacking. The study aim was to determine CKD incidence rates in these at-risk groups by practice- and guideline-based definitions.

Methods: The Center for Kidney Disease Research, Education, and Hope (CURE-CKD) registry is curated from electronic health records with clinical and administrative data from two large non-profit healthcare systems. CKD incidence (95% CI) in adults was calculated over 4, two-year time periods during 2010-2017 adjusted for age, sex, and race/ethnicity. CKD was identified by 2 definitions: 1. Practice-based, CURE-CKD: At least 2 laboratory measures for CKD ≥90 days apart (estimated glomerular filtration rate - eGFR <60 mL/min/1.73m^2, urine albumin/creatinine ratio - UACR ≥30 mg/g, or urine protein/creatinine ratio - UPCR ≥150 mg/g) or CKD administrative code; 2. Guideline-based, Kidney Disease Improving Global Outcomes (KDIGO): At least 2 eGFRs <60 mL/min/1.73m^2 or 2 UACRs/UPCRs >30 mg/g/≥150 mg/g ≥90 days apart.

Results: Overall adjusted CKD incidence rates declined over 2010-2017 by both definitions with lower rates by KDIGO (Table). By CURE-CKD, CKD incidence increased in the HTN group.

Conclusions: The practice-based CURE-CKD definition produced higher estimates of CKD incidence than the stricter guideline-based KDIGO definition. CKD incidence declined in all groups, except for HTN by the CURE-CKD definition, and was highest in patients with DM/HTN. Targeting these at-risk conditions for control may mitigate new onset CKD in these groups.

Funding: Other U.S. Government Support

Table: Adjusted CKD incidence rates per 1000 person-years (95% CI)

	2010-2011	2012-2013	2014-2015	2016-2017
Overall				
CURE-CKD (N=2,172,467)	65.9 (65.3-66.5)	62.0 (61.6-62.4)	52.3 (52.0-52.6)	52.6 (52.3-52.9)
KDIGO (N=2,181,246)	58.6 (58.0-59.2)	39.8 (39.5-40.1)	30.8 (30.6-31.0)	28.1 (27.9-28.3)
DM/HTN				
CURE-CKD (N=435,847)	124.0 (121.1-126.8)	130.4 (129.0-131.8)	104.5 (103.6-105.4)	97.0 (96.1-97.9)
KDIGO (N=444,947)	94.6 (92.2-97.0)	80.3 (79.2-81.4)	61.5 (60.8-62.2)	51.8 (51.2-52.4)
DM/no HTN				
CURE-CKD (N=439,432)	92.8 (91.4-94.2)	48.9 (48.0-49.8)	39.0 (38.3-39.7)	42.6 (41.6-43.6)
KDIGO (N=440,408)	87.5 (86.1-88.9)	30.2 (29.4-31.0)	17.3 (16.8-17.8)	12.5 (12.0-13.0)
PDM/HTN				
CURE-CKD (N=189,809)	66.9 (63.7-70.1)	63.5 (62.0-65.0)	48.7 (47.7-49.7)	42.3 (41.4-43.2)
KDIGO (N=193,307)	55.6 (52.6-58.6)	41.2 (40.0-42.4)	30.8 (30.0-31.6)	25.9 (25.2-26.6)
PDM/no HTN				
CURE-CKD (N=268,176)	59.6 (58.4-60.8)	35.3 (34.3-36.3)	24.8 (23.9-25.7)	21.4 (20.5-22.3)
KDIGO (N=268,957)	58.4 (57.2-59.6)	26.4 (25.5-27.3)	17.2 (16.4-18.0)	11.0 (10.2-11.8)
HTN				
CURE-CKD (N=1,127,090)	36.0 (35.2-36.8)	46.9 (46.4-47.4)	38.8 (38.4-39.2)	39.9 (39.5-40.3)
KDIGO (N=1,132,287)	28.7 (28.0-29.4)	29.7 (29.3-30.1)	21.9 (21.6-22.2)	20.7 (20.4-21.0)

The at-risk population differs by definition of CKD.

PO0964

New Diagnostic Model for the Differentiation of Diabetic Nephropathy from Non-Diabetic Nephropathy in Chinese Patients

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Background: The differential diagnostic criteria of non-diabetic nephropathy (NDRD) and diabetic nephropathy (DN) usually depend on the 2007 KDOQI guideline, which is not accurate enough. Renal pathological biopsy is the gold standard for diagnosis, which is an invasive method and may cause several complications. This study aimed to construct a new noninvasive evaluation method for the differentiation of DN and NDRD.

Methods: We retrospectively screened 1030 patients (January 2005-March 2017). Variables were ranked in terms of importance, and random forest (RF) and support vector machine(SVM) were then used to construct the models. The final model was validated using an external group (338 patients, April 2017-April 2019), and compared with previous models.

Results: A total of 929 patients were assigned for model development. Ten variables were selected for model development. The area under the receiver operating characteristic curve (AUCROC) for the RF and SVM methods were 0.953 and 0.947. A total of 329 patients were analyzed for external validation. The AUCROC for the external validation of the RF and SVM method were 0.920 and 0.911.

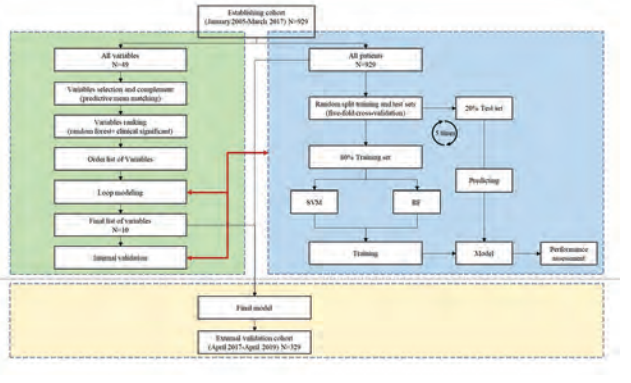
Conclusions: We successfully constructed predictive model for DN and NDRD by machine learning methods, which were better than traditional ways.

Funding: Government Support - Non-U.S.

Performance for SVM and other models in external validation

	Models	Sensitivity	Specificity	PPV	NPV	AUCROC
Isolated DN vs. Isolated NDRD	SVM	0.8671	0.8889	0.9257	0.8073	0.9108
	RF	0.9048	0.8636	0.8986	0.8716	0.9203
	Model-2008	0.8926	0.7059	0.7297	0.8807	0.8855
	Model-2014	0.8581	0.8529	0.8986	0.7982	0.9167
Isolated DN vs. non-DN	SVM	0.7174	0.8897	0.8919	0.7127	0.8462
	RF	0.7348	0.8986	0.8986	0.7348	0.8548
	Model-2008	0.7324	0.7647	0.7027	0.7901	0.8206
	Model-2014	0.6875	0.8832	0.8919	0.6685	0.8412

AUCROC, area under the ROC curve; NPV, negative predictive value; PPV, positive predictive value; SVM, support vector machine; RF, random forest



Analysis flow for the development and evaluation of the model

PO0965

A Simulation Model for CKD Progression Among Patients with Type 2 Diabetes in the United States

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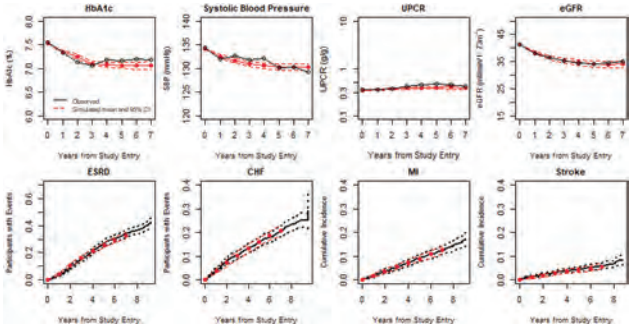
Background: Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) are at a higher risk of end-stage renal disease (ESRD), cardiovascular diseases and mortality. Modeling CKD progression in patients with T2D can help guide disease management for reducing clinical and economic burdens of CKD.

Methods: We developed a discrete-state and discrete-time microsimulation model for predicting changes of underlying risk factors over time and the progression of kidney disease, coronary heart disease, and cerebrovascular disease among patients with T2D and CKD. Transition probabilities were modeled as patient-level characteristics and risk factors, current disease state, and treatment status, with model parameters derived from individual-level data and summary data in published literature. Changes in risk factors for ESRD (urine albumin to creatinine ratio [UACR], estimated glomerular filtration rate [eGFR]), and risk equations for ESRD, myocardial infarction (MI), congestive heart failure (CHF), stroke, and death without ESRD were developed using longitudinal data of a T2D subpopulation in the Chronic Renal Insufficiency Cohort (CRIC). This model underwent calibration and validation against the CRIC patients with T2D and CKD over a 7-year follow-up period.

Results: At baseline, 1,441 CRIC participants with T2D and CKD (mean age: 61.6 years) were available for model development and validation. Concordance between observed and predicted outcomes for the five risk equations ranged from 0.71 to 0.90. The simulated event rates of ESRD, CHF, MI and stroke using estimated changes in key risk factors, and the related 95% confidence intervals covered the observed event rates in CRIC.

Conclusions: The model provided reliable estimates of disease progression among T2D patients with CKD. Modeling disease progression in this population will allow assessment of the impact of early detection and interventions, which may alter the economic and quality of life burden of CKD.

Funding: Commercial Support - Bayer US LLC



PO0966

Joint Model of eGFR Slope: Data from LEADER in Patients with Type 2 Diabetes and High Risk of Cardiovascular Events

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Background: The LEADER cardiovascular (CV) outcome trial (NCT01179048) suggested liraglutide provides renal benefits vs placebo in patients with type 2 diabetes and high CV risk. Aiming to improve the modeling of eGFR slope (surrogate marker of renal outcomes), this *post hoc* analysis compared a joint model with the usual random slope model.

Methods: Two models were applied: 1) random slope model for eGFR using an effect modifier for treatment (liraglutide vs placebo) in change from baseline; 2) joint model using two processes (the same random slope model *and* a hazard model for time to a composite endpoint [all-cause death or ESRD]). These processes were correlated using predicted patient-level effects of eGFR across time, adjusting eGFR slopes for dropouts due to the composite. Those with renal impairment (eGFR <60 mL/min/1.73 m^2 and UACR ≥30 mg/g) at baseline were also analyzed.

Results: Comparing the joint vs random slope models, average eGFR slopes were decreased for liraglutide (-1.77 vs -1.70 mL/min/1.73 m^2/year) and placebo (-2.03 vs -1.96 mL/min/1.73 m^2/year) for all participants (Table). For those with renal impairment, the eGFR slopes estimated using the two models were markedly different for both liraglutide (-2.49 vs -2.08 mL/min/1.73 m^2/year) and placebo (-3.50 vs -3.04 mL/min/1.73 m^2/year). A 1 mL/min/1.73 m^2 lower eGFR value at baseline increased risk of the composite by 3% and change from baseline of -1 mL/min/1.73 m^2 increased it by 6% for all participants. Respective values for those with renal impairment were 6% and 13%.

Conclusions: Liraglutide reduced eGFR slope vs placebo in both models. Joint modeling, which utilized dropout due to death or ESRD, altered the estimation of eGFR slope in LEADER, with a more marked decrease in the high risk group vs the random slope model. It did not change the liraglutide vs placebo treatment effect. Joint modeling may be useful in analyzing future trial data.

Funding: Commercial Support - Novo Nordisk A/S

Table: Random slope model and joint model of change in eGFR correlated to the composite of all-cause death or end-stage renal disease (ESRD)

	Random slope model, estimate [95% CI]	Joint model, estimate [95% CI]	Percentage change in slope, joint vs random slope model
Total population (N=9340)			
Longitudinal process, mL/min/1.73 m²/year			
Annual slope (placebo)	-1.96 [-2.07; -1.84]	-2.03 [-2.15; -1.92]	-3.9%
Annual slope (liraglutide)	-1.70 [-1.81; -1.59]	-1.77 [-1.88; -1.65]	-3.9%
Annual slope (liraglutide vs placebo)	0.26 [0.11; 0.41]	0.27 [0.12; 0.42]	N/A
Time-to-event process (9.8%)*			
Log hazard ratio (liraglutide vs placebo)†	N/A	-0.15 [-0.28; -0.02]	N/A
Association baseline eGFR (per 1 mL/min/1.73 m²)		-0.03 [-0.03; -0.03]	
Association change in eGFR from baseline (per 1 mL/min/1.73 m²)		-0.06 [-0.07; -0.05]	
Patients with eGFR <60 mL/min/1.73 m² and UACR ≥30 mg/g (N=1044)			
Longitudinal process, mL/min/1.73 m²/year			
Annual slope (placebo)	-3.04 [-3.44; -2.66]	-3.50 [-3.91; -3.10]	-15.1%
Annual slope (liraglutide)	-2.08 [-2.44; -1.71]	-2.49 [-2.87; -2.11]	-19.9%
Annual slope (liraglutide vs placebo)	0.97 [0.47; 1.47]	1.02 [0.50; 1.53]	N/A
Time-to-event process (26.7%)*			
Log hazard ratio (liraglutide vs placebo)‡	N/A	-0.07 [-0.32; 0.19]	N/A
Association baseline eGFR (per 1 mL/min/1.73 m²)		-0.06 [-0.07; -0.05]	
Association change in eGFR from baseline (per 1 mL/min/1.73 m²)		-0.13 [-0.16; -0.10]	

*Proportion of events in % (total population: placebo=10.5%, liraglutide=9.1%; patients with renal impairment: placebo=29.7%, liraglutide=23.9%).
†Hazard ratio (95% CI) prior to applying eGFR model to the total population: 0.85 (0.75; 0.97).
‡Hazard ratio (95% CI) prior to applying eGFR model to the renal impaired population: 0.78 (0.61; 0.98).
CI, confidence interval; eGFR, estimated glomerular filtration rate; N/A, not applicable; UACR, urinary albumin-to-creatinine ratio.

PO0967

Large Database Longitudinal Assessment of Electrolyte Abnormalities in Diabetic Patients Receiving SGLT2 Inhibitors

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Background: In diabetic patients, the osmotic diuresis and natriuresis induced by sodium glucose co-transporter 2 (SGLT2) inhibitors produces changes in the serum level of electrolytes such as potassium, magnesium and calcium. Incidence of electrolyte abnormalities induced by these agents in a 'real-world' setting has not been studied.

Methods: We included all patients with diabetes who were prescribed canagliflozin, empagliflozin or dapagliflozin at our healthcare system between 2012-2019. Demographics, baseline medication use, comorbidities, and laboratory values were obtained by querying a centralized research repository. Serum electrolyte levels at SGLT2 inhibitor initiation were compared to electrolyte levels in the 6 months after initiation and the most extreme post-baseline levels were used to determine incidence of electrolyte abnormalities.

Results: In total, 1630 patients were included. Average age was 61 (SD 11) years, 63% identified as male, 71% as white. Hypertension was present in 85%, congestive heart failure in 20%; 18% had an estimated glomerular filtration rate (eGFR) <60 mL/min/m^2 and 12% had uncontrolled diabetes (A1C>10g/dL). ACE inhibitor/ARB use was present in 80% and 5% of patients (n=81) had elevated potassium (>5mEq/L) at baseline. In the first 6 months after drug initiation in patients without elevated potassium at baseline (n=1549), 12% experienced new hyperkalemia (>5 mEq/L) with 4% of patients experiencing a potassium level >5.5 mEq/L. Potassium >6 mEq/L was seen in 1%. Ten percent of patients with eGFR≥60 mL/min/m^2 experienced hyperkalemia when compared to 21% of patients with eGFR<60 mL/min/m^2 (p<0.01). Hyponatremia (<135 mEq/L) was seen in 12% of patients, with values <130 mEq/L seen in 2%. Hypomagnesemia (<1.5 mg/dL) was present in 3% and hypocalcemia (albumin-corrected calcium<7 mg/dL) was seen in 0.1%.

Conclusions: Patients with eGFR≤60 mL/min/m^2 are particularly at high risk of developing hyperkalemia post-SGLT2 initiation. Effective monitoring and treatment strategies are needed to mitigate risks associated with hyperkalemia.

Funding: Commercial Support - Relypsa Fellowship grant

Incidence of electrolyte abnormalities (%)

Hyperkalemia (>5 mEq/L)	12%
Hyponatremia (<135 mEq/L)	12%
Hypomagnesemia (<1.5 mg/dL)	3%
Hypocalcemia (<7 mg/dL)	0.1%

PO0968

Hyperkalaemia Risk and Mortality in Patients with Diabetes

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Background: Diabetes mellitus (DM) is associated with micro- and macrovascular complications, including chronic kidney disease (CKD) and cardiovascular events. Renin-angiotensin-aldosterone system inhibitors (RAASi) are recommended for the management of these conditions; however, their usage may increase the risk of hyperkalaemia (HK), a potentially fatal electrolyte imbalance.

Methods: Patients with type 1 or 2 DM aged ≥18 years were identified from linked primary and secondary care data from the UK Clinical Practice Research Datalink and Hospital Episode Statistics, respectively. DM and relevant complications/comorbidities (CKD; history of major adverse cardiovascular events [MACE] comprising arrhythmia, heart failure, myocardial infarction and stroke) were identified through READ codes recorded during the study period (2008–June 2018) or the five-year look-back period (2003–2007). Index date was the latter of 1st January 2008 or initial DM diagnosis. Event rates (adjusted for age and sex) of HK (serum potassium [SK^+] ≥5.0 mmol/L; ≥5.5 and ≥6.0 mmol/L were also explored) and all-cause mortality (ACM) were estimated over the follow-up period (from index date to the first of: death, loss to follow-up, end of study). Accumulation of complications/comorbidities over time resulted in re-classification.

Results: 288,871 DM patients were included with a mean follow-up of 5.87 (standard deviation [SD] 3.23) years. Available follow-up (1,000 patient-years [PYs]) was 1,038 for DM; 149 for DM + CKD; 129 for DM + MACE and 89 for DM + CKD + MACE. ACM incidence increased in line with increasing comorbidity burden, to 146.73 per 1,000 PYs in the DM + CKD + MACE cohort. At the SK^+ threshold of ≥5.0 mmol/L, the incidence of HK was highest in patients with CKD (779.27/635.26 per 1,000 PYs with/without MACE, respectively) and lower in patients without CKD (384.13/246.83 per 1,000 PYs with/without MACE, respectively). The same between-cohort pattern was observed at thresholds of ≥5.5 and ≥6.0 mmol/L. CKD and/or MACE was associated with higher levels of RAASi prescription (61.91% vs 74.86%–76.28%).

Conclusions: DM patients with CKD and/or MACE are at increased risk of HK and ACM. Routine monitoring of SK^+ and prompt management of HK episodes could improve clinical outcomes in DM patients, particularly those with CKD and/or a history of MACE.

Funding: Commercial Support - AstraZeneca

PO0969

Cumulative Average and Variability of Blood Glucose, Blood Pressure, and Lipids Are Associated with Incidence of Albuminuria, but Not Reduced Kidney Function, Among Patients with Type 2 Diabetes

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Background: We evaluated the effect of cumulative average and variability of fasting blood glucose, blood pressure and lipids on the incidence of albuminuria and reduced estimated glomerular filtration rate (eGFR) among a population with diabetes.

Methods: The study was based on the Kailuan cohort in Tangshan of China. The study baseline was the 2014-2015 circle of health examination. Totally, 1569 patients with type 2 diabetes identified in the 2008-2009 circle, with participation of at least 3 circles of health examination (3-5 times) between 2008 and 2015, and with negative finding in dipstick test and a normal eGFR at baseline were included. The occurrence of albuminuria (urine albumin to creatinine ratio≥30mg/g) and eGFR<60ml/min/1.73m^2 (with an absolute decline of >10%) was ascertained during 2016-2017. eGFR was determined with the CKD-EPI creatinine equation in the 2014-2015 circle and corresponding cystatin-C equation in the 2016-2017 circle. Cumulative average and intraindividual standard deviation (SD) of fasting blood glucose (FBG), systolic blood pressure (SBP), triglycerides and low-density lipoprotein cholesterol (LDL-C) were calculated. Multivariable logistic regression was used to estimate the association of the average and SD values of each variable with the events.

Results: The mean age of the population was 61.8±8.6 years, with a male dominance (77.6%). In the 2016-2017 circle, there were 499 events of albuminuria and 184 of reduced eGFR occurred. Cumulative average, but not SD of FBG, was significantly associated with incident albuminuria, with odds ratios (ORs) and 95% confidence interval of 1.20 (1.11-1.29) per 1 mmol/L increase. Both average and SD of SBP were associated with incident albuminuria with ORs of 1.17 (1.07-1.28) per 10 mmHg increase of average SBP and 1.16 (1.06-1.28) per 5 mmHg increase of SD of SBP. Triglycerides was associated with incident albuminuria with OR of 2.15(1.47-3.13) per one log-transformed value increase. However, no associations between the cumulative average and SDs of FBG, SBP, triglycerides and LDL-C and occurrence of reduced eGFR were found.

Conclusions: Cumulative exposure of FBG, SBP and triglycerides, as well as variability of SBP, could increase the risk of albuminuria among patients with type 2 diabetes.

Funding: Government Support - Non-U.S.

PO0970

The Application of Estimated Glomerular Filtration Rate Equations in Diabetic Kidney Disease Patients

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Background: To evaluate the application of formulas based on serum creatinine and cystadin-C levels in Chinese patients with type2 DM.

Methods: 224 type-2 DM patients were included in this study. Take the 99mTc-DTPA-GFR (sGFR) which standardization by Body Surface Area(BSA) as the golden standard. Estimated GFR (eGFR) was calculated respectively with abbreviated MDRD equation, modify and abbreviated MDRD equation, Cockcroft-Gault equation, CKD-EPI equation, RuJin equation, EPI-Cys2 equation. eGFR were compared with 99mTc-DTPA-GFR (sGFR).

Results: (1)Bland-Altman analysis results demonstrated that consistency of EPI-Cys2 equation and RuJin with sGFR were better than other equation, but all the equation were above the limite professional point. The slopes of EPI-Cys2 equation were closer to the identical line. (2)Bias of EPI-Cys2 equation was smaller than other equations. EPI-Cys2 equation underestimated actual GFR and other equations overestimated GFR. 30% and 50% accuracy rate of Ruijin equation and EPI-Cys2 equation were higher than other equations. (3)As to diagnosis CKD in DM patients, EPI-Cys2 equation was more sensitive and acurrate, and the cut-point of EPI-Cys2 equation and Ruijin equation was closer to 60ml/min.

Conclusions: All six equations show bias in estimating actual GFR. Compared with the equations induced by plasma creatine, EPI-Cys2 equation was more accurate and efficient, and followed by Ruijin equation. All equations should be amended when applying to Chinese DM patients.

Funding: Government Support - Non-U.S.

PO0971

Advanced CKD Augments the Risk of Hypoglycemia with Insulin Use

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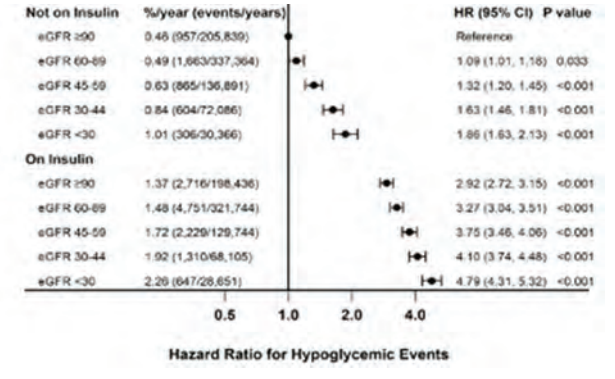
Background: Both insulin use and CKD are known risk factors for hypoglycemia in type 2 diabetes (T2D) but it is unclear whether advanced CKD augments the risk of hypoglycemia with insulin use.

Methods: We analyzed a national veteran cohort (N =944,891) with T2D defined by ICD-9 codes and outpatient serum creat measurements from 1/2008 to 12/2010. Index date was defined as the date of first outpatient serum creat measurement. Duration of T2D was calculated by the first occurrence of ICD-9 codes for T2D, HbA1C > 6.5% or use of anti-diabetic meds from 10/1999 to the index date. Baseline comorbidities were similarly defined by ICD-9 codes. Insulin use at index date was determined by prescription data. Hypoglycemic episodes requiring medical attention were defined by ICD-9 codes and tracked from index date until 2/2016. A multivariate logistic regresssion model of baseliine variables including demographics, duration of T2DM, HbA1C, retinopathy, BMI, other anti-diabetic meds and comorbidities was used to develop propensity scores of baseline insulin use (22% were on insulin at baseline). A propensity score matched cohort (N = 324,064) was used to relate baseline insulin use and CKD stages with subequent hypoglycemic episodes in Cox regression models.

Results: Baseline mean age was 65±11 yrs, 19% black and mean eGFR 71±24. There were 16,048 of hypoglycemic episodes over 1,529, 224 years of follow up. There was a graded increase in incidence rate of hypoglycemic events by CKD stages and insulin use (Fig). In a Cox regression model adjusted for propensity scores as well as above covariates, compared to eGFR >90 with no insulin use (Fig), the risk of serious hypoglycemic episodes was highest in the stage 4/5 CKD group on insulin (HR 4.79, 95% CI 4.31 to 5.32). Interaction p = 0.018 for insulin use and CKD stages for the risk of hypoglycemia.

Conclusions: Advanced CKD augments the risk of hypoglycemia with insulin use. Whether novel anti-diabetic agents are safer than insulin for the risk of hypoglycemia in advanced CKD needs to be studied.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support



PO0972

The Effect of Microalbuminuria on Long-Term Outcomes in Elderly Patients with Diabetes

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Background: In current aging society, the number of elderly diabetes is rapidly growing worldwide. Despite strong evidence on the prognostic power of microalbuminuria in patients with diabetes, it remains uncertain that moderately increased urinary albumin excretion can identify elderly diabetes at high risk of ESRD (end stage renal disease) or mortality. This longitudinal study evaluated incidence of ESRD and mortality according to albuminuria amounts focusing on elderly diabetes.

Methods: We retrospectively identified 3,065 elderly (aged ≥65 years) diabetes. The primary outcomes were incidence of ESRD (considering competing risk with death) and all-cause death. The association between albuminuria (normoalbuminuria, urine albumin to creatinine ratio [uACR] <30mg/g, microalbuminuria, uACR 30-300mg/g, and macroalbuminuria, uACR >300mg/g) and outcomes focusing on elderly (≥65 years) and very elderly (≥75 years) with diabetes were evaluated.

Results: The age was 71.1 (5.0) years and the duration of diabetes was 13.4 (8.7) years. Median follow-up duration was 89 (19.6) months. Overall, microalbuminuria and macroalbuminuria were observed in 25.5% and 9.4% of subjects, respectively. For normoalbuminuria, microalbuminuria, and macroalbuminuria, probability of ESRD and cumulative all-cause death at 8 years was 1.0%, 6.3%, and 29.7% (P<.0001), and 13.1%, 27.4%, and 31.7% (P<.0001), respectively. Using proportional-hazards regression models, albuminuria amounts were independently associated with increased risk of ESRD (fully adjusted hazard ratios [HR] including kidney function: 3.92 [1.29-6.70] for microalbuminuria, 11.16 [6.47-19.24] for macroalbuminuria). The HR of all-cause death were 1.46 (1.21-1.76) for microabuminuria and 1.42 (1.08-1.86) for macroalbuminuria. The associations between albuminuria amounts and the risk of ESRD and all-cause death were consistent in very elderly (≥75 years).

Conclusions: We demonstrated that microalbuminuria is a risk factor of incident ESRD and death even in elderly diabetes, as well as in very elderly. Further studies are needed to determine whether albuminuria can be a therapeutic target in this population.

PO0973

Risk of Cardiovascular Disease, CKD, and Cardiovascular Mortality According to 2017 ACC/AHA Blood Pressure Categories in Diabetes

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Background: The association between blood pressure (BP) and cardiovascular disease (CVD) and chronic kidney disease (CKD) in diabetes patients remains unclear.

Methods: By using an analysis based on the National Health Insurance Database of Korea, 8, 922, 940 persons were screened between 2009 to 2014. We determined the BP status of 490,352 persons: Level 1 ((systolic <120 mmHg and diastolic <80 mmHg, n = 109,427), level 2 (systolic 120-129 mmHg and diastolic <80 mmHg, n = 98,360), level 3 (systolic 130-139 mmHg or diastolic 80-89 mmHg, n= 188,728), and level 4 (systolic ≥140 mmHg or diastolic ≥90 mmHg, n= 93,837).

Results: Overall, 490,352 diabetes patients were analysed over a mean follow-up of 5 years and 6,508 CVD events occurred. Compared to people with BP levels 1, the adjusted hazard ratios (HRs) for CVD in people with BP levels 2, 3, and 4 were 1.07 (95% confidence interval [CI], 0.98-1.16), 1.12 (95% CI, 1.04-1.20) and 1.17 (95% CI, 1.08-1.26), respectively. There were also increased risks of CKD [1.18 (95% CI, 1.12-1.24) and 1.22 (95% CI, 1.15-1.29)] and CVD mortality [1.31 (95% CI, 1.09-1.56) and 1.91 (95% CI, 1.58-2.32)] among subjects with BP levels 3 and 4 compared with those with BP level 1.

Conclusions: These findings provide evidence supporting the 2017 ACC/AHA guidelines for BP targets in diabetes patients.

Funding: NIDDK Support

Table 1. Multivariate-Adjusted HR (95 % CI) of Cardiovascular Disease, Chronic Kidney Disease and Mortality according to Baseline Blood Pressure Levels.

	Total subjects			Men			Women		
	No.	person-years	Adjusted HR*	No.	person-years	Adjusted HR*	No.	person-years	Adjusted HR*
Cardiovascular disease									
Level 1	1,158	715,547	1	812	412,629	1	345	302,917	1
Level 2	1,245	642,522	1.068 (0.984-1.159)	867	392,266	1.050 (0.952-1.157)	378	250,256	1.085 (0.935-1.259)
Level 3	2,610	1,252,219	**1.118 (1.041-1.201)**	1,971	832,173	**1.125 (1.037-1.220)**	639	400,045	1.054 (0.920-1.208)
Level 4	1,495	613,304	**1.166 (1.075-1.264)**	1,121	406,244	**1.210 (1.101-1.331)**	373	207,016	1.016 (0.869-1.187)
Chronic kidney disease									
Level 1	2,247	99,415	1	1,761	56,777	1	486	42,638	1
Level 2	2,073	88,944	**1.144 (1.081-1.212)**	2,104	54,028	**1.121 (1.051-1.196)**	569	34,916	**1.220 (1.077-1.380)**
Level 3	6,003	269,991	**1.179 (1.121-1.239)**	5,034	114,454	**1.175 (1.111-1.242)**	949	55,537	**1.159 (1.034-1.299)**
Level 4	3,395	91,792	**1.220 (1.154-1.291)**	2,832	53,752	**1.224 (1.149-1.302)**	563	28,010	**1.275 (1.092-1.357)**
Cardiovascular disease mortality									
Level 1	169	712,557	1	128	410,191.9	1	41	302,365.45	1
Level 2	213	639,745	**1.265 (1.030-1.554)**	140	389,982.7	1.104 (0.865-1.409)	73	249,762.68	**1.683 (1.142-2.481)**
Level 3	422	1,227,688	**1.313 (1.092-1.587)**	308	829,300.4	1.204 (0.974-1.489)	114	399,387.24	**1.548 (1.073-2.232)**
Level 4	346	609,795	**1.914 (1.578-2.321)**	267	403,376.6	**1.911 (1.531-2.386)**	79	206,418.6	**1.708 (1.195-2.614)**

HR: hazard ratio, No.: number of events.

Table 1

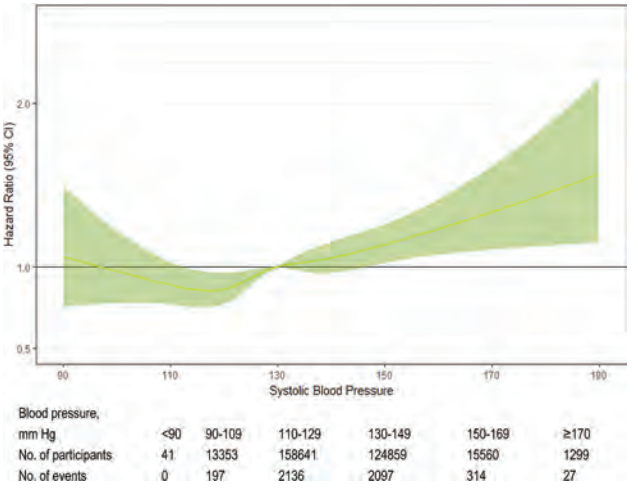

Figure 1. Hazard ratios for cardiovascular disease according to systolic blood pressure in diabetes men patients.

PO0974

Cardiovascular Disease and Medication Use by CKD Risk Groups in People with Type 2 Diabetes: A Post Hoc Analysis from CAPTURE

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Background: The CAPTURE study estimated the contemporary (2019) prevalence of cardiovascular disease (CVD) in people with type 2 diabetes across 13 countries. This post hoc analysis describes the occurrence of CVD and medication use by chronic kidney disease (CKD) risk groups.

Methods: CAPTURE was a multinational, cross-sectional, non-interventional study conducted between December 2018 and September 2019. Data on CVD diagnoses, estimated glomerular filtration rate (eGFR), urine albumin level and glucose-lowering agents (GLA)/CVD medication use was collected during routine visits. Participants were categorized by CKD risk by eGFR and urine albumin thresholds according to the KDIGO classification.

Results: Of 9823 participants, 7923 (81%) had eGFR data, 6482 (66%) had urine albumin creatinine ratio (UACR) data, and 5829 (59%) had both measures available. The distribution by eGFR (>89, 60–89, 30–59, <30 ml/min/1.73m²) was 35%, 44%, 18% and 3%, respectively, and by UACR (<30, 30–300, >300 mg/g) 67%, 25% and 8%, respectively. By KDIGO risk group (low, moderate, high, very high), CVD prevalence was 29%, 44%, 53% and 59%, respectively. Use of GLA decreased with increasing CKD except for insulin which increased. Use of renin angiotensin aldosterone system inhibitors was 49–72% across risk groups (Table).

Conclusions: This post hoc CAPTURE analysis demonstrated a positive association between CVD prevalence and CKD risk. CVD medications with proven CVD benefits, including GLA, were underused.

Funding: Commercial Support - Novo Nordisk

Table. Cardiovascular disease and selected medication use according to KDIGO risk categories in CAPTURE population (N=5829)

KDIGO Classification: risk for CKD progression	Low risk	Moderately increased risk	High risk	Very high risk
N (%)	3370 (58)	1391 (23.9)	565 (9.7)	503 (8.6)
CVD	979 (29.1)	607 (43.6)	299 (52.9)	299 (59.4)
AsCVD	852 (25.3)	508 (36.5)	257 (45.5)	246 (48.9)
RAAS inhibitors	1658 (49.2)	883 (63.5)	405 (71.7)	344 (68.4)
SGLT2i	664 (19.7)	276 (19.8)	80 (14.2)	38 (7.6)
GLP-1 RA	443 (13.1)	185 (13.3)	56 (9.9)	47 (9.3)
Biguanides	2850 (84.6)	1147 (82.5)	381 (67.4)	200 (39.8)
Insulins, any	1088 (32.3)	584 (42.0)	311 (55.0)	326 (64.8)

Albuminuria (mg/g): eGFR (ml/min/1.73m²) per KDIGO risk categories: Low risk: (<30:>89) and (<30:60–89). Moderately increased risk: (<30:45–59); (30–299:>89); (30–299:60-89). High risk: (<30:30–44); (30-299:45–59); (≥300:>89) and (≥300:60–89). Very high risk: (<30:≤29); (30–299:30-44); (30–299:≤29); (≥300:45–59); (≥300:30–44) and (≥300:≤29). The total proportion of people within each risk category is calculated from the overall population (N=5829) from CAPTURE (N=9823) who had both eGFR and albuminuria information available. Proportion of people with CVD and AsCVD and specified medication use are based on number of patients in the respective risk category. AsCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide receptor agonists; KDIGO, The Kidney Disease: Improving Global Outcomes; RAAS, renin angiotensin aldosterone system; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

PO0975

Cardiovascular Autonomic Dysfunction Is Associated with Decline in Kidney Function in Type 2 Diabetes and Healthy Controls

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Background: Cardiovascular autonomic dysfunction is a prevalent and severe complication in type 2 diabetes. We assessed the impact of cardiac autonomic dysfunction on change in kidney function and albuminuria in a cohort of persons with type 2 diabetes and healthy controls.

Methods: In 2013 we recruited 60 persons with type 2 diabetes and 30 controls. Estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (UAER) were measured at baseline and follow up. Cardiovascular reflex tests were performed, and continuous parameters of cardiovascular autonomic function was assessed from heart rate variability in a 5-minute resting ECG.

Results: For the follow up, 32 persons with type 2 diabetes and 21 controls were willing to participate and included in the analyses. Median [IQR] follow-up time was 6.2 [6.0 to 6.3] years. At baseline, mean ± SD age was 60 ± 10 years, median known diabetes duration was 12 [5 to 21] years and mean Hba1c in the type 2 diabetes group was 54 ± 11 mmol/mol. At baseline, mean eGFR was similar between groups (type 2 diabetes: 79 ± 21 ml/min/1.73m^2 and controls: 86 ± 12 ml/min/1.73m^2 p=0.183) and median UAER was higher (p<0.001) in the type 2 diabetes group (33.5 [6.5 to 107.5] mg/24-h) than controls (5.5 [5.0 to 6.5] mg/24-h). During follow up, eGFR decreased in both groups (type 2 diabetes: -1.0 (95%CI: -1.4 to -0.5) ml/min/1.73m^2/year p<0.001 and controls: -0.7 (95%CI: -1.1 to -0.3) ml/min/1.73m^2/year p=0.001) and the change was similar between groups (p=0.179). Albuminuria did not change. After adjustment for age, sex, smoking, Hba1c, body mass index, heart rate, 24-hour systolic blood pressure, plasma cholesterol, baseline UAER and baseline eGFR, a lower response in heart rate variability during Valsalva (p=0.016) and a lower SDNN (p=0.029) were significantly associated with a steeper yearly decline in eGFR. Cardiovascular autonomic function was not associated with change in albuminuria.

Conclusions: Cardiovascular autonomic dysfunction assessed by heart rate variability was associated with steeper decline in kidney function during 6 years of follow up. Cardiovascular autonomic dysfunction may be a marker of higher risk of decline in eGFR. Whether there is a causal link remains to be established.

PO0976

Changes in Cardiac Microvascular Function in Persons with Type 2 Diabetes in Relation to Kidney Function

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Background: The myocardial flow reserve (MFR) reflects the function of both large epicardial arteries and the microcirculation. Coronary artery calcium score (CACS) is a measure of coronary atherosclerosis. Cardiac ^{82}Rb PET/CT provides a measurement of both MFR and CACS. Knowledge on changes in MFR and CACS over time and the impact of kidney function on these changes is lacking

Methods: In 2013 we recruited 60 persons with type 2 diabetes (T2D) and 30 non-diabetic controls (C); all free of overt cardiovascular disease. All underwent a cardiac ^{82}Rb PET/CT scan. In 2019, survivors (n=82) were invited for a repeated cardiac ^{82}Rb PET/CT after a similar protocol. 29 with T2D and 19 C participated.

Results: Median [interquartile range] duration between visits was 6.2 [6.0–6.3] years. The Table summarizes kidney function, MFR and CACS at the 2 visits. MFR was lower in persons with T2D compared to C but change in MFR was similar between groups (p=0.62) and did not differ between visits within the groups (C:p=0.51, T2D:p=0.08). CACS was higher in persons with T2D compared to C at both visits. CACS increased between visits within both groups (C:p=0.015, T2D:p<0.001), and the change was higher in T2D (p=0.002). In the total cohort, lower eGFR at baseline was associated with higher decline in MFR (p=0.027), but not after adjustment (p=0.70). Increase in CACS was higher in men (p=0.03), but not after adjustment (p=0.07). Changes in MFR and CACS were not associated with other risk factors at baseline.

Conclusions: MFR was lower in T2D compared to C but did not change significantly in either of the groups when evaluated over 6 years. Kidney function had no independent impact on changes in MFR or CACS

	Type 2 diabetes (n=29)	Controls (n=19)	P (unadjusted)	P (adjusted)
UAER visit 1 (mg/24-h)	27.3 [6.5, 145]	5.5 [5.0, 6.5]	<0.001	
eGFR visit 1 (ml/min/1.73m2)	81.1 (21.5)	87.6 (11.1)	0.23	
MFR visit 1	2.6 (0.7)	3.3 (0.7)	0.001	0.83
MFR visit 2	2.4 (0.6)	3.2 (0.9)	<0.001	0.46
MFR difference	-0.27 [-0.48, 0.06]	-0.20 [-0.65, 0.50]	0.62	0.32
CACS visit 1	180 [22, 275]	0 [0, 54]	<0.001	0.03
CACS visit 2	560 [136, 981]	18 [0, 116]	<0.001	0.04
CACS difference	301 [72, 830]	9 [0, 62]	0.002	0.12

Adjustment included; age, sex, BMI, eGFR, urinary albumin excretion rate, 24-h systolic BP, heart rate, total cholesterol and smoking

PO0977

Risk of Hospitalization for Heart Failure (HHF) by eGFR and Urinary Albumin-to-Creatinine Ratio (UACR): Pooled Analyses from the CANVAS Program and CREDENCE

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Background: People with type 2 diabetes (T2D) are at particularly elevated risk of cardiovascular (CV) events including heart failure (HF) if they have chronic kidney disease (CKD). Albuminuria and eGFR are each associated with increased risk, leading to recommendations for annual assessment of these parameters. We analyzed the combined effects of eGFR and UACR on risk of HHF, and the effect of canagliflozin (CANA) on reducing risk, in patients with T2D using pooled data from the CANVAS Program and CREDENCE.

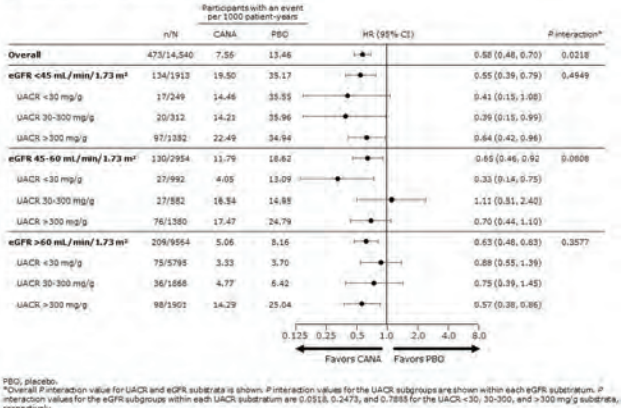
Methods: The CANVAS Program enrolled 10,142 patients with T2D and CV disease or high CV risk. CREDENCE enrolled 4401 patients with T2D and CKD. Risk of HHF was examined in subgroups by baseline eGFR (<45, 45-60, and >60mL/min/1.73m^2) and UACR (<30, 30-300, and >300mg/g). Hazard ratios (HR) and 95% CI were estimated using a Cox proportional hazards model.

Results: In placebo-treated participants (**Figure**), the risk of HHF was generally lowest in people with UACR <30 and eGFR >60, and highest in those with eGFR <45 and UACR >300. HHF rates increased 6.5-fold between those with UACR <30 and >300 and eGFR >60 at baseline and almost 10-fold as eGFR declined from >60 to <45 in patients with UACR <30 at baseline. CANA reduced the risk of HHF overall with some evidence of treatment heterogeneity by UACR and eGFR (*P* interaction=0.0218).

Conclusions: People with T2D and reduced eGFR, increased albuminuria, and especially both, were at increased risk of HHF. The risk of HHF was reduced overall by CANA.

Funding: Commercial Support - Janssen Scientific Affairs, LLC

Figure. HHF by eGFR and UACR.



PBO, placebo.
*Overall P interaction value for UACR and eGFR substrata is shown. P interaction values for the UACR subgroups are shown within each eGFR substratum. P interaction values for the eGFR subgroups within each UACR substratum are 0.0518, 0.2473, and 0.7855 for the UACR <30, 30-300, and >300 mg/g substrata, respectively.

PO0978

The Predictive Value of Diabetic Retinopathy on Subsequently Diabetic Nephropathy in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Prospective Studies

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Background: Studies have already demonstrated diabetic retinopathy (DR) was associated with an increased risk of diabetic nephropathy (DN) in patients with type 2 diabetes (T2D), whereas the predictive value of DR on subsequent DN for T2D were not illustrated. Therefore, we conducted a meta-analysis of prospective cohort studies to assess the predictive value DR on further DN risk in patients with T2D.

Methods: The PubMed, EmBase, and the Cochrane library were systematically searched for eligible prospective cohort studies through March 2020. The predictive value of NR were assessed using sensitivity, specificity, positive and negative likelihood ratio (PLR and NLR), diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUC).

Results: Ten prospective cohort studies recruited a total of 635 patients with T2D were selected for this study. After pooling all studies, we noted the pooled sensitivity, and specificity of DR for predicted DN were 0.64 (95%CI: 0.54-0.73), and 0.77 (95%CI: 0.60-0.88), respectively. The pooled PLR and NLR of DR for predicted DN were 2.72 (95%CI: 1.42-5.19), and 0.47 (95%CI: 0.33-0.67), respectively. The summary DOR for the relationship between DR and subsequent DN for T2D patients was 5.53 (95%CI: 2.00-15.30), and the AUC of DR for predicted DN was 0.73 (95%CI: 0.69-0.77). The predictive value of DR for subsequent DN could affect by mean age, percentage male, and study quality.

Conclusions: This study found significant associations between DR and subsequent DN risk for patients with T2D, while the predictive value of DR was mild. Further prospective study should be assessed for the predictive value of DR on other conditions in T2D patients with specific characteristics.

Funding: Government Support - Non-U.S.

PO0979

Cellular Proteomic Phenotypes Underlying Plasma Signature of 10-Year Risk of Kidney Failure

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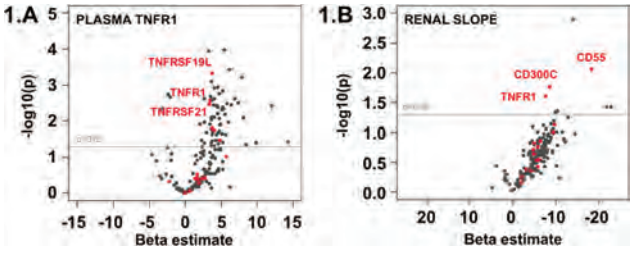
Background: A robust circulating proteomic signature of 10-year risk of kidney failure (KRIS) in a large prospective three-diabetes cohort study was recently identified (Niewczas et al, Nat Med 2019), but the source of the KRIS proteins remains unknown. Therefore, we aimed to evaluate potential contributions of the peripheral blood mononuclear cells (PBMC) and its subset, CD14, to the KRIS in a proteome-wide fashion.

Methods: Our study group consisted of a sample of Joslin Kidney Study participants with Type 2 Diabetes (n=16) with an average eGFR of 59±23 mL/min/1.73m^2 and median albuminuria of 57 (8, 312) at baseline. Within a median of 12 years, our study group experienced a median annual renal function decline of -1.4 (-2.6, -0.5) mL/min/1.73m^2/yr. We obtained PBMC and CD14 lysates using cell density and immunomagnetic separation techniques. Cell lysate samples were subjected to aptamer proteomics (1305 proteins).

Results: In the targeted evaluation, six out of 17 KRIS proteins in PBMC lysates associated significantly with the top KRIS protein in plasma (TNFR1 $_{PBMC}$:β: 3.4, p=0.003) (Fig.1A). TNFRSF members and IL17F accounted for most of these associations. TNFR1 $_{PBMC}$ was also associated with the renal slope (TNFR1 $_{PBMC}$:β: -7.6, p=0.025) (Fig.1B). In the untargeted evaluation, 68 proteins were associated with the renal slope (MAPKAPK3, ILT-2, and IL17R, among others). CD14 cellular KRIS patterns did not robustly associate with the phenotypes of our interest.

Conclusions: Our pilot study suggests potential contributions of the PBMC to the plasma KRIS that requires validation in a larger population. We also demonstrate the potential for biomarker and novel drug target discoveries using an approach that relies on the proteomics in white blood cell subpopulations.



PO0980

Investigations on Urinary mRNA Biomarkers That Reflect Pathologic Features of Patients with Diabetic Kidney Diseases

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Background: Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease worldwide. Despite that histological severity of DKD is a well-established predictor of adverse renal outcomes, investigations on the identification of non-invasive biomarkers that can reflect intrarenal status are scarce. The purpose of this study was to discover urinary mRNA biomarkers of DKD and to examine their associations with the degree of various pathologic features.

Methods: We collected and analyzed urinary samples obtained from 68 patients with biopsy-proven DKD and 32 healthy controls. Using two public GEO dataset (GPL22945 and GPL24120), we compared renal transcriptomic profiles of DKD and healthy living kidney donors and selected candidate genes for DKD (|fold change| > 2 and p < 0.001, compared to controls). The levels of selected candidate genes were measured by quantitative real-time polymerase chain reaction using urine cell pellet.

Results: Mean estimated glomerular filtration rate and urinary protein-to-creatinine ratio of enrolled patients were 45.5 mL/min/1.73 m^2 and 7.4 g/g creatinine, respectively. A total of 30 candidate genes were selected based on the analysis of GEO dataset, among which 22 genes were significantly elevated in urines of patients with DKD compared to controls. In particular, urinary *col1a1* levels were significantly higher in patients with advanced glomerular pathologic scores, while urinary *cx3cr1* and *sox4* levels were significantly lower in these patients. The expression of urinary *cx3cr1* levels was also lower in patients with more severe IFTA. On the other hand, urinary *pdk4* levels showed positive correlation with its scores. Urinary *c3* and *nnmt* levels were positively correlated with the severity of interstitial inflammation and arterial hyalinosis, respectively. Finally, we found significant correlation between the amount of urinary protein-to-creatinine ratio and urinary levels of *nnmt*, *thbs2*, *plk2*, and *cola1a1*.

Conclusions: Urinary mRNAs could reflect the degree of intrarenal pathologic status in patients with diabetic kidney disease.

Funding: Government Support - Non-U.S.

PO0981

Association Between the Urinary Proteome and Diabetic Retinopathy in the DIRECT-Protect 1 and 2 Trials

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Background: Diabetic retinopathy (DR) is a complication of paramount importance in type 1 and type 2 diabetes. Given the association of DR and diabetic kidney disease (DKD), we investigated the association between the urinary proteome and the presence and deterioration of DR in individuals with type 1 and type 2 diabetes.

Methods: Baseline proteomic analysis was performed in both the DIRECT-Protect 1 and 2 studies in a random selection of 800 and 821 subjects respectively. The DIRECT-Protect studies were designed to assess the effect of candesartan in relation to development of DR endpoints. DIRECT-Protect 1 was considered the discovery cohort and DIRECT-Protect 2 the validation cohort. Endpoints were defined as a two-step (RET2) or three-step (RET3) change in DR score according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Urinary peptide levels were correlated to baseline DR score in the discovery cohort. Thereafter, identified peptide fragments were investigated for association to baseline DR score in the validation cohort and for development of endpoints in both cohorts, adjusted for sex, age, diabetes duration, smoking, total cholesterol, HbA_{1c}, systolic blood pressure, urinary albumin excretion rate, serum creatinine, and randomization group at baseline.

Results: Follow-up ranged from 4.0-4.7 years. Eleven out of 427 peptide fragments were inversely associated to baseline DR in the discovery cohort after adjustment. In multivariate Cox regression analyses lower alpha-1 type I collagen (COL1A1) (seq. ApGD~, GKNG~, and LDGA~) was significantly ($p<0.05$) associated to the development of RET2 and lower COL1A1 (seq. LDGA~) and COL3A1 (seq. EDGK~) to RET3. However, when attempting to validate these results, only a KER12 fragment was inversely associated to baseline DR in the validation cohort, as well as to development of RET3. Furthermore, lower levels of one COL1A1 fragment (seq. AEGS~) was associated to development of RET2 in the validation cohort.

Conclusions: Several urinary peptide fragments were associated to the presence and worsening of DR in type 1 diabetes. However, this could not be validated in type 2 diabetes, and the identified peptide fragments were not conclusively associated to deterioration of DR across both cohorts.

PO0982

Urinary Cubilin Shedding Predicts Progressive Diabetic Nephropathy in Type 1 Diabetes Mellitus

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Background: Diabetes mellitus (DM) is the leading cause of end-stage renal disease worldwide. Microalbuminuria(MA) is considered a gold standard to diagnose diabetic nephropathy (DN) however its detection of early kidney damage is questionable. Therefore, there is an emergent need for novel biomarkers to capture early molecular alterations preceding MA. Cubilin is a 460 kd size protein lacking a transmembrane domain and is coexpressed with megalin facilitating albumin endocytosis in proximal tubule epithelial cells. We hypothesize that cubilin trafficking is compromised and is amenable to urinary shedding in DM. We propose that urinary cubilin shedding predicts DN.

Methods: This study assessed urinary IL-8, cubilin, monocyte chemoattractant factor (MCP-1), NGAL and vitamin D binding protein (VDBP) levels by ELISA (normalized for creatinine) across three groups of individuals with type 1 diabetes (T1D): Group 1(n=9) preserved normal kidney function, group 2 (n=10) developed proteinuria (albumin excretion >200microgram/min) and group 3 (n=9) developed progressive DN >40% decline in glomerular filtration rate (GFR) and proteinuria during follow-up of ~10 years. Urine samples for these assessments were obtained from the baseline examination of the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort. All patients had normal urine albumin excretion and kidney function. Duration of diabetes was comparable between groups (13.5 years±1.1). Mann-Whitney U and Kruskal Wallis tests were used to compare groups.

Results: Urinary IL-8 levels were (pg/gr) 229 ± 71, 270 ±146 and 549 ± 41.5 (NS) respectively. Urinary cubilin excretion(pg/gr) was 23±71, 38±9.2 and 47±8.8 ($p<0.05$). A urinary cubilin excretion >30 pg/mg predicted progressive DN with a 67% sensitivity and 89% specificity and an area under the ROC curve of 0.81($p<0.05$). Urinary MCP-1, NGAL and VDBG levels did not significantly differ across the groups.

Conclusions: We demonstrated that urinary cubilin shedding is a reliable biomarker for predicting progressive DN in T1D preceding microalbuminuria. Although not statistically significant urine IL-8 levels were elevated in patients with significant proteinuria and decline in GFR. The role of urinary cubilin shedding as a biomarker for the diagnosis and treatment of diabetic nephropathy at an early stage should be examined in a larger patient population.

PO0983

Comparison of Natriuretic Peptides as Risk Markers for Mortality and Cardiovascular and Renal Complications in Persons with Type 1 Diabetes

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Background: Assessment of natriuretic peptides, N-terminal pro-brain natriuretic peptide (NT-proBNP) and Midregional Proatrial Natriuretic Peptide (MR-proANP), represents a useful addition for evaluating risk of cardiovascular and renal complications. Only very few studies have compared these two risk markers. We compared the value of NT-proBNP and MR-proANP as risk markers for mortality and development of cardiovascular and renal complications in persons with type 1 diabetes (T1D).

Methods: Plasma NT-proBNP and MR-proANP were measured (using commercially available kits) in 664 persons with T1D and various degrees of albuminuria. Endpoints were traced through National Registers and laboratory records and comprised mortality (n=57), composite cardiovascular events (CVE, n=94), heart failure (HF, n=27), end-stage kidney disease (ESKD, n=21) and decline in estimated glomerular filtration rate (eGFR) ≥30% (n=93). Median follow-up ranged from 5.1-6.2 years. From Cox regression models Hazard ratios (HRs) were assessed per doubling of NT-proBNP or MR-proANP with 95% confidence interval in models adjusted for cardiovascular risk factors: sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA_{1c}, BMI, eGFR and urinary albumin excretion rate and additionally with mutual inclusion of MR-proANP and NT-proBNP.

Results: Of the 664 persons (55% male), mean±SD age was 55±13 years, eGFR 81±26 ml/min/1.73m^2, median (IQR) MR-proANP was 74 (49-116) pmol/L and NT-proBNP 70 (29-162) pg/L. Higher NT-proBNP level was associated with higher risk of mortality (HR 1.5 (1.2-1.8)), CVE (HR 1.3 (1.1-1.5)) and HF (HR 1.7 (1.3-2.1)) independent of cardiovascular risk factors ($p<0.001$) and MR-proANP ($p<0.004$). Higher MR-proANP level was associated with higher risk of mortality (HR 1.7 (1.1-2.7)), CVE (HR 1.6 (1.1-2.2)), HF (HR 2.8 (1.5-5.2)) and ESKD (HR 3.1 (1.2-7.8)) independent of cardiovascular risk factors ($p<0.03$), however, after addition of NT-proBNP significance for all endpoints was lost. None of the markers were significantly associated with decline in eGFR ≥30%.

Conclusions: Higher NT-proBNP concentration was independently associated with mortality and cardiovascular events. Our results suggest that NT-proBNP may be useful singly or in combination with MR-proANP for risk-stratification in persons with T1D.

Funding: Private Foundation Support

PO0984

The Importance of Addressing Multiple Risk Markers in Type 2 Diabetes: Results from the LEADER Trial

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Background: The benefit of multifactorial intervention in type 2 diabetes (T2D) was demonstrated in the small Steno-2 study in microalbuminuric T2D. Larger studies in more diverse cohorts are limited. We investigated the importance of multiple risk-marker improvement for micro- and macrovascular outcomes in the LEADER trial.

Methods: LEADER (n=9340, ClinicalTrials.gov number NCT01179048) randomized patients with T2D to liraglutide or placebo (1:1) in addition to standard of care. We categorized patients according to number of risk markers with a clinically relevant change at year 1 of treatment and investigated subsequent risk of an expanded cardiovascular outcome (MACE-6) or nephropathy. We defined clinically relevant change as: body weight loss ≥5%, HbA_{1c} reduction ≥1%, systolic blood pressure reduction ≥5 mmHg, LDL reduction ≥0.5 mmol/L, eGFR reduction ≥0 ml/min/1.73m^2 and urinary albumin-to-creatinine ratio reduction ≥30% of baseline value. Numbers of risk markers with change were classified as: none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4). Cox regression analyzed risk of the outcomes adjusted for continuous baseline levels of the risk markers and treatment group.

Results: Compared to patients with no risk-marker change, risk of cardiovascular disease was lower for patients with 2 (HR [95% CI] 0.81 [0.66–0.98] or 3 (0.80 [0.65–0.99]) risk-marker changes, and risk of nephropathy was lower for those with 3 (0.50 [0.35–0.72]) or ≥4 (0.48 [0.31–0.73]) risk-marker changes (Table). Test for trend with number of improved risk markers as a continuous variable: p=0.004 and $p<0.001$, respectively.

Conclusions: Improvement in multiple risk markers within 1 year translates into reduced risk of micro- and macrovascular outcomes in T2D, underscoring the benefit of pleiotropic antidiabetic treatments.

Funding: Commercial Support - Novo Nordisk A/S

Table: Outcomes according to total number of risk markers improved at year 1 from randomization

Number of improved risk markers	Outcome	N (%)	IR	HR	[95% CI]	p value
G0 (n=802)	Cardiovascular outcome	149 (18.6)	4.9	Reference group		
	Nephropathy	55 (6.9)	1.8			
G1 (n=2408)	Cardiovascular outcome	448 (18.6)	4.8	0.96	[0.79–1.16]	0.65
	Nephropathy	192 (8.0)	2.1	1.06	[0.77–1.46]	0.73
G2 (n=2656)	Cardiovascular outcome	458 (17.2)	4.5	0.81	[0.66–0.98]	0.03
	Nephropathy	179 (6.7)	1.7	0.73	[0.53–1.02]	0.07
G3 (n=1844)	Cardiovascular outcome	315 (17.1)	4.4	0.80	[0.65–0.99]	0.04
	Nephropathy	93 (5.0)	1.3	0.50	[0.35–0.72]	0.0002
G4+ (n=928)	Cardiovascular outcome	157 (16.9)	4.4	0.80	[0.63–1.02]	0.07
	Nephropathy	48 (5.2)	1.3	0.48	[0.31–0.73]	0.0006

Expanded cardiovascular outcome (from year 1) defined as MACE-6: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure. Nephropathy defined as new-onset macroalbuminuria, doubling of serum creatinine and eGFR ≤45 ml/min/1.73m^2, continuous renal replacement therapy, or renal death. IR: events per 100 patient years of observation. G0: subjects with zero clinical responses at year 1 (reference group), G1–G3: subjects with 1–3 clinical responses, G4+: subjects with ≥4 clinical responses at year 1. HR: compares subgroups G1–G4 to G0. Cox regression model adjusted for treatment (liraglutide vs placebo), baseline body weight, HbA_{1c}, systolic blood pressure, LDL cholesterol, eGFR and urinary albumin-to-creatinine ratio. CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HR, hazard ratio; IR, incidence rate; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events.

PO0985

Associations of Circulating Angiopoietins with Renal Function Decline and Progression to ESKD in CKD Stage 3 Patients with Diabetes

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Background: The literature on plasma angiopoietins (Ang) levels in patients with diabetes and CKD Stage 3 is sparse. The data pertaining the association of Ang with progression of renal decline and development of ESKD is similarly limited. This study aimed to investigate relationships between circulating angiopoietins with risk of progressive renal decline and ESKD in diabetic patients with already existing moderate renal impairment.

Methods: We prospectively studied 214 T1D patients and 144 T2D patients over a follow-up period of 7-15 years to determine eGFR slope and ascertain time of onset of ESKD. Serial measurements of serum creatinine were used to estimate the rate of eGFR decline. Fast decliners were defined as eGFR loss ≥ 3.0 ml/min/year. We quantified Ang1, Ang2 and Tie-2 present on the SOMAscan proteomic platform in baseline plasma samples in diabetics as well as in 79 non-diabetics. We examined the association of plasma levels of each Ang and the rate of fast renal decline using logistic regression models.

Results: There were 143 and 75 fast decliners in T1D and T2D (Median eGFR slope -6.2 ml/min/year in both cohorts), respectively. In regression models adjusted for baseline eGFR, HbA1c, ACR and type of diabetes, Ang1 (OR (95% CI): 0.77 (0.61, 0.96)) or Ang1/Ang2 ratio (OR: 0.74 (0.59, 0.94)) was significantly associated with protection against fast renal decline. Neither Ang2 (OR: 1.21 (0.96, 1.51)) nor Tie-2 (OR: 1.12 (0.89, 1.39)) was associated with the rate of fast renal decline. Patients with Ang1 levels above median and Ang2 below median had very low cumulative incidence of ESKD of 30%. The lowest baseline Ang1 levels were observed in non-diabetic controls (Median (25^{th}, 75^{th} percentiles): 757 (641, 1189)) and the highest values were observed in slow decliners (Median: 1565 (1093, 2522)), while fast-decliner levels (Median: 1248 (934, 1916)) fell between the two other sub-groups.

Conclusions: Elevated Ang1 levels or the ratio of Ang1/Ang2 had a protective effect against fast renal decline and progression to ESKD. As such, Ang1 and Ang2 may be useful targets for preventing or delaying the onset of renal function decline and ESKD in diabetes.

Funding: NIDDK Support

PO0986

Microscopic Hematuria Is a Risk Factor for ESKD in Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Microscopic hematuria is rarely observed in patients with diabetic nephropathy (DN). Some studies have reported that hematuria is a risk factor for end-stage kidney disease (ESKD) in glomerulonephritis, but association of hematuria with renal prognosis in DN is unknown.

Methods: The present study is a retrospective cohort study of patients with DN confirmed by renal biopsy between June 1981 and December 2014. The participants were followed until October 2018 or death. Exposure of interest is the presence of hematuria (U-RBC >5) and main outcome was the occurrence of ESKD. The association of hematuria with ESKD was evaluated using Cox hazard model with adjustment for clinically relevant factors [age, sex, eGFR, proteinuria, body mass index, systolic blood pressure (SBP) and pathological evaluations].

Results: Patients who had microscopic hematuria at the time of renal biopsy were defined as the hematuria group (N = 91), and the remainder as the non-hematuria group (N = 306). Hematuria group had more proportion of male, higher SBP, more proteinuria, and lower eGFR compared with non-hematuria group. Pathological findings revealed that glomerular, tubulointerstitial, and vascular lesions in the hematuria group were significantly more severe than those in non-hematuria group. During a median follow-up period of 80 months, 44 and 52 patients developed ESKD in the hematuria group and non-hematuria groups, respectively. Survival analyses showed that incidence of ESKD was significantly higher in the hematuria group (P <0.0001). The significance remained robust even after adjustment for confounding factors (adjusted HR 1.64, 95% CI; 1.03-2.60). In the subgroup analyses, the associations of hematuria with ESKD among male and overt proteinuria (≥0.5 g/day) were stronger than those among female and micro proteinuria (<0.5 g/day), respectively (P values for interaction <0.1 and <0.03, respectively).

Conclusions: The presence of microscopic hematuria is an independent risk factor for ESKD in diabetic nephropathy.

PO0987

A Profile of Multiple Circulating TNF Receptors Associated with Early Progressive Renal Decline in Type 1 Diabetes: Similar to Profiles in Autoimmune Disorders

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Background: This study comprehensively evaluated the association between known circulating tumor necrosis factor (TNF) superfamily ligands and receptors and the development of early progressive renal decline (PRD) leading to end-stage kidney disease (ESKD) in Type 1 diabetes (T1D).

Methods: The Macro-Albuminuria Study comprised of 198 individuals, and the Micro-Albuminuria Study consisted of 148 individuals. All individuals had normal renal function and were followed for 7-15 years to determine estimate glomerular filtration rate (eGFR) slopes and to ascertain onset of ESKD. Plasma concentrations of 25 TNF superfamily proteins were measured using proximity extension assay applied in the OLINK proteomics platform.

Results: In the both studies risk of early PRD, determined as eGFR loss greater than or equal to 3 ml/min/1.73m^2/year, was associated with elevated circulating levels of 13 TNF receptors out of 19 examined. In the Macro-Albuminuria Study, we obtained similar findings for risk of progression to ESKD. These receptors comprised: TNF-R1A, -R1B, -R3, -R4, -R6, -R6B, -R7, -R10A, -R10B, -R11A, -R14, -R21, and -R27. Serial measurements showed that circulating levels of these TNF receptors had increased before the onset of PRD. In contrast, none of the 6 measured TNF ligands showed association with risk of early PRD.

Conclusions: The disease process that underlies PRD which leads to ESKD in T1D is enriched with up-regulated levels of multiple TNF receptors, a profile also seen in autoimmune disorders. The mechanisms of this enrichment may be causally related to the development of PRD in T1D and must be investigated further. Some of these receptors may be used as new predictors of risk of ESKD.

Funding: NIDDK Support, Private Foundation Support

PO0988

Associations Between TNFR-1, TNFR-2, and KIM-1 with Kidney and Cardiovascular Outcomes: Results from the CANVAS Trial

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Background: Tumor Necrosis Factor Receptor (TNFR)-1, TNFR-2 and Kidney Injury Molecule-1 (KIM-1) are blood-based biomarkers that are known to predict kidney outcomes in patients with diabetic kidney disease. We sought to examine the association of baseline TNFR-1, TNFR-2 and KIM-1 with cardiovascular (CV) and kidney outcomes in patients with type 2 diabetes mellitus (T2DM) in the CANagliflozin cardioVascular Assessment Study (CANVAS) study, and secondly, whether these markers modified the effect of the SGLT2 inhibitor canagliflozin (CANA) on these outcomes.

Methods: The CANVAS trial randomized participants with T2DM at high CV risk to CANA or placebo. Plasma TNFR-1, TNFR-2 and KIM-1 were measured with immunoassays (proprietary multiplex assay performed by RenalytixAI, NY, USA). Associations between the 3 biomarkers and the CV (nonfatal myocardial infarction, stroke, or CV death) and kidney outcome (40% eGFR decline, end-stage kidney disease, or renal death) were assessed using multivariable adjusted Cox regression.

Results: We included 3548 (82% of original cohort of 4330) CANVAS participants with available baseline plasma samples (mean age 62.8 y, 33.0% female, mean eGFR 76.9 mL/min/1.73 m^2, median uACR 11.6 mg/g, median TNFR-1, TNFR-2 and KIM-1: 2578 pg/mL, 9684 pg/mL, and 110 pg/mL). During a mean follow-up of 5.6 y, 554 CV and 137 kidney outcomes occurred. After adjustment for demographics and clinical characteristics, each doubling of baseline TNFR-1, TNFR-2, KIM-1 was significantly associated with higher risk of kidney outcomes: TNFR-1, HR 3.74 (95% CI 2.28, 6.15); TNFR-2, HR 2.68 (95% CI 2.01, 3.57); KIM-1, HR 1.50 (95% CI 1.23, 1.82). The biomarkers were not associated with the CV outcome. The protective effect of CANA on the CV and kidney outcome (HR 0.56, 95% CI 0.40, 0.78) was consistent regardless of baseline TNFR-1, TNFR-2, or KIM- 1 (all P-interaction>0.10).

Conclusions: Higher levels of TNFR-1, TNFR-2 and KIM-1 were independently associated with a higher risk of kidney but not CV outcomes in patients with T2DM at high CV risk. The baseline markers did not modify the effect of CANA on these outcomes.

Funding: Commercial Support - Janssen Research & Development, LLC

PO0989

The Clinical Importance of Phenyl Sulfate as a Predictive Marker of Albuminuria in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the major causes of end-stage renal diseases (ESRD), and it is important to prevent from onset or progression of DKD. However, it is difficult to identify type 2 diabetes patients who are at risk of developing progressive DKD based only on measurements of glomerular filtration rate and albuminuria. Therefore, specific biomarkers are needed for a breakthrough in the good management of DKD.

Methods: Among 777 patinets in a multi-center clinical study in diabetic nephropathy cohort (U-CARE), 362 patients with full data were selected. The plasma PS, PCS, IS and TMAO level were measured by LCMS/MS. The correlation between these level and various factors were calculated using the Spearman Rank-Order Correlation. Multiple regression analysis and a logistic regression analysis were used to identify the factors associated with PS, IS, PCS, TMAO, suPAR, urine acid or the development of 2-year ACR deterioration, respectively.

Results: As we previously reported (Kikuchi et al. Nat. Commun. 2019, ASN 2019), serum PS level significantly related with the basal albuminuria level in U-CARE study. In addition, logistic regression analysis showed among known ACR predictive factors, PS was the only factor which significantly related 2-year progression of albuminuria especially in patients with microalbuminuria. We next examined the relationship between albuminuria or renal function with IS, PCS, TMAO which were well-known as gut derived uremic solutes as well as PS. In addition, we examined the relationship between albuminuria or renal function and suPAR, uric acid. As a result, IS, PCS, suPAR were inversely correlated with eGFR. PS, IS, suPAR and uric acid were correlated with albuminuria. Among them, PS and uric acid were the factor which significantly correlated with the 2-year albumin-creatinine ratio (ACR) deterioration. Furthermore, we clarified that serum PS concentration level was high even in same patients who are preserved renal function (eGFR>60 ml/min/1.73cm^2), and high PS concentration patients were significantly increased 2-year ACR deterioration rate.

Conclusions: PS is a predictive marker of albuminuria in the patients with microalbuminuria in DKD.

PO0990

Virtual Patient Simulation in Diabetic Kidney Disease: Successful Strategy for Improving Recognition and Management

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Background: We sought to determine if virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists related to recognition and management of diabetes kidney disease (DKD).

Methods: The intervention comprised a patient presenting at two different time points in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a McNemar's test to determine *P* values. The activity posted August 30, 2019; initial data was collected through November 7, 2019.

Results: 139 nephrologists completed the activity (all decisions within at least 1 case) and were included. Significant improvements were observed after CG: 1st Patient: Diagnose CKD stage 3b: 28% absolute improvement (19% pre-CG vs 47% post-CG; P<.01) Diagnose T2D: 33% absolute improvement (5% pre-CG vs 38% post-CG; P<.01) Initiate SGLT2 inhibitor: 53% improvement (17% pre-CG vs 70% post-CG; P<.01) Order patient education: 15% improvement (52% pre-CG vs 67% post-CG; P<.01) 2nd Patient: Diagnose CKD stage 3a: 33% absolute improvement (24% pre-CG vs 57% post-CG; P<.01) Diagnose T2D: 41% absolute improvement (10% pre-CG vs 51% post-CG; P<.01) Initiate SGLT2 inhibitor: 36% improvement (48% pre-CG vs 84% post-CG; P<.01) Initiate ACE inhibitor: 18% improvement (82% pre-CG vs 100% post-CG; P<.01) Order patient education: 14% improvement (59% pre-CG vs 73% post-CG; P<.01)

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia.

Funding: Commercial Support - Janssen

PO0991

Effect of Multidisciplinary Care Models on Glomerular Filtration Rate for Patients with Diabetic Kidney Disease: Systematic Review and Meta-Analysis

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Background: Since 2015, the Kidney Disease Improving Global Outcomes guidelines advocate for comprehensive conservative care for diabetic nephropathy (DN) patients. Multidisciplinary care (MCD) models are such strategies that offer integrated care to delay renal disease progression, reduce micro- and macrovascular complications of diabetes, increase the quality of life, and reduce associated costs. Prior reviews have assessed the effect of MCDs in all-cause mortality, hospitalization rate, and need for temporal or permanent renal replacement therapy. However, to date, there are no reviews on their impact on glomerular filtration rate (GFR).

Methods: We conducted a systematic search of observational and randomized trials on DN GFR assessments. We searched Ovid and PubMed databases. Following the STROBE and CONSORT recommendations, we assessed the quality of evidence and any selection/information bias from our resulted pool of evidence. Our primary outcome was GFR quantifications between MCD vs. non-MCD DN treated patients. We performed a meta-analysis of these measurements using random and fixed effects models and examined inter-study heterogeneity with meta-regression models.

Results: There were 93 records from our systematic search. We screened titles and abstracts and retrieved eight records (9,892 participants) for qualitative and quantitative assessments. By subgroup analyses, MCD had a statistically significant effect on GFR among younger patients (<65 years, x0.53-fold increase in GFR vs. non-MCD) with long-term follow-up (>2 years, x0.57-fold increase in GFR vs. non-MCD) (Table).

Conclusions: Based on eight records with significant sample size, MCDs might have a positive effect on GFR if implemented earlier (preferably before age 65). However, this benefit might not be seen immediately, rather in the long-term. We suggest implementing these approaches as standard of care for DN.

Subgroup	Pooled SMD (95% CI)	Sample size	I-squared
Age ≥65 vs <65 years	0.53 (0.40, 0.65)	1,011	62%, p = 0.07
Follow-up time < 2 vs ≥ 2 years	0.57 (0.43, 0.70)	917	43%, p = 0.19

PO0992

Outcomes of Diabetic vs. Non-Diabetic Patients in the GCC Dialysis Outcomes and Practice Patterns Study

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Background: Diabetes is a common comorbidity among hemodialysis (HD) patients in the Gulf Cooperation Council (GCC) countries, higher than any other region participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Objectives of this analysis were to describe the prevalence of glycated-hemoglobulin (HbA1c) measurement, distribution of HbA1c, and association of HbA1c with mortality among participants in the GCC DOPPS.

Methods: 2,274 HD patients were analyzed from 6 GCC (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates) participating in DOPPS phase 5 (2012-2015) and 6 (2015-2018). Diabetic status was based on cause of ESKD or medical chart diagnosis. Cox regression was used to assess the associations of diabetes (among all GCC patients) and baseline HbA1c (among diabetic patients) with mortality adjusted for demographics, comorbidities, creatinine, and Kt/V.

Results: Overall 60% of GCC DOPPS participants were diabetic (country prevalence ranged from 45% in Saudi Arabia to 74% in Kuwait). Compared to non-diabetic patients, patients with diabetes were older (60 vs. 47) on dialysis fewer years (1.5 vs. 3.0), and had higher BMI (27.6 vs. 24.9). Diabetes was associated with elevated mortality; adjusted HR(95% CI)=1.69(1.21-2.34). Measurement of HbA1c within the four months prior to enrollment was variable – ranging from 0% in Bahrain and 33% in Saudi Arabia to 60-78% in the other GCC countries. Among diabetic patients with HbA1c measured, median [IQR] HbA1c was 6.8 [5.8-7.1]. A moderate U-shaped relationship with HbA1c and mortality was observed after adjustment.

Conclusions: Although diabetes is highly prevalent in the GCC HD population, measurement of HbA1c remains variable among this population. The relationship of HbA1c with mortality appears similar to that see in other DOPPS regions. Further investigation related to frequency of measurement and control of HbA1c via treatment is warranted.

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PO0993

Self-Management and Progression of Patients with Diabetic Kidney Disease (DKD): A Retrospective Cohort Study

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Background: Few specifics were proved effective to delay DKD progression while accumulating evidence supported potential merits of self-management on it. This study aimed to evaluate the association between self-management and progression of non-dialysis CKD3-5 DKD patients.

Methods: Data including demographics, procedure notes, laboratory findings, and medication of the included cohort were analyzed. The cohort was divided into self-management group and control group based on previous self-management exposure. The between-group comparison of renal function at 2 years and survival analysis were conducted.

Results: Total 92 patients were included(47 in self-management group and 45 in control group). Declined serum creatinine level and preserved eGFR were detected in self-management group after 2 years both with no significant difference(P =0.695,0.922), while significantly higher serum creatinine level(P=0.010) and decreased eGFR with no evident significance(P =0.059) after 2 years were found in control group. We defined eGFR<5ml/min/1.73 m2, initiation of renal replacement therapy and death as composite endpoints, and performed time-to-event survival analysis. Ten endpoint events in self-management group(mean survival time 221.31±12.97 weeks) and 17 in control group(mean survival time 168.63±15.03 weeks) were recorded, with significant difference between group comparison(χ2=6.319,P =0.012). Further Cox proportional hazards regression with three adjusted models showed that self-management engagement was an independent factor associated with reduced risk of incident endpoints.

Conclusions: The findings documented predisposing preserved renal function of patients with self-management at 2 years and self-management engagement as an independent factor for decreased risk of endpoints, indicating its potential benefits on delaying DKD progression.

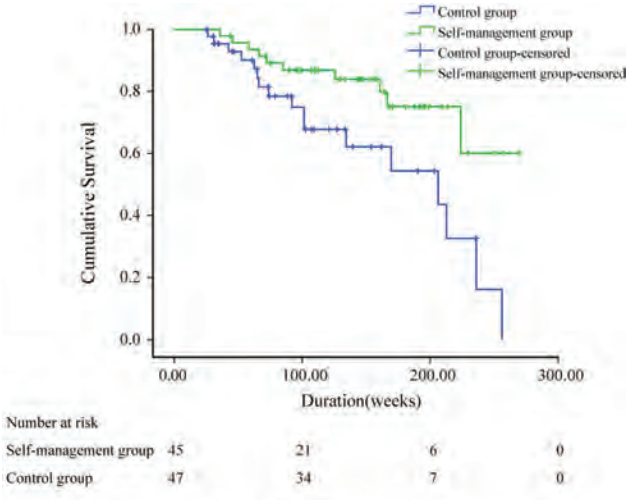

Fig 1. Survival function of self-management group and control group.

PO0994

Attitude Toward Care and Dietary Patterns Differ in CKD and Transplant Patients with and Without Diabetes

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Background: Diabetes mellitus requires dietary changes and increased interaction with the health care team over that required by kidney disease alone. We compared dietary adherence and attitudes in pts with kidney disease with and without diabetes in inner-city Brooklyn.

Methods: A face-to-face survey was conducted in a random convenience sample of pts from CKD (23) and transplant (33) clinics. Diet was studied by 24-hour recall using ASA24 software. Healthy Eating Index was calculated using the HEI-15 score. The Beliefs in Medicine Questionnaire (BMQ) was used to elicit attitudes toward the healthcare environment. Comparisons were by t-test.

Results: 15 (45%) transplant (TXP) and 13 (57%) CKD pts had diabetes (DIAB). DIAB were older than pts without diabetes (NODIAB) (62.1±1.98 vs 50.4±2.4 yrs, p<0.0001) but age did not correlate with any finding. Mean creat was 1.83±0.15 mg/dl and did not differ between CKD and TXP, or DIAB and NODIAB. Mean HbA1c was 8.0± 0.28, time with diabetes was 97.7±20.3 months and did not differ between clinics. DIAB were more likely to agree that their health depends on medications in the future (1.36±0.12 vs 2.00±0.26, p=0.024), less likely to believe that if doctors had more time, they would prescribe fewer medications (3.61±0.25 vs 2.79±0.28, p=0.034) and less likely to believe that medicines are poisons (4.5±0.14 vs 3.93±0.23, p=0.039). DIAB pts ate fewer carbohydrates (137.4±11.6 vs 211.8±13.4, p<0.0001), less sugar (44.7±5.6 vs 89.4±9.5, p<0.0001), less fiber (10.9±1.1 vs 16.1±1.4, p<0.005), less vitamin C (54.2±9.9 vs 110.2±23.3, p=0.031), less fruit (0.3±0.1 vs 1.96±0.6, p=0.015) and less refined grains (3.01±0.43 vs 4.61±0.59, p=0.035). There was no difference for HEI score, total caloric or protein intake.

Conclusions: In our population: 1. Approximately 50% of our pts had diabetes. 2. Pts with diabetes had a more positive opinion of the healthcare environment.and ate fewer carbohydrates, sugars and refined grains but less fresh fruit, fiber and vitamin C. 3. Education of our pts with kidney disease and diabetes should reinforce their attitudes towards the healthcare environment while encouraging an eating plan that includes fruits and vegetables, as pts appear to be focusing on restricting sugar and carbohydrates and plant based eating has been shown to be beneficial for pts with kidney disease.

PO0995

Racial and Ethnic Similarities of Adherence to Diabetic Hemoglobin A_{1c} Testing and Control Measures Between Providers and Patients in Federally Qualified Health Centers in Eastern North Carolina

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Background: Type 2 Diabetes is a chronic metabolic disorder that occurs when there is a dysregulation of insulin production and cellular insulin response, leading to hyperglycemia. The test for glycated hemoglobin, HbA1C, is the basic blood test used for diagnosis. There is limited exploration of the relationship between adherence to HbA1c testing, diabetes control, and congruent provider/patient race and ethnicity. This study examines the correlations among HbA1c testing, provider race/ethnicity, and patient race/ethnicity.

Methods: Twelve consecutive monthly diabetes reports and dashboards compiled by the Rural Health Group, starting on October 1, 2018, were retrieved and analyzed in the investigation of the racial and ethnic similarities of HbA1c adherence to diabetic testing and control measures between providers and patients in the Federal Qualified Health Center in eastern North Carolina. Comparative statistical analyses permitted the juxtaposition of the comparison groups of patients and providers: White, Black, Hispanic, or other.

Results: As per adherence with the order of testing, there were no statistically significant differences found for White, Black, or Hispanic patients when they were seen by different providers. However, as per adherence to diabetes control measures, Black patients seen by Black providers were much more likely to have an HbA1c < 7% (52% when seen by a Black provider vs. only 45% when seen by a White provider, p-value = 0.0001, 95% confidence interval). Similarly, White patients had an HbA1c < 7% 50% of the time when seen by White providers, but only 43% of the time when seen by Black providers (p-value < 0.05). Therefore, patients who are the same race as their providers are statistically more likely to have an HbA1c, which reflects adherence to diabetes control measures.

Conclusions: Patients who are the same race/ethnicity as their providers did not play a significant role on HbA1c testing than patients who are the same race/ethnicity as their provider. However, patients who are the same race/ethnicity as their provider were more likely to have a HbA1c < 7%, which was statistically significant and reflected adherence to diabetes control measures. This finding was particularly true of White patients to White providers and with Black patients to Black providers.

PO0996

Low Serum Transferrin Saturation Is Associated with Incident Diabetes in Veterans with CKD

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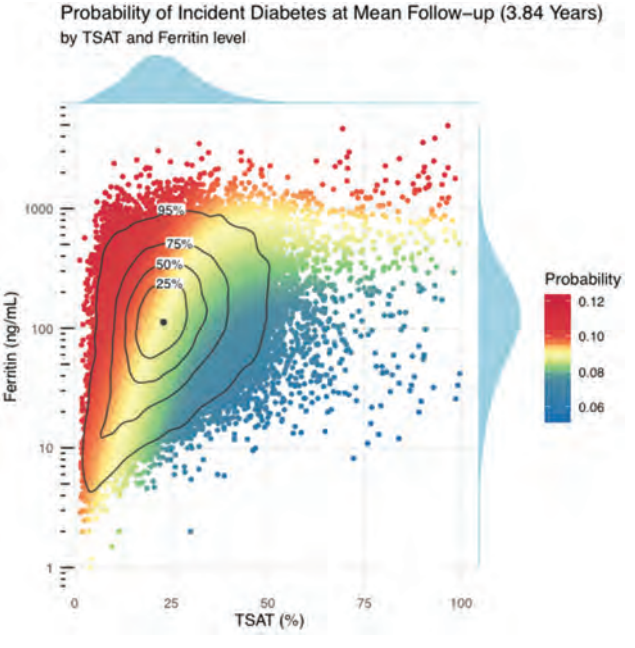
Background: Chronic kidney disease (CKD) is associated with increased risk for new-onset diabetes. Decreased circulating iron, as expressed by low transferrin saturation (Tsat), is associated with diabetes in the general population, but it has not been investigated if Tsat or ferritin is independently associated with incident diabetes in CKD.

Methods: We developed a historical cohort using the Veterans Affairs Informatics and Computing Infrastructure. We identified non-diabetic Veterans with CKD (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. Veterans with diabetes, end-stage renal disease, genetic or chronic disorders affecting iron metabolism, or those who received intravenous iron or erythropoietin stimulating agents within 3 months of the iron indices were excluded. A generalized additive Cox model was applied to the cohort to explore the joint dose-response relationship of the hazard for incident diabetes following the iron assay. A contour surface plot relating the covariate-adjusted hazard for incident diabetes to both Tsat and ferritin was developed using cubic regression splines.

Results: Of the 1,159,371 Veterans with CKD, 54,990 met the inclusion criteria. The mean±SD for age and eGFR were 73.8 ± 11.8 years and 43.8 ± 10.4 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 23.0 (16.9, 29.7) % and 112.1 (56.0, 210.0) ng/mL. Over the mean follow-up period of 4 years, the risk of diabetes was inversely associated with Tsat, while it was positively correlated with serum ferritin. The surface contour map suggests that lower Tsat range (<20%) has a stronger relationship with diabetic risk than serum ferritin.

Conclusions: In Veterans with pre-dialysis CKD, decreased Tsat is closely associated with incident diabetes risk, while increased ferritin exacerbates the risk.

Funding: Veterans Affairs Support



PO0997

Association of Glomerular Hyperfiltration with Glycemic Control and Serum Uric Acid Among NHANES Participants with Diagnosed Diabetes Mellitus

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Background: Glomerular Hyperfiltration (GH) is the earliest sign of diabetic kidney disease (DKD) even prior to the development of albuminuria. Some studies have reported that improvement in glycemic control reduces GH. Since elevated serum uric acid (SUA) level may herald worse diabetes outcomes including a higher likelihood of DKD, we sought to examine the association of GH status with glycemic control and SUA among diabetics.

Methods: We examined the National Health and Nutritional Examination Survey (NHANES) data from 1999 through 2016, comprising adults (age ≥ 20 years, n= 47,133, projected to N=214.9 million US population). We defined diagnosed diabetes cases as those who reported being diagnosed by a doctor or using glucose-lowering medications (n= 5,783, N=19.3M) and defined GH as eGFR ≥120 ml/min/1.73m2 (CKD-EPI) vs. normal-filtration as 60 ≤ eGFR <120 (GH: n=110, non-GH: n=3115). Cases with eGFR<60 were excluded (n= 2,558). We assessed the association of GH with average glycemic control (HbA1c) and SUA levels adjusted for demographic characteristics, diabetes duration, and diabetes treatment, using univariate and multivariable regression models.

Results: The prevalence of GH in persons under 10 years of diabetes was 2.7% but significantly less after 10 years (1.1%, p= 0.003). GH was more likely in younger age, female sex, Hispanic ethnicity, higher A1c, higher SUA, and those with no diabetes treatment. In the multivariable model, female sex was the strongest predictor followed by Hispanic ethnicity, higher SUA, and younger age [Table].

Conclusions: GH is more common in the first 10 years of diabetes and associated with higher SUA. It is more common among females, Hispanic race, and younger diabetes patients. Further studies should examine the potential role of sex, ethnicity, age, and SUA in the mechanism of GH among persons with diabetes.

Regression model for variables associated with Glomerular Hyperfiltration (GH) among patients with diagnosed diabetes

Variables	Odds Ratio (95% CI)	P-Value
Age (per SD)	0.91 (0.89, 0.92)	<0.0001
Gender (Female vs. Male)	16.34 (5.10, 52.34)	<0.0001
Ethnicity (Hispanic vs. White)	3.10 (1.39, 6.90)	0.006
HbA1c (per SD)	1.01 (1.00, 1.02)	0.06
SUA (Hypouricemia vs. Reference)	2.28 (1.13, 4.62)	0.02

PO0998

Continuous Glucose Monitoring in a Diabetic Hemodialysis Patient

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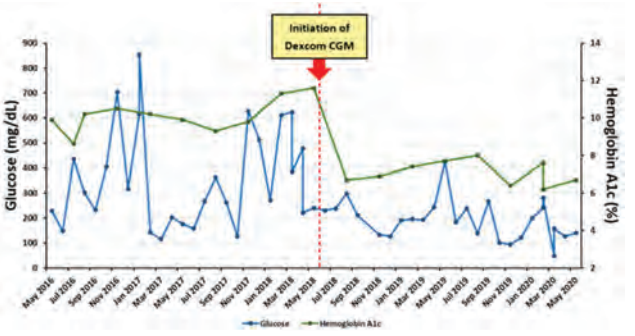
Introduction: Diabetes is the leading cause of end stage renal disease (ESRD) in the US. Patients with diabetic kidney disease (DKD) are susceptible to hypo- and hyperglycemia via multiple pathways. Continuous glucose monitoring (CGM) provides automated, less invasive glucose measurements (updated every 5 minutes) and more comprehensive glucose data vs. conventional self-monitored blood glucose (SMBG), and glycemic benefits for CGM use have been established. However, CGM use has been limited in diabetic hemodialysis (HD) patients as devices are not currently approved for use in this population.

Case Description: We describe a 48-year old male with ESRD due to DKD receiving HD. At the age of 26, the patient was diagnosed with diabetes after presenting with recurrent skin infections and unexplained weight loss. He was initially treated with glyburide which was changed to metformin, and was later transitioned to an insulin pump. Over time he developed DKD which progressed to ESRD by the time he was 41 years old. His diabetes was also complicated by neuropathy and retinopathy with right-eye blindness. For two decades, the patient utilized SMBG with capillary fingerstick measurements to monitor his glycemic status. During this time he had wide fluctuations in his glucose levels with asymptomatic hypo- and hyperglycemia, and his HbA1c levels were typically 10-12%. Due to poor glucose control, his endocrinologist advised him to use CGM (Dexcom G5, later transitioned to Dexcom G6, San Diego, CA). Since transitioning to CGM, the patient reports 1) greater adherence to glycemic monitoring, 2) improved hypoglycemia detection, 3) minimal lifestyle interruption, and 4) improved quality of life. In addition, he has less glycemic variability, increased time-in-target glucose range, and improved HbA1c levels to 6-8%.

Discussion: This case demonstrates CGM is a practical method for glucose assessment with the potential to improve glycemic control in diabetic ESRD patients. Further studies are needed to determine the comparative effectiveness of CGM vs. SMBG in diabetic HD patients.



PO0999

ESKD due to an Atypical Cause of Diabetes Mellitus

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Introduction: Diabetes mellitus (DM) is the most common cause of chronic kidney disease (CKD) in the United States. This case describes CKD caused by an atypical, potentially reversible cause of type 2 DM.

Case Description: A 70 year-old male presented to our Hypertension Clinic with new onset lower extremity edema, CKD, and hypertension. He had had type 2 DM for 20 years complicated by retinopathy and gastroparesis. Although body mass index was 29.8, he required more than 100 units of long-acting insulin daily. His blood pressure measured 200/115 and had been refractory to multiple medications. Initial laboratory evaluation demonstrated creatinine 2.7 mg/dL, glucose 245 mg/dL, urine protein-to-creatinine (uPCR) of 8.5, hemoglobin A1c of 7.5%, and negative serum and urine protein electrophoresis. Echocardiogram revealed severe left ventricular hypertrophy. CT of his abdomen demonstrated a 4 x 4 cm pancreatic cystic mass which had been biopsied 15 years previously and showed no malignant cells. Due to persistent gastrointestinal complaints, imaging was repeated 2 years later and demonstrated an increase in the pancreatic mass size to 5.8 x 5.1 cm without any evidence of metastasis. Further laboratory evaluation demonstrated C-peptide 2.4 ng/ml (normal) and glucagon 1760 ng/L (normal <208 ng/L). Elevated pancreatic polypeptide and chromogranin A levels confirmed the diagnosis: glucagonoma. He declined surgery and was intolerant of octreotide. Although uPCR decreased to a nadir of 1.5 with improved blood pressure control, his kidney function progressively declined and he required hemodialysis (HD). HD only minimally improved his nausea and vomiting. His physical condition declined over the course of a year, until he entered hospice and expired. At time of death, his pancreatic lesion measured 6 cm.

Discussion: Glucagonomas are rare tumors with an incidence of approximately 0.1 cases per 100,000, most commonly presenting in the 5th decade of life. Secondary causes of DM should be considered in patients without obesity, normal C-peptide levels despite advanced disease, and/or a pancreatic mass. Additionally, glucagon excess or mechanical obstruction by a pancreatic mass may cause gastrointestinal complaints attributed to uremia or diabetic gastropathy. Timely diagnosis and resection could prevent this disease cascade of diabetes, nephropathy, and end-stage kidney disease.

PO1000

Effects of Canagliflozin on Cardiovascular, Renal, and Safety Outcomes by Baseline Loop Diuretic Use: Data from the CREDENCE Trial

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Background: Canagliflozin (CANA) reduces the risk of cardiovascular (CV) events and kidney failure in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Inherent in its mechanism of action is enhanced natriuresis and osmotic diuresis. It is unclear if the efficacy or safety of CANA is modified by concomitant diuretic use.

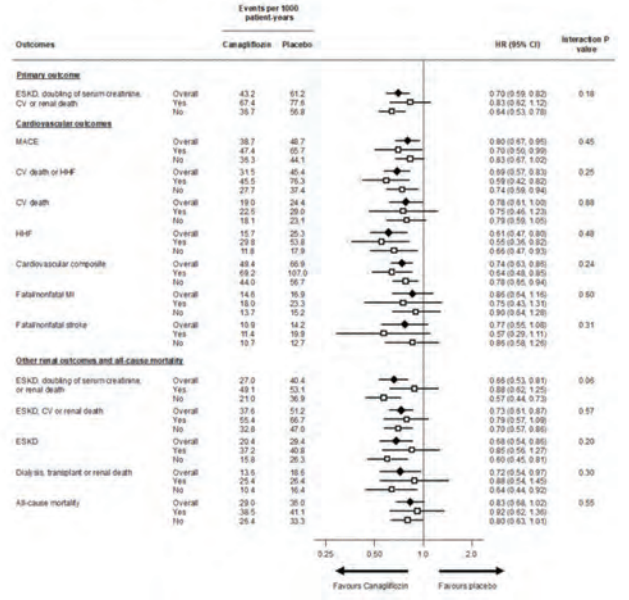
Methods: CREDENCE randomized participants with T2DM and CKD to CANA or matching placebo. The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, CV or renal death. We estimated effects on key efficacy and safety outcomes by baseline use of loop diuretics.

Results: Of 4401 CREDENCE participants, 955 (21.7%) received loop diuretics at baseline. These participants were older (mean age 63.5 vs 62.7 y; P=0.01), with a longer diabetes duration (17.0 vs 15.5 y), lower eGFR (49.7 vs 58.0 mL/min/1.73m^2), and were more like to have a history of heart failure (27.6 vs 11.3%; all P<0.0001). Unadjusted event rates were higher in those using loop diuretics (Figure). Effects of CANA on the primary outcome and other CV and renal outcomes were consistent irrespective of loop diuretic use. The risk of renal-related adverse events, acute kidney injury, and volume depletion was not elevated by loop diuretic use (data not shown; all $P_{interaction}$>0.05).

Conclusions: CANA reduces the risk of CV and renal outcomes in people with T2DM and CKD irrespective of baseline use of loop diuretics, without additional adverse effects.

Funding: Commercial Support - Janssen Scientific Affairs, LLC

Figure. Effect of canagliflozin on cardiovascular and renal outcomes by baseline use of loop diuretics



Cardiovascular composite includes cardiovascular death, nonfatal MI, nonfatal stroke and hospitalization for unstable angina. MACE: major adverse cardiovascular events; CV: cardiovascular; HHF: hospitalization for heart failure; ESKD: end-stage kidney disease; MI: myocardial infarction; HR: hazard ratio; CI: confidence interval.

PO1001

Acute Declines in eGFR During Treatment with Canagliflozin (CANA) and Its Implications for Clinical Practice: Insights from CREDENCE

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Background: CANA slows progression of chronic kidney disease (CKD) in people with type 2 diabetes. CANA also induces a reversible acute decline in estimated glomerular filtration rate (eGFR), which is believed to be a hemodynamic effect. Predictors of the initial decline and its association with long-term eGFR trajectories and safety outcomes are unknown.

Methods: This post hoc study of CREDENCE included 4289 patients with type 2 diabetes and CKD who had eGFR measured at both baseline and week 3. Participants were categorized by percentage decline in eGFR at week 3: greater than 10% decline; between 0 and 10% decline; and no decline. Baseline characteristics associated with acute eGFR drop >10% were evaluated using logistic regression. Long-term eGFR decline and safety outcomes were estimated in each eGFR decline category by linear mixed effects models and Cox regression after adjustment for laboratory measures and medication use.

Results: More participants in the CANA (956 [45%]) versus placebo (PBO) group (450 [21%]) had an acute eGFR decline >10% (p<0.001). A >30% decline occurred infrequently (89 [4%] with CANA and 39 [2%] with PBO; p<0.001). In the CANA but not in the PBO group, older age (OR CANA 1.17, 95% CI 1.05–1.31; per 10 years) and

history of heart failure (OR CANA 0.77, 0.59–0.99) were associated with a higher and lower likelihood of an acute eGFR decline >10%, respectively (both p interaction<0.05). Following the initial eGFR change, long-term eGFR trajectories were similar across eGFR decline categories (all p>0.05). Safety profiles were also similar except when the drop unusually exceeded 30%, in which case adverse events and renal related adverse events occurred more frequently. Results were consistent in subgroup analysis by baseline eGFR (30-<45, 45-<60, and 60-<90 mL/min/1.73m^2).

Conclusions: Although acute eGFR declines >10% occurred in nearly half of all patients following initiation of CANA, the benefit of CANA compared with PBO was observed regardless of the acute eGFR decline and safety profiles were similar.

Funding: Commercial Support - Janssen Scientific Affairs, LLC

PO1002

The SGLT2 Inhibitor Canagliflozin Reduces the Plasma Markers TNFR-1, TNFR-2, and KIM-1 in the CANVAS Trial

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Background: Tumor Necrosis Factor Receptor (TNFR)-1, TNFR-2 and Kidney Injury Molecule-1 (KIM-1) are biomarkers known to predict kidney outcomes in patients with type 2 diabetes (T2D). We assessed the effect of the SGLT2 inhibitor canagliflozin (CANA) on TNFR-1, TNFR-2 and KIM-1 in CANVAS study participants to determine whether early changes were associated with subsequent kidney outcomes.

Methods: The CANVAS trial randomized participants with T2D at high cardiovascular risk to CANA or placebo (PBO). TNFR-1, TNFR-2 and KIM-1 were measured with immunoassays (proprietary multiplex assay performed by RenalytixAI, NY, USA) at baseline, and years 1, 3, and 6. Mixed effects models for repeated measures assessed the effect of CANA vs PBO on TNFR-1, TNFR-2 and KIM-1. The association between early change (baseline to year 1) for each of the 3 markers and the kidney outcome (40% eGFR decline, end-stage kidney disease, or renal death) was assessed using multivariable adjusted Cox regression.

Results: Among 2872/4330 (67%) CANVAS participants with available plasma samples at baseline and follow-up, median baseline TNFR-1, TNFR-2 and KIM-1 were 2559, 9612, and 108 pg/mL. Difference between CANA and PBO in TNFR-1, TNFR-2, and KIM-1 during follow-up were 2.8% (95%CI −3.4, −1.3; P<0.001), −1.9% (95%CI −3.5, −0.2; P=0.028) and −26.7% (−30.7, −22.7; P<0.001). Increases in TNFR-1 and TNFR-2, but not KIM-1, at year 1 were independently associated with a higher risk of the kidney outcome (Table).

Conclusions: CANA reduces TNFR-1, TNFR-2 and KIM-1 in patients with T2D at high cardiovascular risk. Early increases in TNFR-1 and TNFR-2 were independently associated with higher risk of kidney disease progression and have the potential to be pharmacodynamic markers of non-response to CANA.

Table

		TNFR-1	TNFR-2	KIM-1
Change at year 1	Quartile 1	0.81 (0.42, 1.55)	0.98 (0.50, 1.92)	0.99 (0.56, 1.76)
	Quartile 2	Ref	Ref	Ref
	Quartile 3	1.31 (0.71, 2.41)	1.94 (1.05,3.59)	0.72 (0.38, 1.35)
	Quartile 4	2.23 (1.28, 3.87)	2.76 (1.52, 5.01)	1.32 (0.74, 2.33)
P-trend		0.004	<0.001	0.496

Multivariable Cox regression analysis adjusted for age, gender, race, treatment assignment, smoking, cardiovascular disease history, HbA1c, systolic/diastolic BP, BMI, LDL, eGFR, log UACR and respective biomarker (TNFR-1, TNFR-2, or KIM-1) as well as change from baseline at year 1 in HbA1c, systolic BP, BMI and log UACR.

PO1003

Canagliflozin Treatment Reduces Formation and Increases Degradation of Collagen Type III in the Canagliflozin Cardiovascular Assessment Study (CANVAS)

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Background: The CANVAS trial investigated the effects of canagliflozin in T2D patients at high risk of cardiovascular (CV) disease. Collagen type III (COL III) is one of the main components of the interstitial extracellular matrix that is significantly upregulated in fibrosis. In the current study, we investigated the impact of canagliflozin treatment on biomarkers of COL III formation (PRO-C3) and degradation (C3M) in the CANVAS trial.

Methods: COL III formation was assessed with the PRO-C3 enzyme-linked immunosorbent assay (ELISA), detecting the cleaved pro-peptide released upon deposition in the extracellular matrix. COL III degradation was assessed with the C3M ELISA, detecting a neo-epitope fragment released after MMP-9 mediated degradation. The change in biomarker measurements at year 3 from baseline were compared between placebo and canagliflozin in plasma (n=2156) and urine (n=2137) samples using a linear model to assess whether biomarker levels were significantly affected by treatment. Urine biomarker levels were corrected for urine creatinine.

Results: Treatment with canagliflozin compared to placebo resulted in significantly lower plasma PRO-C3 levels -0.52 ng/mL (p=0.0054; 95% CI: -0.88, -0.15), with mean levels rising in the placebo group (0.48 ng/mL) but remaining stable in the intervention group (-0.04 ng/mL). Urinary PRO-C3 levels were increased 293.19 ng/mmol (p<0.001; 95% CI: 158.87, 427.51), with mean levels increasing 24.23 ng/mmol in the placebo group and 317.42 ng/mmol in the intervention group. Urinary C3M levels were increased 833.01 ng/mmol (p<0.001; 95% CI: 481.27, 1184.74), with mean levels decreasing -337.71 ng/mmol in placebo and increasing 495.30 ng/mmol on treatment. There was no correlation between the change in plasma and urine PRO-C3 (r=0.07).

Conclusions: The reduction in PRO-C3 levels in plasma and the increase in urine C3M levels following treatment with canagliflozin suggest an anti-fibrotic effect of canagliflozin. Further research is necessary to understand the mechanism for canagliflozin's effects on fibrosis.

Funding: Commercial Support - Janssen Research & Development, LLC

PO1004

Canagliflozin and Risk of Genital Infections and Urinary Tract Infections in People with Diabetes Mellitus and Kidney Disease in the CREDENCE Trial

Amy Kang,[1] Brendon L. Neuen,[1] Hiddo J. L Heerspink,[2] Gian Luca Di Tanna,[1] Bruce Neal,[1] Hong Zhang,[3] Carinna Hockham,[1] Rajiv Agarwal,[4] George L. Bakris,[5] David M. Charytan,[6] Dick de Zeeuw,[2] Tom Greene,[7] Adeera Levin,[8] Carol A. Pollock,[11] David C. Wheeler,[12] Bernard Zinman,[10] Kenneth W. Mahaffey,[9] Vlado Perkovic,[1] Meg J. Jardine.[1] *[1]The George Institute for Global Health UNSW Sydney, Sydney, NSW, Australia; [2]Rijksuniversiteit Groningen, Groningen, Netherlands; [3]Peking University First Hospital, Beijing, China; [4]Indiana University School of Medicine, Indianapolis, IN; [5]University of Chicago, Chicago, IL; [6]NYU Langone Health, New York, NY; [7]University of Utah Health, Salt Lake City, UT; [8]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [9]Stanford University, Stanford, CA; [10]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada; [11]University of Sydney - Camperdown and Darlington Campus Burkitt-Ford Library, Sydney, NSW, Australia; [12]University College London, London, United Kingdom.*

Background: Genital mycotic infections (GMI) and urinary tract infections (UTI) are common in patients with diabetes. We assessed the effects of canagliflozin on the risk of these infections in the CREDENCE trial population.

Methods: The CREDENCE trial randomised people with type 2 diabetes and albuminuric stage 2 and 3 chronic kidney disease to canagliflozin 100mg daily or placebo. We analysed the risk of GMI and UTI with canagliflozin compared to placebo overall and in subgroups. The primary analysis was conducted in the on-treatment population. When canagliflozin increased risk, we determined patient risk factors for GMIs using multivariable Cox regression models.

Results: Overall 31/2905 (1.1%) men and 32/1492 (2.1%) women experienced 91 GMIs and 166/2905 (5.7%) men and 300/1492 (20.1%) women experienced 669 UTIs. 58/669 (8.7%) UTIs but no GMIs were reported as serious. Most participants continued treatment following their first infection with similar recurrence rates in the canagliflozin and placebo groups. Canagliflozin increased the risk of GMI (HR 3.83 [95% CI 2.08-7.06] p<0.0001). The hazard ratio (HR) for canagliflozin compared to placebo was consistent across most subgroups, though canagliflozin led to a greater increase in risk in those with a BMI>30 kg/m^2 compared to those with a BMI<30 kg/m^2 (HR 5.91 vs 1.36, p interaction=0.03) and in men compared to women (HR 9.30 vs HR 2.10, p interaction=0.04). In those who were randomised to canagliflozin, independent risk factors for GMI were higher BMI (HR 1.53 [95% CI 1.29-1.83] per 5 units p<0.0001) and longer diabetes duration (HR 1.18 [95% CI 1.01-1.40] per 5 years p=0.04). Canagliflozin did not affect the risk of UTI (HR 1.08 [95% CI 0.90-1.29] p=0.42) overall or in any subgroup.

Conclusions: Canagliflozin increased risk of GMI but not UTI. The proportional increase in GMI with canagliflozin was greater in men and people with higher BMI.

Funding: Commercial Support - Janssen sponsored the CREDENCE trial but did not sponsor this post-hoc analysis

PO1005

Canagliflozin and Risk of Skin and Soft Tissue Infections in People with Diabetes Mellitus and Kidney Disease in the CREDENCE Trial

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Background: The skin's hypertonic microenvironment has a protective antimicrobial function that may be disrupted by sodium glucose cotransporter 2 inhibitors (SGLT2i). We aimed to describe skin and soft tissue infections (SSTI) in the CREDENCE trial and determine whether canagliflozin affects the risk of SSTIs.

Methods: We performed a post-hoc analysis of the CREDENCE trial that randomised people with type 2 diabetes and albuminuric stage 2 and 3 chronic kidney disease to either canagliflozin 100mg daily or placebo. Adverse events were assessed by two blinded authors following predetermined criteria for SSTI with discrepancies resolved by consensus. We analysed the risks of SSTIs in the on-treatment population as the more conservative approach, with sensitivity analyses conducted in the intention-to-treat population, for serious events only and for participant subgroups. Univariable time-to first-event regression models were assessed.

Results: Overall 373/4397 (8.5%) participants experienced 478 events comprising 252 bacterial skin infections (including 2 episodes of necrotising fasciitis), 94 fungal skin infections, 109 other skin infections and 23 soft tissue infections. Of these, 136/478 (28%) were serious. Canagliflozin did not increase the risk of SSTI (HR 0.85 [95% Confidence Interval (CI) 0.69-1.04] p=0.11), with similar results in the intention-to-treat population (HR 0.88 [95% CI 0.73-1.07] p=0.20), in analyses confined to serious SSTI (HR 0.83 [95% CI 0.58-1.21] p=0.33) and participant subgroups (all p interaction≥0.10). Both cases of necrotising fasciitis were in patients assigned to canagliflozin and the participants recovered after drug was withdrawn.

Conclusions: Canagliflozin did not increase the risk of skin and soft tissue infections overall or in any subgroup, in CREDENCE trial participants with type 2 diabetes mellitus and albuminuric chronic kidney disease.

Funding: Commercial Support - Janssen sponsored the CREDENCE trial but did not sponsor this post-hoc analysis

PO1006

Early Change in Albuminuria with Canagliflozin (CANA) Predicts Kidney and Cardiovascular (CV) Outcomes

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Background: The association between early changes in albuminuria and kidney and CV events is primarily based on trials of renin-angiotensin system blockade. It is unclear whether this association is similar with sodium-glucose cotransporter 2 inhibitors.

Methods: In this post-hoc analysis of the CREDENCE trial in patients with type 2 diabetes and chronic kidney disease, we assessed the effect of CANA versus placebo on albuminuria at week 26, and the association of early changes in urinary albumin:creatinine ratio (UACR) for the first 26 weeks with kidney and CV outcomes using multivariable Cox regression. Kidney and CV outcomes were defined as (1) end-stage kidney disease, doubling of serum creatinine or death due to kidney disease, (2) major adverse cardiovascular events (MACE) and (3) hospitalization for heart failure (HHF) or CV death.

Results: This analysis included 3836 participants (87.2%) with complete data for early changes in UACR. CANA lowered UACR by 31% (95%CI 27–36%) at week 26 and increased the likelihood of achieving a 30% UACR reduction (OR 2.69, 95%CI 2.35–3.07). We observed log-linear associations of early changes in UACR during 26 weeks with kidney and CV outcomes (all p trend <0.001; Table). Each 30% UACR reduction was independently associated with a lower hazard for clinical outcomes, overall and in each treatment arm (all p <0.001).

Conclusions: In people with type 2 diabetes and CKD, canagliflozin results in early and sustained reductions in albuminuria, which was independently associated with long-term kidney and cardiovascular outcomes.

Table: Adjusted HRs (95% CIs) of early changes in UACR at week 26 for kidney and CV outcomes

		Kidney outcome	MACE	HHF or CV death	HHF
UACR change at week 26	<-30%	0.55 (0.24–0.52)	0.81 (0.56–1.16)	0.72 (0.49–1.07)	0.65 (0.38–1.13)
	-30% to <0%	0.70 (0.48–1.02)	0.92 (0.63–1.36)	0.79 (0.52–1.21)	0.89 (0.51–1.58)
	0% to <30%	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	≥30%	1.76 (1.26–2.47)	1.33 (0.94–1.90)	1.55 (1.08–2.24)	1.78 (1.08–2.84)
Each 30% reduction in UACR		0.71 (0.67–0.76)	0.92 (0.88–0.96)	0.86 (0.81–0.90)	0.82 (0.76–0.88)

PO1007

Effects of Canagliflozin on Major Adverse Cardiovascular Events in Patients with Different Baseline Levels of Type 2 Diabetes Disease Severity: Results from the CANVAS Program

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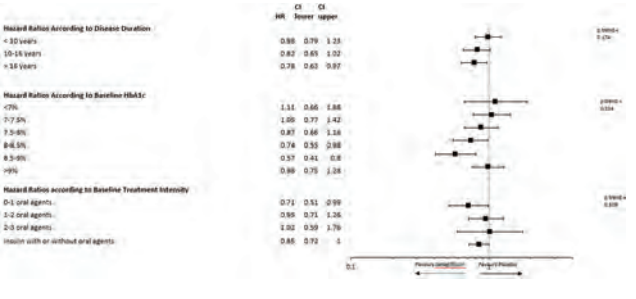
Background: Patients with type 2 diabetes mellitus (T2DM) included in trials of sodium-glucose cotransporter 2 inhibitors are heterogeneous in terms of disease severity. We assessed the effects of canagliflozin compared to placebo on cardiovascular and renal outcomes in the CANVAS program according to severity of T2DM as indicated by intensity of treatment, duration of diabetes and glycaemic control.

Methods: We compared effects on major adverse cardiovascular events ([MACE], defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) according to three indicators of T2DM severity at study baseline: number of glucose lowering treatments or insulin therapy (0-1, 2, 3+, insulin), duration of diabetes (<10, 10-16, >16 years) and HbA1c (<7.0, 7.0-7.5, 7.5-8.0, 8.0-8.5, 8.5-9, >9.0%). We also assessed effects on other pre-specified cardiovascular outcomes, and an adjudicated composite of end-stage kidney disease, renal death or sustained 40% decline in estimated glomerular filtration rate. We assessed for constancy of hazard ratios across subgroups by fitting an interaction term that tested for linear trend.

Results: Of 10,142 participants in the CANVAS Program, 1011 experienced a MACE during a mean follow-up of 3.6 years. The effect of canagliflozin on MACE in the overall population (HR 0.86, 95 % CI 0.75-0.97) was consistent irrespective of the number of glucose lowering treatments (p=0.509), duration of diabetes (p=0.174) and baseline HbA1c (p =0.314). Effects were also consistent across different levels of T2DM disease severity for all other outcomes studied.

Conclusions: The proportional risk reductions achieved with canagliflozin were comparable regardless of diabetes duration, number of therapies or HbA1C at baseline.

Funding: Commercial Support - Janssen



PO1008

Kidney Effects of Empagliflozin in People with Type 1 Diabetes

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Background: Empagliflozin lowers the risk of cardiovascular and kidney events in type 2 diabetes (T2D). In the empagliflozin in type 1 diabetes (T1D) clinical program (EASE), glycemic control, weight and blood pressure improved with empagliflozin as adjunct to insulin treatment, though diabetic ketoacidosis risk was higher with use of the 10 and 25mg doses vs the 2.5mg dose. The kidney effects of empagliflozin in T1D remain incompletely understood.

Methods: Here we report changes in kidney parameters in phase 3 placebo-controlled trials EASE-2 (empagliflozin 10/25mg; 52-week; n=730) and EASE-3 (empagliflozin 2.5/10/25mg; 26-week; n=975).

Results: Mean±SD baseline estimated glomerular filtration rate (eGFR in mL/min/1.73 m²) in EASE-2/EASE-3 was 97.3±18.2 and 98.5±18.2 and median (interquartile range) baseline urinary albumin-to-creatinine ratio (UACR in mg/g of creatinine) was 6.2 (2.7,14.1) in both studies. After 26 weeks of treatment in EASE-3, mean placebo-corrected eGFR changes with empagliflozin 2.5mg (n=230), 10mg (n=228) and 25mg (n=234) were -0.14 (p=0.87), -2.57 (p=0.004) and −3.56 (p<0.0001), respectively. Mean placebo-corrected eGFR changes with empagliflozin 10mg and 25mg were −2.09 (p=0.02; n=226) and −2.60 (p=0.002; n=228) after 52 weeks in EASE-2, respectively. Changes in eGFR 3 weeks after end of therapy (FU) returned to above baseline levels. In participants with UACR <30mg/g, no significant changes in urinary albumin-to-creatinine ratio (UACR) were observed. In a pooled analysis (EASE-2 + EASE-3), in participants with baseline UACR ≥30 mg/g, UACR decreased by 16% (p=0.27) and 30% (p=0.02) with empagliflozin 10mg (n=71) and 25mg (n=77) vs placebo (n=65), respectively, at 26 weeks. In EASE-3, in people with baseline UACR ≥30 mg/g, treatment with empagliflozin 2.5mg (n=36) for 26 weeks did not significantly attenuate UACR vs placebo (n=34). Hematocrit and serum albumin increased in EASE-2 and EASE-3 with empagliflozin treatment while serum uric acid decreased; changes in these parameters returned to near baseline values at the FU visit after 26 and 52 weeks of treatment.

Conclusions: In conclusion, empagliflozin doses >2.5 mg/day as adjunct therapy to insulin in T1D resulted in short-term changes in kidney markers comparable to changes observed with SGLT2 inhibitor use in T2D.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

PO1009

Empagliflozin Is Associated with Increased Plasma Lipid Metabolites in Type 1 Diabetes

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Background: Sodium glucose cotransporter-2 (SGLT2) inhibition reduces the risk of cardiorenal complications in people with diabetes, possibly by altering energy substrate pathways. It has been hypothesized that SGLT2 inhibitors improve mitochondrial efficiency and may induce a shift towards increased lipid utilization as an energy substrate. In this exploratory, *post-hoc* analysis, we investigated the effects of SGLT2 inhibition on plasma lipid and tricarboxylic acid (TCA) cycle metabolites in patients with type 1 diabetes (T1D).

Methods: In the ATIRMA trial (NCT01392560), patients with T1D were assessed under clamped euglycemia and hyperglycemia at baseline and after 8 weeks of empagliflozin treatment. Plasma samples from the ATIRMA trial were analyzed for lipid and TCA cycle metabolites using the ZipChip method.

Results: Of the 15 lipid metabolites, 5 increased during clamped euglycemia in response to empagliflozin (Figure) while 1 increased after treatment during clamped hyperglycemia. Of the 3 TCA cycle metabolites, 2 increased during clamped euglycemia in response to empagliflozin. None of the metabolites decreased significantly after empagliflozin treatment.

Conclusions: In patients with T1D, SGLT2 inhibition increased plasma TCA cycle metabolite levels, suggesting an impact on mitochondrial function. Lipid metabolite levels were also increased after SGLT2 inhibition, suggesting a possible increase in beta oxidation. Further work is needed to determine if these changes contribute to cardiorenal protection with SGLT2 inhibitors.

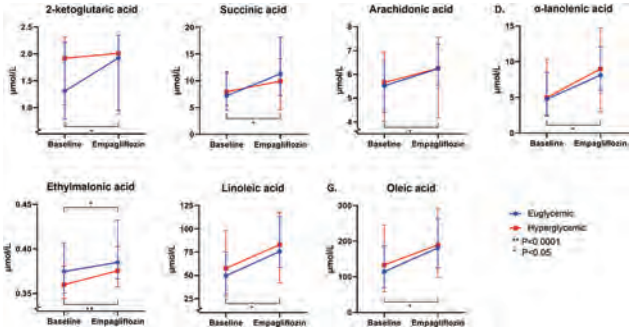

Figure Plasma concentrations of (A.) 2-ketoglutaric acid, (B.) succinic acid, (C.) arachidonic acid, (D.) α-lanolenic acid, (E.) ethylmalonic acid, (F.) linoleic acid, and (G.) oleic acid during clamped euglycemia and hyperglycemia at baseline and post 8 weeks treatment with empagliflozin. Data shown are medians ± Q_1/Q3. Succinic acid levels significantly increased after treatment during clamped euglycemia.

PO1010

Effect of Dapagliflozin on Risk for Fast Decline in eGFR: Analysis from DECLARE-TIMI 58 Trial

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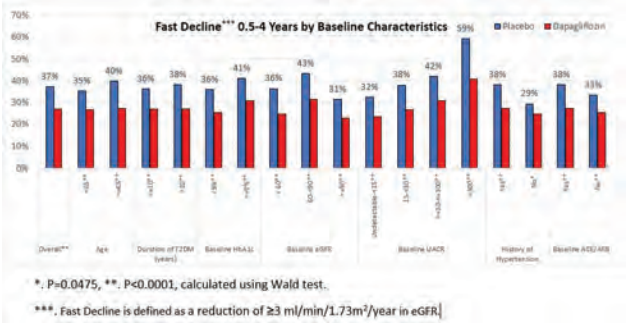
Background: SGLT2 inhibitors may lead to short term decrease in eGFR with later stabilization and long-term reduction in risk for end stage kidney disease. Fast decline (FD) in eGFR can be defined as reduction of ≥3 ml/min/1.73m²/year and is associated with poor long-term renal prognosis. In this post hoc analysis we studied the effect of dapagliflozin (dapa) on risk for FD in the DECLARE-TIMI 58 trial.

Methods: In DECLARE-TIMI 58, 17,160 patients with T2D and established or increased risk for CVD, with mean baseline eGFR of 85.2 ml/min/1.73m², were randomized to dapa vs. placebo and followed for median of 4.2 years. The risk for FD was compared between treatment arms.

Results: In the time frame of 0.5 years (after stabilization) to 4 years, the proportion of patients with FD was reduced with dapa vs. placebo (26.8% vs. 37.1%, respectively, p<0.0001) and in all subgroups assessed (Figure). The mean (SD) reduction in eGFR per year was 6.3 (3.7) vs. 0.0 (2.5) ml/min/1.73m²/year in FD (N=4,788) vs. non-FD (N=10,224) patients. In patients that had FD, mean (SD) reduction in eGFR was -5.9 (3.2) vs. -6.6 (4.1) ml/min/1.73m²/year in dapa vs. placebo arm, while in patients that did not have fast decline it was 0.2 (2.5) vs. -0.2(2.5) ml/min/1.73m²/year, respectively. The proportion of patients with FD during entire study period (i.e. 0-4 years) was also reduced with dapa vs. placebo (33.6% vs. 37.0%, respectively, p<0.0001).

Conclusions: Dapa reduced the risk for FD in eGFR in a broad population of patients with T2D and relatively preserved renal function, irrespective of patients' baseline characteristics.

Funding: Commercial Support - AstraZeneca



PO1011

Comparative Effectiveness of SGLT2 Inhibitors, GLP1 Receptor Agonists, DPP4 Inhibitors, and Sulfonylureas on Risk of Kidney Outcomes: Emulation of a Target Trial Using Healthcare Databases

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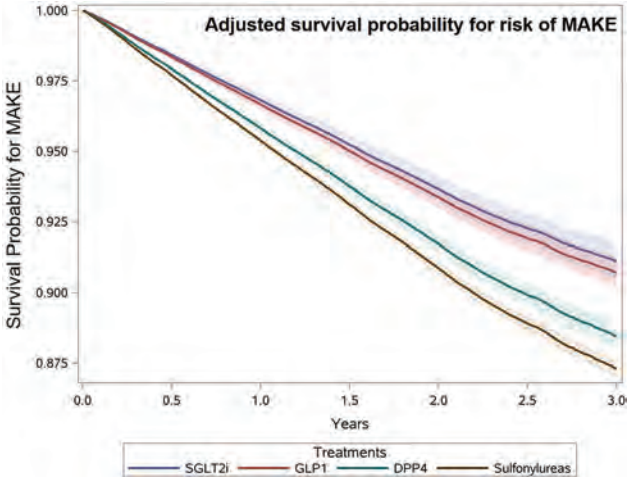
Background: The comparative effectiveness of SGLT2i, GLP1, DPP4, and sulfonylureas on risk of kidney outcomes among people with type 2 diabetes mellitus is not known.

Methods: We built a cohort of 216,558 US Veterans initiated on SGLT2i, GLP1, DPP4, or sulfonylureas and followed them for up to 3 years. The outcome was defined as the risk of the major adverse kidney events (MAKE) of estimated glomerular filtration rate (eGFR) decline >50%, end stage kidney disease, or all-cause mortality. Risks were estimated using survival models adjusted for pre-defined covariates as well as covariates identified by a high-dimensional variable selection algorithm through application of generalized propensity scores.

Results: During follow up, there were 14612 (6.75%) MAKEs. Adjusted KM curve for risk of MAKE across treatment arms are presented. Compared to those treated with sulfonylurea, treatment with SGLT2i, GLP1, and DPP4 was associated with lower risk of MAKE (HR=0.68 (0.63-0.74), HR=0.72 (0.67-0.77), and HR=0.90 (0.86-0.95), respectively). Both SGLT2i and GLP1 had lower risk of MAKE than DPP4 (HR=0.76 (0.70-0.82), and HR=0.79 (0.74-0.85), respectively). The associations were consistent regardless of metformin use at baseline. Analyses by eGFR category suggested that compared to the sulfonylureas arm, those in the SGLT2i and GLP1 arms exhibited lower risk of MAKE in all eGFR categories. Compared to DPP4, both SGLT2i and GLP1 exhibited reduced risk of MAKE in eGFR >90 to ≥60, <60 to ≥45, and <45 ml/min/1.73 m².

Conclusions: Among patients with diabetes mellitus type 2, treatment with SGLT2i or GLP1 compared to DPP4 or sulfonylureas was associated with lower risk of adverse kidney outcomes.

Funding: Veterans Affairs Support



PO1012

Renal Outcomes and All-Cause Death Associated with SGLT-2 Inhibitor vs. Other Glucose-Lowering Drugs (CVD-REAL 3 Korea)

Eun Sil Koh,[1] Kyungdo Han,[3] Hyewon Lee,[2] You-Seon Nam,[2] Eric T. Wittbrodt,[4] Peter Fenici,[5] Mikhail Kosiborod,[6] Hiddo J. L Heerspink,[7] Soon-Jib Yoo,[8] Hyuk-Sang Kwon.[1] *[1]The Catholic University of Korea Yeouido Saint Mary's Hospital, Yeongdeungpo-gu, Seoul, Republic of Korea; [2]AstraZeneca Korea Co Ltd, Seoul, Republic of Korea; [3]Soongsil University Department of Statistics and Actuarial Science, Dongjak-gu, Seoul, Republic of Korea; [4]AstraZeneca, Gaithersburg, MD; [5]AstraZeneca, Cambridge, United Kingdom; [6]Saint Luke's Mid America Heart Institute, Kansas City, MO; [7]University Medical Center Groningen, Groningen, Netherlands; [8]The Catholic University of Korea Bucheon Saint Mary's Hospital, Bucheon, Gyeonggi-do, Republic of Korea.*

Background: Real-world evidence from routine clinical practice elucidating the effects of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) on renal outcomes and mortality in patients with type 2 diabetes (T2D) is limited.

Methods: Using data from the Korean National Health Insurance Service database from January 2014 to December 2017, a total of 701,674 patients were identified with T2D. We divided these patients into new-users of SGLT-2i and new-users of other glucose-lowering drugs (oGLD). Using propensity scores, patients in the two groups were matched 1:1. We examined for the risk of end-stage renal disease (ESRD) and all-cause death.

Results: There were 45,016 patients in each group, and baseline characteristics were well-balanced between groups: mean age 58.1 ± 10.6 years; mean estimated glomerular filtration rate (eGFR) 89.2 ± 27.4 ml/min/1.73m²; 8% of patients had proteinuria. We identified 167 incident ESRD and 1,070 all-cause deaths during follow-up. Use of SGLT-2i *versus* oGLD was associated with a lower risk of ESRD (HR: 0.47; 95% confidence interval [CI]: 0.34 to 0.65) and all-cause death (HR: 0.82; 95% CI: 0.73 to 0.93). In a subgroup analysis by eGFR, initiation of SGLT2i vs oGLD was associated with lower risk of progression to ESRD among patients with eGFR 60-90 and <60 ml/min/1.73m² and lower risk of all-cause death associated with SGLT-2i *versus* oGLD was observed across the entire range of renal function.

Conclusions: In this large nationwide study of Korean patients with T2D, initiation of SGLT-2i *vs* oGLD was associated with lower risk of ESRD and all-cause death.

Funding: Commercial Support - AstraZeneca

PO1013

Cardiovascular Outcomes with SGLT-2 Inhibitors vs. GLP-1 Receptor Agonists in Patients with Type 2 Diabetes and CKD: A Systematic Review and Network Meta-Analysis

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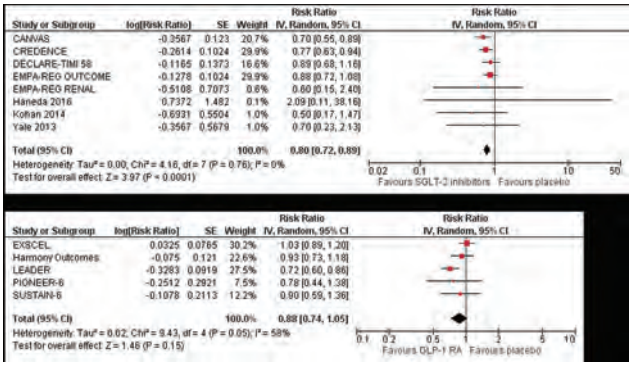
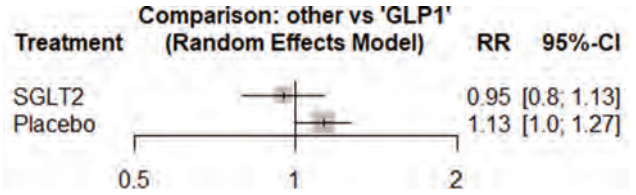
Background: Type 2 diabetes mellitus (DM) and chronic kidney disease (CKD) increase the risk of cardiovascular disease. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are known to reduce cardiovascular disease. However, no study compared the effect of SGLT-2 inhibitors on cardiovascular diseases with that of GLP-1 RAs in CKD patients.

Methods: We performed a systematic literature search up to March 2020. We selected randomized control trials. First, we performed meta-analysis to compare SGLT-2 inhibitors vs placebo and GLP-1 RA vs placebo. Next, we performed a network meta-analysis to compare SGLT-2 inhibitors with GLP-1 RA indirectly. Risk ratios (RRs) with corresponding 95% confidence interval (CI) were synthesized.

Results: Total thirteen studies were selected. SGLT-2 inhibitors led to a risk reduction in MACE (RR [95% CI]; 0.80 [0.72-0.89], p <0.0001). On the other hand, GLP-1 RAs did not show significant difference with high heterogeneity (0.88 [0.74-1.04], p =0.15, I^2=58%) (Figure 1). The network meta-analysis did not show significant difference between SGLT-2 inhibitors and GLP-1 RA (0.90 [0.77-1.08]) (Figure 2).

Conclusions: In patients with type 2 DM and CKD, SGLT-2 inhibitors were associated with decreased risk of MACE, but GLP-1 RA did not. Network meta-analysis did not reveal significant difference between SGLT-2 inhibitors and GLP-1 RA.





PO1014

Comparative Effectiveness of SGLT2 Inhibitors vs. Other Antihyperglycemics on Risk of Kidney Outcomes: A Cohort Study

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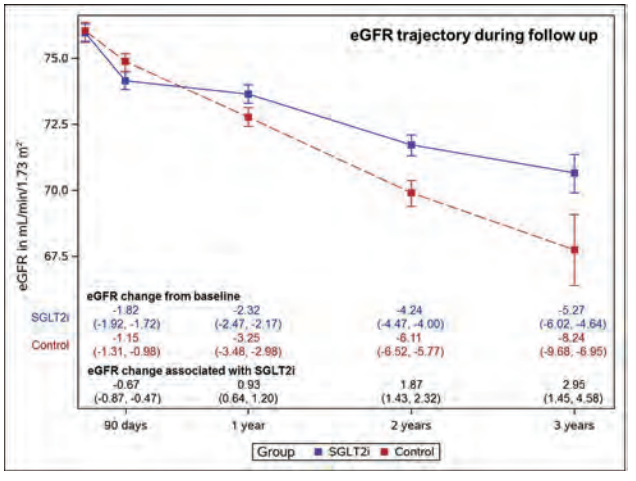
Background: In randomized controlled trials, sodium-glucose co-transporter-2 inhibitor (SGLT2i) reduced the risk of adverse kidney outcomes. We aimed to examine the comparative effectiveness of SGLT2i and other antihyperglycemics on the risk of major adverse kidney events (MAKE) of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease, or all-cause mortality.

Methods: We built a cohort of 379,191 new users of SGLT2i or other antihyperglycemics. Risk of MAKE during follow up served as the primary outcome. Pre-defined covariates and covariates identified by a high-dimensional variable selection algorithm were used to build a propensity score. Linear mixed models were used to estimate the longitudinal change of eGFR and body mass index (BMI) and survival analyses were used to estimate the risk difference of MAKE.

Results: Compared to other antihyperglycemics, SGLT2i use was associated with 0.98 (0.48, 1.53) ml/min/1.73m^2 less annual reduction in eGFR, 0.24 (0.17, 0.32) kg/m^2 more annual decrease in BMI, and reduced risk of MAKE (HR=0.68 (0.64-0.73)). SGLT2i use was associated with reduced risk of MAKE in eGFR≥90, ≥60 to <90, ≥45 to <60, and ≥30 to <45 ml/min/1.73m^2 and in participants with and without albuminuria. The association was evident in per-protocol analyses which required continuation of the antihyperglycemic medication during follow up (HR=0.64 (0.60-0.70)), and in analyses requiring concurrent use of metformin in at least the first 90 days of follow up (HR=0.63 (0.57-0.69)).

Conclusions: Among people with diabetes mellitus type 2, SGLT2i use was associated with eGFR preservation, greater decline in BMI, and reduced risk of MAKE compared to other antihyperglycemics.

Funding: Veterans Affairs Support



PO1015

Correlation of Anti-Albuminuric Effect by SGLT2 Inhibitor with Tubulointerstitial Impairment

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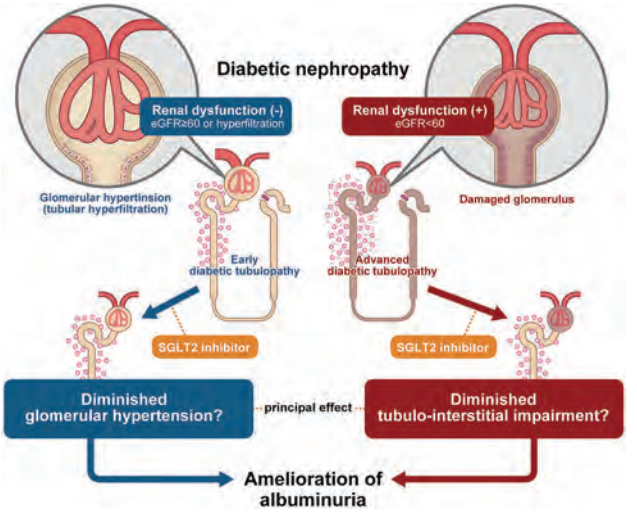
Background: This study aimed to examine the anti-albuminuric effect of SGLT2 inhibitor (SGLT2i) in patients with or without renal dysfunction, and to investigate factors associated with the effect of SGLT2i.

Methods: Patients with diabetic nephropathy were enrolled and received 50 mg of Iplagliflozin. Their blood and urine were sampled at 0 M, 1 M and 12 M. Patients with renal dysfunction (DF; eGFR<60) and with normo-renal function (NF; eGFR≥60) were separately analyzed.

Results: In all patients (n=22), urine albumin-to-Cr ratio (ACR) was reduced at 1M and maintained until 12M (median: 236.2 at 0M, 115.0 mg/gCr at 1M), however, eGFR was not changed. In DF, ACR was also decreased (median: 311.8 at 0M vs 107.0 mg/gCr at 1M, n=10). In NF, ACR was similarly decreased at 1M. Next, the patients in DF and NF were divided by %ACR reduction (high responder: HR, low responder: LR). In NF, only %change of eGFR at 12M was significantly different (-6.5±8.6% in HR vs +5.0±7.6% in LR). In DF, MCP-1 at 1M (-33.0±7.3% in HR vs +45.9±33.1% in LR) and %change of NAG at 12M showed significant difference (-33.6±13.5% in HR vs +6.8±28.3% in LR), however, there was no difference in eGFR. Univariate analysis showed significant correlation between %ACR reduction and %MCP-1 at 1M (R=0.734, p=0.016) or %NAG at 12M (R=0.714, p=0.047) in DF whereas no significant correlation was observed in NF. Multivariate analysis confirmed the results.

Conclusions: In patients with normo-renal function, restoring glomerular hyperfiltration might be important for anti-albuminuric effect of SGLT2i. However, in patients with renal dysfunction, the effect of SGLT2i seemed to be associated with reduced tubulointerstitial damages.



Anti-albuminuric effect of SGLT2 inhibitor in patients with or without renal dysfunction

PO1016

SGLT2i Prescribing for Type 2 Diabetes and Comorbid Conditions Among 24 US Healthcare Organizations

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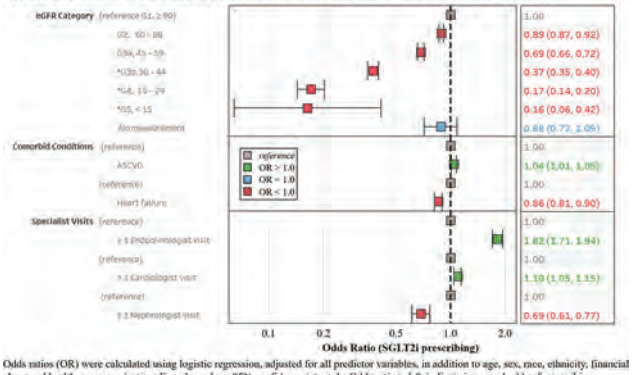
Background: Sodium glucose cotransporter-2 inhibitors (SGLT2i) are among several glucose-lowering therapies available. Clinical guidelines for type 2 diabetes recommend use of SGLT2i for people with ASCVD, heart failure (HF), or CKD when eGFR is adequate, to control glycemia, reduce cardiovascular risk, and slow progression of kidney disease.

Methods: Using an EHR-derived dataset from 24 AMGA member health care organizations (HCOs), we identified 248,469 patients with type 2 diabetes aged 18–85 who had ≥1 ambulatory encounter with a primary care provider and ≥1 prescription for a glucose-lowering medication other than metformin and insulin in the past year (9/2018–8/2019). Patients with end stage kidney disease or hospice care were excluded. We explored the proportion of patients with an SGLT2i prescribed in the past year, and used logistic regression to describe differences by eGFR category, comorbid conditions, and specialist visits, adjusted for all predictor variables, age, sex, race, ethnicity, financial class, and HCO.

Results: Across HCOs, median proportion of patients with an SGLT2i prescribed was 22% (range, 12–39%). Prescribing decreased with eGFR category from G1 to G4 (Figure 1). SGLT2i prescribing was lower for patients with HF and those who saw a nephrologist, marginally higher for patients with ASCVD and those who saw a cardiologist, and substantially higher for patients who saw an endocrinologist.

Conclusions: There was significant variation in SGLT2i prescribing across HCOs. While guidelines emphasize use of SGLT2is among patients with ASCVD, HF, or CKD, our findings suggest these recommendations have not been widely adopted in clinical practice. Endocrinologists may play an important role in prescribing new glucose-lowering medications, while nephrologists may be hesitant to prescribe medications for type 2 diabetes.

Figure 1: Association of eGFR category, comorbid conditions, and specialist visits with SGLT2i prescribing



Odds ratios (OR) were calculated using logistic regression, adjusted for all predictor variables, in addition to age, sex, race, ethnicity, financial class, and health care organization. Error bars show 95% confidence intervals. Odds ratio > 1.0 indicate increased odds of prescribing. eGFR was calculated from serum creatinine measurements using the CKD-EPI equation, reported in mL/min/1.73m². Reference groups for specialist visits are patients with no visits with the respective specialist.
* Indications for SGLT2i initiation and continued use vary by individual medication within the class for eGFR G3b, and are contraindicated for eGFR G4+.

PO1017

Dulaglutide and Kidney Function-Related Outcomes in Type 2 Diabetes: Post Hoc Analysis from the REWIND Trial

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Background: Over the median follow-up of 5.4 years in the REWIND trial, which included participants with type 2 diabetes (T2D) and multiple cardiovascular (CV) risk factors, dulaglutide (DU) use was associated with a reduction in composite renal outcomes, defined as the first occurrence of new macroalbuminuria, sustained decline in estimated glomerular filtration rate (eGFR) of ≥30% (using the modification of diet in renal disease [MDRD] equation), or chronic renal replacement therapy. This posthoc analysis evaluated the potential effects of dulaglutide on renal outcomes using an alternative endpoint definition that is commonly used in renal outcomes studies; defined as the composite endpoint of sustained eGFR decline ≥40% (using the chronic kidney disease-epidemiology collaboration [CKD-EPI] equation), end-stage renal disease (ESRD), or all-cause death.

Methods: REWIND participants were randomized (1:1) to DU 1.5 mg once weekly or placebo. Cox proportional hazards model for time-to-first event analysis was used to determine the risk of renal outcomes. Subgroup analyses were conducted by baseline eGFR and albuminuria status.

Results: At baseline, treatment groups had similar eGFR values (mean±SD: DU=77.6 ± 19.4 mL/min/1.73 m²; placebo=77.1 ± 19.6 mL/min/1.73 m²). The incidence rate of the composite endpoint was significantly lower for the DU group compared with placebo. This effect was consistent regardless of baseline eGFR or albuminuria status (Table).

Conclusions: Treatment with DU 1.5 mg was associated with a 17% risk reduction in the composite renal outcome, suggesting potential delay in progression of diabetic kidney disease in patients with T2D at CV risk.

Funding: Commercial Support - Eli Lilly and Company

Table: Kidney function-related outcomes with dulaglutide 1.5 mg treatment

Endpoint	Dulaglutide N=4949 n (%) or n/N (%)	Placebo N=4952 n (%) or n/N (%)	Hazard Ratio (95% CI)	P value
Composite endpoint				
Sustained eGFR[a] decline ≥40%, ESRD[b], all-cause death	676 (13.7%)	800 (16.2%)	0.83 (0.75, 0.92)	<0.001
Composite endpoint components				
Sustained eGFR[a] decline ≥40%	156 (3.2%)	214 (4.3%)	0.72 (0.58, 0.88)	0.002
ESRD[b]	31 (0.6%)	43 (0.9%)	0.78 (0.49, 1.25)	0.308
Renal replacement therapy	16 (0.3%)	21 (0.4%)	0.85 (0.44, 1.65)	0.626
Sustained eGFR<15[c] mL/min/1.73m²	21 (0.4%)	32 (0.6%)	0.69 (0.39, 1.21)	0.191
All-cause death	536 (10.8%)	592 (12.0%)	0.90 (0.80, 1.01)	0.072
Subgroup analysis for the composite endpoint				
eGFR ≥60 mL/min/1.73 m²	438/3904 (11.2%)	534/3870 (13.8%)	0.80 (0.70, 0.90)	Interaction P=0.205
eGFR <60 mL/min/1.73 m²	225/944 (23.8%)	257/988 (26.0%)	0.92 (0.77, 1.10)	
UACR <30 mg/g	276/2917 (9.5%)	321/2863 (11.2%)	0.84 (0.72, 0.99)	Interaction P=0.893
UACR ≥30 mg/g	364/1707 (21.3%)	428/1760 (24.3%)	0.86 (0.74, 0.98)	

[a]eGFR was calculated using CKD-EPI equation; Sustained eGFR decline ≥40% is based on two consecutive eGFR values. [b]ESRD is defined as renal replacement therapy (chronic dialysis or renal transplant) or sustained eGFR<15. [c]Sustained eGFR<15 defined as two consecutive eGFR values <15 mL/min/1.73 m²; eGFR units: mL/min/1.73 m². ESRD=end stage renal disease; N=total number of patients, n=number of patients with events; UACR=urinary albumin/creatinine ratio.

PO1018

Efficacy and Safety of Cotadutide, a Dual GLP-1 and Glucagon Receptor Agonist, for Patients with Type 2 Diabetes Mellitus and CKD

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Background: Cotadutide is in development for nonalcoholic steatohepatitis and type-2 diabetes mellitus (T2DM). GLP-1 analogues have been shown to delay the development of macroalbuminuria in patients (pts) with T2DM. The glycemic and renal effects of cotadutide were assessed in a phase 2a, randomized, controlled trial.

Methods: The trial enrolled 41 pts with T2DM (HbA1c: ≥6.5—≤10.5%) and chronic kidney disease (CKD) stage G3 (estimated glomerular filtration rate [eGFR]: ≥30–<60 mL/min/1.73m²), on insulin and/or oral therapy, with a BMI of 25—45 kg/m². Pts were randomized to once-daily subcutaneous cotadutide (n=21), titrated up to 300 μg, or placebo (PBO; n=20) for 32 days. Endpoints included glucose response via mixed meal tolerance test (MMTT), HbA1c, body weight (BW), eGFR, urinary albumin creatinine ratio (UACR), and C-peptide levels. The trial was powered based on a 2-sided alpha of 0.1.

Results: Cotadutide significantly reduced MMTT glucose AUC vs baseline (-26.7%, 90% CI: -34.6 to -18.8) and vs PBO (3.7%, 90% CI: -3.8 to 11.2; $P<0.001$), with a 35.2% reduction in insulin dose ($P=0.012$). Cotadutide significantly reduced BW (-3.7%) and HbA1c (-0.7%; both $P<0.001$). After 32 days of cotadutide treatment, no significant changes were observed in eGFR or blood pressure. Fasting C-peptide levels in the cotadutide group increased significantly vs PBO (LS mean change: 0.88 μg/L, 90% CI: 0.57 to 1.19, $P<0.001$). In pts with baseline micro- or macroalbuminuria (n=18), UACR was reduced by 50.6% vs PBO ($P=0.0504$). Serious adverse events (AEs) were balanced between treatment arms; treatment-related AEs were more frequent with cotadutide (71%) vs PBO (35%). The most common AEs were nausea (cotadutide, 33%; PBO, 20%) and vomiting (cotadutide, 24%; PBO, 5%). Pulse rate was significantly increased (11 beats per minute; $P<0.001$) by day 32.

Conclusions: In pts with T2DM and CKD, cotadutide improved overall glycemic control and glucose responses to an MMTT with acceptable tolerability. Improvements in albuminuria suggest that cotadutide may be beneficial in this population to slow long-term progression of CKD. Further exploration of this effect is warranted.

Funding: Commercial Support - AstraZeneca

PO1019

Dulaglutide Treatment in Patients with Type 2 Diabetes and Moderate-to-Severe CKD Improves Kidney Fibrosis Biomarker Levels

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Background: The AWARD-7 clinical trial demonstrated that once-weekly dulaglutide slowed the decline in estimated glomerular filtration rate (eGFR) and decreased urine albumin/creatinine ratio compared to insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (CKD). Lower levels of urinary C3M (a marker for type III collagen degradation) and increased level of serum PRO-C6 (a marker for type VI collagen formation) are reported to correlate with CKD progression and lower eGFR.

Methods: This exploratory analysis evaluated changes in urinary C3M and serum PRO-C6 with dulaglutide 1.5 mg treatment as compared to insulin glargine in AWARD-7 in overall study population and the macroalbuminuria subgroup.

Results: At baseline, the macroalbuminuria subgroup had numerically higher serum PRO-C6 levels and lower urinary C3M levels than the total population for both treatment groups. At baseline, both biomarker levels were comparable between treatment groups. At week 26 and 52 of treatment in the overall population, urinary C3M levels were significantly elevated and serum PRO-C6 levels were significantly reduced in the dulaglutide 1.5 mg group compared with insulin glargine group. These effects were consistent in participants with baseline macroalbuminuria (Table).

Conclusions: Dulaglutide was associated with decreased levels of biomarkers for type VI collagen formation and increased type III collagen degradation, suggesting a potential effect to reduce kidney fibrosis. These anti-fibrotic effects could be a potential mechanism for the beneficial effects observed with dulaglutide treatment on CKD in type 2 diabetes.

Funding: Commercial Support - Eli Lilly and Company

Table: Changes in kidney fibrosis biomarker levels on treatment with dulaglutide 1.5 mg and insulin glargine in total population and in macroalbuminuria subgroup.

Parameters		Overall study population				Participants with baseline macroalbuminuria (Baseline UACR >300 mg/g)			
		Dulaglutide 1.5 mg		Insulin Glargine		Dulaglutide 1.5 mg		Insulin Glargine	
		N	LSM ± SE (ng/mL)	N	LSM ± SE (ng/mL)	N	LSM ± SE (ng/mL)	N	LSM ± SE (ng/mL)
Serum PRO-C6	Baseline	157	15.2 ± 0.4	172	16.0 ± 0.4	65	19.4 ± 0.9	77	20.5 ± 0.9
	Week 26 % CFB	149	-4.6 ± 1.9[#]	163	5.7 ± 2.0	60	-2.0 ± 3.5[#]	74	15.2 ± 3.9
	Week 52 % CFB	150	-0.2 ± 2.2[#]	150	8.0 ± 2.3	62	3.3 ± 3.8[#]	64	19.8 ± 4.3
Urinary C3M	Baseline	108	22.9 ± 1.7	109	21.3 ± 1.6	47	18.8 ± 1.9	55	16.6 ± 1.6
	Week 26 % CFB	89	10.9 ± 8.2[#]	98	-10.0 ± 8.5	37	18.5 ± 13.3[#]	49	-8.9 ± 9.0
	Week 52 % CFB	100	20.7 ± 8.8[#]	90	-16.9 ± 8.4	44	7.1 ± 12.1[#]	44	-20.4 ± 8.8

Results were analyzed in the safety population using a model of mixed effects for repeated measures of log transformed values with the following covariates: baseline biomarker value, eGFR, HbA1c, blood pressure, categorical groups indicating geographical region/macroalbuminuria, CKD stage, treatment, time, and treatment by time. *p<0.05 vs. insulin glargine; #p<0.01 vs. insulin glargine. CFB=change from baseline; UACR=urine albumin-to-creatinine ratio.

PO1020

Once-Weekly Exenatide Effects on eGFR Slope and Urine Albumin-to-Creatinine Ratio (UACR) as a Function of Baseline UACR: An EXSCEL Post Hoc Analysis

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Background: GLP-1 RA effects on major kidney outcomes in unselected T2D patients at high cardiovascular (CV) risk are modest or neutral. However, GLP-1 RA may provide renal benefits in those at high risk of worsening kidney disease. We examined once-weekly exenatide (EQW) effects on eGFR slope and UACR change, as a function of baseline UACR, in a subset of EXSCEL participants.

Methods: Of 14752 EXSCEL participants, eGFR slope was assessed in those with baseline UACR and ≥1 post-baseline eGFR (n=3503 [23.7%]) via mixed model repeated measures (MMRM) analysis (median follow-up 3.3 years). UACR percent change from baseline to first post-baseline measurement (median time 8.9 months) was assessed in those with baseline and ≥1 follow-up UACR (n=2828 [19.2%]) via ANCOVA of log-transformed UACR, with baseline UACR as a covariate.

Results: Participants with baseline UACR measurements were generally similar to the overall EXSCEL population, and balanced across treatment arms. EQW improved eGFR slope, compared with placebo, in patients with baseline UACR>100mg/g (+0.79 mL/min/1.73m2/year [95% CI 0.24–1.34]) and UACR>200mg/g (+1.32 mL/min/1.73m2/year 95% CI [0.57–2.06], but not at lower UACR thresholds (Figure A). No difference in EQW effect on eGFR was observed as a function of baseline eGFR, CV disease history, RAAS inhibitor use, or SBP. EQW, compared with placebo, reduced UACR by 28.2% in patients with baseline UACR>30 mg/g. This effect was consistent in subgroups with higher baseline UACR (baseline UACR>100 mg 22.5%; baseline UACR>200 mg 34.5%) (Figure B).

Conclusions: This post-hoc EXSCEL analysis suggests that EQW reduces UACR, with improvement in eGFR slope specifically in participants with elevated baseline UACR.

Funding: Commercial Support - AstraZeneca

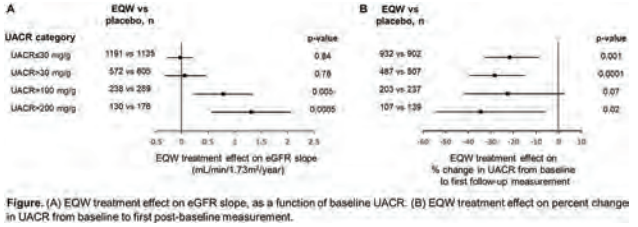

Figure. (A) EQW treatment effect on eGFR slope, as a function of baseline UACR. (B) EQW treatment effect on percent change in UACR from baseline to first post-baseline measurement.

PO1021

Hemoglobin A_{1c} Reduction with the GLP-1 Receptor Agonist Semaglutide Is independent of Baseline eGFR: Post Hoc Analysis of SUSTAIN and PIONEER Programs

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Background: Hyperglycemia is an established risk factor for the development and progression of chronic kidney disease. The glucagon-like peptide-1 receptor agonist semaglutide is approved for the treatment of type 2 diabetes (T2D) across a wide range of estimated glomerular filtration rates (eGFRs). We investigated whether baseline eGFR affected glycated hemoglobin (HbA_{1c}) reduction with semaglutide.

Methods: This *post hoc,* trial-level analysis considered all SUSTAIN (1–10) and PIONEER (1–10) trials where renal impairment was not an exclusion criteria and where the number of subjects receiving semaglutide with eGFR <60 mL/min/1.73m² was >10. It included data for once-weekly subcutaneous semaglutide (SUSTAIN 4–6, pooled 0.5 and 1.0 mg; SUSTAIN 10, 1.0 mg only) and once-daily oral semaglutide (PIONEER 5 and 6, 14 mg); comparator data were not analyzed. Subjects receiving semaglutide were grouped by baseline eGFR; the eGFR subgroups evaluated were selected according to number of subjects meeting eGFR cut-offs (≥60 and <60 mL/min/1.73 m² in SUSTAIN 4, 5, and 10; <45, 45 to <60 and ≥60 mL/min/1.73 m² in SUSTAIN 6 and PIONEER 5 and 6). Within each trial, absolute estimated change in HbA_{1c} from baseline to end of treatment (EOT) was compared between eGFR subgroups using a linear mixed model.

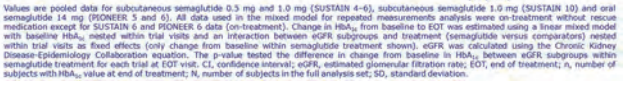
Results: Mean HbA_{1c} at baseline ranged from 7.9% to 8.7% across the subgroups. Semaglutide significantly reduced HbA_{1c} at a comparable magnitude across eGFR subgroups in all trials (mean reduction of 1.0–1.7% from baseline to EOT; p>0.148 for difference between eGFR subgroups within each trial; Figure).

Conclusions: Semaglutide (subcutaneous and oral) is an effective glucose-lowering agent in subjects with T2D, independently of baseline eGFR, including in those with chronic kidney disease.

Funding: Commercial Support - Novo Nordisk

Mean change in HbA_{1c} from baseline to end-of-treatment by eGFR subgroup for semaglutide in SUSTAIN 4–6 and 10 and PIONEER 5 and 6

Trial and eGFR subgroup, (mL/min/1.73 m²)	Trial duration (weeks)	Mean (SD) baseline eGFR (mL/min/1.73 m²)	Mean (SD) baseline HbA_{1c} (%)	n/N	Mean change in HbA_{1c} from baseline to EOT (%-point)	[95% CI]	Semaglutide by eGFR groups	p-value
SUSTAIN 4	30							
<60		52.7 (6.5)	8.2 (1.0)	22/29	−1.7	[−2.1;−1.3]		0.15
≥60		97.9 (15.7)	8.2 (0.9)	549/693	−1.4	[−1.5;−1.3]		
SUSTAIN 5	30							
<60		50.6 (7.6)	8.3 (0.9)	18/20	−1.6	[−2.0;−1.2]		0.94
≥60		93.4 (15.3)	8.4 (0.8)	201/243	−1.6	[−1.8;−1.5]		
SUSTAIN 6	104							
<45		34.1 (8.2)	8.6 (1.4)	137/193	−1.4	[−1.6;−1.2]		0.49
45 to <60		52.6 (4.2)	8.6 (1.4)	155/223	−1.4	[−1.6;−1.2]		
≥60		86.8 (13.7)	8.7 (1.5)	900/1,215	−1.4	[−1.5;−1.3]		
SUSTAIN 10	30							
<60		49.4 (6.9)	8.1 (0.9)	8/14	−1.7	[−2.1;−1.2]		0.95
≥60		94.6 (14.5)	8.2 (1.0)	233/276	−1.7	[−1.8;−1.6]		
PIONEER 5	26							
<45		37.8 (4.8)	8.0 (0.8)	54/65	−1.2	[−1.5;−1.0]		0.71
45 to <60		51.3 (3.9)	8.0 (0.7)	60/83	−1.1	[−1.3;−0.9]		
≥60		65.5 (5.8)	7.9 (0.7)	12/15	−1.1	[−1.5;−0.6]		
PIONEER 6	≤83							
<45		37.4 (5.8)	8.0 (1.5)	121/167	−1.1	[−1.3;−0.9]		0.28
45 to <60		52.3 (4.4)	8.1 (1.6)	217/267	−1.0	[−1.2;−0.9]		
≥60		84.5 (13.6)	8.2 (1.6)	952/1,150	−1.1	[−1.1;−1.0]		



Values are pooled data for subcutaneous semaglutide 0.5 mg and 1.0 mg (SUSTAIN 4–6), subcutaneous semaglutide 1.0 mg (SUSTAIN 10) and oral semaglutide 14 mg (PIONEER 5 and 6). All data used in the mixed model for repeated measurements analysis were on-treatment without rescue medication except for SUSTAIN 6 and PIONEER 6 data (on-treatment). Change in HbA_{1c} from baseline to EOT was estimated using a linear mixed model with baseline HbA_{1c} nested within trial visits and an interaction between eGFR subgroups and treatment (semaglutide versus comparators) nested within trial visits as fixed effects (only change from baseline within semaglutide treatment shown). eGFR was calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation. The p-value tested the difference in change from baseline in HbA_{1c} between eGFR subgroups within semaglutide treatment for each trial at EOT visit. CI, confidence interval; eGFR, estimated glomerular filtration rate; EOT, end of treatment; n, number of subjects with HbA_{1c} value at end of treatment; N, number of subjects in the full analysis set; SD, standard deviation.

PO1022

Effects of Semaglutide on CKD Outcomes: A Post Hoc Pooled Analysis from the SUSTAIN 6 and PIONEER 6 Trials

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Background: The SUSTAIN 6 cardiovascular outcomes trial (CVOT) indicated a benefit on kidney disease with subcutaneous (s.c.) once-weekly (OW) semaglutide vs placebo (PBO) in subjects with type 2 diabetes (T2D) at high CV risk. The PIONEER

6 CVOT reported CV safety with oral once-daily (OD) semaglutide in a similar cohort. This *post hoc* analysis evaluated the potential benefit of semaglutide vs PBO on chronic kidney disease (CKD) outcomes.

Methods: Data from 6,480 subjects (SUSTAIN 6: N=3,297; median follow-up, 2.1 years; mean baseline [BL] estimated glomerular filtration rate [eGFR], 76 mL/min/1.73 m^2; PIONEER 6: N=3,183; median follow-up, 1.3 years; mean BL eGFR, 74 mL/min/1.73 m^2) were pooled for semaglutide (0.5 and 1.0 mg s.c. OW, 14 mg oral OD) or PBO. Time to onset of persistent eGFR reduction (≥30, ≥40, ≥50, ≥57% [corresponding to doubling of serum creatinine]) was evaluated overall and by BL eGFR subgroup (≥30–<60, ≥60 mL/min/1.73 m^2). Analyses used a Cox proportional-hazards model with treatment group and eGFR subgroup and interaction between both as fixed factors stratified by trial.

Results: In the overall population, hazard ratios (HRs) for onset of persistent eGFR reductions with semaglutide vs PBO were not statistically significantly different from 1, but estimated HRs were <1.0, favoring semaglutide. Estimated HRs for semaglutide vs PBO in the eGFR ≥30–<60 mL/min/1.73 m^2 subgroup were generally lower than in the overall population; semaglutide significantly reduced the risk of developing a persistent 30% eGFR reduction vs PBO (p=0.03; Figure). No significant interactions between treatment and eGFR subgroup were observed.

Conclusions: This analysis of semaglutide CVOTs supports the possibility of a smaller magnitude of eGFR decline with semaglutide vs PBO and suggests a potential kidney disease benefit of semaglutide vs PBO in people with T2D and established CKD.

Funding: Commercial Support - Novo Nordisk

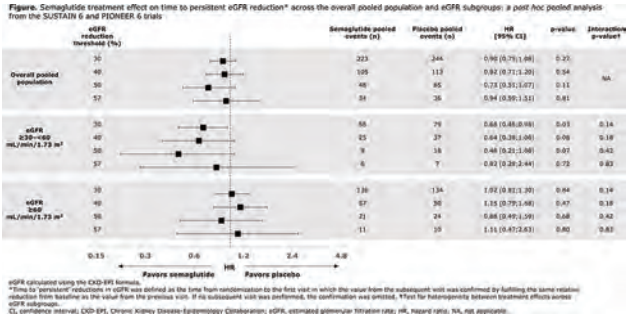

Figure. Semaglutide treatment effect on time to persistent eGFR reduction* across the overall pooled population and eGFR subgroups: *a post hoc pooled analysis from the SUSTAIN 6 and PIONEER 6 trials*

PO1023

Impacts of Glucagon-Like Peptide 1 Analogues and Sodium Glucose Cotransporter 2 Inhibitor on Type 2 Diabetes Patients with Renal Impairment

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Background: Diabetes mellitus (DM) is a progressive multifactorial disease associated with cardiovascular complications. To prevent the progression of cardiovascular complications in DM patients, we examined impact on cardiac function between glucagon like peptide-1(GLP-1) analogue and sodium-glucose cotransporter-2 (SGLT-2) inhibitors to treat type 2 diabetes patients with renal impairment.

Methods: A total of 156 type 2 DM patients with renal impairment were recruited for this study. All patients were divided into two groups according to the anti-diabetic agents at baseline : Group G; 0.9mg/day liraglutide, n=72, Group S; n=84; 5mg/day dapagliflozin, n=52, empagliflozin n=32. Blood glucose levels, glycosylated hemoglobin (HbA_1c), serum creatinine, and albuminuria were obtained 12 months before and every 3 months for 36 months. Echocardiography, cardio-ankle vascular index(CAVI) were obtained every 12 months for 36 months.

Results: HbA1c and systolic blood pressure were significantly decreased after ADAs. The eGFRs were gradually decreased in both groups. Albuminuria was decreased significantly after initiation of ADAs. Left ventricular mass index (LVMI) and left atrial volume index (LAVi) were significantly decreased in both groups. Cardiac systolic function indicated by ejection fraction and diastolic function indicated by E/e'or left atrial dimension were remained or improved only in group G. Moreover, arterial stiffness indicated by cardio-ankle vascular index (CAVI) was improved in group G (Table1).

Conclusions: These findings suggest that liraglutide and SGLT-2 inhibitor for type 2 DM patients with renal impairment have similar effects on renal function including eGFR and albuminuria and left ventricular and atrial volume. However, liraglutide could provide more benefit for arterial stiffness than SGLT-2 inhibitors.

Table 1 : Clinical Data

		at baseline	after 12 months	after 24 months	after 36 months
LVMI(g/m2)	Group G	135.8 ± 45.8	110.2 ± 30.3*	114.5 ± 41.5*	107.2 ± 38.2*
	Group S	130.0 ± 43.9	113.2 ± 36.5*	106.4 ± 34.2*	115.9 ± 29.5*
LAVI(mL/m2)	Group G	25.6 ± 6.7	22.3 ± 5.2*	21.4 ± 5.7*	20.8 ± 5.8*
	Group S	24.0 ± 3.5	21.8 ± 3.8*	21.7 ± 3.5*	22.7 ± 4.3**
E/e	Group G	12.9 ± 3.0	10.4 ± 2.5*	9.4 ± 2.4*	9.8 ± 3.1*
	Group S	12.4 ± 3.3	10.6 ± 3.9*	12.5 ± 3.7	12.9 ± 3.9
CAVI	Group G	10.2 ± 1.7	9.9 ± 1.3	9.9 ± 1.1	9.9 ± 1.2
	Group S	10.3 ± 2.0	10.5 ± 1.9	10.6 ± 1.7*†	10.6 ± 1.7*†

* : p<0.01, ** : p<0.05 vs at baseline, † : p<0.05 vs Group G

PO1024

AKI Associated with Semaglutide

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Introduction: Recently there have been post-marketing reports of AKI and worsening CKD in patients taking glucagon-like peptide-1 (GLP-1) receptor agonists. Clinical details of these patients have not been published. Herein we report two patients who suffered rapid worsening of renal function after being prescribed semaglutide (Ozempic).

Case Description: Patient 1. An 83-year-old woman with diabetes, hypertension, and CKD was seen in Apr 2020 for increasing leg edema. In Nov 2019 she had been prescribed weekly semaglutide injections. At that time serum creatinine was 1.59 mg/dL (eGFR 30 mL/min/1.73m^2) and serum albumin 3.3 g/dL. Rate of decline of eGFR for the previous 6 years had been 1.5 mL/min/1.73m^2/yr. Attempts to increase the dose of semaglutide from 0.25 mg to 0.5 mg resulted in nausea and vomiting the day following the injection, so the drug had been stopped at the end of March 2020. She had no intercurrent illnesses, hospitalizations, or change in other medications. Examination revealed BP 162/82 and 3+ peripheral edema. Serum creatinine was 3.50 mg/dL (eGFR 11), serum albumin 2.9 g/d, and urine protein/creatinine ratio (UPCR) 4.9 g/g. Urinalysis revealed 3+ protein. Renal biopsy showed diffuse and nodular glomerulosclerosis with acute interstitial lymphocytic and eosinophilic infiltration and acute tubular injury. There has been no recovery of renal function in the 2 months since semaglutide was discontinued. **Patient 2.** A 65-year-old male with diabetes, hypertension, and CKD was initially seen in 2012 for CKD management. BP was well controlled and eGFR stable in the 30-35 range with UPCR of 400-500 mg/g for the next 7 years. In Nov 2019 he was started on weekly semaglutide 0.25 mg increased after 2 weeks to 0.5 mg, after which eGFR decreased to 22 in Mar 2020 accompanied by an increase in UPCR to 1333. The patient denied GI symptoms but did complain of decreased appetite and fatigue. Semaglutide was stopped with resolution of symptoms. His most recent eGFR is 24.

Discussion: AKI has been observed in both clinical trials with GLP-1 receptor agonists and post-marketing clinical experience. Most of these events have occurred in patients who experience adverse GI symptoms. To our knowledge, Patient 1 is the first reported case with biopsy findings. Patients developing new symptoms after starting semaglutide should have laboratory tests performed and the drug discontinued if there is worsening renal function.

PO1025

Association of Atrasentan Plasma Exposure with Variability in Responses in Proxies of Kidney Protection and Fluid Retention: A Post Hoc Analysis of the SONAR Trial

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Background: Atrasentan reduced urinary albumin:creatinine ratio (UACR) and the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease in the SONAR trial. However, in this high risk population, atrasentan was also associated with fluid retention in some patients. We evaluated whether plasma exposure to atrasentan could explain between-patient variability in UACR response, a surrogate for kidney protection, and in B-type natriuretic peptide (BNP), as a biomarker of fluid expansion.

Methods: All patients received 0.75 mg atrasentan for six weeks in the active run-in (enrichment) period. Individual area under the concentration time curve (AUC) was estimated using a population pharmacokinetic model. Subsequently, the association between atrasentan AUC as well as baseline clinical characteristics with UACR and BNP response was estimated with linear regression in univariable and multivariable analyses.

Results: The median atrasentan AUC was 43.8 ng.h/mL which varied considerably among patients [2.5^{th}-97.5^{th} percentiles: 12.6 to 197.5 ng.h/ml]. Median UACR change at the end of enrichment was -36% and BNP change was 8.7%, which also varied among patients [UACR; 2.5^{th}-97.5^{th} percentiles: -76.2 to 44.5%; BNP;-71.5 to 300.0%]. Atrasentan AUC, along with certain clinical characteristics at baseline such as age, eGFR, and hemoglobin, was independently associated with greater UACR reduction (β -7.0% per ng.h/ml AUC; p<0.01) and greater BNP increase (β 4.5% per ng.h/ml AUC; p<0.01).

Conclusions: Atrasentan plasma exposure varied among individual patients and in addition to other patient characteristics, explained the between-patient variability in UACR and BNP response.

Funding: Commercial Support - The SONAR trial was sponsored by Abbvie

PO1026

Effect of Oral Supplementation with Curcumin in Diabetic Subjects with Proteinuric Kidney Disease: A Randomized Controlled Trial

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Background: Proteinuria remains one of the most important risk factors associated with kidney disease progression. Curcumin is a powerful antioxidant, and different studies have demonstrated the increased expression of cytoprotective proteins through the Keap1/NrF pathway. We conducted a randomized controlled trial in proteinuric diabetic patients to assess the effect of curcumin on proteinuria

Methods: The trial was conducted between May, 2016 and September, 2019. We included diabetic patients over 18 years of age, with an estimated GFR by CKD EPI > 15 ml/min/1.73 m2 and proteinuria > 1 gram/g despite optimal dose or contraindication to RAAS blockade. We excluded patients without DM, renal replacement therapy, kidney transplantation, or pregnancy. The study group received 3.22g of turmeric powder equivalent to 1.67g of curcumin, divided into three doses every 8 hours for 24 weeks. Primary outcome was proteinuria at the end of follow up. Secondary outcomes included eGFR and blood pressure control. Our power calculation estimated a total of 100 patients. Results were analyzed on an intention to treat basis

Results: 100 diabetic patients were included. The mean age was 58.1 ± 10.3 years, 67% were female, 98% were hypertensive and the mean eGFR and 24h proteinuria were 35.9 ± 16.5 ml/min/1.73 m2 and 4.0±2.9 g/g, respectively. After 24 weeks of follow up, no significant differences were observed between groups for proteinuria, eGFR or blood pressure control (Table 1)

Conclusions: In this randomized double blinded controlled trial in diabetic subjects with nephrotic range proteinuria and moderate CKD, curcumin administration was not effective in proteinuria reduction or eGFR preservation. ClinicalTrials.gov Identifier: NCT03019848

Funding: Government Support - Non-U.S.

Table 1. Results

	Total Cohort (N=100)	Curcumin (N=54)	Placebo (N=46)	P
Age (years)	58.1 ± 10.3	59.3 ± 9.3	57.4 ± 11.4	NS
Gender(M/F)	33 / 67	31 / 23	36 / 10	p < 0.05
Hypertension (N / %)	98 / 98	54 / 55.1	44 / 44.8	NS
Baseline eGFR (ml/min/1.73m2)	35.9 ± 16.5	34.3 ± 15.7	37.8 ± 17.3	NS
Final eGFR (ml/min/1.73m2)	33.7 ± 15.4	34.6 ± 15.9	32.5 ± 14.8	NS
Baseline 24h proteinuria (g/g)	4.1 ± 3.4	3.8 ± 3.3	4.5 ± 3.5	NS
Month 3 proteinuria (g/g)	4.2 ± 5.1	4.2 ± 6.2	4.2 ± 3.4	NS
Final Proteinuria (g/g creatinina)	3.5 ± 2.8	3.5 ± 2.9	3.6 ± 2.7	NS
Baseline SBP (mmHg)	139 ± 18	138 ± 19	139 ± 18	NS
Final SBP (mmHg)	138 ± 18	140 ± 17	136 ± 20	NS
Baseline DBP (mmHg)	81 ± 12	81 ± 12	81 ± 11	NS
Final DPB (mmHg)	74 ± 8	75 ± 7	73 ± 8	NS

PO1027

Effect of Praliciguat, a Once-Daily, Oral Soluble Guanylate Cyclase Stimulator, on Albuminuria in Patients with Diabetic Kidney Disease: A Randomized, Double-Blind, Phase 2 Trial

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Background: Impaired nitric oxide (NO) signaling has been implicated in the progression of diabetic kidney disease (DKD). Praliciguat (PRL) is a soluble guanylate cyclase stimulator that amplifies NO signaling in vitro and reduces proteinuria and fasting plasma glucose in the ZSF1 rat model of DKD.

Methods: We evaluated the safety and efficacy of PRL in adults (25-75 y) with type 2 diabetes, eGFR 30-75 mL/min/1.73 m^2, urine albumin creatinine ratio (UACR) 200-5000 mg/g, hemoglobin A1c (HbA1c) <12%, systolic blood pressure (BP) 110-160 mmHg, on stable glucose-lowering and renin angiotensin system-inhibition therapy. Participants were randomized 1:1:1 to placebo (PBO), PRL 20 mg, or PRL 40 mg daily for 12 weeks. Two first morning void specimens for UACR were collected at baseline and weeks 1, 4, 8, 12. Adverse events, 24 h BP and serum chemistry were also assessed. The primary efficacy endpoint was change from baseline (CFB) in UACR to weeks 8 and 12 analyzed by mixed-effects repeated measures model to compare pooled PRL vs PBO.

Results: A total of 156 participants enrolled and 140 completed treatment. Of the 156, 66% were men, 71% were White, 24% Black, and 54% Latino. Model estimates of mean UACR CFB [90% CI] [intent-to-treat (ITT)] were -28% [-36, -18] for pooled PRL and -15% [-27, 0] for PBO; PBO-adjusted UACR CFB was -15% [-31, 4] (p=0.17). Quality checks identified a site with data inconsistent with that from the overall study population. In a post-hoc sensitivity analysis excluding this site, PBO-adjusted UACR CFB for PRL was -20% [-33,-5], nominal p=0.03. PBO-adjusted CFB for other variables at week 12 (ITT) were: 24 h systolic BP -4.2 mmHg [-7.5, -0.8], 24 h heart rate 3.4 bpm [1.6, 5.2], HbA1c -0.27% [-0.50,-0.03], and cholesterol -10.1 mg/dL [-19.2, -1.0]. Mediation analyses indicated that ~75% of the UACR decline was independent of SBP decrease. Both praliciguat doses were well tolerated.

Conclusions: PRL did not significantly reduce UACR in the primary ITT analysis, but favorable trends in UACR, BP, and metabolic variables warrant further clinical study of PRL in DKD.

Funding: Commercial Support - Cyclerion Therapeutics

PO1028

Preexisting CKD Increases Risk of Metformin Monotherapy Failure in US Veterans with Type 2 Diabetes

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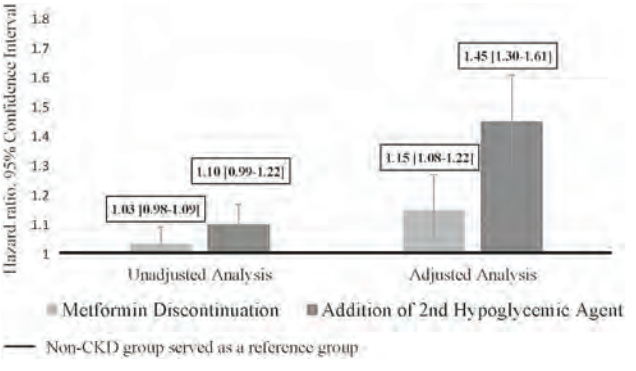
Background: Metformin (MET) is increasingly used for treatment of type 2 diabetes (T2D) in patients with chronic kidney disease stage 3 (CKD3); however, it is unknown if rates of MET monotherapy failure differs in patients with and without CKD3.

Methods: This was a retrospective study including 21,142 US Veterans with T2D and estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m^2 who initiated MET monotherapy between 01/2010 and 03/2017. CKD3 was established as eGFR 30-59 ml/min/1.73m^2. MET monotherapy failure defined as the 1st 90-day gap in MET refill (MET discontinuation) or the addition of 2nd hypoglycemic agent (HA) during 3-yr follow up was compared between patients without and with CKD3 using univariate and multivariate Cox regression analyses adjusted for case-mix.

Results: The mean ± SD age for the total cohort was 59.9 ±1 0.2 yrs, 94.3% were males, 79.7 and 17.3% were Whites and Blacks, respectively. Preexisting CKD3 was present in 1,363 (6.5%) patients. Baseline patients' characteristics were similar between two groups except CKD patients were older (68.7 vs. 59.3 yrs in non-CKD) and had lower eGFR (54.1 vs. 87.4ml/min1.73m^2 in non-CKD). In Kaplan-Meyer analysis there were no difference in rates of MET discontinuation or addition of 2nd HA in patients without and with CKD3 (p=0.2 and p=0.09, respectively). However, in the adjusted analyses, patients with CKD3 had a significantly higher risk of MET discontinuation or addition of 2nd line HA (HR, 95% CI 1.15, 1.08-1.22 and 1.45; 1.30-1.61, respectively), as compared with no CKD (Figure 1).

Conclusions: In newly treated patients with T2D the presence of preexisting CKD stage 3 was associated with increased risk of MET monotherapy failure. MET discontinuation may be expected in CKD3 patients with the prorgession of CKD; however, our findings of the increased risk of addition 2nd HA warrant further studies to understand whether hypoglycemic efficacy of MET monotherapy is reduced in CKD stage 3.



PO1029

Utilization of Glucose-Lowering Medications Among US Medicare Beneficiaries with CKD Between 2007 and 2016

Julie Zhao,[1,2] Eric D. Weinhandl,[1,2] Angeline M. Carlson,[1] Wendy L. St. Peter.[1,2] *[1]University of Minnesota, Minneapolis, MN; [2]Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN.*

Background: Selecting effective and safe glucose-lowering medications for chronic kidney disease (CKD) patients is challenging. Twelve classes of glucose-lowering medications are on the US market today. Information regarding utilization of glucose-lowering medications in patients with CKD is limited.

Methods: We evaluated an adult CKD population from Medicare 5% random sample 2007-2016, provided by the United States Renal Data System. Yearly cohorts of patients with CKD and type 2 diabetes were created. Descriptive statistics were used to report proportions of patients using glucose-lowering medications. To test overall trends in glucose-lowering medication classes, linear probability models with adjustment for age, sex, race/ethnicity, CKD stage, and low-income subsidy (LIS) status were used.

Results: Use of metformin, newer glucose-lowering medication classes (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors), and newer insulin analogs (aspart, lispro, glulisine, detemir, glargine, degludec) showed statistically significant upward trends during the study timeframe. Sitagliptin was the most commonly prescribed DPP-4 inhibitor; use increased from 5.6% in 2007 to 15.0% in 2016. Use of linagliptin (approved in 2011) increased from 0.1% in 2011 to 6.0% in 2016. Compared with other GLP-1 receptor agonists, use of liraglutide (approved in 2010) increased more (0.3% in 2010 to 3.6% in 2016), and use was higher in 2016. Use of SGLT2 inhibitors (canagliflozin, empagliflozin, or dapagliflozin) remained very low in 2016, but use was increasing. Use of newer analog insulin therapy increased, especially insulin detemir (2.4% in 2007 to 11.7% in 2016). Insulin was the most highly used single medication class in 2016. The most highly used dual combination therapies in 2016 were metformin and sulfonylureas and metformin and insulin. Combination therapy was less common as CKD stage increased.

Conclusions: Use of metformin and newer glucose-lowering medication classes is increasing in CKD patients with type 2 diabetes. We anticipate that percentages of CKD patients using these newer agents will increase.

PO1030

Role of Roxadustat in Improving Erythropoiesis-Stimulating Agent (ESA)-Resistant Anemia in Patients on Maintenance Hemodialysis

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Background: Roxadustat, an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, is shown to stimulate erythropoiesis thus improving iron metabolism. Again, while hyperglycemic states are known to be associated with a decreased tissue hypoxia response, to date, roxadustat has not been revaluated for its role in improving anemia in patients with or without diabetes in clinical settings.

Methods: A total of 64 hemodialysis patients being treated with epoetin α (9000 units weekly) participated in the study after giving informed consent. They were switched from intravenous epoetin α to oral roxadustat (100 mg 3 times weekly) therapy and were assessed 8 weeks later for improvements in anemia, as well as for changes in parameters for iron metabolism and C-reactive protein (CRP).

Results: The study included 39 patients without diabetes (mean age, 71.1 ± 12.1 years; mean dialysis vintage, 7.5 ± 7.4 years; mean GA, 16.2 ± 2.9%) and 27 patients with diabetes (mean age, 70.3 ± 10.3 years; mean dialysis vintage, 5.9 ± 5.5 years; mean GA, 24.9 ± 5.5%). As shown in Table, after 8 weeks the Hb concentration was significantly increased from 10.3 ± 0.8 g/dL at baseline to 10.7 ± 1.3 g/dL in patients without diabetes (P = 0.03) but was not increased in patients with diabetes (from 10.4 ± 0.6 at baseline to 10.5 ± 1.1 g/dL). Again, the serum iron, ferritin concentrations and the transferrin saturation ratio were decreased, irrespective of whether or not they had diabetes, with no change shown in serum CRP level.

Conclusions: Switching hemodialysis patients with ESA-resistant anemia from ESA to roxadustat led to improvements in anemia only in those without diabetes, while study results suggested the involvement of mechanisms, other than impaired iron utilization or inflammation, in the impairment of hematopoiesis in those with diabetes.

Funding: Private Foundation Support

Effects of Roxadustat on HD Patients without or with Diabetes

		without DM			with DM	
	Week 0	Week 4	Week 8	Week 0	Week 4	Week 8
Hb (g/dL)	10.3±0.8	10.9±1.2*	10.7±1.3*	10.4±0.6	10.4±1.0	10.5±1.1
iron (μg/dL)	53.3±17.7	49.1±25.7	45.6±20.1*	43.4±19.9	37.1±20.5*	37.6±24.9*
ferritin (g/dL)	49.7±36.2	40.7±47.5*	46.6±62.1	35.8±36.7	19.1±17.0*	15.6±22.2*
TSAT	0.19±0.05	0.15±0.08*	0.15±0.10*	0.16±0.06	0.12±0.07*	0.10±0.07*
CRP (mg/dL)	0.27±0.03	0.22±0.05	0.30±0.19	0.22±0.09	0.25±0.09	0.27±0.10

* p<0.05

PO1031

Efficacy and Safety of Roxadustat in Patients with Dialysis-Dependent CKD, Anemia, and Diabetes Mellitus

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Background: Roxadustat is an oral hypoxia inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Diabetes mellitus (DM) is a growing health problem often associated with CKD. The risk of cardiovascular (CV) events and CV mortality is significantly increased in patients with CKD and DM. Thus, evaluation of safety and efficacy of roxadustat in the subgroup of patients with CKD and DM is of clinical importance.

Methods: Pooled data from three pivotal, phase 3, randomized, open-label, epoetin alfa-controlled studies of roxadustat for the treatment of anemia in patients with dialysis-dependent (DD) CKD were assessed in patients with a history of DM at baseline. Efficacy endpoints were: mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy, time to first blood/RBC transfusion during the treatment period, and mean monthly IV iron use during weeks 28–52. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs)

Results: In the DD-CKD study population, 47% (1830/3890) of patients had DM (roxadustat 915; epoetin alfa 915). Baseline characteristics were generally similar between treatment groups. Mean (SD) Hb levels (g/dL) at baseline were 9.87 (1.15) in the roxadustat group and 9.88 (1.18) in the epoetin alfa group. Patients achieved a significantly larger least-squares mean (LSM) [SEM] CFB in Hb levels (g/dL) with roxadustat vs. epoetin alfa (0.94 [0.032] vs. 0.62 [0.031]), corresponding to a LSM difference of 0.32 (95% CI: 0.23, 0.40) (p<0.0001). Risk for blood/RBC transfusion was significantly reduced in the roxadustat vs. epoetin alfa group (HR, 0.72 [95% CI: 0.56, 0.93]; p=0.0121). Mean (SD) monthly IV iron (mg) use was lower in roxadustat- vs. epoetin alfa-treated patients: 58.0 (222.0) vs. 67.4 (146.5) (p<0.0001). TEAE rates were comparable between treatment groups and to those in the overall DD-CKD study population

Conclusions: Roxadustat was efficacious vs. epoetin alfa for increasing Hb levels, reducing the risk for blood/RBC transfusion, and lowering mean monthly IV iron use in patients with DD-CKD and DM. Safety and tolerability profiles were similar to the overall population and consistent with that observed in this patient subgroup.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO1032

Efficacy and Safety of Roxadustat in Patients with Non-Dialysis-Dependent CKD, Anemia, and Diabetes Mellitus

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Diabetes mellitus (DM) is a growing health problem often associated with CKD. In patients with DM, 37.0% have CKD (Stages 1–4), of which 52.5% have moderate-to-severe CKD (State 3 or 4). The risk of cardiovascular events and mortality is significantly increased in patients with CKD and DM. Thus, evaluation of the safety and efficacy of roxadustat in patients with CKD and DM is of clinical importance.

Methods: Pooled data from three pivotal, phase 3, randomized, double-blind, placebo-controlled studies of roxadustat for the treatment of anemia in patients with non–dialysis-dependent (NDD) CKD were assessed in the subgroup of patients with a history of DM at baseline. Primary and key secondary endpoints were mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy and time to first blood/RBC transfusion in the first 52 weeks, respectively. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs).

Results: In the NDD-CKD study population, 57% (2433/4277) of patients had DM (roxadustat=1337, placebo=1096). Baseline characteristics were generally similar between the treatment groups. Mean (SD) Hb levels (g/dL) at baseline were 9.12 (0.71) in the roxadustat group and 9.10 (0.71) in the placebo group. Patients achieved a larger mean (SD) CFB in Hb levels (g/dL) with roxadustat vs. placebo (1.81 [0.93] vs. 0.14 [0.98]), corresponding to a least-squares mean difference of 1.71 (95% CI: 1.61, 1.81) (p<0.0001). The risk for blood/RBC transfusion was significantly reduced in the roxadustat vs. placebo group (HR, 0.28 [95% CI: 0.21, 0.36]; p<0.0001). TEAE rates were comparable between treatment groups and with those reported in the overall NDD population.

Conclusions: Roxadustat was efficacious vs. placebo for increasing Hb levels and reducing the risk for blood/RBC transfusion in patients with NDD-CKD and DM. The safety and tolerability profile was similar to the overall NDD-CKD population.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO1033

Effects of Veverimer on Serum Bicarbonate and Physical Function in Patients with Diabetes and CKD: Subgroup Analysis from a Randomized Trial

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Background: Metabolic acidosis (MA) is a complication of CKD and has deleterious effects on kidney function, bone (demineralization), and muscle (protein catabolism). Patients (pts) with diabetes and CKD are prone to functional limitations that adversely affect their quality of life. Veverimer, an investigational non-absorbed polymer that binds gastrointestinal hydrochloric acid, is being developed to treat MA in CKD.

Methods: TRCA-301E is a multicenter, Phase 3, randomized, blinded, placebo-controlled trial in 196 pts with CKD (eGFR 20-40 ml/min/1.73 m^2) and MA (serum bicarbonate 12-20 mEq/L) who were treated for up to 1 yr with veverimer or placebo, with dose titration targeted to achieve a normal serum bicarbonate.

Results: Compared with placebo, veverimer significantly increased serum bicarbonate and significantly improved physical function as reported on the Kidney Disease and Quality of Life-Physical Function Domain (KDQOL-PFD) and the 5-times repeated chair stand test (RCS) with a safety profile that was similar to placebo (Wesson, *The Lancet* 2019). In the subgroup with diabetes (n=70, veverimer; n=57, placebo), mean age was 63years, mean baseline eGFR was 28.5 mL/min/1.73 m^2, and mean serum bicarbonate was 17.3 mEq/L; 10% were on background oral alkali. In the veverimer group, at Week 52, mean serum bicarbonate increased by 4.39 mEq/L (P<0.05 vs. placebo) and significantly more pts had a ≥4mEq/L increase or normalization of serum bicarbonate (64% v 38%, P< 0.01). Pt-reported limitations of physical function (KDQOL-PFD) (e.g. walking several blocks, climbing a flight of stairs) significantly improved in the veverimer group (+12.5 v +0.3, P<0.001) as did objective physical performance on the RCS at Week 52 (P<0.0001). There was no significant effect of the presence or absence of diabetes on the effect of veverimer on improvement in either measure of physical function (rank-based ANCOVA, P≥0.6).

Conclusions: Few interventions for CKD have improved QOL or physical functioning. Our study demonstrates that veverimer is an effective treatment for diabetic pts with MA in CKD. Treatment with veverimer significantly improved how these pts felt and functioned.

Funding: Commercial Support - Tricida, Inc.

PO1034

Monocyte-to-Lymphocyte Ratio, an Independent Risk Factor of Survival and Cardiovascular Disease in Hemodialysis Patients: Results from the International MONDO Consortium

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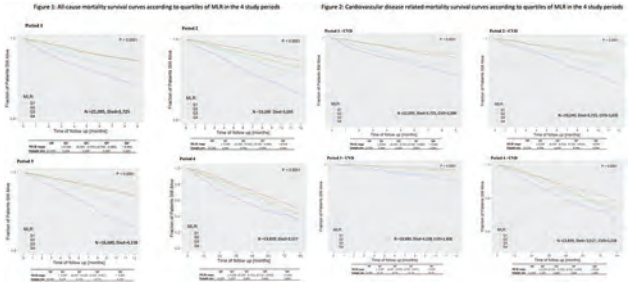
Background: Patients with ESRD have a high prevalence of chronic inflammation and higher risk of death. Monocytes have a crucial inflammatory role, but there has been limited study to date. This analysis studed the independent relationship between MLR, all-cause and cardiovascular (CV) mortality in a large and ethnically diverse haemodialysis population

Methods: Four cohorts were described by phases of haemodialysis exposure. Kaplan-Meier (KM) curves were applied to explore the association between MLR quartiles with all-cause and CV mortality in the 4 cohorts. Cox proportional hazards models with spline terms (adjusted for age, gender, race, body mass index, diabetic (DM) and congestive heart failure (CHF)) were applied to explore the association between MLR levels and all-cause mortality in the cohorts

Results: 21,095 patients were included in acute phase cohort; 19,240 in the early-stable phase cohort, 16,680 in the mid-stable cohort, and 13,839 in the late-stable phase cohort. Notably, patients with higher baseline MLR by quartile tended to be older, male and with a higher percentage of DM and CHF as comorbidities. Lower lymphocyte count and higher neutrophil count, NLR, CRP were associated with higher MLR quartile, consistent with the observed association with other markers of inflammation and malnutrition: lower albumin, phosphate and higher ferritin. Adjusted all-cause and CV mortality was observed to be higher in patients with higher MLR quartile both in the KM and spline analyses (Fig1/2)

Conclusions: There is a positive relationship between higher levels of MLR and adjusted all-cause and CV mortality across all phase cohorts, including long-term follow-up in this large and ethnically diverse haemodialysis population. Higher prevelence of DM and CHF are seen in patients with higher levels of MLR. This work supports findings made previously in more restricted cohorts and warrants further mechanistic investigation



PO1035

Warfarin Increases the Risk of Vascular Calcification in Haemodialysis Patients: A Multicenter Case-Control Study

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Background: Vascular calcifications (VC) are highly prevalent in maintenance haemodialysis patients and it is a recognized risk factor for increased mortality. Previous experimental studies showed the relation between warfarin which has been prescribed frequently in dialysis patients and VC. The aim of this study is to investigate the association between VC and warfarin use in haemodialysis patients.

Methods: This was a cross-sectional, observational, multicenter study. VC were assessed using Adragao (AS; pelvis and hands) and Kauppila (KS; lateral lumbar spine) scores in 76 haemodialysis patients from six centers. There were 32 patients (4.5%) being treated with warfarin for at least 1 year out of a total 711 haemodialysis patients and we included 44 control patients with matching parameters of age, sex and dialysis vintage to the study. Clinical characteristics, concomitant treatments, laboratory results were recorded and possible risk factors related to VC were analyzed.

Results: Of the patients, 47% were females, mean age was 65.8 ± 9 years, 23% were diabetics, their mean dialysis vintage was 68.39 ± 38.5 months and mean Kt/V 1.66 ± 0.27. No significant differences in clinical characteristics and basic laboratory results were found between control and warfarin group. In warfarin group, median Kauppila score was higher than control [11 vs 6.5, (25%-75% percentile, 5 vs 15), P=0.032] and percentages of Kauppila score >6 patients were higher, as well (76,6% vs 50%; P=0.029). Median Adragao score was not significantly different between two groups [7 vs 6, (%25,%75 percentile 6 vs 8), P=0.177]. Logistic regression analysis revealed that warfarin treatment was independently associated with Kauppilla scores of >6 (OR 3.28, 95% CI 1.17-9.22, P=0.024).

Conclusions: The results of this study showed that warfarin is a strong risk factor for vascular calcifications, especially in aorta of haemodialysis patients.

Table 1. Basic characteristics of the patients and summary of the results

Parameter	Warfarin (+) n=32	Warfarin (-) n=44	P value
Age (mean±SD)	67.6±9	64.54±8.3	0.143
Female/Male	14; 43%/18; 56%	22; 50%/ 22; 50%	0.646
Dialysis vintage (months, mean±SD)	74.9±44.2	63.6±33.4	0.209
Kt/V	1.62±0.2	1.7±0.2	0.205
Diabetes mellitus +/-(n,%)	6, 18%	12, %27	0,427
Warfarin usage time (months, mean±SD)	65.9±9.7	NA	NA
Kauppilla score (median,min-max)	11 (1-24)	6,5 (1,20)	**0,032**
Kauppilla score >6 (n, %)	23, 76.6%	22, 50%	**0,029**
Adragao score (median, min-max)	7 (2-8)	6 (0-8)	0,177
Adragao score ? 3 (n, %)	30, 93.7%	41, 93.1%	0,638
Serum calcium (mean±SD)	8.82±0.5	8.78±0.5	0.778
Serum phosphorus (mean±SD)	4.62±0.87	4.84±0.89	0.279
Serum parathyroid hormone (mean±SD)	376.23±192.8	457.36±251.2	0.116
Serum albumin (mean±SD)	3.81±0.38	3.91±0.52	0.361
Serum hemoglobin (mean±SD)	11.43±1.1	11.6±1.57	0.595
Serum C-reactive protein (mean±SD)	14.3±12.2	13.8±15.4	0.881

PO1036

Paradoxical Effect of Aldosterone on Cardiovascular Outcome in Maintenance Hemodialysis Patients

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Background: Patients with end-stage kidney disease have an increased risk of cardiovascular (CV) events and left ventricular diastolic dysfunction (LVDD) is known to contribute to high occurrence of CV mortality. Although high serum aldosterone level is involved in the development of CV complications in general population, this association is unclear in patients undergoing hemodialysis (HD). We aimed to determine the impact of serum aldosterone on LVDD and CV mortality among HD patients.

Methods: We performed a prospective cohort study of maintenance HD patients without CV disease. Patients were divided into two groups according to the median level of serum aldosterone. All patients underwent echocardiography to evaluate diastolic dysfunction. Proportions of LVDD and CV mortality were compared between high and low aldosterone groups.

Results: We enrolled a total of 60 adult patients (mean age 57.9±12.1 years, male 30.0%). Low aldosterone group had an increased left ventricular diastolic dimension compared with high aldosterone group (52.2±8.4 vs. 50.3±5.2 mm, p=0.033). The E/e' ratio and the proportion of LVDD were significantly higher in the low aldosterone group than the high aldosterone group. Multivariate logistic regression revealed that low log-aldosterone (odds ratio (OR) 0.403; 95% confidence interval (CI) 0.188-0.862) and large left atrial dimension (OR 1.308; 95% CI 1.114-1.536) were independent risk factors for LVDD. During the mean follow-up period of 5.2 years, the cumulative incidence rates of CV mortality were significantly higher in low aldosterone group (log-rank test, p=0.027). In addition, cox regression analysis demonstrated that low serum aldosterone was an independent predictor of CV mortality in HD patients (hazard ratio 0.505; 95% CI 0.294-0.869, p=0.014).

Conclusions: Low serum aldosterone was not only associated with LVDD but also an independent predictor of CV mortality among HD patients.

Funding: Clinical Revenue Support

PO1037

Variations in the Thrombin Generation Profile and Clotting Factor Levels in the Patients Undergoing Maintenance Hemodialysis

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Background: Chronic kidney disease (CKD) patients are at high risk of cardiovascular disorders and thrombosis. CKD-V patients undergoing maintenance hemodialysis exhibit varying degrees of hemostatic dysregulation. Endogenous thrombin potential (ETP) is important to the pathogenesis of vaso-occlusive complications. This study investigated ETP and its relevance to circulating coagulation factor levels in CKD-V patients.

Methods: Citrated blood samples from 95 patients with CKD-V were collected prior to maintenance hemodialysis. Normal human plasma (NHP) was used for referencing purposes. Plasma levels of coagulation factor VII, IX, X and XIII were measured by ELISA. ETP was measured using a kinetic fluorogenic method. Such parameters as peak thrombin, lag time (LT) and area under the curve (AUC) were compiled. Correlation analysis between peak thrombin and coagulation factors was carried out by using GraphPad Prism software.

Results: CKD-V patients did not show any significant difference in factor VII levels (110.6 % vs 112.5 %) and factor X (81.5 % vs 88.2 %). Factor IX levels were elevated (124.3 %) in the CKD-V group in comparison to NHP (100.5 %) similarly factor XIII levels were significantly higher in CKD-V (104.8 %) in comparison to NHP (82.3 %). In the ETP studies, CKD-V patients showed a wide variation in ETP parameters. Peak thrombin levels (107.1 nM vs 168.3 nM) and AUC (589.8 nM*min vs 815.7 nM*min) were lower while lag time was higher (2.89 min vs 2.17 min) in the CKD-V group in comparison to NHP. Coagulation factor VII, IX and X correlated with peak thrombin levels (r = >0.3) whereas factor XIII did not show any significant correlation.

Conclusions: These studies demonstrate that CKD-V patients exhibit a decreased generation of endogenous thrombin with simultaneous consumption of coagulation factors suggesting an ongoing activation of coagulation system. Almost 10% of the CKD-V patients exhibit increased levels of peak thrombin values which correlated with relatively higher levels of clotting factors suggesting a decreased activation of ETP. These studies suggest that a majority of CKD-V patients are in a sustained state of ongoing thrombin generation which may contribute to the observed thrombotic complications in these patients.

PO1038

Physical Activity and Mortality in Adults Undergoing Hemodialysis: A DIET-HD Cohort Study

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Background: People receiving maintenance hemodialysis (MHD) are at higher risk of cardiovascular disease (CVD) and death. Regular exercise training reduces CVD mortality in people with coronary heart disease, but the potential survival benefits for adults undergoing MHD are unproven. We assessed the association between self-reported physical activity (PA) and mortality in a very large cohort of people receiving MHD.

Methods: DIET-HD is a prospective, multinational study of adults undergoing MHD in Europe and South America. We classified participants as sedentary, exercises up to once a week ('occasional PA'), or exercises twice a week or more ('frequent PA'), using a self-reported question. We balanced the baseline characteristics, including socio-demographic factors, comorbidities, blood chemistry and dietary intake, across the PA groups using propensity scores. We conducted weighted Cox proportional hazards models with double robust estimators to assess the association between PA and mortality.

Results: Of the 8043 participants initially included in the DIET-HD study, 6147 (76%) had information on PA. 1226 (20%) exercised frequently, 1981 (32%) occasionally and 2940 (48%) were sedentary. During a median follow-up of 3.82 years (19 677 person-years), 2337 (38%) deaths occurred, of which 1050 (45%) were from CVD causes. After propensity score-weighing and adjustment for potential confounders, PA was associated with a lower risk of all-cause mortality, CVD mortality and non-CVD mortality (Table). We observed a dose-dependent effect of PA for CVD death.

Conclusions: Regular PA is associated with a lower risk of CVD mortality in adults receiving MHD. Until randomised control trials assess whether PA improves survival in MHD, it should be considered as part of the clinical management of MHD patients.

Funding: Government Support - Non-U.S.

PA level	Adjusted Hazard Ratio	Pooled P	P trend
Sedentary	1		
Occasional	0.80 (0.72 to 0.89)	0.0001	0.002
Frequent	0.82 (0.71 to 0.95)		
CV mortality:			
Sedentary	1		
Occasional	0.82 (0.70 to 0.96)	0.009	0.007
Frequent	0.77 (0.62 to 0.94)		
Non-CV mortality:			
Sedentary	1		
Occasional	0.81 (0.69 to 0.94)	0.02	0.13
Frequent	0.88 (0.72 to 1.08)		

PO1039

Impact of Age on the Association of Pre-ESRD Uric Acid with Post-Transition Mortality Among US Veterans

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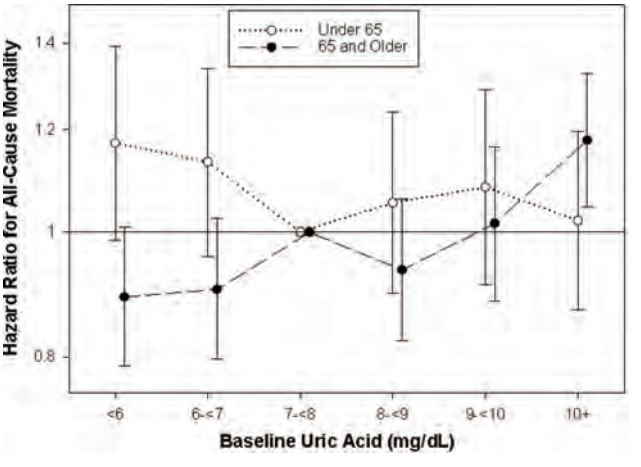
Background: Elevated uric acid is a marker for gout and higher mortality in kidney disease patients. In a prior analysis we demonstrated that higher pre-dialysis uric acid was associated with higher post-transition outcomes. As higher uric acid is more commonly found in older patients, we examined the differences in the association between pre-dialysis uric acid and mortality post-transition to dialysis across age groups.

Methods: From US veterans who transitioned to dialysis between 10/2007-03/2015, we identified 9,110 patients with a uric acid measured 3 months before transitioning to ESRD. We examined the association of pre-ESRD uric acid category with all-cause mortality post-transition using Cox proportional hazards models adjusted for case-mix covariates, and additional adjustments for laboratory values and eGFR, separately in patients less than 65 or >= 65 years.

Results: The mean age of the cohort was 66±11 years old, 2% female, and 36% African American. The 3-month prelude uric acid average was 8.13 ± 2.29 mg/dL. 4,521 patients died during follow-up (median follow up time of 25 months). Compared to the reference group (7-<8mg/dL) in the fully adjusted model, lower uric acid led to a lower risk and the highest category of uric acid had an 18% higher risk of mortality in those 65 years or older. There was no significant association between uric acid and mortality among patient younger than 65. Wald Test for interaction showed a significant difference in association (p value: 0.0029). [Figure]

Conclusions: Elevated uric acid pre-transition is associated with a higher risk of mortality post-transition among older Veteran patients. In older patients, prelude uric acid can be informative of post-transition outcomes. Further study of this relationship is warranted to determine if uric acid should be more closely monitored in patients transitioning to dialysis and to further understand why age modifies the clinical impact of uric acid.



PO1040

Hemodiafiltration Reduces All-Cause Mortality in Korean Hemodialysis Patients: A Propensity-Matched Cohort Study

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Background: On-line hemodiafiltration(OL-HDF) is currently the most advanced hemodialysis modality. Several studies have found that high convection volume OL-HDF reduces the mortality in dialysis patients compared with that of conventional hemodialysis(HD). Most randomized controlled trials to demonstrate the effect of

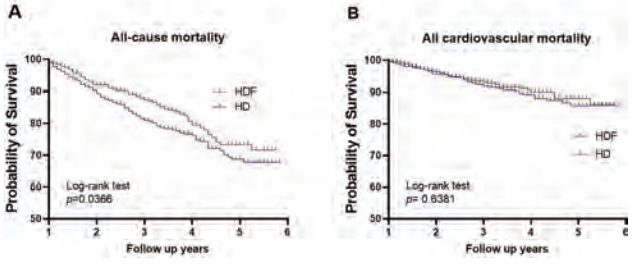
OL-HDF on survival benefit have failed. To date, the survival rate of OL-HDF has not been investigated in a large number of Koreans.

Methods: Using data from the Korean Society of Nephrology, The total 85,643patients undergoing hemodialysis between 2014 and 2019 were divided into two groups receiving only conventional HD and only OL-HDF with thrice sessions per week, dialysis vintage ≥3months, and ≥18years of age. Demographic characteristics, hemodialysis patterns, and overall survival were analyzed between the groups.

Results: The study included 8,955patients(750 OL-HDF, 8,205 conventional HD) with a median follow-up of 2.58(interquartile range 0.50–4.66)years. The mean age was younger, more male genders, and the dialysis vintage was slightly longer in patients with OL-HDF group compared with these of conventional HD group. We performed propensity score matching in 1:1 with the covariate of age, gender, cause of ESRD, and dialysis vintage. Compared with conventional HD, OL-HDF was associated with improved all cause-mortality(hazard ratio 0.659, 95% confidence interval 0.465 to 0.934). In cardiovascular mortality, no statistical difference was observed between the groups.

Conclusions: Our results indicate that OL-HDF was associated with reduced mortality without harmful effects on nutritional status across patient subgroups of age, sex and cause of ESRD, dialysis vintage.

Comparison of cumulative probabilities of survival between HD and HDF groups



Predictors of all-cause mortality in univariate & multivariate cox analyses

covariate	Unadjusted			Adjusted*		
	HR	95% CI	*P value*	HR	95% CI	*P value*
HDF(reference: HD group)	0.76	0.586 to 0.985	0.038	0.659	0.465 to 0.934	0.019
Age (per 1-yer increment)	1.062	1.050 to 1.074	<0.001	1.062	1.046 to 1.079	<0.001
Male (reference: female)	1.178	0.889 to 1.562	0.254	1.385	0.919 to 2.086	0.119
Primary disease						
Ref: Diabetes						
Hypertension	0.955	0.690 to 1.325	0.782	0.739	0.472 to 1.157	0.186
Glomerulonephritis	0.474	0.273 to 0.822	0.008	0.794	0.381 to 1.657	0.539
Cystic kidney disease	0.833	0.265 to 2.618	0.755	1.605	0.384 to 6.701	0.516
Others	0.744	0.402 to 1.377	0.347	0.999	0.401 to 2.493	0.999
Unknown	0.976	0.645 to 1.476	0.907	0.82	0.431 to 1.493	0.456
Vascular access						
AV Fistula Graft (Ref)						
CVC/ other	1.88	1.212 to 2.915	0.005	1.414	0.741 to 2.698	0.293
previous HD duration (years)	1.085	1.022 to 1.153	0.008	1.062	0.966 to 1.168	0.210
previous KT	0.685	0.219 to 2.140	0.515			
ESA dose	1.039	1.011 to 1.068	0.007	1.02	0.973 to 1.068	0.414
Systolic BP	0.997	0.989 to 1.005	0.447			
Diastolic BP	0.984	0.970 to 0.998	0.022	1.003	0.988 to 1.020	0.676
BMI	0.973	0.917 to 1.037	0.428			
Hb	0.766	0.668 to 0.880	<0.001	0.843	0.718 to 0.990	0.037
Albumin	0.338	0.237 to 0.483	<0.001	0.455	0.294 to 0.704	<0.001
Creatinine	0.813	0.762 to 0.867	<0.001	0.931	0.859 to 1.008	0.079
Calcium	0.85	0.696 to 1.037	0.110	1.14	0.888 to 1.463	0.305
Phosphorous	0.777	0.687 to 0.878	<0.001	1.05	0.911 to 1.211	0.498
PTH	0.998	0.997 to 0.999	0.003	0.999	0.998 to 1.000	0.073
Ultrafiltration	1.114	0.941 to 1.320	0.210			
NPCR	0.916	0.562 to 1.495	0.727			
SPKTV	0.766	0.446 to 1.317	0.335			

PO1041

Energy Homeostasis Gene Polymorphisms and Survival of Hemodialysis Patients

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Background: Patients who undergo hemodialysis (HD) therapy have an increased risk of death compared to the general population. Single nucleotide variants (SNVs) of energy homeostasis influence the susceptibility to diabetes mellitus (DM), dyslipidemia, and coronary artery disease (CAD). We investigated whether selected SNVs related to energy homeostasis are associated with mortality risk in HD patients.

Methods: The study included 471 HD patients who were tested for 11 SNVs in *FOXO3*, *IGFBP3*, *FABP1*, *PCSK9*, *ANGPLT6*, and *ANGPLT8* genes using HRM analysis and TaqMan assays. FOXO3, IGFBP3, L-FABP, PCSK9, ANGPLT6, and ANGPLT8 plasma concentrations were measured by ELISA in 71 HD patients. The Kaplan-Meier method and Cox proportional hazard models were used for survival analyses.

Results: Patients with *ANGPLT8* rs737337 CC genotype had over 3-fold increased risk of death compared with the carriers of the major allele (log-rank test p=0.002; HR 3.4; 95%CI 1.5–7.7;p=0.003). rs737337 CC genotype was in particular a risk factor for cardiac (2e-4; 5.5; 2–15.1; 8E-4) and cardiovascular deaths (0.004; 4; 1.5–10.7; 0.007). The associations mentioned above remained significant after adjustment for gender, DM, CAD, age at RRT onset, BMI and CRP (p=0.03, 0.004 and 0.02 for overall survival, cardiac and cardiovascular deaths, respectively). *ANGPLT8* rs737337 was also associated with an increased risk of diabetic nephropathy (OR 1.8;95%CI 1.1–2.9; p=0.02). Plasma ANGPLT8 levels were increased in patients diagnosed with CAD (p=0.028). Bearers of *IGFBP3* rs3110697 variant A allele had increased risk of cardiovascular mortality (HR 1.3; 95%CI 1–1.6; p=0.02, adjusted p=NS). *IGFBP3* rs3110697 positively correlated with the diagnosis of CAD (p=0.006), myocardial infarct (p=0.01) and dyslipidemia (p=0.02) as well as with CRP concentrations (p=0.005). Carriers of *FOXO3* rs4946936 CT genotype had increased risk of cardiac death (HR 1.6; 95% CI 1.1–2.4; p=0.03, adjusted p=NS), whereas FOXO3 rs2802292 TT genotype was associated with decreased risk of vascular mortality (HR 0.4; 95%CI 0.2–0.8; p=0.005). The association remained significant after adjustment (p=0.002). The analyzed proteins did not correlate with the survival probability of HD patients.

Conclusions: *ANGPLT8* rs737337, *IGFBP3* rs3110697, *FOXO3* rs2802292, and rs4946936 are prognostic factors of survival among HD patients.

Funding: Government Support - Non-U.S.

PO1042

Short-Term Association of Pre-Dialysis Calculated Serum Osmolality and Its Per-Quarter Change with Mortality in Maintenance Hemodialysis Patients

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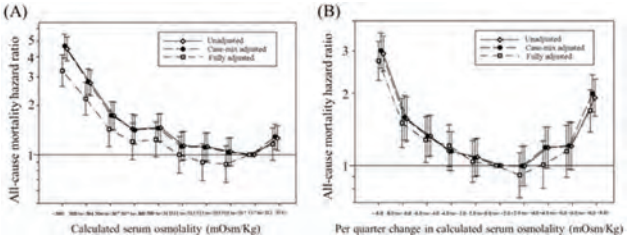
Background: Homeostatic regulation of serum osmolality (SOsm) is critical for normal cellular function. Since kidney plays an important role in maintaining homeostasis, patients with kidney dysfunction might be unable to maintain homeostasis. However, it is unknown if SOsm can predict risk of mortality in maintenance hemodialysis (HD) patients.

Methods: We identified 16,402 patients who transitioned to maintenance HD in a large U.S. dialysis organization over 5 years (2007-2011) and had available calculated pre-dialysis SOsm (Sodium and Potassium and blood urea nitrogen (BUN) and Glucose) at baseline. We used the equation with the best fit between measured and calculated SOsm as follows: 2x([Na, in mmol/L]+[K, in mmol/L])+[Glucose, in mg/dL]/18+[BUN in mg/dL]/2.8. We divided the patients into ten groups based on their calculated SOsm (SOsm updated at quarterly intervals as a proxy of short-term exposure): <300, 300–<304, 304–<307, 307–<309, 309–<311, 311–<313, 313–<315, 315–<317, 317–<321 (reference group) and ≥321 mOsm/Kg, and calculated SOsm's per quarter change from the date of first dialysis: <-8.0, -8.0–<-6.0, -6.0–<-4.0, -4.0–<-2.0, -2.0–<0, 0–<+2.0 (reference group), +2.0–<+4.0, +4.0–<+6.0, +6.0–<+8.0and ≥+8.0 mOsm/Kg. All-cause mortality risk was estimated using multivariable Cox models.

Results: The patients were 56% male, 48% non-white, and the mean age was 63 ± 13 (mean ± SD) years. Those with low calculated SOsm tended to be older. In time-varying analysis, the association between all-cause mortality showed that patients with the lowest calculated SOsm had the highest hazard ratio after fully adjusted (Figure A). We observed a U-shaped association between all-cause mortality and per quarter change in calculated SOsm such that SOsm change levels ±8.0 mOsm/Kg were associated with higher mortality risk (Figure B).

Conclusions: This result suggests that short-term and a wide range of changes in serum osmolality may increase the risk of all-cause mortality in hemodialysis patients.



PO1043

Survival Differences Among ESRD Patients in the Mainland United States, Hawaii, and Pacific Islands

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Background: Asians and Native Hawaiians and other Pacific Islanders (NHOPIs) are collectively the fastest growing racial minorities in the US. While certain Asian subgroups and NHOPIs have a high prevalence of kidney disease risk factors, there are sparse data

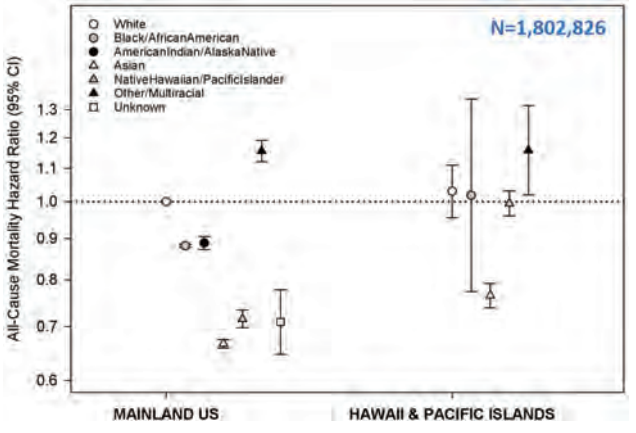
examining ESRD outcomes in these populations. As Hawaii is among the states with the highest representation of Asians and NHOPIs, we compared ESRD survival among Asians, NHOPIs, and other racial groups residing in the Mainland US vs. Hawaii and the Pacific Islands.

Methods: Using United States Renal Data System (USRDS) data, we examined the impact of geographic residence in the Mainland US vs. Hawaii and the Pacific Islands on associations of race and mortality among incident ESRD patients who transitioned to dialysis over 2010-16. HRs for all-cause mortality were estimated using Cox models adjusted for sociodemographics, comorbidities, dialysis characteristics, pre-ESRD nephrology care, BMI, laboratory tests, and medications.

Results: Compared with White incident ESRD patients residing in the Mainland US, Asians and NHOPIs in the Mainland US had lower mortality risk: HRs (HRs) (95%CIs) 0.67 (0.66-0.67) and 0.72 (0.70-0.73), respectively. When examining Asians and NHOPIs residing in Hawaii and the Pacific Islands, survival benefit was attenuated in Asians and was diminished to the null in NHOPIs (ref: White incident ESRD patients in Mainland US): HRs (95%CIs) 0.77 (0.74-0.79) and 1.00 (0.96-1.03), respectively.

Conclusions: In the Mainland US, Asians and NHOPIs had lower mortality risk compared with Whites. However, in Hawaii and the Pacific Islands, this survival benefit was diminished in Asians and was mitigated in NHOPIs. Further studies are needed to determine the factors contributing to the differential ESRD mortality risk across racial groups residing in the Mainland US vs. Hawaii and the Pacific Islands.

Funding: NIDDK Support



PO1044

Association of All-Cause Mortality with Pre-Hemodialysis Pulse Pressure in Chronic Hemodialysis Patients

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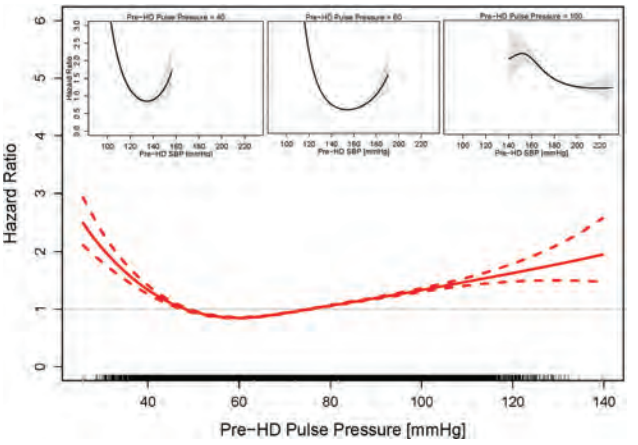
Background: Pulse pressure (PP) reports cardiac and vascular conditions, where high PP values are associated with atrial fibrillation, aortic insufficiency, arterial stiffness, low PP values may be associated with aortic valve stenosis, cardiac insufficiency. However, the association of pre-hemodialysis (pre-HD) PP with mortality among hemodialysis patients is not well understood. In this study, we aim to explore the extent to which PP is associated with mortality.

Methods: We analyzed pre-HD PP (calculated as pre-HD SBP minus pre-HD DBP) between 1/2001 and 12/2012 in hemodialysis patients treated in U.S. Fresenius Medical Care facilities. A 3-months baseline period was defined as months 4 to 6 after hemodialysis initiation, all-cause mortality was noted during follow-up. Only patients who survived baseline were included. Censoring events were renal transplantation, modality change, or study end. We built Cox proportional hazards models with spline terms, allowing us to model nonlinear effects of pre-HD PP as a continuous variable and its relationship with all-cause mortality.

Results: We included 152,625 patients. Mean age was 60.8 years, 59% were white and 56% were male. During a median follow-up of 26.0 months 40.4% patients died. We found that for patients with pre-HD PP between 49.2 mmHg and 74.7 mmHg, were associated with better survival. In contrast, a PP below 49.2 mmHg and above 74.7 mmHg were associated with higher mortality. Similar nonlinear effects are seen in SBP for a given pre-HD PP value (see Fig. 1). Figure 1: Association between pre-HD pulse pressure and all-cause mortality. HRs (solid line) and 95% CIs (dashed lines) of pre-HD pulse pressure. The tick marks on the x-axis represents individual patients.

Conclusions: The association of pre-HD PP with mortality is nonlinear, a better understanding will provide further insights into disentangling the associated mediators affecting its dynamics. Our findings may aid risk stratification.

Funding: Commercial Support - Fresenius Medical Care North America



PO1045

Risk Factors and Mortality in Dialysis Patients with Abdominal Aortic Aneurysm

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Background: In the general population, abdominal aortic aneurysm (AAA) is associated with increased mortality. Once diagnosed, AAA can be followed noninvasively or corrected surgically. Vascular disease is common in dialysis patients, but there is limited information on the incidence and outcomes for AAA in this population. To address this question, we queried the United States Renal Data System (USRDS) for risk factors associated with diagnosis of AAA, survival of patients diagnosed with AAA, and overall risk factors for mortality.

Methods: Incident dialysis patients from 2005–2014 from the USRDS were queried. ICD-9 and ICD-10 codes were used to define a diagnosis of AAA and identify clinical co-morbidities. Cox proportional hazards (CPH) modeling was used to determine the adjusted hazard ratio (aHR) and 95% confidence intervals (CI) for death.

Results: From a total cohort of 868,799, we identified 22,121 subjects with a diagnosis of AAA. When compared to patients without the diagnosis, AAA patients were older and had higher percentages of white race, male gender, tobacco use, Charleson comorbidity index (CCI), and hypertension as end stage renal disease (ESRD) etiology, but lower percentages of diabetes as ESRD etiology. A bivariate CPH model of survival showed that AAA patients had significantly increased mortality compared to patients without a AAA diagnosis (HR=1.29, p-value<0.0001). However, in the final CPH model, patients with a AAA diagnosis had a decreased risk of mortality (aHR=0.85, 95% CI 0.844–0.860), after controlling for age, CCI, and other demographic and comorbid variables.

Conclusions: ESRD patients with a diagnosis of AAA are more likely to be older, white, male, smokers with hypertension as the cause of ESRD. Patients with AAA are less likely to have diabetes as an etiology of ESRD. AAA is associated with a decreased risk of death, which suggests that AAA in the ESRD population by itself may not increase mortality, but the comorbid factors that come with it do.

Funding: Private Foundation Support

PO1046

Composite Comorbidity Scoring System to Predict Mortality in a Saudi Dialysis Population

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Background: Most uremic patients starting hemodialysis (HD) have multiple comorbidities, resulting in a high risk of mortality. Our aim was to establish and evaluate a personal scoring system in which we included associated comorbidities, age and, other HD related factors known to predict mortality.

Methods: All patients referred to DaVita-KSA, from October 2014 to December 2019, to continue hemodialysis therapy, were included in this analysis. Cox proportional hazards model was used to identify factors influencing all-cause mortality. A personal scoring system was established based on the score assigned to each factor, according to its weight as predictor of death, judged on the value of the relative risk generated in the preliminary analysis. An index of co-morbidity was calculated for each patient that corresponded to the sum of scores assigned to each factor. Patients were divided into 4 groups according to percentile rank of their comorbidity index (Group1: low risk, Group 2: moderate, Group 3: high, Group 4: very high) and compared in terms of global and annual mortality rates and survival using Log rank analysis

Results: 3983 patients (2177 males, 55%) were included with a mean age of 52.5± 16.8 years. Diabetic and hypertensive nephropathies accounted for 78.1 % of all causes of ESRD. After a cumulative follow-up period of 7635 years, 15.3% of patients were transferred to other facilities, 8.7% were transplanted and 14.5% were deceased.

Conclusions: This new scoring system appears to be easily established at our clinics and may constitute a good predictor for all-cause mortality in our HD population.

The mortality parameters in the study groups

Groups		Total	Group 1	Group 2	Group 3	Group 4	p
Number		3983	882	867	1237	997	
Comorbidity score		[0-22]	[0-3]	[4-5]	[6-8]	>=9	
Mortality, %	Rate	14.5	3.6	8.4	14.5	29.4	<0.0001
	CL 95%	[13.3-15.7]	[2.4-4.9]	[6.5-10.3]	[12.3-16.6]	[26-32.7]	
Annual mortality, % patient-years	Rate	7.6	1.5	4.3	8.2	18.1	<0.0001
	CL 95%	[6.9-8.2]	[1-2]	[3.5-5.2]	[7-9.4]	[16.1-20.2]	
Survival rate, months	0	100	100	100	100	100	<0.0001
	3	98.2	99.9	99.3	98.7	95	
	6	96.7	99.6	98.3	97.4	89.6	
	12	94	98.8	97.6	94.1	89.6	
	24	86.7	96.9	93.2	86.6	71	
	60	65.3	92.6	68.8	59	37.8	
Relative mortality risk	Rate		1	2.9	5.7	12.9	<0.0001
	Ci, 95%		Reference	[1.9-4.4]	[3.9-8.3]	[8.9-18.5]	

PO1047

Mortality and Cost Track Yearly Changes in ESRD Quality Incentive Program Performance

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Background: Patients treated in dialysis facilities that receive payment reductions under the ESRD QIP experience higher mortality and cost (Medicare payments) during the same performance year. We asked whether these outcome measures track with yearly changes in the QIP payment reduction.

Methods: Mortality and cost per patient year were analyzed using claims files for dialysis patients enrolled in the traditional Medicare fee-for-service program for performance years 2010-2016.

Results: The table displays index-year mortality and cost (columns) according to the facility QIP payment reduction (PR) for the prior year (rows) and the direction of the change in QIP PR in the index-year (worse, unchanged, better). In almost all cases, mortality and cost were higher for patients in facilities that did worse in QIP and lower for patients in facilities that did better. For example, patients treated in dialysis facilities that received a 1.5% QIP PR in the prior year experienced 18.7% mortality if the index-year PR was unchanged, 16.9% mortality if the index-year PR was lower (≤1%) and 24.5% mortality if the index-year PR was higher (2%).

Conclusions: Patient mortality and average Medicare payments track with changes in facility QIP PRs. The finding suggests that facility efforts to improve QIP performance may translate into improved mortality and lower costs to Medicare. Moreover, it is unlikely that the observed association between outcome measures and QIP is attributable to unmeasured patient case-mix, which tends to be relatively stable from year to year. The findings suggest that the ESRD QIP captures meaningful aspects of quality and value.

Funding: Other U.S. Government Support

Prior Year QIP Payment Reduction (PR)	Mortality, by Change in QIP PR			Medicare Payment, by Change in QIP PR		
	Worse	Unchanged	Better	Worse	Unchanged	Better
0.0%	16.8%	15.6%	n.a.	$79,971	$76,227	n.a.
0.5%	17.1%	16.6%	16.1%	$81,864	$81,334	$78,384
1.0%	21.2%	16.3%	16.4%	$91,018	$75,786	$79,187
1.5%	24.5%	18.7%	16.9%	$91,816	$85,555	$81,323
2.0%	n.a.	24.6%	19.7%	n.a.	$98,216	$83,937

PO1048

Comparison of ESRD Quality Incentive Program (QIP) Performance and Dialysis Facility Compare (DFC) Star Rating

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Background: The DFC quality of patient care star rating system reached its 5-year mark in 2020 and the ESRD QIP surpassed its 10-year mark. Both programs have undergone considerable changes in a continuing effort to help patients make informed decisions when selecting a provider while also incentivizing high quality care. We assessed whether ESRD QIP scores and payment reductions aligned with facilities' star ratings in calendar year (CY) 2018.

Methods: Payment year (PY) 2020 QIP scores and payment reductions (PR) and CY 2018 star ratings (1-5 stars) were obtained from DFC public data files. Comparisons between the two programs were assessed with cross-tabulations of PR categories and star ratings and with t-tests comparing mean QIP Total Performance Scores (TPS) among adjacent PR and star rating levels.

Results: Facilities with higher PY 2020 QIP scores tended to receive higher star ratings. Among facilities with no PR (N=3,929), 79.4% received 4 or 5-stars and 91.7% of facilities with a 2% PR received 1 or 2-stars. The average facility TPS decreased by approximately 10 points with each decrease in star rating, with significant differences between all categories (Table 1).

Conclusions: The ESRD QIP and the star rating program have distinct goals which have led to differences in their design and methodology, such as the use of the small facility adjuster in the ESRD QIP and non-overlapping measures between the two programs. Nevertheless, there is strong overall correspondence between the two programs in their assessments of facility quality of care. These results are reassuring, in that QIP scores and star ratings are providing a consistent message about dialysis facility quality of care in most cases.

Funding: Other U.S. Government Support

Table 1. Mean TPS by PY 2020 QIP Payment Reduction and CY 2018 5-star Rating (N=6,703)

QIP PR	Facility %	Mean TPS (SD)	Star Rating	Facility %	Mean TPS (SD)
0.0%	58.6%	70.8* (8.7)	5	27.6%	74.3* (9.8)
0.5%	24.0%	53.8* (2.8)	4	29.0%	63.6* (9.0)
1.0%	12.0%	44.3* (2.8)	3	33.6%	54.3* (9.9)
1.5%	4.1%	34.1* (2.9)	2	7.1%	44.9* (11.7)
2.0%	1.3%	21.9 (5.7)	1	2.6%	36.3 (13.6)

*t-test with p<.0001 vs. adjacent category.

PO1049

Comparison of 5-Year Survival Rate Between Hemodialysis and Peritoneal Dialysis Patients: A Prospective Cohort Study with Propensity Score Matching

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Background: Chronic Kidney Disease patients who require dialysis have increased worldwide. However, whether hemodialysis (HD) or peritoneal dialysis (PD) independently affects prognosis is still controversial.

Methods: A multicenter prospective observational study was conducted from 1 January 2012 to 31 March 2018. Total of 646 HD patients and 72 PD patients were enrolled from Hiroshima Chronic kidney disease outcomes cohort study (Hi-COCS) in Japan. We excluded patients whose follow-up period was less than 3 months. One to one propensity score matching was performed to compare the survival rates between HD and PD patients and to find the factors that would affect prognosis.

Results: Of 621 HD patients and 71 PD patients, the mean average age was 74.2±12.5, 49.7% patients had DM, and 19.2% patients had CVD. The median follow-up period was 41 months. Total of 130 patients were selected with 1:1 propensity score matching (65 HD patients and 65 PD patients). In the PS matched cohort, there was no difference between the two groups in the 5-year survival rates of the overall events. (HD 71.2% vs PD 71.2%, respectively, $P = 0.97$) PD group had better survival rate of CVD events and it was significantly different between the two groups ($P = 0.043$). Multivariate Cox proportional hazard model showed that adjusted hazard ratio (HR) of overall events and CVD events were 1.06 (95% confidence interval (CI); 0.53-2.10, $P = 0.96$) and 4.90 (95% CI 1.37-23.8, $P = 0.014$), respectively. Age, non-HDL cholesterol and CRP were associated with prognosis in overall events. Only non-HDL cholesterol was associated with prognosis in CVD events.

Conclusions: In this study, we found out that 5-year survival rate was not significantly different between the HD and PD patients in overall events. However, PD group had better survival rate of CVD events than that of HD patients. It suggests that PD may potentially have treatment advantage for patients who have high risk factors of CVD events.

PO1050

Effects of Dialysate Magnesium Concentrations on Mortality: Results from the MONDO Initiative

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Background: Dialysate magnesium (DMg) is known to be positively associated with serum Mg levels in hemodialysis (HD) patients (pts). We aimed to study the associations between different DMg levels and mortality in HD pts.

Methods: We conducted a retrospective cohort study to examined the associations of different DMg levels (1.0, 1.5, or 2.0 mEq/L) and all-cause mortality. In-center HD pts treated in KfH and MONDO with constant DMg levels during their first year of observation were studied. The primary outcome variable was a 1-year mortality risk. In a second step, we used 1:1 propensity score matching (based on age, gender, catheter, and vintage) to create 4 matching groups: 1)DMg 1.0 versus 1.5 mEq/L (KfH and MONDO), 2)DMg 1.5 versus 2.0 mEq/L (only KfH), 3)1.0 versus 2.0 mEq/L (only KfH). The associations between different DMg levels and mortality after matching were evaluated by Cox proportional hazards models, Kaplan Meier survival curves, and the Log Rank test, respectively.

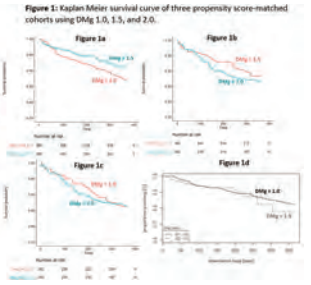
Results: We studied 32,117 pts from KfH [69 years, 64% males, 42% diabetics, 48% catheter; DMg 1.0: 31,460 (98%), DMg 1.5: 395 (1%) and DMg 2.0: 262 (1%)]; 15,211 pts from MONDO [57 years, 58% males, 41% diabetics, 24% catheter; DMg 0.75: 2,481

(16%), DMg 1.0: 12,508 (82%) and DMg 1.5: 222 (1%)]. Propensity score-matching created 4 well-balanced cohorts with DMg of 1.0 v.s. 1.5(KfH and MONDO), DMg 1.5 v.s. 2.0 and 1.0 v.s. 2.0 (KfH), respectively. Survival analysis show that DMg 1.5 is not statistically associated with survival benefits compared to 1.0 in both data sets (Table 1, Figure 1 a, d). In addition, compared to both DMg 1.0 and 1.5, we do not observe a survival benefit of DMg 2.0 in KfH's data (Table 1, Figure 1b, c).

Conclusions: Increased DMg was not associated with a survival benefit in either the KfH or MONDO datasets. One of the limitations is the lack of detailed dialysate information. Further studies directly addressing the association between serum Mg and DMg are needed to further delineate the complex relationship between DMg and patient outcomes.

Table1: Hazard Ratio of comparing different DMg groups in KfH [after matching]

	HR	95% CI	P-value
DMg 1.5 vs. 1.0	0.68	(0.44, 1.0)	0.08
DMg 2.0 vs. 1.0	1.00	(0.63, 1.60)	0.93
DMg 2.0 vs. 1.5	1.20	(0.74, 2.00)	0.44



PO1051

Risk of Hypokalemia in Hyperkalemic Hemodialysis Patients

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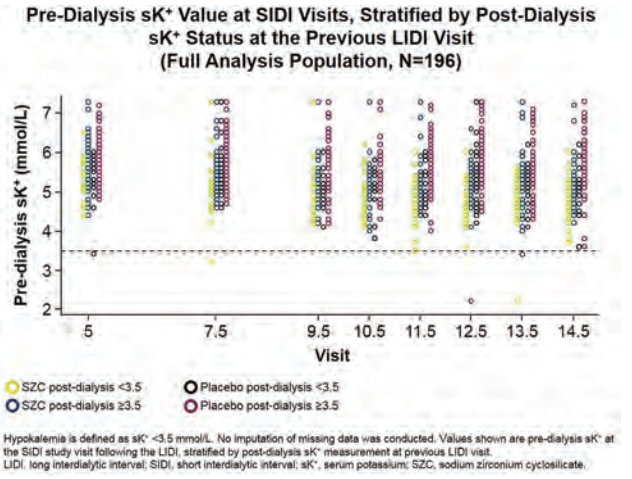
Background: Combined pre- and post-dialysis hypokalemia is associated with increased mortality risk. The Phase 3b DIALIZE study (NCT03303521) showed that sodium zirconium cyclosilicate (SZC) reduces pre-dialysis serum potassium (sK^+) and is well tolerated in hemodialysis patients (pts) with hyperkalemia. In this *post-hoc* safety analysis of DIALIZE, we report hypokalemia events in the SZC and placebo (PBO) arms.

Methods: In DIALIZE, 196 pts were randomized blindly 1:1 to receive PBO (n=99) or SZC (n=97) 5 g starting dose once daily on non-dialysis days (4 days/week [wk]) for 8 wks, comprising a 4-wk SZC or PBO dose-titration phase (max 15 g) to achieve target pre-dialysis sK^+ 4.0–5.0 mmol/L, and a 4-wk stable-dose evaluation phase. In this *post-hoc* analysis, the proportions of pts with hypokalemia (sK^+ <3.5 mmol/L) pre-dialysis, post-dialysis, and combined pre- and post-dialysis at the same visit were tabulated by visit. Pts' current pre-dialysis sK^+ stratified by post-dialysis sK^+ (≥3.5 vs <3.5 mmol/L) at the previous visit was also assessed.

Results: The frequency of pre-dialysis hypokalemia was comparable between SZC and PBO, with 5 pts in each arm accounting for 7 and 5 events, respectively. The proportion of pts with post-dialysis hypokalemia at each visit was greater with SZC than PBO. For all but 2 SZC pts with post-dialysis hypokalemia, pre-dialysis sK^+ returned to ≥3.5 mmol/L at the next visit (**Figure**). In each arm, 1 pt had combined pre- and post-dialysis hypokalemia.

Conclusions: Despite the efficacy of SZC in lowering pre-dialysis sK^+, SZC was not associated with a clinically significant increase in the frequency of pre-dialysis hypokalemia. Treatment with SZC vs PBO did not increase the frequency of combined pre- and post-dialysis hypokalemia which is associated with increased mortality risk.

Funding: Commercial Support - AstraZeneca



PO1052

Electrolyte Changes in Contemporary Hemodialysis: An Analysis of the Monitoring in Dialysis (MiD) Study

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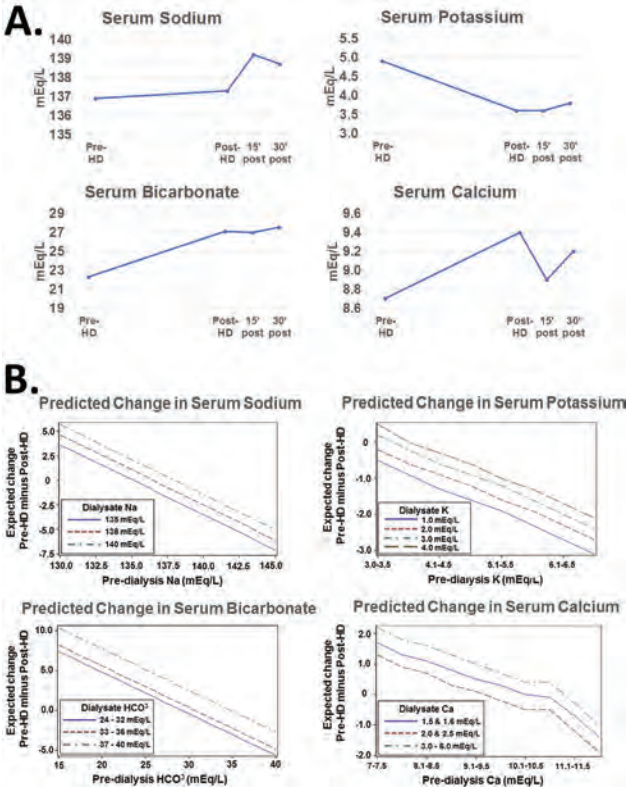
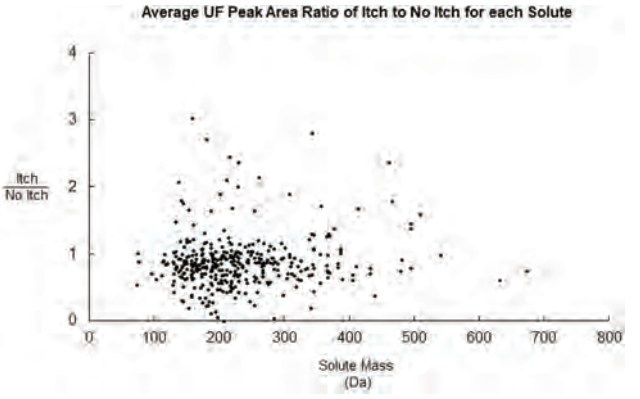
Background: There is a paucity of data examining electrolyte concentrations during and immediately after hemodialysis (HD) sessions. We describe these changes and provide predictive nomograms based on HD prescriptions and pre-HD electrolytes.

Methods: We leveraged patient (n=66) and HD session-level pre- and post-HD laboratory data (n=1,713) from the Monitoring in Dialysis study and fit mixed effects regression models to analyze differences between pre-, 15-minutes post-, and 30-minutes post-HD levels (compared with immediately post-HD) of electrolytes, blood urea nitrogen, creatinine, and albumin as well as the association of post-HD values with dialysate prescriptions.

Results: Serum bicarbonate, calcium, and albumin increased (mean increase 4.9mEq/L±0.3, 0.7mEq/L±0.1, and 0.4g/dL±0.03, respectively), and potassium, magnesium, and phosphorus decreased immediately post-HD (mean -1.2mEq/L±0.1, -0.3mEq/L±0.03, and -3.0mg/dL±0.2, respectively). Hypokalemia and hypophosphatemia were present in 34% and 67% of immediately post-HD samples, respectively. Changes were observed in electrolyte concentrations at 15- and 30-minutes post-HD compared to immediately post-HD (Fig. A: observed changes; Fig. B: predictive nomograms of post-HD electrolytes).

Conclusions: Contemporary HD results in marked changes in electrolyte concentrations during and after the treatment. We report a high frequency of post-HD hypokalemia and hypophosphatemia and present predictive nomograms relating post-HD changes to dialysate prescriptions. Whether the abnormalities observed in potassium and phosphorus post-HD predispose to adverse symptoms and arrhythmia is unclear and requires further research.





PO1053

Metabolomic Analysis Fails to Identify Uremic Solutes Associated with Pruritus in Hemodialysis Patients

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Background: Uremic pruritus is a debilitating symptom in hemodialysis (HD) patients. That uremic solutes contribute to pruritus is suggested by the improvement after transplantation. We aimed to identify solutes associated with pruritus using metabolomic analysis comparing plasma of HD patients with severe pruritus and mild/no pruritus.

Methods: Plasma and ultrafiltrate (UF) samples from 12 HD patients with severe pruritus (Itch) and 24 HD patients with mild/no pruritus (No Itch) were analyzed. Pruritus was assessed using a 100-mm visual analogue scale with severe defined as >70 mm and mild/no defined as <10 mm. Plasma and UF were analyzed using a metabolomics platform (Metabolon Inc.). Solutes were first identified as uremic based on the finding of higher average peak areas in all 36 HD patients than in 16 controls with normal kidney function. Solutes were deemed uremic if their HD/control ratio was >4 in plasma and/or UF with a false discovery rate of <0.05. Peak areas of each solute in the Itch and No Itch HD patients were then compared to identify uremic solutes associated with pruritus.

Results: HD vintage, spKt/V_{urea}, and lab values were similar in both groups (Table). Metabolomic analysis identified 593 uremic solutes. No difference in the levels of these uremic solutes was found between the Itch and No Itch patients using a false discovery rate < 0.05 (Figure).

Conclusions: Metabolomic analysis did not reveal any uremic solutes associated with pruritus in HD patients. The role of uremic solutes in pruritus remains to be established.

Funding: Veterans Affairs Support

Characteristics

	Itch (12)	No Itch (24)
Visual analogue scale (mm)	87±9	1.5 ± 2
HD vintage (yrs)	7 ± 3	7 ± 5
spKt/Vurea	1.56 ± 0.13	1.61 ± 0.21
Phos (mg/dl)	5.1 ± 1.7	6.0 ± 2.2
Ca (mg/dl)	9.1 ± 0.9	9.0 ± 0.9
PTH (pg/ml)	364 ± 236	363 ± 227

PO1054

Combined Value of Geriatric Nutritional Risk Index, Body Composition, and Bone Mineral Density for Predicting Mortality of Hemodialysis Patients

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Background: Prognostic utility of the geriatric nutritional risk index (GNRI) and the association between body mass index and bone mineral density (BMD) in hemodialysis (HD) patients are uncertain. We assessed the combined predictive value of GNRI, body composition, and BMD in HD patients.

Methods: Pre-dialysis laboratory data, same-day post-dialysis body composition parameters by the Body Composition Monitor (Fresenius), and radius, lumbar spine, and femoral bone mineral density (BMD) using dual energy X-ray absorptiometry were assessed in HD patients at baseline. The data were compared according to GNRI tertiles (T). Logistic regression analysis was used to assess GNRI T1. Kaplan-Meier survival and Cox proportional hazard analyses were conducted. Comparison of multiple receiver operating characteristic curves was performed to assess whether mortality prediction accuracy improved after adding GNRI, body composition, and BMD to established risk factors.

Results: Among 264 patients (male: 65%, diabetes: 42%), mean age was 65±12 years and the median dialysis vintage was 79 (39–144) months. GNR T1, T2, T3 were 88 (85–91), 94 (93–95), 98 (97–101), respectively. GNRI T1 patients showed older age, lower male frequency, and lower serum albumin, body cell mass index (BCMI), lean tissue index, fat tissue index (FTI), lumbar spine, femoral neck, and right distal mid-third radius BMD, but higher overhydration/extracellular fluid than patients with GNRI T2 or T3 (P<0.05). FTI (OR: 0.88), femoral neck BMD (OR: 0.05), age (OR: 1.03), C-reactive protein (OR: 1.37) and hemoglobin (OR: 0.70) were significant predictors of GNRI T1 (P<0.05). Patients with GNRI T1 showed significantly lower 2-year survival and GNRI T was significant predictor for 2-year all-cause mortality [Hazard ratio (T1-2): 2.07 (0.56-9.83), (T1-3): 8.59e+9 (2.45-3.39e+37), P<0.05]. Area-under-the curve for all-cause mortality using established risk factors (age, sex, diabetes, serum phosphate) was 0.66, improving to 0.79 by adding GNRI alone or to 0.81 by adding GNRI, FTI, and femoral neck BMD (P<0.05).

Conclusions: Associations of GNRI, body composition, and BMD were confirmed in HD patients. Combining GNRI, body composition, and BMD to established risk factors improved mortality prediction in HD patients.

Funding: Private Foundation Support

PO1055

Predicting Intradialytic Hypotension with Continuous Hemodynamic Monitoring Throughout Hemodialysis

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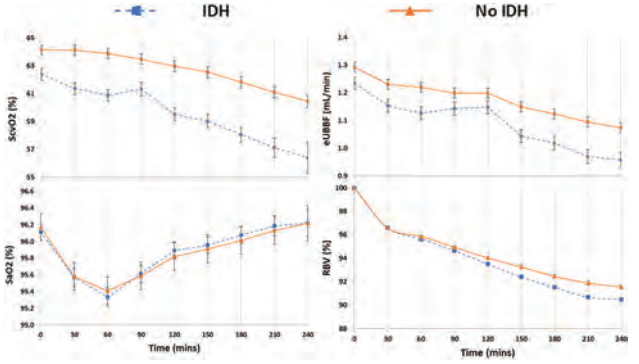
Background: Intradialytic hypotension (IDH) remains one of the most common complications associated with hemodialysis (HD). The CritLine Monitor (CLM) measures relative blood volume (RBV) and blood oxygen saturation (O_2Sat), but uncertainties remain in application of these parameters for predicting IDH. We looked at differences in CLM parameters based on whether an IDH episode was imminent or not as a function of time into a HD session to investigate whether their prognostic ability is dependent on the time into HD.

Methods: We studied routinely collected data from 17 US dialysis clinics. IDH was defined by systolic blood pressure (SBP) below 90 mmHg. The CLM directly measures RBV and O_2Sat, interpreted as arterial O_2Sat (SaO_2) for all sessions with a fistula or graft and as central venous oxygen saturation ($ScvO_2$) for those with a central venous catheter. For sessions with $ScvO_2$, we also calculated estimated upper body blood flow (eUBBF). We extracted each parameter every 30 minutes through each treatment. We compared

variables dependent on whether IDH occurred in the subsequent 30 minutes. Separate linear mixed effects regression models were used at each timepoint, with each CLM parameter as the dependent variable, IDH status as a dummy-coded predictor and subject as a random effect to account for repeated measures on individuals.

Results: We studied 2,791 patients and 197,526 sessions, 160,094 (81%) with SaO_2 and 37,432 (19%) with $ScvO_2$ data. IDH occurred in 13% of sessions. RBV was not different in the first 90 minutes for patients approaching IDH compared to those who were not, but was lower thereafter. Differences between the groups were observed throughout HD for $ScvO_2$ and eUBBF, but not SaO_2.

Conclusions: The ability for RBV to predict IDH depends on the time of onset. $ScvO_2$ and eUBBF better predict IDH than SaO_2, reflecting the dependence of $ScvO_2$ on cardiac output while SaO_2 more reflects pulmonary function.



Time course of CLM parameters based on whether IDH will occur in the following 30 mins or not

PO1056

Time of Hemodialysis and Risk of Intradialytic Hypotension and Intradialytic Hypertension

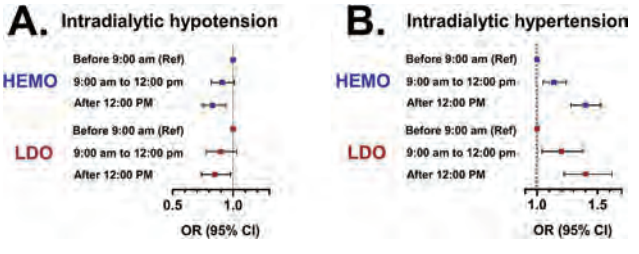
Murad Alostaz,[1,2] Simon Correa,[2,3] Sushrut S. Waikar,[4] Finnian R. McCausland.[2,3] *[1]University of California Los Angeles, Los Angeles, CA; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Boston Medical Center, Boston, MA.*

Background: Blood pressure (BP) fluctuates throughout the day following a circadian pattern. BP control is of utmost importance in patients with ESRD undergoing hemodialysis (HD), and both intradialytic hypotension (IDH) and intradialytic hypertension (HTN) are associated with adverse CV events and death. Whether the risk of IDH and intradialytic HTN varies according to the time of the day of the HD session is unknown.

Methods: Random effects logistic regression models examined the association of HD start time (before 9:00 am [timecat1], 9:00 am to 12:00 pm [timecat2], and after 12:00 PM [timecat3]) with IDH and intradialytic HTN among adults undergoing thrice-weekly maintenance HD (N= 1,938 patients/n=64,503 sessions from the Hemodialysis [HEMO] Study, and N=3,408 patients/n=33,590 from a contemporary large dialysis organization [LDO]). IDH was defined as nadir intra-HD SBP <90mmHg if pre-HD SBP <160mmHg or <100mmHg if pre-HD SBP ≥160mmHg, and intradialytic HTN was defined as any increase in post-HD SBP compared to pre-HD SBP. Models were adjusted for demographics, CV comorbidities, HD dose, HD flux, pre-HD BUN, pre-HD SBP, UFR, HD vintage and HD session length.

Results: Mean age was 58 years and 56% were female in HEMO; mean age was 63 years and 42% were female in LDO. Compared to timecat1, timecat2 and timecat3 were associated with with a 9% (aOR 0.91, 95% CI 0.82-1.01) and a 17% (aOR 0.83, 95% CI 0.75-0.94) lower risk of IDH in HEMO, respectively (Fig 1A). Conversely, compared to timecat1, a monotonic increase in the risk of intradialytic HTN was observed for timecat2 (aOR 1.14, 95% CI 1.05-1.24) and timecat3 (aOR 1.40, 95% CI 1.28-1.53) in HEMO (Fig1B). These findings were consistent in LDO (Fig 1).

Conclusions: In two diverse and large cohorts of HD, we observed a monotonic decrease in the risk of IDH and a monotonic increase in the risk of intradialytic HTN as HD start time progressed throughout the day. Whether HD treatment allocation to certain times of the day in hypotensive-prone or hypertensive-prone patients improves outcomes deserves further investigation.



PO1057

Association Between Pulse Pressure and Extracellular to Intracellular Water Ration in Hemodialysis Patients

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Background: Optimal fluid management is a challenge in patients with end-stage kidney disease (ESRD) on maintenance hemodialysis (HD). Multifrequency bioimpedance spectroscopy (MBIS) is a non-invasive method to estimate body composition, including estimates of extracellular water (ECW) and intracellular water (ICW) and the ratio between both spaces (ECW/ICW). Pulse pressure is a significant risk factor of cardiovascular disease and death in general and dialysis population. Our study aimed to analyse the correlation between systolic, diastolic and pulse pressure with body composition status in ESRD patients before HD.

Methods: We performed a retrospective single-centre cohort study in 93 HD patients. The body composition was measured using the portable whole-body MBIS device, Body Composition Monitor-BCM(®) (Fresenius Medical Care, Bad Homburg, Germany). Blood pressure was measured with OMRON monitors.

Results: The mean age of patients was 64 ± 13 years, mean dialysis vintage 63 (1-352) months, 61% were men, all patients had arteriovenous fistula as vascular access. Sixty-nine (74.2%) patients were fluid overload (FO) with > 1.1 L overhydration. Other data are presented in table 1. We found a statistically significant correlation between the pulse pressure and ECW/ICW ratio (r=0.258; P=0.033) in FO patients. In contrast, there was no significant correlation between systolic, diastolic blood pressure and ECW/ICW ratio in FO patients.

Conclusions: Only pulse pressure and not systolic or diastolic blood pressure values measured before HD are associated with ECW/ICW ratio in FO patients.

Descriptive data of the patients included in the study (N=93)

Variable	All patients (N=93) Mean ± SD	Fluid overload patients (N=69) Mean ± SD	NOT fluid overload patients (N=24) Mean ± SD	P value
Age (years)	64.3 ± 13	64.3 ± 13	64.1 ± 12	0.943
Dialysis vintage (months)	63.2 ± 64	65.8 ± 68	55.8 ± 49	0.509
Systolic blood pressure (mmHg)	151 ± 21	151 ± 22	149 ± 19	0.708
Diastolic blood pressure (mmHg)	78 ± 13	79 ± 13	75 ± 12	0.168
Pulse pressure (mmHg)	73 ± 21	72 ± 22	75 ± 21	0.654
MBIS: Extracellular water (ECW) (L)	18.1 ± 4.2	19.03 ± 4.2	15.4 ± 3.1	<0.0001
MBIS: Intracellular water (ICW) (L)	18.8 ± 4.4	19 ± 4.5	18.3 ± 4.4	0.527
MBIS: ECW/ICW	0.97 ± 0.14	1.01 ± 0.13	0.84 ± 0.1	<0.0001
MBIS: Overhydration (L)	2.14 ± 1.9	2.83 ± 1.6	0.16 ± 1	<0.0001

MBIS= multifrequency bioimpedance spectroscopy; HD=hemodialysis

PO1058

Plasma Refill Rate: A Potential Hemodynamic Marker of Intradialytic Hypotension During Hemodialysis

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Background: Intradialytic hypotension (IDH) is difficult to predict. Continuous hematocrit monitoring (CHM) measures relative blood volume to provide non-invasive dynamic monitoring during hemodialysis (HD). We used CHM data with time-updated ultrafiltration rate (UFR) to estimate plasma refill rate (PRR), a potential mediator of hemodynamic status, and studied its relationship to IDH.

Methods: We used CHM performed at 17 Renal Research Institute HD units from 2017 to 2019 to calculate intradialytic PRR standardized to weight and height. We defined IDH as 1) systolic blood pressure (SBP) <90 mmHg and 2) a drop in SBP ≥20 mmHg or in mean arterial pressure ≥10 mmHg associated with symptoms. IDH-prone was defined as having >20% of treatments with IDH. Uni- and multivariable mixed-effects logistic regression were used to evaluate factors associated with low initial PRR (lower quartile) within the first 10 minutes of HD. Bi- and multinomial logistic regression were used to evaluate the relationship between initial PRR and IDH. Data are presented as mean±SD or aOR; 95% CI.

Results: We studied 2,637 patients (61±15 yrs, 57% male, 51% white) with 184,044 total treatments, interdialytic weight gain (IDWG) 2.1±1.4 kg, and UFR 9.5±4.6 ml/kg/h. IDH occurred in 13.7% and 15.8% of treatments by definitions 1 and 2, respectively. PRR (ml/kg/h) over all sessions was 5.0±8.8, 8.4±6.0, 7.9±7.2, and 7.4±11.4 at 10m, 1h, 2h, and 3h, respectively, with substantial variability at both patient and treatment levels. Older age, low BMI, female sex, black race, low albumin, and multimorbidity were associated with low initial PRR. Patients with low initial PRR were more likely to be IDH-prone by definition 1 (aOR 1.95; 1.01-3.72) and definition 2 (aOR 1.50; 0.87-2.56). Patients with low initial PRR were more likely than patients with high initial PRR to be IDH-prone by definition 1 (aOR 2.12; 1.50-2.74).

Conclusions: The dynamics of PRR vary during an HD session and has promise as a marker of hemodynamic instability. We found that several patient and treatment factors classically associated with IDH were also associated with low initial PRR, independent of

IDWG, SBP, and UFR, and that low PRR was associated with IDH. Further investigation into the predictive utility of PRR throughout HD may offer novel insights to extend the use of CHM.

Funding: NIDDK Support

PO1059

Hypoaldosteronism in Chronic Hemodialysis Patients Causes Intradialytic Hypotension and Is Improved with Fludrocortisone

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Background: Intradialytic hypotension (IDH) affects up to 30% of chronic hemodialysis (CHD) pts and hypoaldosteronism (HA) is common in these pts. Aldosterone (aldo) exerts potent non-genomic hypertensive effects via its arterial aldo receptor & enhanced sympathetic nervous system activity.

Methods: We identified 11 consecutive CHD pts with severe IDH & normal cosyntropin stimulation tests that had HA. Mean PRA was 3.3 +/-7.7 ng/mL/hr & serum aldo was 2.9 +/- 1.6 ng/dL. All pts had failed low temperature dialysate, UF and Na modeling and maximum doses of midodrine. We studied pre & post HD SBP & DBP, number of episodes of systolic BP <100 & mean UF volume (Kg) for the 13 dialysis treatments pre fludrocortisone (FC), 1 month post FC & 6 months post FC. FC dose was 0.1 mg BID. The mean pt age was 69 +/- 11 years & dialysis duration was 5.1 +/- 2.3 years.

Results: The mean +/- SD pre & post HD SBP & DBP & the mean number of hypotensive episodes were significantly improved at 1 & 6 months post-FC (Table 1). No changes occurred in UF volume. 4 pts have remained on FC for 2 years or more without side effects and with sustained good results.

Conclusions: Refractory IDH is associated with HA in CHD pts. FC therapy decreases IDH episodes as well as improves pre & post SBP & DBP & can be used safely in CHD pts.

Table 1. Results for pre & post HD SBP & DBP, Hypotensive episodes & UF volume.

	Pre-FC	1 Month Post-FC	Month 6 Post-FC	P-value (with Box-Correction)
Pre-SBP mmHg	117.9 (20.5)	131.8 (16.3)	131.0 (19.6)	**<0.001**
Pre-DBP mmHg	64.9 (12.6)	71.7 (16.0)	70.0 (16.0)	**0.002**
Post SBP mmHg	106.0 (14.5)	122.6 (17.9)	114.9 (17.2)	**<0.001**
Post-DBP mmHg	58.0 (11.1)	65.2 (16.0)	60.4 (11.0)	**<0.001**
Number of Episodes SBP <100	2.9 (2.3)	1.0 (1.4)	1.4 (1.6)	**<0.001**
UF in kg	3.4 (9.1)	3.2 (2.2)	3.3 (1.9)	0.780

PO1060

Feasibility and Benefits of Hemodialyzer Filtration of Contaminated Water in Poor Rural Communities in Ghana

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Background: Contaminated water supplies for drinking water are a source of health problems in poor communities. Hemodialyzers with a pore size of 0.003 micrometers have been known to be effective in preventing transfer of bacteria and most viruses. Our NGO, "Easy Water for Everyone," investigated prospectively the incidence of diarrhea, before and after implementation of water treatment utilizing reused hemodialyzers in poor villages lacking electricity and sanitation in Ghana.

Methods: Data were collected monthly regarding the incidence of diarrhea and death in households of 8 villages that have no electricity during February to November 2018. In 4 "study" villages the main source of drinking water (river), was processed after the first 5 (pre) months through a set of 8 hemodialyzers that produced purified water at ~250 L per hour. River water was pumped weekly into an elevated holding tank to be drawn by gravity through the dialyzers whenever the faucet was opened. Manual back flushes (4x/day) by trained villagers maintained high output of clean water. The same data collection in 4 "control" villages where the polluted water was not (yet) treated during the same 10 month period. We also assessed the function of the devices over ≥11 months of use in 9 villages.

Results: [1] Monthly rates of diarrhea in the study villages decreased from 18 to 5 per 100 villagers from the pre to the post period for a rate reduction by 72 % (rate ratio = 0.27). In the control group the average monthly rate during the same calendar months decreased by 23% (p >0.05) from the first to the second 5 months. After >11 months of daily filtration in 9 villages (population ~2000) none of the filters had to be replaced, suggesting that daily back-flush management prevented hemodialyzer clogging.

Conclusions: We demonstrated feasibility and success of sustaining a simple and efficient treatment of infected water for entire villages in absence of available electricity. The continuous function over >11 months indicates low cost of the device over time. The reduction in diarrhea from before to after initiation of the hemodialyzer filtration device is large. The simplicity of hemodialyzer filtration by gravitational feed, low cost and relative ease suggest wider application to other needy villages.

Funding: Private Foundation Support

PO1061

Combining a Heparin-Grafted Dialyzer with a Citrate-Enriched Dialysate Offers Acceptable Dialysis Adequacy Avoiding Systemic Anticoagulation: Results of the Randomized Noninferiority Evocit Study

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Background: The combined use of a heparin-grafted membrane with a citrate-enriched dialysate is a hemodialysis (HD) strategy with low circuit clotting rates while avoiding systemic anticoagulation. Its adequacy in comparison to HD using systemic anticoagulation is unknown.

Methods: Prevalent HD patients were recruited for a randomized crossover non-inferiority trial powered at >90% to detect a prespecified non-inferiority threshold of 10% $spKt/V_{urea}$ (NCT03887468). HD using a heparin-grafted dialyzer in combination with a 1.0 mmol/L citrate-enriched dialysate ("evocit") was compared to HD using a heparin-grafted dialyzer, systemic unfractionated heparin and bicarbonate-based dialysate ("evohep"). Each treatment arm lasted 4 weeks: 3x4hours HD/week with fixed blood and dialysate flow rates and midweek biological analyses.

Results: 26 patients received 617 HD sessions: 307 evocit and 310 evohep sessions. Mean $spKt/V_{urea}$ was 1.46±0.23 for evocit and 1.50±0.24 for evohep sessions (p=0.06). Mean of the paired difference in $spKt/V_{urea}$ was 0.04 with a 95%CI of -0.002 to 0.08, the upper bound of the estimate lying within the prespecified non-inferiority threshold (i.e. <0.15). Urea reduction rate (RR) was 71.5±5.5% vs 72.1±5.7% and bèta2microglobulin RR 37.4±8% vs 37.8±8% for evocit and evohep sessions. Processed blood volume was 75.4±3L vs 75.8±1.5L and online Kt was 47.3±5L vs 48.3±4L for all evocit and evohep sessions. Circuit thrombosis leading to premature treatment end occurred in 13/307 (4.2%) of evocit sessions (n=6), but in none of the evohep sessions (p=0.0002), with a median 36(20-46)min treatment time shortening without impact on effective treatment times overall (236±12 vs 238±4min for evocit vs evohep). Retransfusion failure occurred in 3/307 (0.98%) of evocit sessions and none of the evohep sessions (p=0.25).

Conclusions: HD avoiding systemic anticoagulation using a heparin-grafted dialyzer with a citrate-enriched dialysate offers recommended $spKt/V_{urea}$ dose and is not inferior to HD using systemic anticoagulation in terms of $spKt/V_{urea}$. Circuit clotting complications occurred at low rates during evocit sessions and did not have clinically significant repercussions on dialysis efficacy.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1062

Cinacalcet Use and the Risk of Gastrointestinal (GI) Bleeding Among Hemodialysis Subjects with Secondary Hyperparathyroidism (SHPT) in the Dialysis Outcome and Practice Patterns Study (DOPPS)

Gill Karminder, Tzu-Chieh Lin, Rohini Hernandez. *Amgen, Inc., Thousand Oaks, CA.*

Background: Cinacalcet is an oral calcimimetic for the treatment of SHPT in US adult hemodialysis (HD) patients. We conducted an observational study to evaluate the potential association between cinacalcet and fatal and non-fatal GI bleeding using data from DOPPS, an observational longitudinal data system of a random sample of patients from dialysis facilities in more than 20 countries.

Methods: The eligibility criteria for study cohort inclusion was individuals ≥18 years of age with ESRD receiving in-center hemodialysis at a DOPPS facility for a minimum of four months during calendar years 2009-2015, in the following countries: Australia, New Zealand, Canada, France, Germany, Italy, Spain, Sweden, Japan, the UK, and the US. Nested within the cohort, we conducted a matched case-control study (1:4 matching ratio) to estimate the association between cinacalcet use and GI bleeding events. We used risk-set sampling and matched on the following: (1) duration of follow-up (a same number of days), (2) time on dialysis (≤1 year, >1 year), (3) age (+/- 1 year), and (4) sex. Multivariable conditional logistic regression models were used to generate adjusted odds ratios (ORs) and 95% confidence intervals (CIs), accounting for baseline comorbidities.

Results: A total of 9,349 HD patients with SHPT met the eligibility criteria for the cohort study, 4,399 subjects from the United States and 4,950 subjects from countries outside the United States. We estimated the incidence rate of hospitalization or death due to GI bleeding (per 1,000 person-years [PYs]) in the US as 10.2 (95% CI: 7.9, 13.3); and 26.4 (95% CI: 23.5, 29.7) in countries outside the US. There was no association between cinacalcet exposure and GI bleeding (fatal or nonfatal events) in HD subjects with SHPT in US (adjusted OR: 0.68 [95% CI: 0.47, 1.00]) and ex-US (adjusted OR: 0.75 [95% CI: 0.50, 1.12]) populations.

Conclusions: Cinacalcet use was not associated with an increased risk of GI bleeding events among US and ex-US adult hemodialysis subjects with SHPT. The study results are broadly generalizable to adult subjects with ESRD receiving center-based hemodialysis in the US and selected countries outside the US.

Funding: Commercial Support - Amgen

PO1063

Medium Cut-Off Dialyzer Improves Erythropoiesis-Stimulating Agent Resistance in a Hepcidin-Independent Manner in Maintenance Hemodialysis Patients

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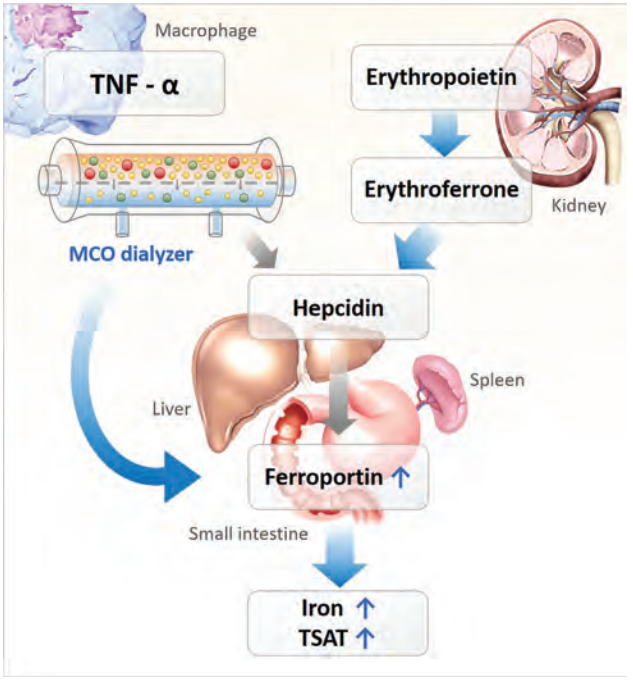
Background: The response to erythropoiesis stimulating agents (ESAs) is affected by inflammation linked to middle molecules in hemodialysis (HD) patients. We evaluated the effect of a medium cut-off (MCO) dialyzer on ESA resistance in maintenance HD patients.

Methods: Forty-nine patients who underwent high-flux HD were randomly allocated to the MCO or high-flux group. The primary outcome was the changes of erythropoietin resistance index (ERI; U/kg/wk/g/dL) between baseline and 12 weeks. The biomarkers associated with iron metabolism and inflammation at 12 weeks were compared between groups.

Results: The MCO group showed significant decrease in the ESA dose, weight-adjusted ESA dose, and ERI compared to the high-flux group at 12 weeks (all $p < 0.05$). In the MCO group, the ESA dose, weight-adjusted ESA dose, and ERI did not change until 8 weeks compared to those at baseline, but decreased significantly at 12 weeks (all $p < 0.01$). Serum iron and transferrin saturation were higher in the MCO group at 12 weeks (both $p < 0.05$). The MCO group showed a greater reduction in TNF-α and lower serum TNF-α level at 12 weeks compared to the high-flux group ($p = 0.025$ and $p = 0.027$), whereas no differences were found in the reduction ratio of hepcidin and serum levels of erythropoietin, erythroferrone, soluble transferrin receptor and hepcidin between groups.

Conclusions: HD with MCO dialyzer improves ESA resistance compared to high-flux HD in maintenance HD patients. The MCO dialyzer provides superior removal of the inflammatory cytokine such as TNF-α and thus improves iron metabolism in a hepcidin-independent manner.



The iron metabolism regulatory pathway Blue arrows indicate dominant effects.

PO1064

Recent Trends in Acute Care Admissions Among Medicare Beneficiaries Undergoing Dialysis

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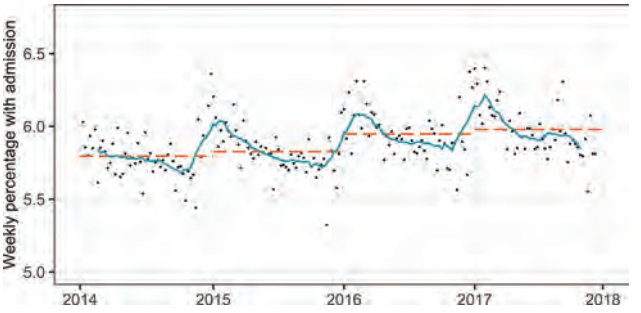
Background: While the rate of hospital admissions has been a bedrock measure of morbidity among dialysis patients, patients today may receive acute care during a hospital admission, observation status, or an emergency department (ED) visit. There are no public reports summarizing the composite rate of these encounters among dialysis patients. We used claims data to estimate rates of acute care admissions in dialysis patients with Medicare fee-for-service coverage.

Methods: Using Medicare Limited Data Sets, we identified all patients with Medicare Part B claims documenting outpatient dialysis from January 2014 to December 2017. For each calendar week (Monday to Sunday), we identified patients with at least one outpatient dialysis session, who were alive at the end of the week, and who were not hospitalized at the last midnight of the week. We calculated the proportion of patients who were admitted to the hospital, observation status (with discharge to home), or an ED (with discharge to home) during the subsequent calendar week. From the time series of weekly admission risks, we fit an autoregressive integrated moving average model, both overall and within strata defined by concurrent enrollment in Medicaid.

Results: From 2014 to 2017, mean weekly incidence of acute care admission increased from 5.8% in 2014 to 6.0% in 2017 ($P < 0.01$ from test of secular trend), as displayed. The incidence of hospital admission was unchanged ($P = 0.35$), whereas the incidence of both observation status admissions and ED visits increased ($P < 0.01$). In 2017, 49% of acute care admission volume was attributed to observation status admissions and ED visits. In patients with Medicare coverage alone and patients with concurrent enrollment in Medicaid, mean weekly incidence of acute care admission increased to 5.2% and 6.9%, respectively, in 2017.

Conclusions: From 2014 to 2017, the incidence of acute care admission increased in dialysis patients with Medicare fee-for-service coverage, mostly because of increasing incidence of observation status admissions and ED visits.

Funding: Commercial Support - Fresenius Medical Care



PO1065

Poor Vitamin K Status Associates with Worse Clinical Outcome Independent of Coronary Artery Calcium and Aortic Valve Calcium in ESRD

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Background: Patients with end-stage renal disease (ESRD) are at high risk of vitamin K deficiency and vascular calcification. The association between vitamin K status and vascular calcification is non-affirmative in clinical observations. We investigated the association of vitamin K status with all-cause mortality in ESRD and the modification effect of vascular calcification in this scenario.

Methods: We studied 493 stable ESRD patients (median age 55 years, 66% males) comprising non-dialysis patients (n=321), prevalent peritoneal dialysis (n=122) and hemodialysis patients (n=50). Plasma dephosphorylated-uncarboxylated matrix-Gla protein (dp-ucMGP), a circulating marker of vitamin K deficiency, and other relevant clinical and biochemical data were determined at baseline. A cohort of 553 controls (median 51 age years, 45% males) was referred to estimate vitamin K status in healthy subjects. Vascular calcification was estimated with coronary artery calcium (CAC, n=237) and aortic valve calcium (AVC, n=223) among ESRD patients undergoing cardiac computed tomography scan.

Results: Plasma dp-ucMGP (median 1445 pmol/L) levels were substantially elevated in ESRD patients compared to healthy subjects (median 376 pmol/L). During median 42 months' follow-up, 92 patients died (19%) and 128 patients (26%) underwent renal transplantation. 1-SD increase of dp-ucMGP associated with increased all-cause mortality (1.19 (1.01-1.40), sub-hazard ratio (95% confidence interval)), with adjustment for age, sex, presence of cardiovascular disease, diabetes, body mass index, inflammation, handgrip strength and dialysis. In subgroup analysis further adjusted for presence of CAC or AVC, dp-ucMGP remained as an independent risk factor of mortality (1.27 (1.03-1.56) and 1.36 (1.05-1.66), respectively). In multivariate linear regression model, increased dp-ucMGP levels were not associated with quantified calcification suggested by CAC ($p=0.11$, $R^2=0.30$) and AVC ($p=0.84$, $R^2= 0.12$).

Conclusions: Vitamin K deficiency is evident in ESRD and strongly associated with an increased risk of mortality which is not modified by the presence of vascular calcification. Plasma dp-ucMGP was not an independent risk factor of calcification quantified by CAC and AVC.

PO1066

Calcium Carbonate-Pre-Added Cheese to Improve Compliance, Nutrition, and Metabolic Balance of Patients on Renal Replacement Treatment

Gianluigi Ardissino,[1] Valentina Capone,[1] Elisabetta Margiotta,[2] Isabella Cropanese,[1] Francesca Raffiotta,[2] Giovanni Montini,[1] Piergiorgio Messa.[2] *[1]Pediatric Nephrology, Dialysis and Transplantation, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy; [2]Nephrology, Dialysis and Transplantation, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy.*

Background: Patients with chronic kidney disease have several dietary limitations that make their diet unappealing with detrimental consequences as adherence to prescriptions, malnutrition and overall poor quality of life. Cheese, an important component of the Western diet, has high phosphorus (P) content thus its consumption is generally restricted in patients on renal replacement therapy (RRT).

Methods: A special cheese was prepared by adding a fixed concentration of CaCO3 (5 gr/L) to cow milk prior to production procedures. The cheese was then provided to a cohort of patients on chronic RTT with the working hypothesis that while eating the modified cheese patients would have benefited from the phosphorus-binding effect of CaCO3. After a run-in period of 1 month, all patients were randomly assigned to receive standard cheese (SC) followed by modified cheese (FriP) or the opposite sequence in a double blind and cross-over fashion for 1 month for each product. The increase in inter-dialysis (48 hrs) P (DP) was regularly and repeatedly (n: 5) measured during each of the 2 periods. A washout period of 1 week was introduced between treatment periods.

Results: Twenty-one patients were enrolled and 16 successfully completed the 2 treatment periods. Drop outs were due to transplantation, COVID-19 infection or to documented non-adherence to the protocol. Observed mean (sd) DP were as follows: Run-in: 2.8 (0.7) mg/dL, SC: 2.8 (0.85) mg/dL, FriP 2.4 (0.61) mg/dL with the latter being significantly lower compared with both other periods. Pre-dialysis P was also lower with FriP compared with SC: 5.00 (1.00) vs 4.66 (0.91) while Pre-dialysis Ca was not diffent: 9.24 (0.73) vs 9.24 (0.63) with SC and FriP, respectively. All patients appreciated both products equally and the mean amount consumed per week was not different: SC: 307 gr vs FriP: 283 gr (p: 0.56). All patients reported a significant gratification by reintroducing cheese consumption in their diet.

Conclusions: In conclusion, FriP cheese may reduce dietary limitations of patients on RRT mith significant benefits on: malnutrition, adherence to P binders prescription and ultimately to quality of life.

PO1067

Efficacy of Double-Dose Influenza Vaccine with a Booster Compared with Standard Dose in Hemodialysis Patients: Randomized Controlled Trial

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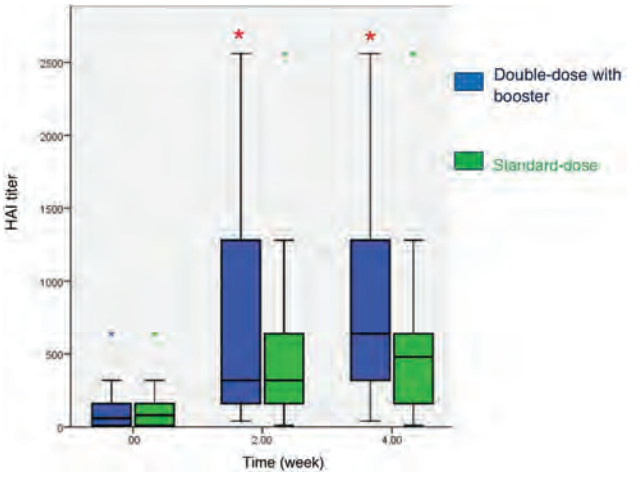
Background: Patients on hemodialysis may be at higher risk of illness and death from infected of influenza virus. The efficacy of dose of influenza vaccine across dialysis patients is uncharacterized. We assessed the efficacy of double-dose and booster influenza vaccine versus standard-dose in hemodialysis patients.

Methods: A prospective, open-label, randomized study with 100 hemodialysis patients were enrolled. Double-dose and booster group(n=50) received two doses of IM inactivated seasonal quadrivalent influenza vaccine and one dose at the next 2 weeks while standard-dose group(n=50) received one dose of vaccine. Demographics and co-morbidity were collected at baseline. HAI titers were assessed prior to vaccination and at 14, 28 days post-vaccination.

Results: Hemodialysis patients had age of 61 years approximately and had similar baseline laboratory and co-morbidity. Double-dose with booster group had higher rate of seroprotection(100% vs 86%, p=0.006) and seroconversion(84% vs 60%, p=0.008) measured by using HAI against H3N2 were different significantly. Moreover, Double-dose with booster group had higher rate of sustained antibody level at 4 weeks after first vaccination measured by using HAI against H1N1(88% vs 52%, p=0.006) and H3N2(84% vs 72%, p=0.003) were significant differences. However, no differences in HAI against B strains were seen. At 4 weeks after first vaccination, HAI against H1N1, H3N2, B/Colorado and B/Yamagata are similar in both groups.

Conclusions: The double-dose with booster influenza vaccine can provide higher seroprotection and seroconversion rates of HAI against in H3N2 but no different in other strains compared to standard-dose. This study is needed to explore the effect of double-dose with booster vaccine against all causes mortality or influenza related outcomes for adults undergoing hemodialysis compared to the standard-dose.

Funding: Private Foundation Support



PO1068

Temporal Trends in Clinical Phenotype, Bacterial Genotype, and Clinical Outcomes in Hemodialysis-Dependent Patients with *Staphylococcus aureus* Bacteremia

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Background: *Staphylococcus (S.) aureus* bacteremia (SAB) is a common and potentially lethal infection among hemodialysis-dependent (HD) patients. The determinants of clinical outcomes in HD patients with SAB are not completely understood. We evaluated temporal trends in SAB-attributable mortality, metastatic infections, and bacterial genotype in HD patients over a 20-year period.

Methods: Hospitalized, non-neutropenic HD and non-HD adults with monomicrobial SAB were prospectively enrolled from Jan 1, 1995 to Dec. 31, 2015. Clinical characteristics, bacterial isolates, and outcome data were collected. Isolates were previously genotyped using *spa* typing. Differences between HD and non-HD patients were estimated using medians/quartiles or counts/percentages with statistical significance evaluated with Mann-Whitney-U or Fisher's Exact test. Proportions of participants experiencing each outcome were calculated overall and by calendar year. Secular trends in proportions were estimated with linear regression and associations between bacterial genotypes, clinical characteristics, and clinical outcomes were estimated using univariate and multivariate logistic regression.

Results: Among 2,347 unique participants, 495 (21.1%) were HD. Compared to the non-HD patients, HD patients were younger (median 57 years (y) vs 60 y, p=0.002) and more likely to be Black (74.6% vs 26% p<0.001), female (48.1% vs 42.1% p=0.019), and to have diabetes (56.2% vs 33.8% p<0.001). HD patients experienced significant increases in the annual prevalence of age- and diabetes-adjusted SAB-attributable mortality (0.49% per year p=0.05), metastatic infections (0.79% per year p=0.028), and infection with the highly virulent Methicillin resistant strain USA300 (0.97% per year, p<0.001). The increase in USA300 infections did not appear to explain the observed increases in metastatic infections (Odds Ratio [OR] 1.33, Confidence Interval [CI] 0.55-3.21) or SAB-attributable mortality (OR 0.57, CI 0.14-2.32).

Conclusions: Clinical characteristics differed significantly between HD and non-HD patients with SAB. Increases in mortality and metastatic infections over time were not explained by the rise in more virulent strains of *S. aureus*, but may be partially explained by changes in patients' characteristics.

PO1069

Hemodialysis-Associated Increased Intraocular Pressure: A Vision-Threatening Complication

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Introduction: Elevation of intraocular pressure (IOP) is a potential complication of hemodialysis (HD). When patients with risk factors for angle closure undergo HD, aqueous humor volume may increase, thus elevating IOP.

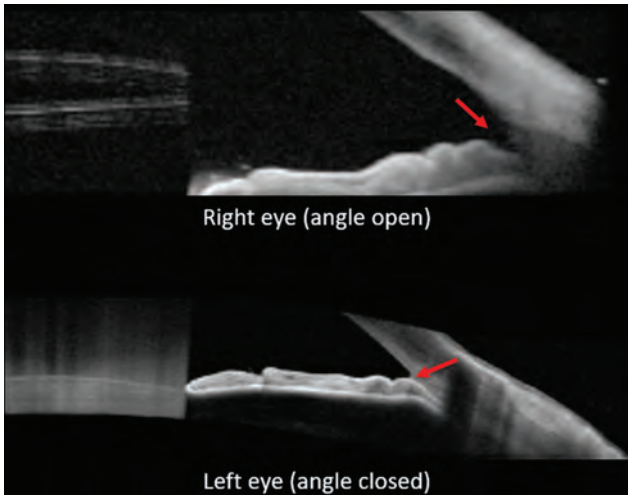
Case Description: A 71M with ESRD secondary to type II diabetes and proliferative diabetic retinopathy reported one month of headache, left-sided eye pain and photophobia, and periorbital redness occurring with dialysis. Ophthalmology diagnosed neovascular glaucoma following an elevated IOP of 36 mmHg in the left eye (normal < 22). Pre-dialysis IOP returned to normal with medical therapy. Dialysis modifications reduced the rate and magnitude of change in plasma osmolality (Table 1). However, elevated IOP and symptoms persisted and he underwent surgery on 5/6/2020 with full resolution of symptoms.

Discussion: Sitprija et al. (1964) first observed increased IOP during HD in 83 of 89 cases. Subsequent studies report that IOP may increase, decrease, or remain unchanged

during HD. One proposed mechanism for increased IOP is as plasma urea is reduced, the aqueous humor lags, becoming hypertonic relative to plasma. The choroid may also thicken, obstructing outflow. We increased dialysate sodium and reduced HD time and dialysate flow. Other strategies include infusing mannitol or hyperosmolar glucose, ultrafiltration to increase plasma oncotic pressure, and more frequent or peritoneal dialysis. Nephrologists should have heightened awareness for angle-closure glaucoma and conditions predisposing to obstruction of aqueous outflow, including proliferative diabetic retinopathy. Headache, ocular pain, or visual changes during dialysis warrant urgent ophthalmic evaluation.

Table 1

Date	Pre-HD IOP (R/L; mmHg)	IOP 3 hrs. into HD (R/L; mmHg)	Net Δ in IOP (R/L; mmHg)	% Δ in IOP (R/L)
4/25/20	9/12	12/25	+3/+13	+33%/+108%
4/29/20	12/25	16/33	+4/+8	+33%/+32%
5/25/20	13/12	15/16	+2/+4	+15%/+33%



Optical coherence tomography on 4/23/20

PO1070

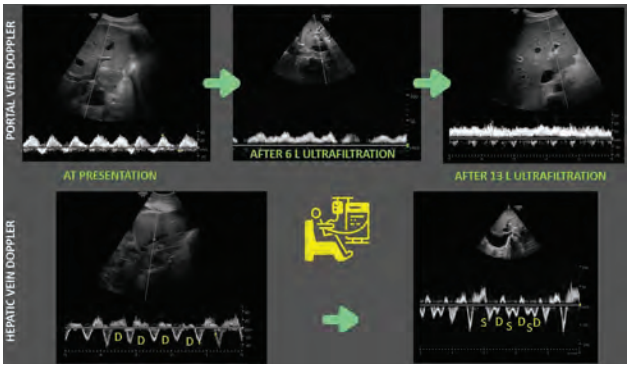
Point-of-Care Ultrasonography to Assess Venous Congestion and Guide Ultrafiltration: Another String to Our Bow?

Saqib Mahmud, Abhilash Koratala. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Point of care ultrasound (POCUS) is rapidly evolving as a valuable adjunct to bedside clinical examination in internal medicine and subspecialties. However, there is no single accurate sonographic application to determine fluid volume status. While sonographic assessment of inferior vena cava (IVC) is popular among novice POCUS users, its isolated use to determine and monitor volume status is subject to numerous limitations. Similarly, lung ultrasound gives an idea of left sided filling pressures but does cannot quantify venous congestion, which can have deleterious consequences in various organ systems including kidney. Novel scoring systems like venous excess ultrasound grading (VExUS) allow objective assessment of volume status using portal and hepatic venous Doppler waveforms in addition to IVC measurements. Herein, we demonstrate the natural history of these waveforms in a patient with advanced chronic kidney disease (CKD) during the course of ultrafiltration.

Case Description: A 39-year-old man with a history of CKD stage 5 presented with generalized weakness, shortness of breath on exertion, worsening leg edema and weight gain despite being compliant with prescribed diuretic therapy. He was admitted and initiated on hemodialysis for refractory volume overload. POCUS showed mild pericardial and pleural effusion as well as an enlarged IVC of ~3cm with <50% collapse. In addition, Doppler ultrasound showed 100% pulsatility of portal vein (normal <30%) with systolic flow reversal and hepatic vein with S wave reversal and only D wave below the baseline. These findings constitute VExUS grade 3, suggestive of severe congestion. While IVC continued to indicate high right atrial pressures, the Doppler waveforms showed parallel improvement with ultrafiltration reaching VExUS grade 1 (mild congestion) at discharge [Figure]. No episodes of intradialytic hypotension occured.

Discussion: POCUS-derived venous waveforms aid in monitoring the effectiveness of decongestive therapy and guide the amount of ultrafiltration.



PO1071

Can the Assessment of Ultrasound Lung Water in Hemodialysis Patients Be Simplified?

Claudia Torino,[2] Rocco Tripepi,[2] Maurizio Postorino,[1] Giovanni Tripepi,[2] Charalampos Loutradis,[3] Pantelis Sarafidis,[3] Francesca Mallamaci,[1,2] Carmine Zoccali.[2] *[1]Nephrology Unit, GOM Reggio Calabria, Reggio Calabria, Italy; [2]IFC-CNR, Reggio Calabria, Italy; [3]Aristoteleio Panepistemio Thessalonikes, Thessaloniki, Greece.*

Background: Lung Ultrasound (US) reliably estimates lung water and it is increasingly applied in clinical practice in dialysis patients. Lung water is measured by applying a semi-quantitative US score summing up the US-B lines detected in 28 lung intercostal spaces (LIS). A simplified assessment restricted to 8 LIS only has been proposed. However, the agreement among the scores has not been studied and their prognostic value has never been compared.

Methods: We included in the analysis 303 HD patients in which the pre-dialysis US-BL score was measured at baseline with both the semi-quantitative and the simplified method. The time needed for performing the 28-LIS and the 8-LIS score by six independent assessors with various experience on lung US assessment was accurately measured. Patients were divided into 4 categories, according to pre-established cut-offs specific for the two methods (28-LIS score: <5;6-15;16-30;>30 US-BL; 8-LIS score: <10;11-20;21-50;>50 US-BL). The prediction power of these scores was assessed by the explained variance (R^2).

Results: The 28-LIS score and the 8-LIS score were highly inter-related (ρ=0.93,P<0.001). During a mean follow-up of 3 years, 112 patients died and 129 experienced a CV event. At univariate and multivariate analysis, both scores were associated to the study outcomes. The R^2 of the 28-LIS score for death was 4.1% and that for CV events 4.6%. The corresponding R^2 of the 8-LIS score were 5.4% (death) and 4.7% (CV events), values close to those of the 28-LIS score. Accordingly, when the two scores were separately added to a clinical model including easily available clinical variables the R^2 of the model including the 28-LIS score (death:31.1%; CV events:23.9%) were again very similar to those of the 8-LIS score (30.7% and 23.1%, respectively). The median time needed to perform the examination was 3:05 min (IQR 2:22–5:00 min) for the 28 LIS score and 1:35 min (IQR 1:16–2:00 min) for the 8 LIS score.

Conclusions: The simplified 8-LIS score is tightly related to the classical 28 LIS score and the two scores hold an almost identical predictive power. Even though the 28-LIS score demands less than 5 minutes, the 8-LIS score can be done in only about 90 sec. and it is therefore better suited for application in everyday clinical practice in hemodialysis units.

PO1072

Longitudinal Assessment of Random Variability in ICH-CAHPS Scores

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Background: The Centers for Medicare & Medicaid Services mandates use of the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH-CAHPS) survey to assess dialysis patients' experience of care. Survey responses, collected twice annually and reported at the facility level, are intended to evaluate facility performance over time and to compare across facilities at a given time. In order to be useful for these purposes, the random variability in ICH-CAHPS scores must be relatively low.

Methods: ICH-CAHPS scores were analyzed among 2735 facilities managed by a large dialysis organization that had at least one ICH-CAHPS score available between 2014 and 2018. The association between Center Global Rating score (1 of the 6 ICH-CAHPS domains) and survey period was assessed using a mixed model with random slopes and intercepts for each facility. Mean squared residuals were calculated for each facility and categorized on the basis of the number of survey responses received at the facility. Facilities with available scores in all 9 survey periods analyzed (N = 1074) were assigned to quintiles based on their position within the distribution of scores in each survey period, and movement across quintiles was assessed longitudinally.

Results: The mean Center Global Rating score in the fall of 2018 was 64.9, with an average increase of 0.2 points per period over the subsequent 8 survey periods. However, random variation in scores was considerable and dependent on the number of survey

responses received. The root mean square error, a measure of random variation, ranged from 6.9 points for facilities with >27 responses to 9.2 points for facilities with 11 to 12 responses. Among facilities with survey responses available in all 9 periods, movement between quintiles was frequent, with 39.7% of facilities occupying 4 of the 5 possible quintiles at least once, and 11.5% occupying all 5 quintiles.

Conclusions: Within facilities, there is substantial random variation in ICH-CAHPS scores over time. This diminishes the utility of ICH-CAHPS for its intended purposes. Improvements to ICH-CAHPS, or development of alternative measures of patient experience, are needed to enable accurate assessment of facility performance and to inform patient care.

PO1073

Implication of Trends in Timing of Dialysis Initiation on Population Incidence of ESRD

Chi-yuan Hsu,[1,2] Rishi V. Parikh,[2] Leonid Pravoverov,[2] Sijie Zheng,[2] David V. Glidden,[1] Thida C. Tan,[2] Alan S. Go.[2,1] *[1]University of California San Francisco, San Francisco, CA; [2]Kaiser Permanente, Oakland, CA.*

Background: In the past two decades, eGFR at start of chronic dialysis worldwide have changed notably. How changes over time in the likelihood of dialysis initiation at any given eGFR level impacts the population burden of ESRD has not been not well-defined.

Methods: We analyzed data from 2001-2015 in successive 3-year intervals among adult members of a large, integrated health care delivery system in Northern California who had ≥1 outpatient serum creatinine in the prior year. One-year risk of initiating chronic dialysis was delineated stratified by starting eGFR levels per 3-year cohort. To assess multivariable-adjusted temporal trends, we evaluated the significance of a 3-year cohort term in a logistic regression model adjusting for age, gender, race, and diabetes mellitus status. We then estimated a potential reduction in dialysis initiation in 2013-2015 using the relative difference between the standardized 1-year risks (95% CI) in 2001-2003 and 2013-2015.

Results: Among those with eGFR 16-17 mL/min/1.73m^2 (N=2753), 14-15 mL/min/1.73m^2 (N=2074), and 10-13 mL/min/1.73m^2 (N=2655), the 1-year risk of initiating dialysis increased for every 3-year period by 11% (adjusted odds ratio [aOR] 1.11 [95% CI:1.03 to 1.21]), 11% (aOR 1.11 [1.03 to 1.20]) and 7% (aOR 1.07 [1.01 to 1.14]) respectively, adjusting for age, gender, race, and diabetes mellitus (Figure). We estimate that incidence of ESRD could have potentially been 16% (95% CI:13% to 18%) lower if there were no changes in system-level practice patterns or patient-related or other factors from 2001-2003 to 2013-2015.

Conclusions: Our data suggest that approximately two thirds of the target 25% relative reduction in new ESRD cases by 2030 called for in the White House AAKH initiative could potentially be achieved by changes in the timing of initiation of chronic dialysis.

Funding: NIDDK Support, Other U.S. Government Support

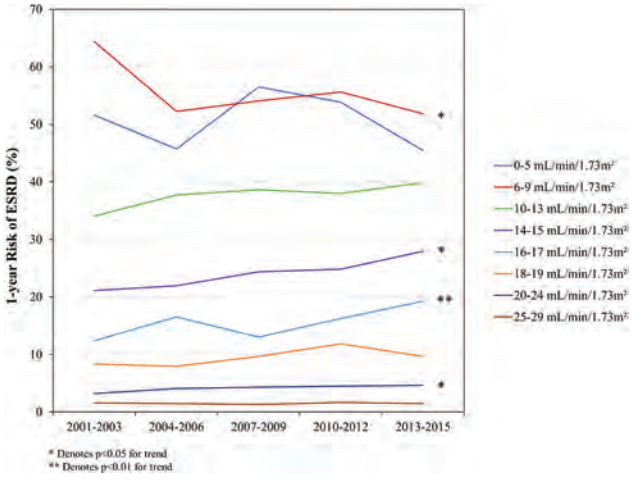

FIGURE: Annual risk of initiating chronic dialysis by calendar year and index eGFR level, 2001-2015.

PO1074

Investigation and Analysis of Post-Dialysis Fatigue in Maintenance Hemodialysis Patients

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Background: post-dialysis fatigue is one of the concerns in recent years. The time of fatigue recovery can be used to predict the hospitalization rate and mortality rate. At the same time, there are few reports on the relationship between maintenance hemodialysis (MHD) and protein energy consumption (PEW). The purpose of this study is to investigate the status of fatigue in MHD patients, analyze the factors affecting fatigue and its correlation with PEW, and provide possible effective interventions.

Methods: 346 MHD patients in our blood purification center were selected. MHD patients were assessed with self-made general data questionnaire, international standard fatigue assessment scale (FAI) and subjective comprehensive nutrition assessment (SGA), and their blood routine and biochemical results were collected for statistical analysis

Results: More than half of patients claimed to experience post-dialysis fatigue. Time to recover from hemodialysis(TIRD) was different: the interquartile range time was 2.00(0.00, 3.00) hours. In the study, 30.1% patients reported no fatigue after hemodialysis. Recovery time in 30.5%% patients was more than 30 minutes to 2 hours, 26.1% was 3 to 4 hours, 12.3% was 5 to 12 hours, 1.0% patients took longer time to recover from a dialysis session. According to the recovery time, these patients were divided into three groups. Among the three groups, SGA score, the ultrafiltration, the serum sodium and bicarbonate level after dialysis showed significant difference. It was showed by the unconditional logistic regression analysis that high SGA(OR=1.312,95%CI 1.163-1.481), scoreultrafiltration (OR=2.15,95%CI 1.24-3.41) and serum sodium (OR=0.83,95%CI 0.71-0.98) were associated of TIRD.

Conclusions: The incidence of post-dialysis fatigue in MHD patients is high. Medical staff should pay attention to the nutritional status of MHD patients, control their weight growth, and maintain the stability of electrolyte and bicarbonate levels such as serum sodium.

PO1075

Recurrent Episodes of Angioedema During Hemodialysis

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Introduction: Angioedema during hemodialysis (HD) is uncommon but can be potentially life-threatening. We report a patient with recurrent episodes of angioedema during HD who posed a diagnostic and therapeutic challenge.

Case Description: A 73 year old male with end stage renal disease was initiated on HD in 2012. He did well on HD till February 2018 when he developed angioedema along with itchiness two minutes after initiation of HD and required intubation for airway support. No medications, food ingestions, contact with any external agents or insect bite were identified which may have triggered the angioedema. His C4 was not low, C1 esterase inhibitor and C1Q binding assay were normal, radioallergosorbent test was negative to aeroallergens, food allergens and latex. As no specific cause for angioedema was identified, a dialyzer reaction was considered. He was being dialyzed via Optiflux F180NR dialyzer (electron beam sterilized polysulfone membrane) since initiation of HD in 2012. He was subsequently dialyzed with other dialyzers including Optiflux F180 NR (sterilized with ethylene oxide), Exeltra 190 (gamma radiation sterilized tricellulose acetate membrane) and Rexeed 15S (gamma radiation sterilized polysulfone membrane). He developed angioedema with each of these dialyzers within a few months of using them and in spite of premedication with intravenous methylprednisolone, diphenhydramine and ranitidine and also rinsing the dialysis circuit with three liters of normal saline prior to HD initiation. These episodes of angioedema occurred within the first 30 minutes of HD initiation and required intubation on two occasions. At this point, a possible reaction to the dialysis blood tubing, which was ethylene oxide sterilized, was considered and the patient was switched to Streamline Express dialyzer (polyethersulfone membrane with pre-attached blood tubing, both sterilized with gamma radiation). The patient has had no further episodes of angioedema since this change was made five months back and has been off steroids for the last two months.

Discussion: In patients with unclear etiology of angioedema during HD, exposure to all components of the HD circuit, including the dialysis blood tubing, should be considered as a potential cause of angioedema and should be systematically ruled out.

PO1076

The Impact of Serum Albumin Levels on Excess Hospital Spending

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Background: National Kidney Foundation K/DOQI guidelines recommend that hemodialysis patients have serum albumin (sA) levels greater than or equal to 4 g/dL. Serum albumin lower than 4 g/dL has long been associated with an increased risk of morbidity and mortality in dialysis patients. Compared to both low and high flux dialyzers, a mean albumin loss of 3g per dialysis session has been observed with medium cut-off (MCO) dialyzers (Kim et al., BMC 2020; Kirsch et al. NDT, 2017) which may decrease sA levels and increase the risk of hypoalbuminemia (serum albumin ≤3.5 g/dL). The aim of this analysis was to estimate the impact of sA levels on hospitalization and associated cost.

Methods: Prior research conducted by Rocco et al. (J. Am. Soc. Nephrol., 1996) identified sA level as a risk factor for hospitalization in ESKD patients receiving dialysis and estimated hospital utilization associated with sA levels. Data from this analysis was used to show that relative to patients with sA ≥4 g/dL, on average each year, patients with sA of 3.5-3.99 g/dL, sA of 3.0-3.49 g/dL, and sA≤ 3.0 g/dL have 3.98, 7.65, and 7.8 more hospital days, respectively. Using an average cost per hospitalization for a dialysis patient of $15,907.18 and the average length of stay (11.3 days) from USRDS, and data from Rocco et al. (1996), we estimated the additional hospital spending associated with reduced serum albumin levels.

Results: Based on previous research demonstrating an association between sA levels < 4 g/dL and increased risk of hospitalization, we estimated the hospitalization costs

associated with having reduced serum albumin. Relative to hemodialysis patients with ≥4 g/dL, we calculated that having a lower average sA level may result in excess healthcare spending of $5,602 for sA of 3.5-3.99 g/dL, $10,769 for sA of 3.0-3.49, and $10,980 for sA less than or equal to 3.0 g/dL.

Conclusions: Lower serum albumin levels are associated with increased hospital admissions, which is estimated to lead to excess hospital spending on average of $5,602-$10,980 per patient per year. Preventing albumin loss in dialysis patients may help to reduce the risk of hospitalization.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO1077

A Pilot Randomized Control Trial of an Energy Management Program for Adults on Chronic Hemodialysis with Fatigue: The Fatigue-HD Study

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Background: How to reduce fatigue and its impact on life participation is a top-ten unanswered research question among patients treated with chronic hemodialysis. We aimed to determine the feasibility of conducting a randomized controlled trial, to investigate an energy management education program for the chronic hemodialysis population.

Methods: We conducted a parallel-arm, 1:1, blinded pilot RCT at six hemodialysis units in Calgary, Canada. Patients who had moderate or severe fatigue on the Fatigue Severity Scale, and met other study eligibility criteria, were invited to participate. Consenting participants were randomized to general self-management education or the Personal Energy Planning (PEP) program, a tailored 7-9 week energy management program that guides participants in practicing efficient energy expenditure during valued life activities. We assessed study eligibility, recruitment and attrition rates. We then computed standardized intervention effects (Cohen's D statistic) on self-reported fatigue and life participation measures, compared to control, at immediate post-intervention and 12 weeks post-intervention.

Results: Of 253 people on hemodialysis screened, 153 were eligible to be approached (clinically stable and English-speaking). 42 (26%) were interested and consented to participate, and 30 met all study eligibility criteria were enrolled (mean age 62.4, 60% male). 22 (73%) enrolled participants completed all study procedures. Medium intervention effects were observed compared to control on the global life participation scale, global life participation satisfaction scale, and COPM-Performance Scale at immediate post-intervention follow-up. At 12-week post-intervention, large and very large intervention effects were observed on the COPM Performance and Satisfaction Scales, respectively, compared to control. Minimal to no intervention effects were seen on other life participation or fatigue measures.

Conclusions: We have shown it is feasible to enroll and follow patients on hemodialysis with fatigue in a randomized controlled trial of an energy management intervention. Since the intervention led to improved life participation on some scales, we have justified the need for, and feasibility of, a larger trial.

Funding: Government Support - Non-U.S.

PO1078

Coffee and Headache in Hemodialysis Patients: The CoffeeHD Trial

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Background: Headache occurs in 40 to 75 % of HD patients. Caffeine circulates unbound in the blood and passes the dialysis membrane. Some suggested that headache can result from caffeine withdrawal. This study aims to compare the incidence of headache and hypotension between patients taking or not coffee during dialysis.

Methods: This is a randomized double-blind multicenter trial. Patients of 3 HD units were included. 156 patients were randomized to two groups, group A was given coffee and group B decaffeinated coffee mid-session for 12 sessions. UF rate was fixed to <13 ml/kg/h. Primary outcome was incidence of headache and secondary outcome incidence of hypotension. This clinical trial received the approval of the ethics committee and was registered on ClinicalTrials.Gov (NCT04057313).

Results: 139 patients completed the trial (6.4% vs 15.4 % of withdrawal in A and B respectively). Baseline characteristics are summarized in Table 1. Incidence of headache was not significantly different between A and B (34% vs 37% respectively, p=0.522), nor the incidence of hypotension (27% vs 26% respectively, p= 0.539). In subgroup analysis, headache was lower in A (p=0.06) in two categories of patients: those with higher potassium dialysate (K=2) and the non-hypertensive patients.

Conclusions: Headache occurred in 34 to 37% of dialysis sessions. There was no difference in headache or hypotensive episodes between patients in the coffee versus decaffeinated group.

Baseline characteristics

	A	B	p
Age	64.3±13	69±11.4	0.016
Sex (M/F)	71.8%/28.2%	59%/41%	0.092
Dialysis Vintage (M)	39[17-84]	27[14-55]	0.086
Smoking (N/Y)	65.4%/34.6%	76.9%/23.1%	0.112
Hypertension (N/Y)	9%/91%	15.4%/84.6%	0.221
Coffee cups daily	2.4±1.4	2.3±1.5	0.783
Coffee intake before session (N/Y)	46.2%/53.8%	47.4%/52.6%	0.873
Diabetes (N/Y)	57.7%/42.3%	46.2%/53.8%	0.149
Headache usually (N/Y)	82.1%/17.9%	85.9%/14.1%	0.513
URR	75.6±5.3	76.5±4.9	0.274
Dialysate K (0/1/2)	5.1%/42.3%/52.6%	7.7%/33.3%/59%	0.468
Pre HD systolic BP	146.5±21.7	140.4±21.1	0.076
Pre HD diastolic BP	76.7±12.8	72.6±11.9	0.036
Pre HD heart rate	71.6±10	68.8±10	0.077

N, No; Y, Yes

PO1079

Physical Activity Levels in Hemodialysis Patients Measure Using a Commercially Available Activity Tracker

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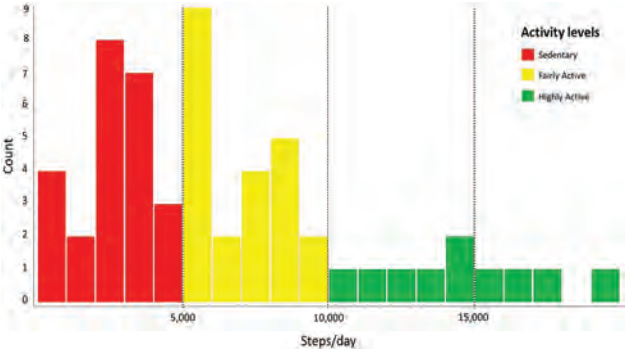
Background: Sedentary life is a major risk factor for all-cause mortality in the general population, more in those with cardiovascular (CV) diseases. Hemodialysis (HD) patients have an increased CV mortality and it has been shown that they are less active than their healthy piers. The use of physical activity (PA) tracking devices could provide an objective measurement of PA in HD patients' everyday lives. We aimed to objectively quantify activity in a large HD population

Methods: This prospective, still ongoing study enrolled HD patients from 4 clinics in NYC beginning in May 2018 and followed them up to 1 year. Patients ≥18 years, HD ≥3 months, able to walk, owning a smartphone, mobile tablet or PC were enrolled. They were provided with a wrist-based tracking device (Fitbit® Charge 2). We present baseline characteristics and PA levels of the first 7 days of wear. Based on their average daily step counts, participants were separated into 3 categories:sedentary, fairly active, or active if they walked less than 5,000, 5,000 to 10,000, or >10,000 steps, respectively

Results: Fifty-six patients were included in this analysis (54±12 years, 71% male, 60% black, 28.6% had diabetes and 23.2% CHF, dialysis vintage 5.8±5.8 years and body mass index of 28.0±7.0 kg/m^2). Participants walked an average of 6,470±4,617 steps per day, median of 5,513 [IQR 3,043-8,268] steps/day. Of the 56 participants, 45%(n=25) were sedentary, 39%(n=22) were fairly active, and 16% (n=9) were active **(fig.1)**

Conclusions: In our study, only a small number of patients exceeded the WHO recommendation of 10,000 steps/day. Overall, 83% of patients walked <10,000 steps/day. Further analysis is needed after completion of the study to assess the impact of a physical activity tracker device on physical activity levels. We hypothesized that the daily use of a tracker will positively impact activity levels and overall self-perceived health



Histogram average daily steps

PO1080

Feasibility and Acceptability of Symptom Monitoring with Feedback Trial (SWIFT) for Adults on Hemodialysis: A Pilot ANZDATA Registry-Based Cluster Randomized Trial

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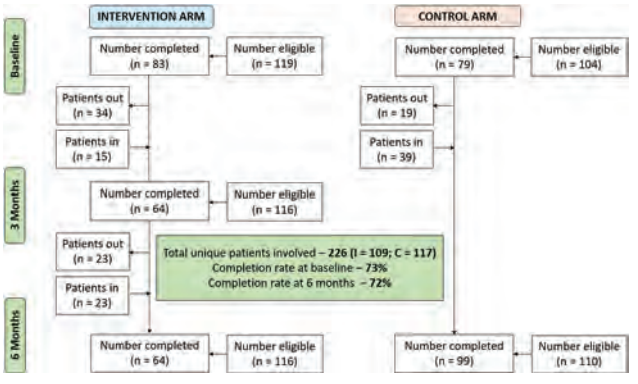
Background: We designed a registry-based randomized trial to test whether the collection and feedback of symptoms improves health-related quality of life (HR-QoL). The pilot study's aim was to determine technical feasibility and patient-clinician acceptability of electronic tablet-based data capture and feedback integrated within the ANZDATA registry.

Methods: Hemodialysis units were cluster randomized to 3-monthly symptom monitoring using the Integrated Palliative Outcome Scale-Renal (IPOS-Renal) with feedback to clinicians plus 6-monthly HR-QoL using EQ-5D-5L questionnaire (intervention group); vs HR-QoL alone (control group). Feasibility and acceptability outcomes included, 1) individualized survey generation using QR codes linked to ANZDATA records; 2) patient completion rate and time; 3) delivery of individualized symptom reports.

Results: Technical feasibility was demonstrated by successful development of a Qualtrics survey platform presented on tablet computers, use of QR reader codes to verify correct patients from ANZDATA, with a link to the relevant survey for the patient's allocation and study timepoint. 226 patients (intervention =109; control =117), from 4 Australian units with median dialysis vintage of 1.6 years, mean age 62 years, 31% females, completed at least one symptom or HR-QoL measure, (72% of eligible patients, range 44-90%). Mean completion time was 6.5 minutes for IPOS-Renal (66% nurse assisted), 3.5 minutes for EQ-5D-5L. Consolidated symptom feedback reports and evidence-based symptom management guidelines for Nephrologists and dialysis nurse managers were delivered electronically within 2 weeks of measurement.

Conclusions: Electronic symptom monitoring in adults on hemodialysis with feedback to clinicians is feasible. These data support the commencement of the definitive trial in 3,072 patients.

Funding: Private Foundation Support, Government Support - Non-U.S.



SWIFT Pilot flow chart

PO1081

Physiological Pre-Dialytic Changes Could Mediate the Effects of Extreme Heat Events on Hospital Admission Risk in Hemodialysis Patients

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Background: Thermoregulatory response to extreme heat events (EHE) includes reduced blood pressure and perspiration. EHE exposure increases the risk of hospitalizations among hemodialysis (HD) patients, though the underlying mechanism for this relationship is unclear. We employed traditional mediation analysis to decompose the total effect between EHE and hospital admissions using pre-HD systolic blood pressure (SBP) and interdialytic weight gain (IDWG) as mediators.

Methods: We assigned EHE exposure metric – calculated using calendar day and location-specific temperature thresholds – to HD patients treated at Fresenius Kidney Care clinics from 2003 to 2012. We used time-to-event methods using varying lag periods followed by VanderWeele's difference method with bootstrapping to test mediators.

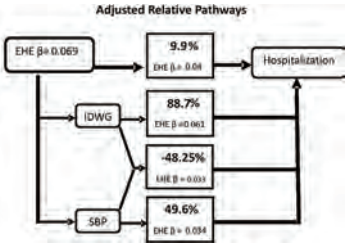
Results: EHE increased the hazard of hospital admission up to 17% after covariate adjustments (n=7,962). In one of the lag periods (two-day EHE exposure before hospital admissions), hazard ratio (HR) estimates from Cox models (Figure) exhibited statistical significance for all pathways. SBP and IDWG as a conjoined mediator suggest protective mediation (-48.3%), whereas IDWG, independent of SBP, accounts for a considerable proportion of the association (88.7%). Half of the association is mediated through SBP, independent of IDWG. Preliminarily, IDWG may have a consistent mechanistic role in hospital admissions after exposure. Also, lagged EHE does yield heterogeneity in mediating effects.

Conclusions: This work is a step forward to understanding potential physiological linkages between EHEs and health complications that may result in hospitalization. Such findings could be critical in discerning potential interventions to minimize the impact of extreme heat among HD patients.

Funding: Other U.S. Government Support

Risk Estimates

Estimate	EHE HR	Indirect Effect
EHE and only confounders	1.07 (0.98, 1.16)	
EHE, confounders, and PRE_SBP, and IDWG	1.01 (0.92, 1.11)	1.06 (1.04, 1.12)
EHE, confounders, and PRE_SBP	1.04 (0.95, 1.13)	1.0010 (1.0005, 1.0020)
EHE, confounders, and IDWG	1.01 (0.92, 1.11)	1.03 (1.01, 1.06)



L: HR and 95% CI for EHE-Hospital association (EHE HR) and for mediation effects of the association (Indirect Effects); **R**: Mediating EHE-Hospital association pathways and its relative proportions

PO1082

Frequency, Risks, and Outcomes of Sepsis Hospitalizations in the ESKD Population in the United States

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Background: Although a biologically plausible link between End Stage Kidney Disease (ESKD) and sepsis exists, little is known about frequency, risk factors, and outcomes of sepsis-related hospitalizations in ESKD patients.

Methods: Of a retrospective cohort of 1,123,731 incident ESKD patients on dialysis (2005 to 2014) from the United States Renal Data System (USRDS), we studied the 508,372 with linked Medicare claims at initiation of dialysis and complete demographic data. Hospitalization data were obtained from Medicare claims with a sepsis hospitalization being identified by previously validated ICD-9 codes. Using Cox proportional hazard models, we examined the risk factors associated with a sepsis hospitalization and effect of a sepsis hospitalization on mortality.

Results: The study cohort was 55% male, 62% white, and had an average age of 70 years. A sepsis hospitalization occurred in 20.8% of the cohort. The overall rate of sepsis hospitalizations was 15.4 per hundred patient years (PHPY), and the trend increased over time from 13.8 PHPY in 2005 to a peak of 16.7 PHPY in 2011. Factors associated with higher likelihood of a sepsis hospitalization included female sex (Hazard Ratio [HR] 1.05, 95% CI 1.03-1.06), age >80 (vs. age <40; HR 1.30, 95% CI 1.24-1.36), dialysis access via catheter (vs. fistula/graft; HR 1.61, 95% CI 1.58-1.63), congestive heart failure (HR 1.28, 95% CI 1.26-1.30), and diabetes mellitus (HR 1.14, 95% CI 1.12-1.16). Compared to white race, minority races had lower likelihood of developing a sepsis hospitalization (Black HR 0.89, 95% CI 0.87-0.90; Hispanic HR 0.82, 95% CI 0.80-0.84; Asian HR 0.79, 95% CI 0.76-0.82; Native American HR 0.80, 95% CI 0.75-0.86). Compared to no hospitalizations, ESKD patients had a twofold increase in mortality following a first non-sepsis hospitalization (HR 2.14; 95% CI 2.12 to 2.16), increasing to ninefold over baseline following a sepsis hospitalization (HR 9.00; 95% CI 8.87-9.13).

Conclusions: Sepsis hospitalizations are frequent and are associated with significant mortality in ESKD patients in the U.S. Further studies need to focus on modifiable risk factors of sepsis and explore optimal therapies for sepsis in ESKD subjects.

Funding: Clinical Revenue Support

PO1083

Optimising Recruitment in Prepare for Kidney Care: A Clinical Trial Comparing Preparation for Dialysis vs. Responsive Management

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Background: Randomised Controlled Trials (RCTs) are core to evidence-based practice, but often close prematurely or are not attempted for fear of recruitment issues. Prepare for Kidney Care ('Prepare') randomises adults aged 80+/65+ with comorbidities to prepare for Renal Dialysis or Responsive Management -a form of conservative care. An RCT of this nature has never been attempted, with concerns about recruitment feasibility. The Prepare RCT integrated the Quintet Recruitment Intervention (QRI) – a complex

intervention designed to rapidly diagnose and address recruitment issues in real-time. We report the root-causes of recruitment issues and how these were overcome using this novel methodology.

Methods: The QRI entailed monthly scrutiny of pre-randomisation screening data, interviews with nephrologists/nurses (n=27) and audio-recorded consultations between clinicians/patients (n=33). Data were triangulated, informing strategies to address recruitment issues.

Results: Recruitment was hampered by logistical issues that varied, requiring bespoke solutions by centre. More challenging to address were the underlying complex issues entwined with routine clinical practice, manifesting as reluctance to approach all eligible patients, and issues with conveying equipoise. Clinicians often only approached patients whom they felt could not decide between dialysis or conservative care, assuming other patients' treatment intentions were fixed. Audio-recorded consultations indicated patients were not necessarily committed to treatments, and preferences were often complicated by misconceptions. Recordings also revealed recruiters' tendencies to unknowingly undermine dialysis, and hesitancy in exploring preferences. The trial team iteratively produced guides/training to support equipoise communication and used presentations/ clinical vignettes to challenge assumptions that patients have fixed treatment plans. As of May 2020, 246 patients have been randomised (48% of target of 512).

Conclusions: Factors hindering recruitment to this challenging RCT were complex, but amenable to change once well-understood. Novel methodologies, like the QRI, can unlock the potential to deliver seemingly impossible- but vitally important- RCTs to improve renal practice.

Funding: Government Support - Non-U.S.

PO1084

Time Course of Tissue Sodium Flux in Maintenance Hemodialysis (MHD) Patients

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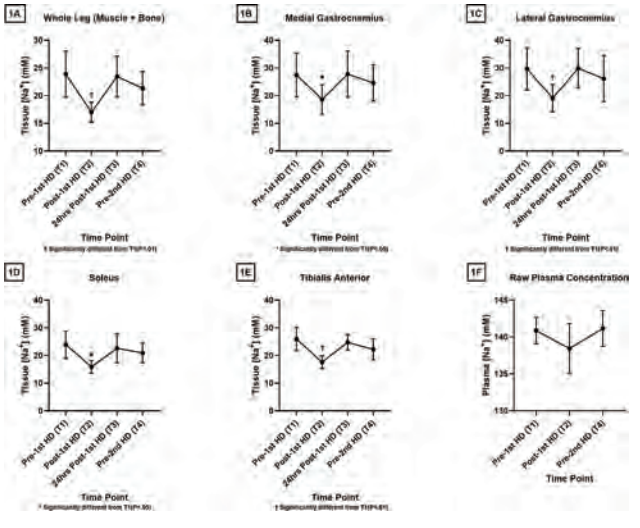
Background: Recent ^{23}Na-MRI studies show that sodium can accumulate in tissues. MHD patients have higher tissue sodium concentration ([Na^+]) than healthy counterparts, while tissue [Na^+] can be partially reduced during hemodialysis (HD). This study aimed to evaluate the magnitude of tissue [Na^+] removed during HD and the time-course for its recalibration.

Methods: Seven HD patients (57% male; 60±12 yr; BMI: 36±10 kg/m^2; spKt/V: 1.4±.32; dialysate [Na^+]: 136±1.90 mEq/L; UFR: 7.2±1.4 mL/kg/hr; thrice-weekly HD) had sequential ^{23}Na-MRI scans (3T system) over 3 consecutive days, including 2 HD days and the non-HD day in between, at 4 time points: pre-first HD (T1), post-first HD (T2), 24 hours post-first HD (T3), and pre-second HD (T4). [Na^+] of the medial (MG) and lateral (LG) gastrocnemius, soleus (Sol), tibialis anterior (TA), and the whole lower leg (WL) were quantified from MRI images. Plasma [Na^+] was also assessed at T1, T2, and T4 by colorimetric enzymatic assays (Piccolo). Repeated measures ANOVA and the nonparametric Friedman test were used to test the differences in tissue and plasma [Na^+] over time.

Results: Tissue [Na^+] was reduced at the end of HD (T2) compared to baseline (T1) in the WL (P=.006), MG (P=.043), LG (P=.006), Sol (P=.029), and TA (P=.006), (Figure 1A-E). For the WL and all 4 examined muscles, tissue [Na^+] at both T3 and T4 did not differ from baseline (all P>.05), indicating that tissue [Na^+] returned to the baseline within 24 hours after last HD. In contrast, plasma [Na^+] did not change over time (P=.067; Figure1F).

Conclusions: We found that tissue [Na^+] was reduced by HD but returned to baseline levels within 24 hours that remained stable until next pre-HD. More studies are needed to determine the mechanisms for these shifts, and whether lifestyle or pharmaceutical interventions can inhibit tissue [Na^+] accumulation or enhance its removal.

Funding: Private Foundation Support



PO1085

Association Between Dialysate Sodium Concentration and Interdialytic Weight Gain in Patients Undergoing Twice Weekly Haemodialysis

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Background: Chronic kidney disease is highly prevalent in the world with more than two million people worldwide requiring renal replacement therapy. Interdialytic weight gain is the change in body weight between two sessions of haemodialysis. Higher interdialytic weight gain has been associated with increased mortality and adverse cardiovascular outcomes. It has long been questioned whether using a lower dialysate sodium concentration during dialysis would reduce the interdialytic weight gain and prevent these adverse outcomes.

Methods: This was a single blind cross-over study of adult patients undergoing twice weekly haemodialysis conducted over two six week periods. Patients were divided into two groups – the first underwent dialysis with dialysate sodium concentration of 137meq/l, the other underwent dialysis with a sodium concentration of 140meq/l. These groups switched over after a six-week period without a washout period. Interdialytic weight gain, pre and post dialysis blood pressures were measured at each dialysis session.

Results: 41 patients were included in the primary analysis after meeting inclusion criteria. Mean age was 61.37 years, and 73% were males. Mean duration for dialysis was 2.53 years. 13% were anuric, 56% were oliguric, and 31% were non-oliguric. 59% of patients had diabetes mellitus and 80% had hypertension. The interdialytic weight gain was not significantly different among the two groups (2.14 for the low DNa (137meq/l) group and 2.35 for the high DNa (140meq/l) group, p = 0.97). Mean blood pressures were as follows. Pre-dialysis: DNa 137meq/l: systolic 152.14 ± 19.99, diastolic 78.99 ± 12.20, DNa 140meq/l: systolic 156.95 ± 26.45, diastolic 79.75 ± 11.25 (p = 0,379, 0.629 respectively). Post-dialysis: DNa 137meq/l: systolic 147.29 ± 22.22, diastolic 77.85 ± 12.82 DNa 140meq/l: systolic 151.48 ± 25.65, diastolic 79.66 ± 15.78 (p = 0,569, 0.621 respectively).

Conclusions: There was no significant difference in the interdialytic weight gain as well as pre dialysis and post dialysis systolic and diastolic blood pressures between the low dialysate sodium concentration and high dialysate sodium concentration. Therefore using a lower dialysate sodium concentration does not appear useful in altering the interdialytic weight gain although further studies with a larger sample size are warranted.

PO1086

Low Sodium Dialysate for Hemodialysis Is Associated with Lower Blood Pressure and Interdialytic Weight Gain, but Not a Lower Pre-Dialysis Serum Sodium

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Background: The use of high dialysate sodium (NaD) concentrations for hemodialysis (HD) is associated with greater interdialytic fluid gain (IDWG). The association with higher blood pressure has not been found routinely. Conversely, use of a lower NaD may improve on these parameters, but may lead to a lower pre-dialysis serum sodium concentration, which may have adverse consequences in this population. We aimed to examine IDWG, blood pressure, calculated serum osmolality and serum Na in HD patients on a high NaD (145) who transitioned to a low NaD (137-138)

Methods: In this retrospective, single-center study of 3-times weekly HD patients without residual kidney function, we queried long-term HD patients who were prescribed NaD of 145 and were then switched to a NaD of 137 or 138, based on change in standard clinic dialysate sodium. Parameters investigated included: pre-HD serum Na and albumin, calculated pre-HD serum osmolality, pre and post-HD weights, and pre and post-HD blood pressures. Paired T-test was used for comparison of each parameter betwee dialysate time periods.

Results: We identified 136 patients who were started on HD with NaD of 145 for at least 1 year, subsequently changed to a NaD of 137-138 for at least 1 additional year. See Figure comparison of parameters.

Conclusions: In patients on 3-times a week HD, long-term use of a high NaD of 145, compared to a low NaD of 137-138, was associated with a higher IDWG, similar to what is found in other studies. A lower NaD was associated with lower pre and post-HD systolic and diastolic blood pressures, but we found no difference in pre-HD serum Na or calculated serum osmolality. The degree of drop in blood pressure during HD on the low NaD caused hypotensive events in some patients. There are some clinical parameter benefits to a lower NaD and serum Na does not appear to suffer.

Funding: Clinical Revenue Support

	Low NaD	High NaD	p-value
Serum Sodium	138.3 ± 2.6	138.2 ± 3.0	0.69
Serum Albumin	3.8 ± 0.4	3.8 ± 0.4	0.95
Post HD wt (kg)	71.5 ± 25.2	72.2 ± 25.1	0.45
Inter-HD wt gain (kg)	2.7 ± 1.1	3.33 ± 1.8	<0.001
Calculated serum Osm	300 ± 8	302 ± 8	0.06
PreHD SBP	151 ± 21	157 ± 18	<0.001
PreHD DBP	80 ± 13	85 ± 12	<0.001
PostHD SBP	138 ± 16	144 ± 16	<0.001
PostHD SBP	74 ± 11	78 ± 9	<0.001
PreHD MAP	104 ± 14	109 ± 13	<0.001
PostHD MAP	95 ± 11	100 ± 10	<0.001

Table 1. Paired T-test comparison of averaged parameters during low and high dialysate sodium HD

PO1087

Medicare Reliance After Implementation of Medicare Payment Reform and the Affordable Care Act Marketplace

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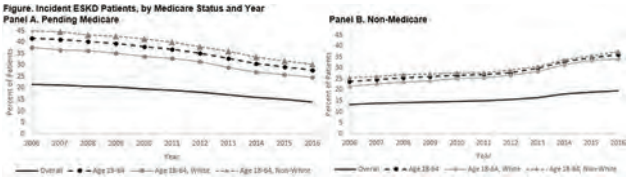
Background: Medicare finances health care for most US patients with ESKD, regardless of age. The 2011 Medicare bundled payment for dialysis reduced Medicare reimbursement for hemodialysis, increasing the difference between Medicare and private insurance that commonly reimburses dialysis providers at higher rates. Passage of the 2014 Affordable Care Act also increased patient access to new private insurance options. These policies may have influenced providers to adjust their payer mix, as dialysis facilities have reported increasing rates of patients not enrolled in Medicare since 2011. This study describes trends in Medicare enrollment among new ESKD patients in 2006-2016.

Methods: From the US Renal Data System, we identified a cohort of incident ESKD patients between 2006 and 2016. We identified each patient's insurance status (Medicare, pending Medicare, non-Medicare) at dialysis initiation and observed changes over time. We report trends for the overall incident population, for patients aged 18-64, and by race.

Results: The proportion of new ESKD patients enrolled in Medicare remained stable between 2006 (65%) and 2016 (67%). There was an increase in non-Medicare coverage (13.2% in 2006, 19% in 2016) and a reduction in pending Medicare applications (21% in 2006, 14% in 2016). These trends were more pronounced among patients aged 18-64 (i.e., not already in Medicare due to age) and among aged 18-64 non-Whites (Figure). Multivariable regression results are pending.

Conclusions: There was a modest shift in payer mix among new patients with ESKD after bundled payment reform in 2011 and private insurance expansion in 2014, with fewer patients applying for or enrolled in Medicare over time. To address concerns among policymakers about facilities encouraging private insurance coverage, future work should examine the implications of these trends on outcomes for patients.

Funding: NIDDK Support



PO1088

The Correlated Case of Dialysis Facility and Hospital Star Ratings

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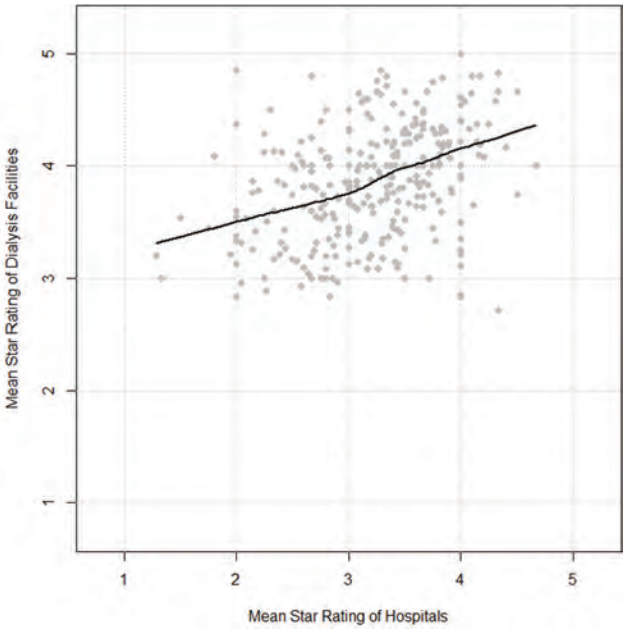
Background: The Centers for Medicaid and Medicaid Services (CMS) periodically releases star ratings for several types of health care facilities, including acute care hospitals and outpatient dialysis facilities. Because respective rating systems utilize disparate quality measures, star ratings of dialysis facilities and nearby hospitals may be weakly correlated. However, hospital quality could influence dialysis patient outcomes. Furthermore, confounding by unmeasured economic, environmental, and social factors could induce correlation. We used public use files to assess whether star ratings of dialysis facilities and hospitals within the same region are correlated.

Methods: We ascertained dialysis facility star ratings from Dialysis Facility Compare and hospital star ratings from Hospital Compare (source: data.medicare.gov). Star ratings were based on quality measures that were accumulated in 2015-2018. We categorized each health care facility into 306 Hospital Referral Regions (HRRs), according to ZIP code. In each HRR, we estimated the mean star rating of all dialysis facilities and the mean star rating of all hospitals. Using loess regression, we estimated the correlation between these HRR-specific means.

Results: The analysis included 6667 dialysis facilities and 3565 hospitals, or approximately 22 dialysis facilities and 12 hospitals per HRR. The mean star rating in dialysis facilities was 3.7 (standard deviation, 1.0) and 3.2 (1.1) in hospitals. As displayed, HRR-specific mean star ratings of dialysis facilities and hospitals were positively and nearly linearly correlated. The correlation coefficient of these HRR-specific means was 0.4.

Conclusions: CMS star ratings of dialysis facilities and hospitals within the same region are positively correlated. Future studies should identify the sources of this correlation.



PO1089

The Budgetary Impact of Point-of-Care Hemoglobin Testing for Hemodialysis Patients

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Background: Point of care (POC) testing in dialysis clinics can improve the quality of care provided to end-stage renal disease (ESRD) patients. The objective of this study was to estimate the budgetary impact of transitioning from weekly lab-based analysis of hemoglobin from each dialysis session to POC testing.

Methods: A budget impact model with a 1-year time horizon was developed. Our model included costs of POC testing in real-time in dialysis clinics compared to requiring the shipment of 3 blood samples per month to a lab for analysis. A non-invasive monitoring technology, the Crit-Line monitor® (CLM) measures hematocrit. Hemoglobin levels can be calculated from the measured hematocrit value. CLM is already used for fluid management in dialysis clinics and can also be used for POC testing. The model took the perspective of a healthcare organization responsible for providing dialysis treatments. The 2020 Medicare reimbursement value for a hematocrit test was used as a proxy value for lab testing costs. Our model also included costs associated with shipping, blood collection tubes, and erythropoiesis-stimulating agent (ESA) which is indicated for the treatment of anemia. Labor costs were excluded as they were considered fixed costs and would not change if POC testing was implemented.

Results: By replacing three blood draws per month, the use of a Crit-Line monitor® to assess hemoglobin levels could save $16.82 USD per patient per month.

Conclusions: The use of Crit-Line monitor® technology for point of care assessment of hemoglobin levels can result in decreased resource use and costs savings of $16.82 USD per patient per month compared to lab-based testing. Point of care testing may also have environmental benefits by reducing emissions associated with shipping samples and decreasing packaging needed to ship samples to a lab for analysis.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO1090

Physician Action on Medication Therapy Management (MTM) Recommendations Within 14 Days Associated with Lower 30-Day Readmission in Dialysis Patients

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Background: We previously reported lower 30-day readmission rates associated with MTM (vs. no intervention) in maintenance dialysis patients.* After aggressive implementation of MTM, we now compare 30-day readmission risk in a more recent

cohort of Full -MTM that requires physician sign-off (including implementation orders) with Partial-MTM (med-rec with or without pharmacist review only) and determined the impact of providing Full-MTM early ≤ 14 days of discharge vs. delayed.

Methods: We reviewed electronic medical records of End-Stage Renal Disease Seamless Care Organization (ESCO) enrolled patients discharged home from acute-care hospitals between Nov 2018-Oct 2019 who returned to participating dialysis units. Patients readmitted ≤3 days, died, or entered hospice ≤30 days were excluded. Time-varying propensity score (from age, dialysis vintage, modality, cause and catheter use, prior hospitalization history, albumin, sex, marital status, and race) matched Cox models were constructed comparing hazard ratios for 30-day readmission between Full- and Partial-MTM exposure groups.

Results: MTM was provided in 1,752 discharges (456 Partial-MTM; 1296 Full-MTM). Of those, 455 Full- and 455 Partial-MTM cases were matched 1:1. Full-MTM had 25% lower risk for 30-day readmission even when compared to discharges that received partial-MTM services (HR 0.75; 95% CI 0.58-0.98). Full-MTM process was completed ≤14 days in 81% cases (n=1054). Of those, 444 early Full-MTM were matched to 444 Partial MTM cases and demonstrated a significantly lower risk for 30-day readmissions (HR 0.74, 95% CI 0.57-0.95), primarily driving the overall results.

Conclusions: Full MTM process is associated with lower 30-day readmission risk compared to Partial-MTM. The results are primarily driven by MTM process completion ≤14 days of discharge. These findings support that timely physician adjudication of pharmacists' recommendations and subsequent actions (i.e. medication changes as needed) influence the effectiveness of MTM programs to impact readmission rates. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document. * = https://doi.org/10.1053/j.ajkd.2019.12.002

PO1091

Use of Predictive Analytics to Inform Integrated Care Programs to Reduce Hospitalizations Among Hemodialysis Patients

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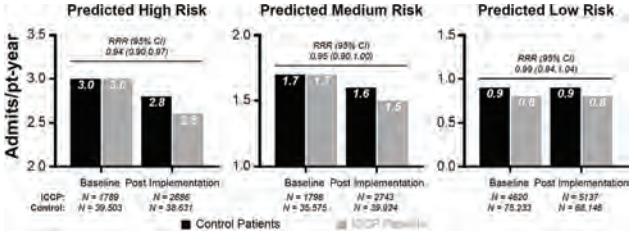
Background: Integrated care for dialysis patients could benefit from identification of those who are at high risk for poor outcomes in order to efficiently deploy clinical resources. We recently developed a hospitalization risk stratification model to triage hemodialysis (HD) patients for clinician contact and assessment within an integrated care clinical program (ICCP). In this analysis, we compared hospitalization rates before and after model implementation for patients enrolled in an ICCP and control patients who were not.

Methods: All patients received our standard level of care consistent with industry best practices and regulations. ICCP patients predicted to be medium and high risk received additional services proportional to predicted risk level. Relative differences in annualized hospitalization rates for HD patients enrolled in an ICCP were compared to controls who were not by calculating relative rate ratios (RRR) and 95% confidence intervals (CI) in the baseline (Feb 2017-April 2018) and postmodel implementation (Jan-Aug 2019) eras. Comparisons were stratified by predicted risk level.

Results: The baseline hospitalization rate was 3.0 admissions/patient-year (pt-yr) for all high-risk patients. Post implementation, hospitalization rates decreased to a greater extent among ICCP patients (-0.4 admissions/pt-yr) versus controls (-0.2 admissions/pt-yr): RRR (95% CI) = 0.94 (0.90, 0.97). The baseline hospitalization rate was 1.7 admissions/pt-yr for all medium-risk patients. Post implementation, hospitalization rates decreased to a greater extent among ICCP patients (-0.2 admissions/pt-yr) versus controls (-0.1 admissions/pt-yr): RRR (95% CI) = 0.95 (0.90, 1.00). No differences were observed among low-risk ICCP patients and low-risk control patients.

Conclusions: These results support the potential utility of predictive analytics to support programs aimed at improving clinical outcomes among HD patients.



PO1092

Healthcare Staff Acceptance of Ultrafiltration Rate Recommendations Made by a Novel Feedback Controller

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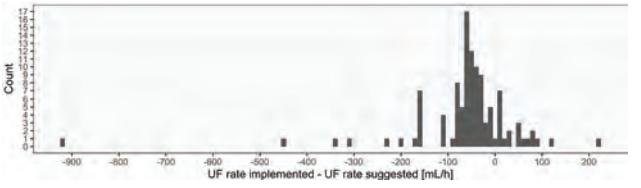
Background: Preciado et al. have identified relative blood volume (RBV) targets during hemodialysis (HD) that are associated with improved patient survival [1]. Attainment of RBV targets requires frequent adjustments to the ultrafiltration rate (UFR) by the dialysis nurse, which is logistically not feasible. We developed a novel proportional-integral controller that takes RBV data from the CLiC® device as an input and provides UFR recommendations to guide the RBV curve into the desired targets. We investigated the degree to which the nurses accepted the UFR recommendations made by this controller.

Methods: We conducted a prospective, interventional study in chronic HD patients at 3 Dialysis Clinics in Manhattan. RBV was measured with the CLiC® device. CLiC® and Fresenius 2008T HD machine data were fed into a research laptop running the UFR Feedback Controller software. UFR recommendations (generated every 10 minutes) were evaluated by dialysis nurses who then either implemented or rejected them as they deemed clinically appropriate.

Results: 56 HD treatments from 14 subjects had analyzable data. Out of 1,038 UFR recommendations, 926 (89.2%) were accepted, while 112 (10.8%) were overridden. For 25 HD treatments which had at least one recommendation overridden, we analyzed the direction and magnitude of disagreement between the Controller-suggested UFR and the implemented UFR (Fig. 1). From the overridden controller recommendations, 20 implemented UFRs were greater than the respective Controller-suggested UFRs, another 70 implemented UFRs were less than 100 mL/h lower than the Controller-suggested UFRs. Together, these two categories made up 83% of all "disagreements" between the nurse and the Controller. Of the total of UFR recommendations overrides, 59.6% were due to staff preference in the absence of clinical symptoms.

Conclusions: There was a high proportion (≈90%) of Controller-UFR recommendations that were accepted by the nurses. Of the few cases where nurses overrode the recommendation, the majority (≈60%) were due to "staff preference", this is likely owed to the fact that the nurses exclusively attended one patient at a time for the entire HD session.

Funding: Commercial Support - Fresenius Medical Care North America



PO1093

Intradialytic Online Multicomponent Total Removed Solute Monitoring in Spent Dialysate by a Novel Miniaturized Optical Sensor

Liisi Leis,[1] Annika Adoberg,[1] Joosep Paats,[2] Jürgen Arund,[2] Kristjan Pilt,[2] Merike Luman,[1,2] Ivo Fridolin.[2] *[1]North Estonia Medical Centre, Tallinn, Estonia; [2]Tallinn University of Technology, Tallinn, Estonia*.

Background: Urea is the most commonly exploited marker of dialysis adequacy, but also other uremic retention solutes accumulate in ESKD patients. Commonly, the uremic solutes are divided into three physicochemical types with the representative markers urea, uric acid (UA); indoxyl sulfate (IS); and β2-microglobulin (B2M). Instead of total dialysate collection for quantification of the amount of uremic solutes removed during dialysis, an optical on-line monitoring has been proposed. The aim of this study was to evaluate intradialytic on-line multicomponent total removed solute (TRS) monitoring in the spent dialysate by a novel miniaturized optical sensor during hemodialysis (HD) and hemodiafiltration (HDF) with different settings.

Methods: Ten ESKD patients (6 M, 4 F; 60.2±16.8 y.o.) on chronic HDF were enrolled into the study. For each patient 5 midweek dialysis sessions (240min; HD: N=1, Qb=200mL/min, Qd=300mL/min, 1,5m^2 ; HDF: N=4, Qb≥300mL/min, Qd≥500mL/min, V_{subst}≥15L, 1,8m^2 and 2,2m^2) were included. Spent dialysate from the drain was monitored on-line by a miniaturized sensor prototype (Optofluid Technologies OÜ, Estonia). For the reference, samples from the spent dialysate drain tube of the HD machine were taken 7, 60, 120, 180 and 240 min after the start of the dialysis session. Concentrations of urea and B2M in the dialysate were determined in the clinical laboratory. Concentrations of IS and UA were determined utilizing the HPLC. TRS values were calculated using the tank weight and the lab or optical tank solute concentrations. t-test was used to determine significant differences between the methods (P≤0.05).

Results: The laboratory and optical TRS values were 489±112mmol and 512±87mmol for urea (R^2=0.215), 4232±712μmol and 4331±756μmol for UA (R^2=0.829), 230±47mg and 231±40mg for B2M (R^2=0.551), 606±339μmol and 616±321μmol for IS (R^2=0.951), being not statistically different for any uremic solutes. The reason for higher correlation for UA and IS is direct measurements of UA and IS by the optical sensor whereas urea and B2M are estimated indirectly.

Conclusions: Novel miniaturized optical sensor successfully carried out intradialytic on-line multicomponent TRS monitoring for the uremic solutes urea, UA, B2M and IS in the spent dialysate.

PO1094

Patient Safety in a Large Multinational Renal Services Provider Network

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Background: Patient safety is considered of paramount importance under any qualified provision of care, but results from routine tracking of incidents have scarcely been reported, even when that may negatively impact survival. **Objectives** To analyze all types of incidents in a multinational renal service provider network during 2019.

Methods: For the last 10 years, our institution has tracked all incidents under a structured process program, as well as, educated our staff in the importance of proactively reporting and analyzing incidents in a quarterly basis at the clinic, by country and globally. Incidents are categorized in 4 different types: A-Patient related; B-Staff and visitors; C-Products and D-Equipment. Different incident codes are assigned to each type (up to 54). Communication to Health Authorities applies in accordance with local country regulations. "Serious incidents" are immediately notified to the Corporate Office and to each Country Medical lead.

Results: A total of 92.923 incidents (2.7 incidents/patient/year) have been reported during 2019 (higher than in 2018: 2.2). This means an increase of 20% in the total number of reported incidents. Total incidents/1000 treatments was 17.2 (12.2 patient-related incidents). Reporting follows a heterogeneous pattern among countries, being lowest in Argentina and highest in the UK. Top 5 reported incidents were as follows: Codes A15 (voluntarily shortened treatment) and A14 (Patient did not show up), both related to patient adherence to treatment, accounted for 36% of total incidents, vascular access (VA) complications (A4) for 10.2%, change of dialyzer and/or blood lines due to clotting (A2) for 8.5% and recurrent minor monitor malfunction (D1) for 7.6% of incidents. Codes related with unexpected death or cardiorespiratory arrest are not present among the total global top 10 incidents.

Conclusions: Detailed tracking of incidents and comparison between countries have potential to increase quality of care and patients outcomes. Room for improvement recently made the Corporate Medical Office to launch new strategies on VA management, anticoagulation and patient compliance, among others. This large series may help other institutions to better monitor and standardize patient safety on dialysis.

PO1095

Incidence of Intradialytic Hypotension Throughout a Hemodialysis Session: Does the Time of Onset Matter?

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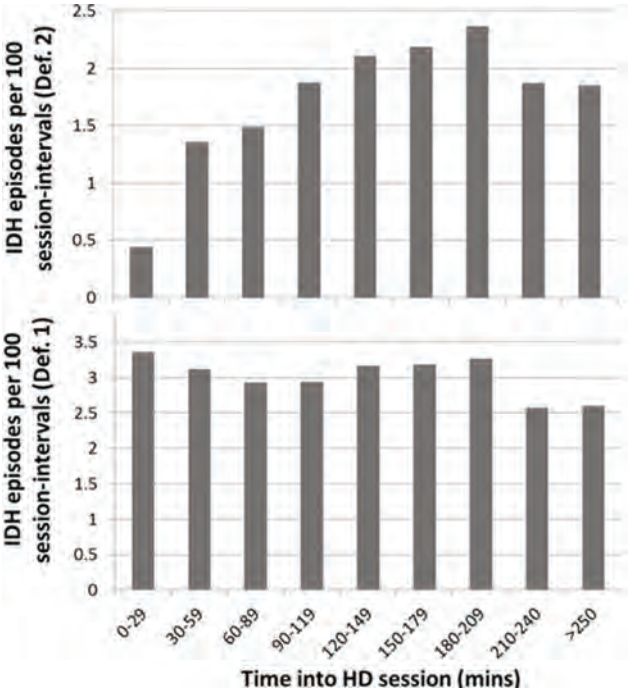
Background: Intradialytic hypotension (IDH) is a common complication of hemodialysis (HD). Probability of IDH would be expected to increase during HD as removed ultrafiltration (UF) volumes increase. We aimed to describe the incidence of IDH throughout HD and associations of the time of IDH with clinical parameters and with survival.

Methods: We studied routinely collected data from 21 US dialysis clinics. IDH was defined as: 1) systolic blood pressure (SBP) < 90 mmHg; and 2) SBP< 90 mmHg and a reduction in SBP > 30 mmHg. Only the first IDH incident per session was included. Time of IDH was defined in 30-minute intervals. Patients who experienced IDH were classed as early- or late-onset based on whether most sessions with IDH had incidents in the first 2 hours or not. Association of early-onset IDH with clinical parameters and mortality were explored with logistic regression and Cox proportional hazard models.

Results: We studied 4,348 patients and 785,682 sessions. For definitions 1 and 2, IDH occurred in 13% and 7% of treatments with a range of 2.6-3.3 and 0.9-2.7 episodes per 100 session-intervals at risk, respectively. IDH occurred in the first 2 hours in 45% and 33% of IDH sessions, respectively. IDH incidence was not associated with time into HD using definition 1; a positive association was observed using definition 2. Adjusted hazard ratios for death comparing early-onset IDH with late-onset were 1.5 and 1.7 for definitions 1 and 2. Early-onset IDH was associated with female sex, higher age and UF rates and lower BMI and SBP.

Conclusions: Early-onset IDH is not uncommon. More consideration of the nature and time of IDH onset, in the context of how it is defined, could help to minimize IDH.



IDH episodes per 100 session-intervals at risk with time into HD session

PO1096

Endothelin 1 and Parameters of Systolic Blood Pressure in Hemodialysis Patients

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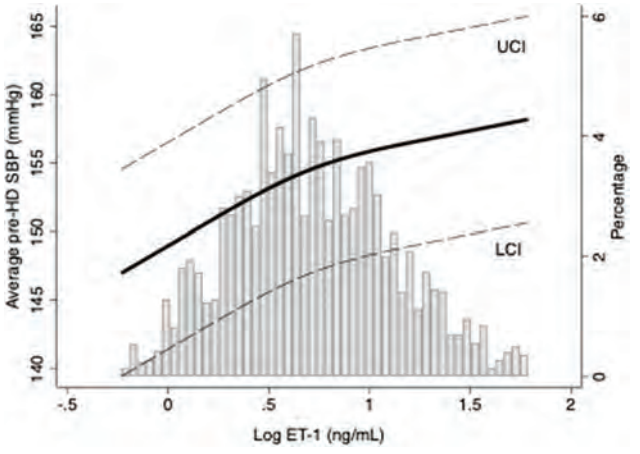
Background: Blood pressure (BP) fluctuates widely during intermittent hemodialysis (HD), with greater variability associated with adverse cardiovascular outcomes. As endothelin-1 (ET-1) is a potent vasoconstrictor, we hypothesized that higher concentrations of ET-1 is associated with higher pre-HD systolic BP (SBP).

Methods: ET-1 concentrations were measured at baseline from the DaVita Biorepository (N=784), a longitudinal prospective cohort study with quarterly collection of clinical data and biospecimens. Unadjusted and adjusted linear mixed effects regression models were fit to determine associations of log-transformed ET-1 with SBP at dialysis (pre-HD, nadir intra-HD, post-HD, drop (pre- minus nadir-HD) and delta (pre- minus post-HD). Multivariable models were adjusted for age, sex, race, access, diabetes, heart failure, cardiovascular disease, peripheral vascular disease and pre-HD SBP.

Results: Mean age was 58 years, 59% were males, 40% black. Mean pre-HD SBP was 152 (± 28) mmHg and mean ET-1 concentration was 2.3 (±1.1) ng/mL. Subjects in higher quartiles of baseline ET-1 tended to be younger, diabetic, have higher SBP and lower serum albumin. In fully adjusted models, each unit increase in SD of log-transformed ET-1 was associated with a 3.0 (95% CI 1.8 to 4.2) mmHg higher pre-SBP; 1.2 (95%CI 0.5 to 1.9) mmHg higher nadir-SBP; 1.6 (95% CI 0.6 to 2.5) mmHg higher post-SBP; 1.2 (95%CI 0.2 to 1.5) mmHg lower SBP drop and 1.6 mmHg (95% CI 0.6 to 1.08) lower delta SBP. In categorical analyses a monotonic increase in pre-SBP was noted in higher quartiles of ET-1 (Q4: 7.8 mmHg increase (95% CI 4.5 to 11.2; P<0.001) compared with Q1. Similar patterns were noted for the other variables of interest.

Conclusions: Higher ET-1 is independently associated with higher SBP in maintenance HD patients. These results suggest a role for studying ET-1 antagonism in HD patients with resistant hypertension.



PO1097

Kidney Transplant Access Among Children and Young Adults on Dialysis in the United States

Yusuke Okuda,[1] Ekamol Tantisattamo,[1] Elani Streja,[1] Marciana Laster,[2] Connie Rhee,[1] Kamyar Kalantar-Zadeh.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]University of California Los Angeles, Los Angeles, CA.*

Background: Only 20% of children and young adults with advanced CKD receive preemptive kidney transplant (KT). This study aimed to investigate secular trends in KT access among incident US dialysis patients who were ≤21 years old.

Methods: In a cohort of incident dialysis patients ≤21 years of age who initiated dialysis between 1995-2014 from the USRDS database, we examined secular trends in the likelihood of receiving KT, using a Cox proportional hazards regression.

Results: Among 24,860 patients, the median (IQR) age at dialysis initiation was 17 (11–20) years of age, among whom 56% were <18 years old. A total of 16,912 (68%) patients underwent a KT during a median (IQR) follow-up of 2.0 (0.9–4.3) years (total follow-up: 82,244 patient-years). The 1-, 2-, and 3-year probabilities of receiving a KT were 23%, 43%, and 55%, respectively. The likelihood of receiving KT slightly improved but decreased after 2005 among patients <18 years old; a decreasing trend was remarkable among patients ≥18 years old [Figure A]. While increasing among patients <18 years old, the likelihood of receiving a deceased donor transplant declined among those ≥18 years old. For a living donor transplant, there were decreasing trends in both age groups [Figure B].

Conclusions: While the likelihood of receiving pediatric KT declined over two decades, there was an increase in deceased donor transplantation among those <18 years old. Since biological factors determine unmet need for KT in pediatric or young adult populations having short waiting time, an old kidney allocation system (KAS), which achieved the goal by transplanting patients with the longest waiting time, may not improve transplant access and outcomes. A new KAS commenced in December 2014, and living donor transplant may provide different trends or improve pediatric KT access, although further long-term studies are needed.

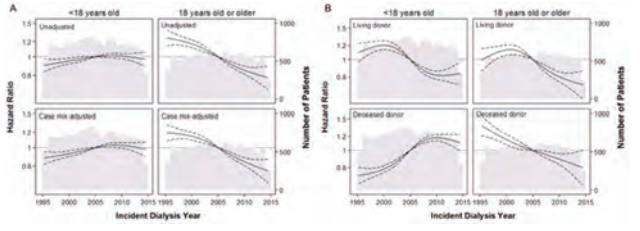


Figure: Time-to-event outcomes for receiving a kidney transplant among pediatrics(<18 years old) and young adults (≥18 years old) between 1995 and 2014.A. Unadjusted and case-mixed adjusted models

B: Stratified into living and deceased donor renal transplantations

PO1098

Nephrologists' Practices, Perspectives, and Experiences Providing Care and Treatment Education to Patients with Varying Amounts of Pre-ESRD Care: A Mixed-Methods Study

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Background: A third of patients newly diagnosed with end-stage renal disease (ESRD) in the U.S. had minimal or no pre-ESRD nephrology care and "crashed" onto dialysis. Little is known about treating nephrologists' practices and perspectives on renal replacement therapy (RRT) information delivery and decision-making for this subset of patients at the time of their ESRD diagnosis and RRT initiation.

Methods: A convergent mixed methods study design was used, and semi-structured interviews were conducted with nephrologists in Philadelphia and the surrounding region. Participants were queried on general practices and perspectives on RRT information delivery and decision-making practices for patients with varying amounts of pre-ESRD nephrology care and also queried on their experiences providing care to patients recently diagnosed with ESRD. Applied thematic analysis was used to analyze the qualitative responses and all quantitative data were fully described.

Results: A total of 15 nephrologists participated. Participants had been practicing nephrology for a median of 7 years and a third of participants were trainees at the time of the interview (i.e., nephrology fellows). The qualitative analyses revealed 12 themes, including: patients' clinical presentation guides RRT initiation, RRT initiation often occurs urgently irrespective of pre-ESRD care, utilize direct communication style during diagnosis, reliance on other providers for patient education, challenges to providing patient education, desire improved access to educational resources, and desire engaging patient in shared decision-making for RRT selection and initiation. Notably, participants identified patient- and institutional-level barriers inhibiting their ability to provide quality care and education to patients presenting with ESRD diagnosis for RRT initiation.

Conclusions: Nephrologists face significant challenges in providing quality care to patients with varying amounts of pre-ESRD nephrology care. Increasing availability of nephrology-trained interdisciplinary staff in outpatient chronic kidney disease clinics and hospital settings to assist providers with the logistics associated with RRT education and initiation has the potential to improve care for patients newly diagnosed with ESRD.

Funding: NIDDK Support

PO1099

Excessive Unfractionated Heparin Dosing During Hemodialysis Explained by Access and Discordance Between Activated Clotting Time and Activated Partial Thromboplastin Time

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Background: Recommendations and practice patterns for heparin dosing during hemodialysis show substantial heterogeneity and are scantly supported by evidence. This study was designed to investigate factors conditioning the dose of unfractionated heparin (UFH) prescribed during maintenance hemodialysis.

Methods: We performed a cross-sectional study assessing UFH dosing, coagulation tests - activated partial thromboplastin time (aPTT) and activated clotting time (ACT) before dialysis start, 1h after start and at treatment end (4h) - and post dialysis measurement of residual blood compartment volume of the dialyzer ("total cell volume") during a single hemodialysis session.

Results: 94 patients, 57% male, with a median dialysis vintage of 34(6-84) months were dialyzed using a total UFH dose of 9271±4066 (range 3000-23050) IU/session (127±58 IU/kg/session). Use of a central venous catheter (n=48, 51%) was associated with higher UFH loading dose (51±22 vs 37±17 IU/kg in patients with arterio-venous (AV) access; $p<0.001$) and higher total UFH dose (158±55 vs 89±32 IU/kg; $p<0.001$). Dialysis sessions using catheters with recent history of thrombotic dysfunction tended to use higher total doses of UFH (174±61 vs 147±49 IU UFH/kg) ($p=0.09$). Compared to baseline values, aPTT increase was significantly higher than ACT increase both 1h (4.7-fold, 95%CI 4.2-5.3 vs 2.0-fold, 95%CI 1.7-2.3) and 4h after dialysis start (3.6-fold, 95%CI 3-4.2 vs 1.6-fold, 95%CI 1.3-1.9) ($p<0.0005$). One and 4h after dialysis start, 75% and 51% of patients presented a >2.5-fold increase in aPTT. Among patients with aPTT increase >2.5-fold at 4h, 84% had an ACT increase of ≤2.5-fold and 52% of ≤1.8-fold ($p<0.001$). No clinically significant clotting of the extracorporeal circuit was noted during the studied sessions. Dialyzer's total cell volume was reduced with a median of 9% (6-21%) without significant effect of UFH dose, aPTT or ACT measurements and catheter use. UFH dose, aPTT, ACT and catheter use were not associated with $spKt/V_{urea}$ either.

Conclusions: Routine clinical practice of UFH dose adaptations based on ACT measurements results in frequent over-anticoagulation according to aPTT results. Higher doses of UFH are used in patients with hemodialysis catheters without evidence that this reduces dialyzer clotting or improves urea clearance.

Funding: Government Support - Non-U.S.

PO1100

Predictors of Extracorporeal Circuit Clotting in Patients Requiring Continuous Renal Replacement Therapy

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Background: Extracorporeal circuit (ECC) clotting frequently occurs during continuous renal replacement therapy (CRRT) resulting in treatment interruption, blood loss and increased resource use. The purpose of this study was to evaluate risk factors for ECC clotting in patients receiving CRRT.

Methods: A retrospective chart review was conducted to identify adult patients who received CRRT at Methodist Le Bonheur Healthcare for a minimum of 24 hours during January 2015 to October 2019. The primary outcome was the occurrence of ECC clotting which was defined as documentation of a thrombotic event in the ECC. Demographic and laboratory data, anticoagulant medications, and CRRT parameters were evaluated for a maximum of 7 days to determine potential risk factors for clotting. Multivariable logistic regression was used to identify predictors of clotting.

Results: A total of 200 patients were included: [108 (54%) male; mean age 56±13 years; mean sequential organ failure assessment score 12±4; 52 (26%) with past medical history of liver disease; 143 (72%) with acute kidney injury; mean duration of CRRT 3.6±2.0 days; 97% receiving continuous venovenous hemodiafiltration]. Overall, 131 (66%) patients experienced an ECC clot with a mean time to first ECC clot of 1.3±1.3 days. Patients receiving an unfractionated heparin (UFH) infusion (n=25) had a lower probability of an ECC clot occurring compared to those receiving no anticoagulation (n=86) (40% and 70%, respectively; p=0.01) and those receiving prophylactic UFH (n=70) (40% and 64%, respectively; p=0.04). Factors associated with an increased odds of clotting in patients not receiving an anticoagulant were non-African American race [odds ratio (OR) 4.0; 95% confidence interval (CI) 1.1-14.6], lower blood flow rates (OR 1.01; 95% CI 1.0-1.03), internal jugular catheters (OR 3.32;95% CI 1.1-9.9), and no history of hypertension (OR 4.79; 95% CI 1.4-16).

Conclusions: This study suggests a high rate of ECC clotting, particularly in patients not receiving anticoagulation. Eligible patients on CRRT should receive an UFH infusion in preference to no anticoagulation or prophylactic UFH.

PO1101

Gram-Negative Bacteraemias in Haemodialysis Patients: Pathogen and Source Identification

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Background: Gram-negative bacteraemia (GNB) in haemodialysis (HD) patients is associated with significant morbidity and mortality. Efforts to reduce rates of bacteraemias caused by Methicillin Resistant Staphylococcus Aureus have been hugely successful. Epidemiological studies now show the re-emergence of gram-negative pathogens, particularly *Escherichia Coli* (*E.Coli*) in causing bloodstream infections. We aimed to determine the source and pathogens responsible for GNB's in our HD cohort.

Methods: Data on all confirmed bacteraemias in HD patients between 2007 and 2018 were collected from clinical and electronic records from the hospital's renal and microbiology databases.

Results: 283 episodes of GNB occurred in 1361 patients over the 12-year period. 58.7% were male. The median age was 71 years (range 26-95). 31.8% had arteriovenous fistulae or grafts, the remainder had dialysis lines, of which 21.2% had dual access. The organisms isolated are shown in table 1. *E.Coli* and *Klebsiella Pneumoniae* were the dominant pathogens, accounting for 40.6% and 15.9% of bacteraemias isolated respectively. The most common sources of infection were HD access related in 31.4% (n=89), urinary tract 18.4% (n=52), hepato-biliary 7.8% (n=22), chest 7.8% (n=22), gastro-intestinal 6.0% (n=17), skin/soft tissue in 4.9% (n=14), other in 4.6% (n=13), no information on 4 patients (1.5%) and unknown source in 50 (17.7%).

Conclusions: *E.Coli* bacteraemias remain a major cause of GNB in our HD population. Dialysis lines are a significant risk factor for bacteraemia, lending further weight to the importance of establishing early definitive vascular access. Resistance trends of gram-negative organisms are of particular and increasing concern. We have noticed changing sensitivity patterns of isolates and it is not clear whether local empiric antibiotic policy is contributing to selection pressures and antimicrobial resistance.

Table 1: Gram negative isolates from blood cultures

Organism	%
Escherichia coli	40.6
Klebsiella Pneumoniae	15.9
Pseudomonas Aeruginosa	7.8
Enterobacter spp	7.8
Proteus mirabilis	6.0
Serratia marcescens	4.9
Other	17

PO1102

Five-Year Outcome of a Retrospective Cohort Study of Patients with Two Hemodialysis Sessions per Week

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Background: The indication of two hemodialysis (HD) sessions per week is a common strategy in patients with chronic kidney disease without social security. Some studies reveal that the indication of fewer HD sessions per week has been shown to be associated with adequate clinical results. **Objective:** To describe the clinical and biochemical status of patients in HD program twice a week in the last five years

Methods: Retrospective cohort study of patients with two HD sessions per week. Their clinical, nutritional status was evaluated by vectors of impedanciometry and quality of life KDQOL-SF 36. The statistical package SPSS V 22.0 was used for data analysis.

Results: Forty-one patients with a mean age of 37.9 ± 12.6 years, 56% women, were analyzed. The mean time with renal replacement therapy was 5.1 years; Average session time was 180 minutes; average ultrafiltration of 2726.8 ± 755.98 ml / session and an average Kt / V single pool of 1.54 ± 0.38. In 59% of patients the cause of CKD was undetermined. 46% of the patients had an arteriovenous fistula. Laboratory tests with Urea Pre-dialysis 164.5 ± 38.9 mg / dL; hemoglobin 10.32 ± 1.9 g / dL; albumin 3.99 ± 0.4 g / dL; phosphorus 5.3 mg / dL; calcium 8.05 ± 0.9 mg / dL; parathyroid hormone 886 ± 747 pg / dL. Body composition BMI 23.6 kg / m2; R (Ω) 622.3; Xc (Ω) 48.4; and phase angle 4.3 °. 44% of the patients had mild malnutrition according to the Score Malnutrion Inflamation classification. The generic dimensions of the KDQOL-SF 36 revealed scores greater than 60 for CKD symptoms and effects, with an SF-12 Physical Health Composite 46.3 and SF-12 Mental Health Composite 56.3.

Conclusions: The costs of hemodialysis (HD) treatment are usually a huge financial burden for health systems and patients. HD sessions twice a week are common practice in many countries in patients without social security. Our results show that this therapy should not be categorized as a suboptimal therapy but as an option for patients with certain clinical characteristics.

PO1103

Feasibility of and Adherence to Using a Wrist-Based Activity Tracker in Hemodialysis Patients

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Background: Wearables allow insights into patient's status outside the clinical setting. We aim to quantify how long patients will use a wearable device before requiring an intervention to improve adherence.

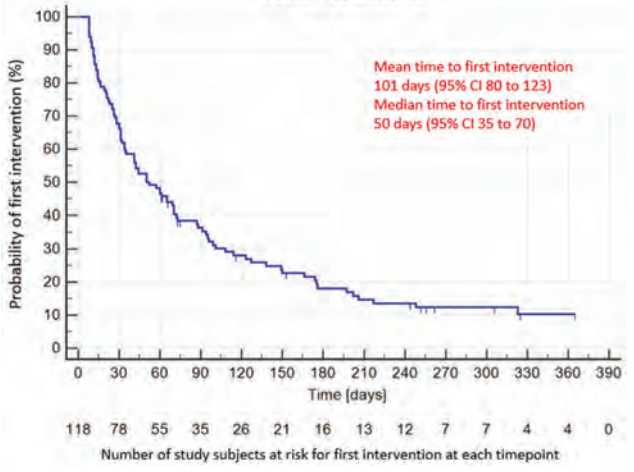
Methods: Hemodialysis (HD) patients were enrolled from 4 clinics in New York City from May 2018 and followed for up to 1 year. Patients ≥18 years, on HD ≥3 months, able to walk, owning a smartphone, mobile tablet or PC were enrolled, provided with a Fitbit Charge 2, and instructed on how to use the device and sync data. If a patient failed to sync data for 7 consecutive days, a SMS or email reminder was sent. Time to first intervention (TFI) was evaluated using Kaplan Meier time-to-event analysis. Predictors of TFI, including gender, age, living situation, and education level, was assessed via univariate Cox Regression. Patients were censored at the end of the observation period.

Results: 125 patients were enrolled into our study and 7 failed screening. At enrollment, patients were 54±12 years old with a dialysis vintage of 5.6±5.8 years; 37% lived alone, 56% were single, 59% unemployed, 64% were African American, and 42% had an education level of some college or higher. 82% of the patients required a text message reminder. Mean and median TFI were 101 days (95% CI 80 to 123) and 50 days (95% CI 35 to 70 days), respectively. The probability of no intervention is shown in Figure 1. None of the a priori defined parameters were significant predictors of TFI.

Conclusions: Majority of patients studied required at least some intervention to maintain the use of a wrist-based wearable device. While most patients require an intervention before 2 months, the patients who maintain use independently after that point are unlikely to require intervention.

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Kaplan Meier curve of time to first intervention



PO1104

Routinely Measured Cardiac Troponin I and NT-ProBNP as Predictors of Mortality in Japanese Hemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study

Masahiro Eriguchi,[1] Kazuhiko Tsuruya,[1] Marcelo Lopes,[2] Brian Bieber,[2] Keith McCullough,[2] Roberto Pecoits-Filho,[2] Bruce M. Robinson,[2] Ronald L. Pisoni,[2] Eiichiro Kanda,[3] Kunitoshi Iseki,[4] Hideki Hirakata.[5] *[1]Nara Medical University, Kashihara, Japan; [2]Arbor Health Care Co, Extendicare Health Services Inc, Milwaukee, WI; [3]Kawasaki Medical School, Kurashiki, Japan; [4]Nakamura Clinic, Urazoe, Japan; [5]Fukuoka renal clinic, Fukuoka, Japan.*

Background: Due to the interplay of chronic kidney disease and the heart, it is common for myocardial damage and strain to be present in hemodialysis (HD) patients. The cardiac troponin I (cTnI) and NT-proBNP are widely used as cardiac biomarkers to evaluate the patients at high risk for cardiovascular disease (CVD). However international The Dialysis Outcomes and Practice Patterns Study (DOPPS) data indicate that these cardiac biomarkers are measured in fewer than 2% of HD patients in real-world practice.

Methods: Pre-dialysis levels of cTnI and NT-proBNP at study enrollment were measured in 1176 prevalent Japanese HD patients (DOPPS phase 5). Cox regression was used to test the association of the cardiac biomarkers with all-cause mortality, adjusting for potential confounders. Subgroup analyses were performed to assess potential effect modification of clinical characteristics: age, systolic blood pressure, HD vintage, diabetes mellitus, CVD, and heart failure.

Results: Median [IQR] cTnI (99th percentile; 0.04 ng/mL) and NT-proBNP levels were 0.018 [0.005, 0.04] ng/mL and 3432 [1580, 8017] pg/mL, respectively. There were 175 deaths during a median [IQR] follow-up of 2.8 [2.3, 2.9] years. Higher levels of both cardiac biomarkers were incrementally associated with mortality after adjustment for potential confounders. Even after adjustment for the alternative cardiac biomarker, the HRs of death for cTnI >0.04 and NT-proBNP >8000 pg/mL versus those references (cTnI <0.01 and NT-proBNP <2000) were 2.67 (95% CI 1.47-4.87) and 2.05 (95% CI 1.10-3.84), respectively and still remained significant. Subgroup analyses showed the associations of both cardiac biomarkers with mortality were consistent between stratified groups. (the p values for interaction were >0.10 for all stratified models).

Conclusions: Routinely measured NT-proBNP and cTnI are strongly associated with mortality among prevalent Japanese HD patients. These associations were still significant even after adjustment for the alternative biomarker, suggesting that cTnI and NT-proBNP may reflect different pathologic aspects for cardiac abnormalities.

PO1105

Paraoxonase 1 Gene Polymorphisms Concerning Dyslipidemia, Related Comorbidities, and Mortality of Hemodialysis (HD) Patients

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Background: Paraoxonase 1 (PON1), a protein product of *PON1*, may prevent atherosclerosis influencing lipid metabolism and exerting antioxidant and anti-inflammatory activities. We focused on *PON1* polymorphisms concerning dyslipidemia, coronary heart disease (CHD), myocardial infarction (MI), ischemic cerebral stroke (ICS), and mortality of HD patients.

Methods: HD subjects (n = 1407, men 782, CHD 542, MI 299, ICS 250) were genotyped for *PON1* polymorphisms by high-resolution melting curve analysis (rs662) or predesigned TaqMan SNV Genotyping Assay (rs854560 and rs705379). Dyslipidemia was diagnosed by K/DOQI guidelines (2003). The TG/HDL-cholesterol ratio of ≥3.8 indicated atherogenic dyslipidemia. Standard diagnostic rules were applied for CHD, MI, and ICS recognition. Survival probability was evaluated by the Kaplan-Meyer method and Cox regression analyses.

Results: The rs662 allele A (OR 1.70, 95% CI 1.07-2.70, P=0.023) and rs854560 TT vs. AA homozygosity (OR 1.59, 95% CI 1.09-2.32, P=0.017) contributed to the prevalence of atherogenic dyslipidemia. *PON1* rs705379 was not associated with frequency of the TG/HDL-cholesterol ratios ≥3.8, but patients showing the TT genotype presented higher values of this ratio (3.92, 0.65–39.4) than possessors of the CC+CT genotypes (3.46, 0.44–49.7, P=0.039) or the CC genotype (3.42, 0.66–34.5, P=0.026). The T allele of *PON1* rs854560 was associated with the higher prevalence of ICS (OR 1.38, 95% CI 1.02-1.85, P=0.034 together with age and diabetic nephropathy) and borderline with MI (OR 1.31, 95% CI 1.0-1.71, P=0.051 together with age, diabetic nephropathy, and male gender). The *PON1* rs705379 TT genotype contributed to mortality from all cardiovascular diseases (HR 1.28, 95% CI 1.04-1.57, n=485, P=0.022), all cardiac diseases (HR 1.33, 95%CI 1.04-1.69, n=354, P=0.023), and CHD and its complications (HR 1.57, 95% CI 1.08-2.27, n=117, P=0.019).

Conclusions: All three tested *PON1* polymorphisms correlate with atherogenic dyslipidemia in HD patients. Associations of *PON1* with dyslipidemia, ICS, and cardiovascular mortality provide arguments for the consideration of PON1 as a therapeutic target in the prevention of atherosclerosis and its complications in uremic subjects.

PO1106

Plasma and Erythrocytes Lipidomic Analysis of Adverse Cardio-Cerebrovascular Outcome in Maintenance Hemodialysis Patients

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Background: Cardio-cerebrovascular diseases are prevalent and devastating in maintenance hemodialysis patients. Lipid metabolism is vital for cardiovascular diseases in non-dialysis population. The disorder of lipid metabolism in dialysis patients is prominent, but the relation of lipids to cardiovascular diseases in dialysis patients is still controversial. Traditional lipids makers failed to identity hemodialysis patients with high risk of cardio-cerebrovascular event. Using high-coverage targeted lipidomic analysis, this study aimed to evaluate the potential of lipids to assess risk of future cardio-cerebrovascular events in hemodialysis patient.

Methods: From July 2013 to August 2019, we followed up the dialysis patients in our dialysis center for stroke and myocardial infarction events, and these patients' plasma and hemocytes were stored at the baseline. Lipidomic analyses were performed on an Exion LC-system coupled with a QTRAP 6500 PLUS system (Sciex). Principal component analysis and orthogonal project to late structures discriminant analysis, and t-test were used to analyze the differences between patients in with /without adverse cardio-cerebralvascular outcome groups.

Results: A total of 45 plasma samples and 117 hemocytes samples were collected. 9 plasma samples and 28 hemocytes samples were from patients with cardio-cerebrovascular events. 539 kinds of lipid metabolites were detected in plasma, 237 kinds of lipid were detected in erythrocytes. Compared with the patients without cardio-cerebrovascular events, the patients with events presented higher level of plasma PS 34:2 and TAG 44:1 (16:1), lower level of plasma TAG 52:6 (16:2), TAG 58:9 (22:5), LPS 18:0, and lower level of erythrocytes Cer d18:1/20:0, Cer d18:1/18:0 and cerd18:1/21:0 (Fold change >1.5 or <1/1.5, P value <0.05).

Conclusions: These findings revealed novel plasma and erythrocytes lipid predictors for cardio-cerebrovascular diseases in hemodialysis patients.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

PO1107

β-Blocker Dialyzability and Adverse Cardiovascular Outcomes in Hemodialysis Patients: A Meta-Analysis

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Background: β-blockers (BB) are one of the most common medications among hemodialysis (HD) patients. There are several BB with different pharmacokinetic properties. Particularly relevant for HD patients is BB dialyzability. In non-dialysis patients, abrupt withdrawal of BB has been associated with adverse cardiovascular events (CVE). HD patients receiving dialyzable BB may also be at increased risk for CVE. This systematic review aims to determine in HD patients if highly dialyzable BB (HDBB) (metoprolol, atenolol, and acebutolol) compared to poorly dialyzable BB (PDBB) (carvedilol, labetalol, bisoprolol, and propranolol) alters CVE and mortality.

Methods: We searched MEDLINE from 1990 through February 2020 for studies of all forms. All cause mortality (ACM) and CVE were our primary outcomes. Random effects models were used to calculate pooled risk ratios (RR).

Results: An initial search identified 1,066 articles. Exclusion criteria eliminated articles that did not include HD participants or did not compare at least two BB. Ultimately, three cohort studies comparing HDBB and PDBB were identified. All studies were retrospective cohort studies of large HD datasets of patients in the U.S. and Canada. The combined population size of the analyzed studies was 38,580 patients: 24,596 on HDBB and 13,984 on PDBB. There was significant heterogeneity between studies, with two suggesting harm associated with HDBB and one suggesting a reduction in mortality. The risk ratio derived from pooled data across these studies was 1.03 (95% CL: 0.88-1.22) for ACM and 0.94 (95% CL: 0.80-1.11) for CVE. Significant heterogeneity was seen with I^2 values of 86% and 84% for ACM and CVE respectively.

Conclusions: After a comprehensive search, only three cohort studies were identified comparing BB of different dialyzabilities. No randomized control trials were identified. The three cohort studies had varying results with two favoring HDBB and one favoring PDBB. Pooled results suggested a greater incidence of CVE in patients on PDBB compared to those on HDBB, while ACM is lower for PDBB than for HDBB. Given the heterogeneity of results it is unclear what type of BB should be used in HD patients. A randomized controlled trial comparing BB of different dialyzabilities is warranted.

Funding: Veterans Affairs Support

PO1108

Pre-Dialysis Transition Predictors of Vascular Access Type in 73,928 Veterans Who Started Hemodialysis Therapy Between 2007-2015

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Background: Studies showed dialysis patients with central venous catheter (CVC) had worse outcomes compared to arterio-venous fistula/graft (AVF/AVG) patients. It is hypothesized that a CVC may be a surrogate for sicker patients. From the US Veteran transition of care (TC-CKD) cohort, we sought to characterize factors associated with initiating dialysis with CVC vs. AVF/AVG access type within a year prior to dialysis transition.

Methods: Among US veterans who transitioned to end-stage renal disease (ESRD) from 2007 to 2015, we examined predictors of access type using adjusted logistic regression. An adjusted reverse cox model was used to examine predictors at time of dialysis initiation to identify time to access placement surgery prior to transition.

Results: Logistic regression showed patients with higher Charlson comorbidity index, multiple preexisting comorbidities, and higher hospital and primary care visit before access surgery, had a higher odds of receiving CVC verses AVF or AVG. Among a subset of 28,759 patients, those who were older, female, black, had dementia, and had higher serum phosphorus, white blood cells, and eGFR are more likely to have CVC. Patients who were married, had higher serum albumin, calcium, sodium, hemoglobin, had slower 1 year eGFR decline, and higher nephrology visits, were less likely to have CVC. Fully adjusted reverse cox regression showed patients with higher serum alkaline phosphatase and blood urea nitrogen were more likely to have AVF/AVG placed closer to time of transition. Among 44,558 patients who had at least 1 VA primary care visit in the year prior to dialysis, patients with ≥2 nephrology visits were more likely to have a AVF/AVG placement surgery in the year prior to transition [figure].

Conclusions: We found that starting dialysis with CVC is a surrogate of adverse outcomes and faster CKD progression, while frequent nephrology visits in a year prior to transition is associated to higher likelihood of AVF/AVG placement.

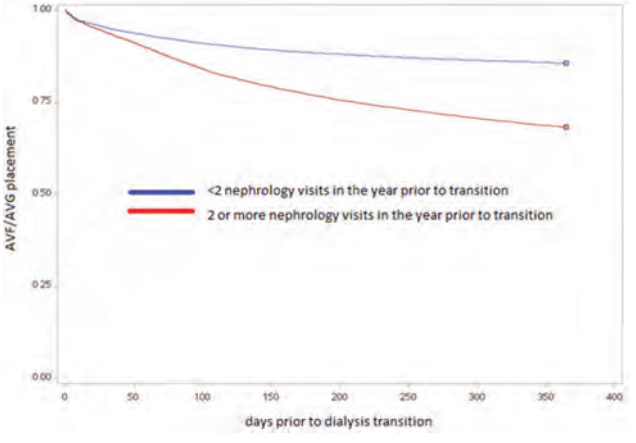

Figure: Time for dialysis transition back to AVF/AVG placement surgery prior to transition.

PO1109

Effect of Treatment According to Intervention Modality with Central Vein Stenosis in Hemodialysis Patients

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Background: A general cause of hemodialysis vascular access failure, a primary cause of morbidity patients undergoing hemodialysis, is central venous occlusion or stenosis. There are several interventions to resolve problem; however whether method is best for dialysis patients. The purpose of this study is to compare which method is best choice to hemodialysis patients.

Methods: We searched Outcomes included the rate of primary patency, assisted primary patency, secondary patency, re-intervention subjects, re-intervention rate regarding balloon angioplasty, nondrug metal stent, drug-eluting balloon, or drug-eluting stent in PubMed, Embase, CENTRAL, Ovid and other relevant websites. We selected and assessed the trials that met the inclusion criteria and conducted a network meta-analysis using the R software.

Results: A total of eighteen studies were included in the network meta-analysis among treatment of intervention group. Overall, 967 patients were reviewed and analyzed for primary and secondary patency rates at 6, 12 months and 24 months post-treatment. Compared with nondrug metal stent, drug-eluting stent group showed a significantly lower secondary patency rates (odds ratio 0.67 [95% credible interval, 0.46–0.92]) at 12 month. However, primary patency and assisted primary patency rates showed no differences among the intervention during observational period. In rank probability, Percutaneous transluminal angioplasty was second in secondary patency rates. However, there is not statistically significant difference in rankgram.

Conclusions: We anticipate that the data of this study will assist physicians in making informed decisions when selecting intervention, such as drug-eluting stent, as a treatment option for central vein stenosis in hemodialysis patients

PO1110

Comparison of Mortality Risk Across Deciles of Cystatin C and Creatinine Among US Veterans

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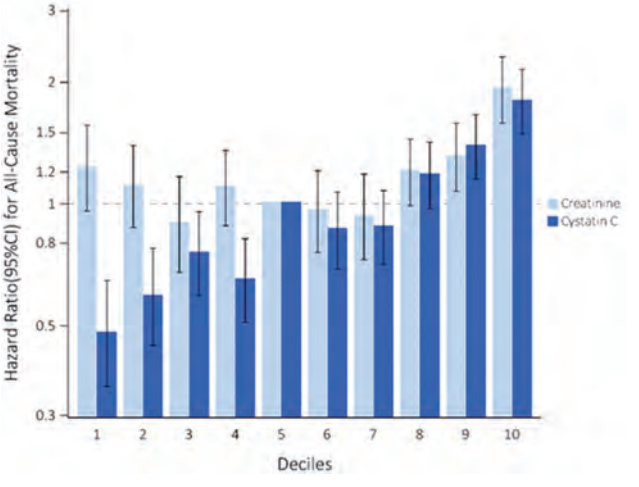
Background: While both creatinine and Cystatin C (CysC) are markers of renal function, a low serum creatinine level can be related to less muscle mass and hence associated with worse outcomes. Prior studies among elderly persons found that higher serum CysC and creatinine levels were predictors of mortality. However, this relationship has not been examined in contemporary cohorts of US veterans. We sought to examine the relationship of creatinine and CysC with mortality risk in US veterans.

Methods: We examined a historical cohort consisting of 7,849 Veterans with baseline CysC and creatinine data between 10/01/2004-09/30/2015. Veterans were divided into deciles of serum creatinine and CysC levels separately. We examined the association of deciles with all-cause mortality using Cox proportional hazards regression adjusted for demographics, comorbidities, and other lab variables using decile 5 as the reference.

Results: The mean age in the cohort was 69±12, 4% were female, 77% were white, 15% were African American. The median (IQR (interquartile range)) for CysC was 1.28 (0.99,1.71) mg/L, for creatinine 1.24 (0.92,1.68) mg/dl. There were 1872/7849(24%) deaths during follow-up(follow-up time median(IQR): 794(461,1244) days). Patients with the highest decile of either CysC or creatinine had the highest mortality risk compared to the reference. Conversely, risk of mortality was incrementally lower for each decile below the reference for CysC while lower creatinine deciles were associated with a null to higher risk of death [figure].

Conclusions: Among US veterans, there is a linear relationship between CysC and mortality risk while the relationship between creatinine and mortality risk is U-shaped. These clinical results indicate that CysC may be a better marker of risk for adverse outcomes than creatinine, as previously shown in epidemiological studies.



Cox proportional hazards model showing the relationship between deciles of creatinine and cystatin C with all-cause mortality (Reference:5th decile). Model adjustments include demographics and comorbidities and lab variables.

PO1111

Comparative Mortality of ESKD from Nephrolithiasis or Urolithiasis in the United States

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Background: Patient with nephro-/urolithiasis (NL/UL), when compared with patients without kidney stone disease, experience higher rates of adverse health outcomes, including increased mortality, cardiovascular morbidity, and progressive kidney disease. Little is known about the epidemiology and outcomes of patients who reach end-stage kidney disease (ESKD) secondary to NL/UL.

Methods: From the USRDS, we identified all patients with incident ESKD who initiated dialysis, 1995-2016. From the Medical Evidence Report (CMS-2728), we ascertained the kidney disease causing ESKD as reported by the patient's nephrologist. Categories included: NL/UL; diabetes; hypertension; glomerulonephritis, polycystic kidney disease (PKD); other urologic; and other/missing/unknown. We also noted patients' age, sex, race, Hispanic ethnicity, Medicaid coverage. Up to 11 comorbid conditions and health behaviors were also abstracted from form CMS-2728. Patients were followed from first dialysis to all-cause mortality, censoring at kidney transplant and end of database (12/2017). Cox proportional hazards regression models, stratified by year, estimated hazard ratios (HR) and corresponding 95% confidence intervals (CI).

Results: We studied 1,979,430 new ESKD patients, of whom 4190 (0.21%) patients had NL/UL as the reported cause of ESKD. Patients with NL/UL had similar age and sex distributions, but more were White (82 vs 66%) and fewer Black (11 vs 28%) or Hispanic (9 vs 13%) than among other causes of ESKD. All-cause mortality during median follow-up of 2.6 years was 173 per 1000 person-years among NL/UL patients. HR and 95% CIs comparing different causes of ESKD with NL/UL, at varying levels of model adjustment, are shown in **Table**.

Conclusions: Compared to patients whose ESKD was attributed to NL/UL, mortality was significantly higher among patients with DM, HTN, and other/unknown/missing cause of ESKD, but lower among patients with GN or PKD as cause of ESKD.

Mortality of Causes of ESKD vs. Nephro-/Urolithiasis [HR (95% CI)]

Nephro-/Urolithiasis (referent)	Adjusted for Year of ESKD	+Demographics and Medicaid	+Comorbidities and Labs
Diabetes	1.28 (1.23, 1.33)	1.46 (1.40, 1.51)	1.32 (1.27, 1.37)
Hypertension	1.23 (1.18, 1.27)	1.24 (1.19, 1.28)	1.16 (1.11, 1.20)
Glomerulonephritis	0.72 (0.70, 0.75)	0.94 (0.90, 0.97)	0.91 (0.88, 0.95)
Polycystic Kidney Disease	0.56 (0.54, 0.58)	0.68 (0.66, 0.71)	0.70 (0.67, 0.73)
Other Urologic Cause	1.12 (1.07, 1.16)	1.06 (1.02, 1.10)	1.02 (0.98, 1.07)
Other, Unknown, or Missing Cause	1.31 (1.26, 1.36)	1.38 (1.33, 1.43)	1.28 (1.23, 1.33)

Complete case analyses

PO1112

Sleep Patterns and Mortality Risk in a Prospective Hemodialysis Cohort

Amy S. You,[1] Sara S. Kalantar,[1] Antoney J. Ferrey,[1] Miklos Z. Molnar,[2] Ronald A. Fischman,[3] Michael A. Fischman,[3] Avedik Semerjian,[3] Yalitzi Guerrero,[1] Tracy Nakata,[1] Csaba P. Kovesdy,[2] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh,[1] Connie Rhee.[1] *[1]University of California Irvine, Irvine, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]Southland Renal Associates, Long Beach, CA.*

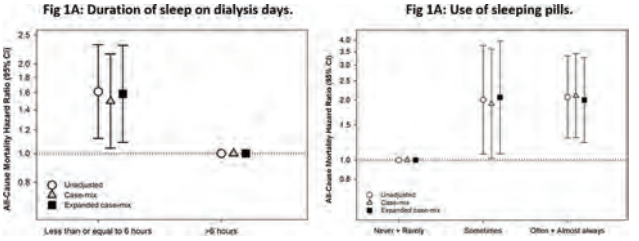
Background: While sleep disorders are common in hemodialysis (HD) patients, the association of sleep patterns and mortality remains uncertain. We sought to examine the association of sleep patterns with survival in a prospective HD cohort.

Methods: Among 452 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease* study, we examined the association between sleep patterns and mortality. Patients underwent protocolized self-reported sleep questionnaires over 3/2014-6/2019. We examined associations of baseline sleep patterns with all-cause mortality using Cox regression adjusted for expanded case-mix covariates.

Results: In the overall cohort, the median (IQR) sleep duration was 6.0 (4.5, 8.0) hours vs. 7.0 (5.0, 8.0) hours on dialysis vs. non-dialysis days, respectively. In analyses examining the association of sleep duration with survival on dialysis days, patients with shorter sleep duration (defined as ≤median) had higher mortality (ref: longer sleep duration >median): adjusted HR (aHR) (95%CI) 1.59 (1.09, 2.31) (**Fig 1A**). Similar findings were observed for patients with shorter sleep duration (defined as ≤median sleep duration) on non-dialysis days (ref: longer sleep duration >median): aHR (95%CI) 1.51 (1.04, 2.19). When surveying patients with regards to having difficulty sleeping at night, those who reported a high frequency (often to almost always) had higher death risk (ref: never/rarely to sometimes): aHR (95%CI) 1.74 (1.17, 2.58). Upon surveying patients with respect to use of sleeping pills, those who reported moderate (sometimes) to frequent use (often/almost always) had higher mortality (ref: never/rare use): aHRs 2.07 (1.08, 3.97) and 2.00 (1.22, 3.28), respectively (**Fig 1B**).

Conclusions: In HD patients, shorter sleep duration, frequent sleeping difficulty, and moderate to frequent use of sleeping pills were associated with higher mortality risk. Future studies are needed to determine if interventions that improve sleeping patterns increase survival in this population.

Funding: NIDDK Support



PO1113

Self-Reported Sleep Patterns in a Prospective Hemodialysis Cohort

Sara S. Kalantar, Amy S. You, Alejandra Novoa, Rene Amel Peralta, Tracy Nakata, Kamyar Kalantar-Zadeh, Connie Rhee. *University of California Irvine, Irvine, CA.*

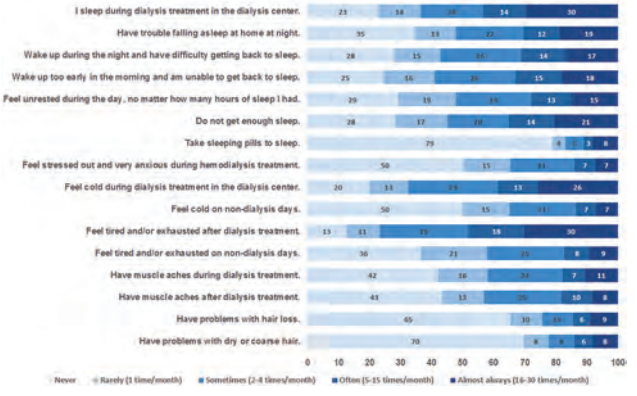
Background: Growing evidence suggests that altered sleep patterns are prevalent in the general population, and are associated with worse health outcomes (obesity, hypertension, cardiovascular disease). However, there has been sparse examination of habitual sleep patterns in chronic kidney disease (CKD) patients, including those receiving dialysis. We thus examined self-reported sleep patterns in a well-defined prospective hemodialysis (HD) cohort.

Methods: Among 452 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* cohort recruited across 16 dialysis clinics, we administered protocolized sleep surveys during routine dialysis treatments over 10/2011-3/2015. Using self-reported questionnaires, patients were queried with respect to their habitual sleep patterns, including survey items related to 1) sleep duration, 2) sleep quality and disturbances, and 3) mental/emotional and physical symptoms potentially linked with sleep alterations.

Results: The mean±SD age of the study population was 55±14 years, among whom 54% were male, 28% were Black, 51% were Hispanic, and 55% had diabetes. In the overall cohort, the median (IQR) sleep duration was 6.0 (4.0, 8.0) and 7.0 (5.0, 8.0) hours on dialysis vs. non-dialysis days, respectively. Over two-thirds to three-quarters of the cohort reported sleeping during dialysis (76%), having difficulties sleeping at night (65%), and having insufficient sleep (72%); sleeping pill use was reported in 21% of patients. Half of the cohort reported stress/anxiety during dialysis, and 87% vs. 64% described feeling tired/exhausted on dialysis vs. non-dialysis days, respectively.

Conclusions: Our findings uncovered a high prevalence of altered sleep patterns in a well-defined prospective HD cohort. Further studies are needed to identify the modifiable and non-modifiable determinants of sleep alterations, as well as their downstream sequelae in dialysis patients.

Funding: NIDDK Support



PO1114

Self-Reported Sleep Apnea-Related Symptoms in a Prospective Hemodialysis Cohort

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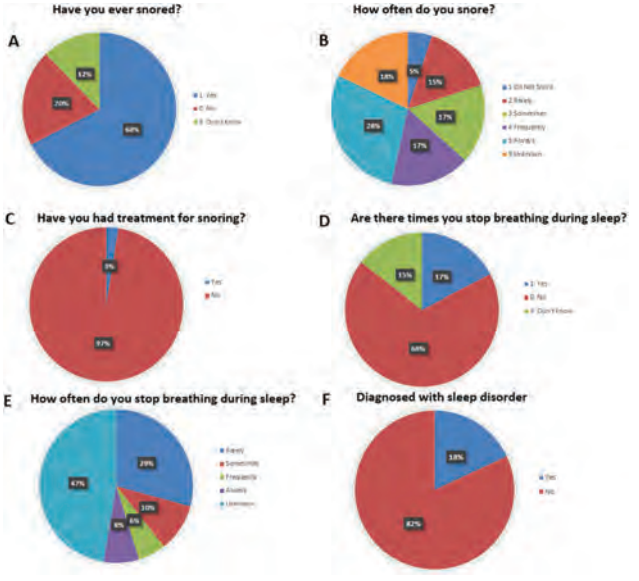
Background: Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder in the general population. While growing data suggests that OSA is more common in hemodialysis (HD) patients, there remains under-diagnosis of this disorder in end-stage renal disease (ESRD) due to symptom overlap with uremia. We thus sought to examine clinical features associated with OSA in a well-defined prospective cohort of HD patients.

Methods: Among 452 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* cohort recruited across 16 outpatient dialysis clinics, we administered protocolized questionnaires querying clinical features of OSA over 10/2011-3/2015. Using self-reported surveys, information was collected regarding OSA-related symptoms including presence and frequency of snoring and apneic events.

Results: The mean±SD age of the study population was 55±14 years, among whom 54% were male, 28% were Black, 51% were Hispanic, and 55% had diabetes. In the overall cohort, 68% of patients reported snoring, among whom 62% reported having frequent (i.e., sometimes, frequent, or always) symptoms. Approximately 17% of patients reported apnea symptoms, among whom 24% reported having frequent events. While over two-thirds of the cohort reported an OSA-related symptom (e.g., snoring, apnea), only 18% were diagnosed with a sleep disorder and 3% had received treatment.

Conclusions: Our findings suggest that clinical features of OSA are common in HD patients, although only a fraction are diagnosed with this disorder and/or undergo treatment for symptoms. Further studies are needed to identify effective OSA screening tools specific to the ESRD population, as well as the impact of OSA interventions in this population.

Funding: NIDDK Support



PO1115

High-Frequency Oscillations of Intradialytic Arterial Oxygen Saturation in Hemodialysis Patients

Xia Tao,[1] Ohnmar Thwin,[1] Priscila Preciado,[1] Matthew S. Cato,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: High-frequency oscillation of arterial oxygen saturation (SaO_2) presenting as repetitive "sawtooth" patterns was observed in sleep apnea patients, but it has never been reported during treatment in hemodialysis (HD) patients. In this study, we explored the prevalence of intradialytic "sawtooth" patterns and their clinical correlates in HD patients.

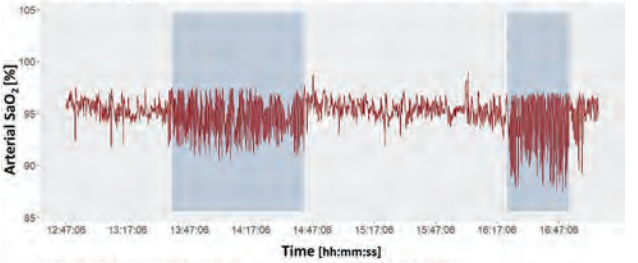
Methods: We prospectively studied chronic HD patients who didn't use breathing devices, cardiac pacemaker, nasal oxygen, alpha blockers, short-acting nitrates, or have history of sickle cell anemia and non-sinus cardiac arrhythmia. During two visits per subject, we used the Crit-Line® Monitor to record SaO_2 at a frequency of 1 Hz, and video recording to capture periods of wakefulness for the entire treatment. SaO_2 data were analyzed for occurrence of "sawtooth" patterns (100% increase in standard deviation lasting ≥10s) and oxygen desaturation episodes (ODE, 3% drop from baseline lasting for ≥10s).

Results: 16 subjects studied were 54±11 years old, 63% males, 69% African Americans. SaO_2 was 94.3±2.1%. "Sawtooth" patterns covered 19.1% of the recorded treatment time, whereas ODE made up only 0.3%. 9 out of 11 subjects who displayed "sawtooth" patterns, showed them in both visits. "Sawtooth" patterns were more likely to occur during the time when subjects were not awake than during wakefulness (25.3% vs. 17.0% of time in each status). Although ODE were rarely seen, 70% were observed during times when "sawtooth" patterns were also present. Figure 1 shows typical SaO_2 "sawtooth" patterns recorded.

Conclusions: Sleep-related breathing disorders are both highly prevalent and underdiagnosed in HD patients and may be underlying the high-frequency oscillations of intradialytic arterial SaO_2 observed in this study. These observations might be useful in identifying sleep-related respiratory abnormalities in HD patients that may warrant diagnostic workup. Further studies are needed to identify sleep-related SaO_2 oscillations and their relationship to clinical outcomes.

Funding: Commercial Support - Renal Research Institute, LLC

Figure 1. Typical "sawtooth" patterns of SaO_2 recorded using the Crit-Line® Monitor



Blue shading indicates time periods during which the subject appeared to be sleeping.

PO1116

CKD and Concomitant Sleep-Disordered Breathing Is Associated with Increased Overall Mortality: A Meta-Analysis

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Background: Sleep-disordered breathing (SDB) is common in advanced chronic kidney disease (CKD) patients. However, the association between CKD with concomitant SDB and overall mortality remains inconclusive. As it has been established that SDB and CKD individually contribute to overall mortality and that a large proportion of CKD patients have concommittant SDB, there comes a question if their morbid effects are compounded together.

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched for eligible publications, including non-transplant CKD patients older than 18 years-old with co-existing SDB. CKD is defined in this study by estimated glomerular filtration rate of <60 mL/min/1.73m^2.

Results: Seven observational studies (n = 186,686) were included in the meta-analyses. 94.2% of patients had end-stage kidney disease (ESKD) requiring hemodialysis (HD), 5.0% had ESKD requiring peritoneal dialysis (PD), and 0.8% had non-dialysis CKD. The mean patient age was 76.8 ± 2.2 years. Most patients were male (53.4%) and caucasian (76.8%). Up to 39.3% of patients had diabetes. The mean body mass index was 26.0 ± 0.6 kg/m^2. Upon analysis, patients with advanced CKD and SDB demonstrated a pooled estimated odds ratios for overall mortality and cardiovascular events were 2.092 (95% CI, 1.594-2.744) and 1.020 (95% CI, 0.929-1.119), respectively compared to patients with CKD alone. No potential publication bias was detected. There were no significant differences in odds ratios for overall mortality, based on subgroup analyses.

Conclusions: Co-existence between advanced CKD and SDB is associated with significantly increased overall mortality, but not cardiovascular (CV) events when compared with CKD alone. The analysis of CV events requires additional studies to corroborate these findings. Moreover, these results suggest clinical interventions should be aimed to prevent the progression of SDB and CKD to mitigate the mortality associated in patients with both diseases.

PO1117

A Randomized, Double-Blind, Phase 2a Study to Evaluate the Tolerability, Feasibility, and Efficacy of AKST1210 in Patients on Hemodialysis with ESRD and Cognitive Impairment

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Background: Studies show that elevated levels of beta-2-microglobulin (b2M) negatively impact cognition. In patients on hemodialysis (HD) for end stage renal disease (ESRD), b2M levels are up to 60-fold higher than in those with normal kidney function; these patients also have a higher prevalence of cognitive impairment. AKST1210 is a device that removes b2M from plasma. To test if removal of b2M could improve cognition, we administered pooled human HD plasma with and without b2M to mice. Mice that received HD plasma with b2M showed a reduction in neurogenesis, neuronal activity, and synaptic markers, while few detrimental effects were seen in mice that received AKST1210 treated HD plasma, suggesting b2M removal is beneficial. Based on robust preclinical data, a clinical study was initiated to assess safety, tolerability, and feasibility of using AKST1210 during HD in subjects with ESRD and cognitive impairment (ESRD-CI).

Methods: In this study, subjects 40 years or older with ESRD-CI are randomly assigned to receive AKST1210 or control during HD sessions for 3 months. Approximately 26 subjects will be recruited and undergo a screening visit, run-in period, treatment visits, and end of study visit. Safety and tolerability will be assessed at every visit. Cognitive assessments will be administered periodically and b2M and proteomics samples collected at specific timepoints.

Results: Primary endpoints are the safety and tolerability of using AKST1210 in subjects with ESRD-CI undergoing HD. Safety is measured by the incidence of treatment-emergent adverse events and serious adverse events. Tolerability is measured by subject retention and compliance with visit completion. Secondary endpoints assess the change from baseline in cognitive assessments and the feasibility of conducting expanded

AKST1210 studies. Exploratory endpoints include plasma analysis to identify biomarkers associated with cognitive function and magnitude of b2M removal.

Conclusions: Preclinical evidence provides the foundation to test if b2M removal may improve cognition in people with ESRD. In this study, safety, tolerability, and feasibility of administering AKST1210 in subjects with ESRD-CI will be assessed. Continued clinical development will be informed by safety and efficacy data emerging from this trial.

Funding: Commercial Support - Alkahest, Inc.

PO1118

Selection of the Best Equation for Serum Osmolality Calculation in Hemodialysis Patients

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Background: Although the serum osmolality (SOsm) is determined by circulating solutes including sodium, potassium, glucose and urea, calculated serum osmolality formula without potassium (2[Na, in mmol/L] + [Glucose, in mg/dL] / 18 + [BUN in mg/dL] / 2.8) is commonly used. Several different equations have been previously described to estimate SOsm. Although in hemodialysis patients it is important to monitor homeostasis by means of estimating SOsm, few studies have examined the accuracy of those equations.

Methods: We identified 20 patients who transitioned to hemodialysis therapy and had repeated SOsm data along with, pre-dialysis sodium, potassium, glucose, and blood urea nitrogen (BUN) on the same day. We compared estimated SOsm by the 13 equations used in the previous literature and measured SOsm.

Results: The patients were 52% male, 33% non-white, and the mean age was 60 ± 17 (mean± SD) years. There were 65 measured SOsm and the mean (± SD) was 310.8 ± 12.0 mOsm/Kg. The following equation provided the best fit between measured and calculated SOsm: 2([Na, in mmol/L] + [K, in mmol/L]) + [Glucose, in mg/dL] / 18 + [BUN in mg/dL] / 2.8 (mean difference, -0.7 mOsm/Kg; 95% confidence interval, -2.12–0.71; P=0.32).

Conclusions: Our result suggests that the equation for estimating serum osmolality in hemodialysis patients should include serum potassium in addition to other components usually used to estimate serum osmolality in non-hemodialysis patient.

Number	Equation	Mean difference	Standard deviation	95% CI	P
1	2Na + (Glu / 18) + (BUN / 2.8)	7.95	5.31	6.54 to 9.36	<0.0001
2	2(Na + K) + (Glu / 18) + (BUN / 2.8)	-0.7	5.34	-2.12 to 0.71	0.32
3	1.75Na + (Glu / 18) + (BUN / 2.8) + 10.1	32.12	4.79	30.85 to 33.39	<0.0001
4	1.86Na + (Glu / 18) + (BUN / 2.8)	27.14	4.99	25.82 to 28.47	<0.0001
5	1.86Na + (Glu / 18) + (BUN / 2.8) + 5	22.14	4.99	20.82 to 23.47	<0.0001
6	1.86Na + (Glu / 18) + (BUN / 2.8) + 9	18.14	4.99	16.82 to 19.47	<0.0001
7	1.86(Na + K) + (Glu / 18) + (BUN / 2.8) + 9	10.1	5.02	8.77 to 11.43	<0.0001
8	2Na + 1.15(Glu / 18) + (BUN / 2.8)	6.79	5.36	5.37 to 8.22	<0.0001
9	1.86(Na + K) + 1.15(Glu / 18) + (BUN / 2.8) + 14	3.91	5.03	2.61 to 5.28	<0.0001
10	1.89Na + 1.38K + 1.08(Glu / 18) + 1.03(BUN / 2.8) + 7.45	8.38	5	7.05 to 9.71	<0.0001
11	1.86(Na + K) + (Glu / 18) + (BUN / 2.8) + 10	9.1	5.02	7.77 to 10.43	<0.0001
12	1.897Na + (Glu / 18) + (BUN / 2.8) + 13.5	8.57	5.07	7.22 to 9.91	<0.0001
13	1.90(Na + K) + (Glu / 18) + (BUN / 2.8) + 5	8.44	5.1	7.09 to 9.79	<0.0001

Na, sodium in mmol/L; K, potassium in mmol/L; Glu, glucose in mg/dL; BUN, blood urea nitrogen in mg/dL; CI, confidence interval

(The list of equations was adapted from J.L. Martin-Calderón et al. Clinical Biochemistry (2015) 48, 529–533)

PO1119

Effect of Dialysate Potassium on Interleukin 6 During Hemodialysis in Patients with ESRD

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Background: Chronic inflammation is associated with poor outcomes in end stage renal disease (ESRD). Pro-inflammatory markers including interleukin-6 (IL-6) increase during hemodialysis. Efflux of intracellular potassium in cell cultures result in activation of inflammasome and release of inflammatory markers. We studied the effect of potassium efflux during hemodialysis on serum IL-6.

Methods: 15 patients with ESRD on chronic maintenance hemodialysis at Hunter Holmes McGuire VAMC were enrolled. Each subject participated in both interventions separated by at least two weeks. Intervention A involved 2K dialysate for the 1st hour followed by 4K for the second hour. Intervention B involved 4K for the 1st hour followed by 2K for the second hour. After first two hours, dialysate potassium was switched to the prescribed concentration for the remaining time Blood was drawn at 0,30,60,90,120,180, and 240 minutes after start of dialysis. Serum IL-6 was measured using ELISA. Data were analyzed using Mixed linear model with $p<0.05$ considered significant.

Results: IL-6 was detectable at baseline and increased during dialysis. However, mean levels of IL-6 were parallel between the 2 interventions (Figure 1.), implying no change in the rate of IL-6 production over time between the 2 interventions (Table 1.)

Conclusions: IL-6 increases during hemodialysis but rate of increase is not affected by dialysate potassium.

Funding: Veterans Affairs Support

Table 1. Linear Mixed Model Serum IL-6

Variable	Estimates	95% CI	P value
Intercept	6.2997	1.3569-11.2424	0.012
Intervention B	-0.6730	-2.9578-1.6118	0.564
Time	0.0079	0.0046-0.0112	<0.001
Intervention B*Time	0.0005	-0.0041-0.0052	0.822

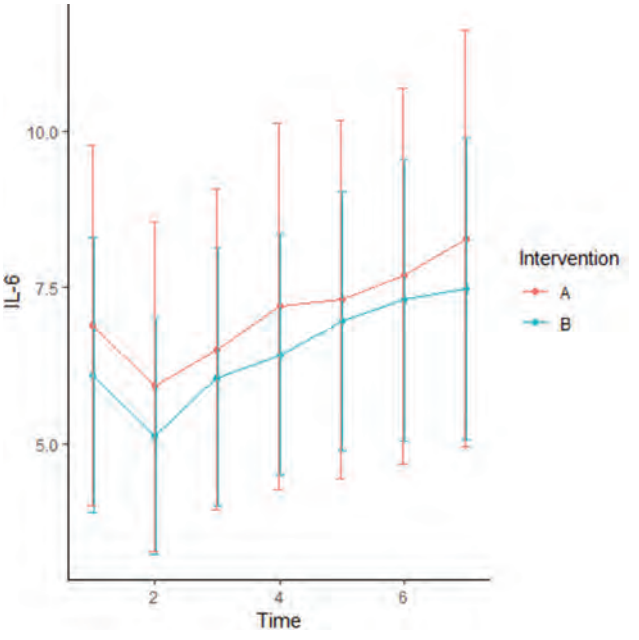

Figure 1. Serum IL-6 at different timepoints between 2 Interventions(Mean±SE)

PO1120

Racial Differences in Physician Trust Among ESRD Patients in Upstate New York

Spencer Dahl, Basil S. Kazi, Fahad Saeed. *University of Rochester Medical Center, Rochester, NY.*

Background: Black patients have worse health outcomes in comparison to White patients, including 2.8 times higher incidence of End Stage Renal Disease, and a significantly higher age stratified risk of death on dialysis. Historically, low levels of physician trust in the healthcare system have been postulated as one of the mediators of healthcare disparities. Previous literature has suggested that black patients are less likely to trust their physicians, however there is a paucity of such data in the dialysis population.

Methods: We surveyed 223/380 (response rate 58%) of hospitalized patients receiving maintenance dialysis in Upstate New York, including 91 white and 82 black patients. We assessed physician trust using the Primary Care Assessment Survey (PCAS). This scale has been previously validated in adult and older adult populations.

Results: We found no difference in the level of trust between black and white patients (3.01 vs 2.95 respectively), assessed on the PCAS scale.

Conclusions: We found no difference in physician trust between black and white patients in our sample. Addressing healthcare disparities is a priority issue for maintenance dialysis patients. Future research to investigate issues related to access to the health care system, health literacy, and socioeconomic status may shed further light into health disparities.

PO1121

Mobile Health (mHealth) Readiness Among Dialysis Patients

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Background: Mobile health (mHealth) is the healthcare use of mobile devices such as mobile phones. mHealth has demonstrated improvement in patient-reported outcome measures, resource efficiencies and cost savings. The aim of this study was to examine the status and correlates of mHealth readiness among individuals on dialysis.

Methods: Cross-sectional 30-item questionnaire, adapted from Bonner's mHealth instrument guided by Khatun's mHealth readiness model, was distributed to people on dialysis from 13 in-center hemodialysis (HD) facilities and 14 home dialysis centers. Proficiency was determined by reported use of applications of increasing level of complexity. We used regression analysis to investigate the relationship between demographic and social factors with proficiency.

Results: 949 patients (632 HD and 317 home dialysis) completed the survey (56% response rate), 38% were female. 73% of respondents reported using the internet: 90% of

them requiring no assistance. 81% of respondents owned smartphones or other internet-capable devices. 70% had intermediate or advanced mHealth proficiency. Main reasons for using mHealth were appointments (56%), communication with healthcare personnel (56%), laboratory results (55%) and obtaining kidney care information (50%). The main reported concerns with mHealth were privacy & security (18%), and cost (6%). mHealth proficiency was lower in older patients: compared to the 45-65 years (yrs) group, respondents in age groups < 45 yrs, 61-70 yrs, and > 70 yrs had adjusted odds ratio (aOR) of 5.04 (95% Confidence Interval: 2.23-11.38), 0.39 (0.24-0.62), and 0.22 (0.14-0.35) respectively. Compared to those with college education, the aOR associated with below high school and high school only were 0.09 (0.05-0.16) and 0.26 (0.18-0.39) respectively. Hispanic ethnicity (aOR 0.49 [0.31-0.75]) compared with non-Hispanic was associated with lower mHealth proficiency, while employment was associated with higher proficiency (aOR 2.26 [1.18-4.32]). Although home dialysis was associated with higher proficiency in the univariate model, we did not observe this in the fully adjusted model.

Conclusions: The majority of dialysis patients surveyed were ready to use, and proficient in, mHealth. These results are encouraging for the nephrology community to increase endorcement of mHealth technologies in patient care.

PO1122

Clinician Perspectives on Access to Kidney Replacement Therapy in Rural Communities

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Background: Patients with chronic kidney disease (CKD) requiring kidney replacement therapy in rural communities are at higher risk of mortality compared with patients in urban areas, and encounter many barriers in accessing care. We aimed to describe clinicians' perspectives of patient access to dialysis and kidney transplantation in rural communities.

Methods: We conducted 28 semi- structured interviews with clinicians (nephrologists, nurses, transplant co-ordinators and social workers) from Australia. Transcripts were thematically analyzed.

Results: We identified five major themes: the tyranny of distance (overwhelming burden of travel, minimizing relocation distress, scarcity of transportation options, concerns for patient safety), supporting navigating of health systems (reliance on local champions, negotiating variability of literacy, providing flexible pathways, frustrating presence of gatekeepers), disrupted care and lacking services (without continuity of care, scarcity of specialist services, fluctuating capacity for dialysis), pervasive financial distress (crippling out of pocket expenditure, widespread socio-economic disadvantage), and awareness of rurality (lacking availability of safe and sustainable resources for dialysis, sensitivity to local needs, dependence on social support, limited options available). Selected quotations are provided in Table 1.

Conclusions: Clinicians felt hampered and frustrated for patients living in rural communities who had limited access to quality care because of geography, financial burden, and complexity and rigidity of the health system. Increased use of telehealth, increased specialist outreach clinics in rural locations and improving flexibility of pathways were suggested to improve access.

Funding: Government Support - Non-U.S.

Table 1. Selected illustrative quotations

Overwhelming burden of travel	Even when I went to the bush (rural), I still had people traveling an hour, two hours to get to me. I know they're going to have to travel for another six hours to get there (transplant hospital).
Minimizing relocation distress	The problem with that is that still from PD catheter insertion to going home still works out to be about at least three months (with patients living away from home). Hopefully for those people that have got the tyranny of distance, more equality with them having actual designated accommodation, designated assistance (will make relocation easier).
Reliance on local champions	We're doing everything by telemedicine (Urban Doctor) and without Nurse on the ground up there (rural location) it would be impossible.
Fluctuating capacity for dialysis	They can't actually have it in their home town. They actually have to travel to somewhere else, look at a home therapy or something else. It's not the way dialysis is set up. It's like a hospital when it goes on bed block, when the dialysis unit in the local town is overwhelmed. I think about a chap [patient] that I was wanting to start on dialysis who was blind and, in a wheelchair, and our nearest chair was going to be over an hour away.
Crippling out of pocket expenditure	I've got one complicated patient who's had a lot of surgical complications post-transplant. And he told me the other day and it actually made me gasp that him and his wife, both on the Pension $20,000 in the red over the last two and a half years. I need a root canal and I don't have X number of thousands of dollars; therefore, I can't have my transplant because I cannot get my dental clearance.
Dependence on social support	If someone doesn't have the support net that is actually a very serious barrier to transplant. It's difficult for these patients who live alone, and don't have a lot of support, so they're the ones who really find it difficult."

PO1123

Estimation and Prediction of Prevalence of Patients Receiving Dialysis in China Based on Claims Data

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Background: The national prevalence of end-stage kidney disease in China has not been well studied. We aimed to estimate the prevalence of patients receiving dialysis and predict the trend using claims data in order to provide evidence for developing prevention strategies.

Methods: Medical claims data from Jan 1, 2013 to Dec 31, 2017 were extracted from a large claims database, which used a two-stage sampling design to obtain a national sample of insured population. Patients receiving maintenance dialysis, including hemodialysis (HD) and peritoneal dialysis (PD), were identified according to medical billings and ICD-10 codes. The age-adjusted prevalence and number of dialysis patients were calculated stratified by year and gender. The Verhulst model was used to predict the short-term prevalence from 2018 to 2025.

Results: From 2013 to 2017, the age-adjusted prevalence of dialysis patients increased from 252.46 per million population (PMP) to 419.23 PMP. In 2017, the age-adjusted prevalence of HD and PD was 384.32 PMP and 34.91 PMP, respectively, and the total number of dialysis patients in China was estimated to be 581,055. The overall trend in the predicted prevalence of dialysis patients was increasing. The predicted prevalence was 533.61 PMP in 2020 and 623.49 PMP in 2025, and the corresponding number of patients was 743,304 and 865,704, respectively.

Conclusions: We have firstly made an attempt to assess the prevalence of dialysis patients in China and establish a national surveillance system based on claims data. It is urgent to formulate prevention and control strategies to reduce the escalating burden of kidney diseases.

Funding: Government Support - Non-U.S.

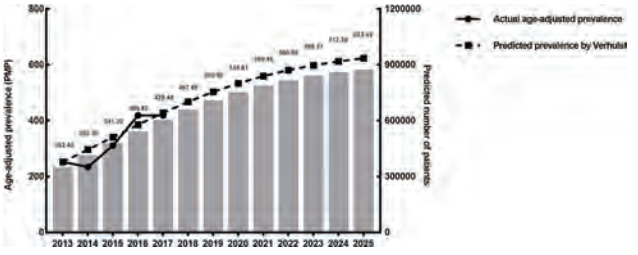

Figure 1. Prediction curve of prevalence and number of dialysis patients in China from 2013 to 2025 Note: The numbers and columns in the figure show predicted prevalence and predicted number of patients using grey Verhulst model, respectively.

Abbreviation: PMP, per million population.

PO1124

Low Socioeconomic Status Increases Risk of Mortality and Hospitalization in Korean Maintenance Hemodialysis Patients

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Background: The number of hemodialysis (HD) patients and medical expenses are growing rapidly in Korea owing to aging society and accompanying diseases such as diabetes. Whether low socioeconomic status (SES) affects poorer HD outcome is controversial. Therefore, this study was performed to evaluate the effect of SES upon mortality and hospitalization in Korean maintenance HD patients.

Methods: We used HD quality assessment data from the year of 2013 and 2015 for collecting demographic and clinical data. The mortality data was collected until Dec 2017. We used insurance status as a proxy indicator of SES in which the subjects were classified into low SES (Medical Aid recipients) and high SES (National Health Insurance beneficiary). We analyzed mortality and hospitalization risk based on SES using Cox proportional hazard model.

Results: A total of 21,786 HD patients from 2013 survey and 35,454 HD patients from 2015 survey were included in the analysis. The ratio between high and low SES group was 76.7% versus 23.3%. The low SES group was younger and showed higher proportion of male, and lower proportion of diabetes, hypertension, and cerebrovascular accidents compared to the high SES group. The crude mortality rate was 93/1,000 person-year in 2013 and 106/1,000 person-year in 2015. After adjusting for age, gender, comorbidity and laboratory parameters, the low SES group showed significantly higher mortality risk compared to the high SES group (hazard ratio 1.151 [95% confidence interval (CI) 1.082-1.225], $P < 0.0001$ in 2013 survey and hazard ratio 1.073 [95% CI 1.009-1.14], $P = 0.0254$ in 2015 survey). The low SES group was also an independent risk factor for hospitalization after adjusting for age, gender, comorbidity and parameters (hazard ratio 1.129 [95% CI 1.09-1.17], $P < 0.0001$ in 2013 survey and hazard ratio 1.142 [95% CI 1.108-1.178], $P < 0.0001$ in 2015 survey).

Conclusions: Low SES independently increases risk of patient mortality and hospitalization in Korean maintenance HD patients

PO1125

Iron Overload in ESRD Treated with Deferoxamine for Chelation

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Introduction: The patient is a 23-year-old female with a history of sickle cell disease, uncontrolled hypertension, and ESRD on HD 3x week for the past 4 years, requiring extensive blood transfusions from hemolysis. Due to the patient's uncontrolled hypertension epoetin alfa was withheld for a few months. The patient presented to Loyola with severe symptomatic anemia, and concerns for iron overload.

Case Description: The patient presented to the hospital with severe anemia and decreased level of consciousness. Labs revealed a Hgb of 5.8g/dl, SBP of 175mmHg, and platelets of 40,000/ml. Hematology was consulted for further evaluation of anemia and thrombocytopenia. Her reticulocyte index was calculated at only 0.10, LDH 206, haptoglobin < 15, with peripheral smear showing no schistocytes or sickles. Iron was 137mcg/dl, transferrin 100, ferritin 4284ng/ml, and iron saturation 98%. Bone marrow biopsy was obtained showing normal cellular marrow for her age and iron laden macrophages. Hgb electrophoresis showed HgS 3.3% indicating that most of the patient's blood was transfused blood volume. Epoetin alfa was restarted and chelation therapy was recommended by hematology for iron overload. The patient was started on deferoxamine 50 mg/kg three times per week following hemodialysis. Most recent labs obtained show a ferritin level decreased to 2378ng/ml after receiving several doses of deferoxamine for over a month.

Discussion: This represents a unique case of iron overload from sickle cell disease along with ESRD leading to transfusion dependence. The treatment of iron overload was from the chelating agent deferoxamine. Initial repeat ferritin levels indicate favorable treatment response without adverse events to date. There are only a few case reports of chelation therapy being used in ESRD. Most of these cases per literature review have been limited to cases of porphyria cutanea tarda. While no repeat iron levels have been obtained due to patient discharge, initial ferritin levels indicate possible treatment response. No adverse side effects have been noted with the patient receiving chelation therapy during her hospital admission.

PO1126

Role of Hemodialysis in Severe Ethanol Poisoning

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Introduction: The treatment for acute ethanol intoxication remains largely supportive. About 1% of patients presenting with ethanol intoxication require the utilization of critical care resources. We present a case of a 19-year-old with altered mental status and a serum ethanol level above assay who required hemodialysis for rapid ethanol elimination and made a full recovery.

Case Description: A 19-year-old male with no past medical history presented with unresponsive after a night of heavy ethanol use. His serum ethanol level was above assay at >550mg/dL. Methanol and ethylene glycol levels were undetectable. He had normal kidney and liver blood tests, without metabolic acidosis. His osmolar gap was attributed purely to ethanol. Given a Glasgow Coma Scale of 3, he was intubated for airway protection. He then developed atrioventricular dissociation and required atropine, and hypotension requiring vasopressor support. A repeat serum ethanol level at 9 hours remained above assay at >550mg/dL and he remained unresponsive at 14 hours. Decision was made to initiate patient on hemodialysis. Two hours into his hemodialysis session, he became conscious and was successfully extubated at a serum ethanol level of 260mg/dL. His neurologic status returned to baseline and he was discharged from the hospital within 24 hours.

Discussion: The patient's ethanol metabolism elimination rate without hemodialysis was calculated to be at 15mg/dL/hour. Using this elimination rate, his initial serum ethanol level was predicted to be about 634mg/dL. Without hemodialysis, it would take roughly 41 hours for complete elimination. While on dialysis, the patient's rate of elimination increased by a factor of four from 15mg/dL/hr to 56mg/dL/hr. Complications of prolonged intubation and cardiac and neurologic toxicity from severe ethanol poisoning in this young patient include life-threatening arrhythmias, and possible permanent neurologic damage which was avoided using hemodialysis to expedite ethanol elimination. This case demonstrates the role and benefit of hemodialysis for a critically ill patient who is experiencing organ toxicity and exposes a need for updated recommendations in this specific set of patients.

PO1127

A Polyethersulfone Membrane with a Direct Thrombin Inhibitor to Decrease Local Thrombus Formation

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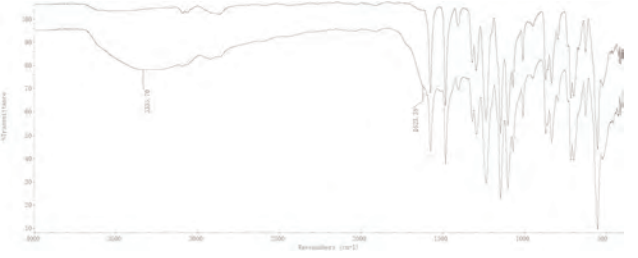
Background: Extracorporeal circulation, such as hemodialysis, is required systemic anticoagulation to avoid thrombus formation. However, conventional anticoagulation methods may induce hemorrhage complications, especially those patients who have bleeding diseases. As dialyzer membrane is the main site of thrombosis. Anticoagulant modification of the dialysis membrane may decrease local clotting of the dialyzer membrane, and doesn't increase the bleeding risk of dialysis patients.

Methods: We chose argatroban(AG), a direct thrombin inhibitor, to modify a polyethersulfone(PES) membrane. Fourier transform infrared spectroscopy(FTIR) was used to confirm that AG was grafted to the PES successfully. Scanning electron microscopy(SEM) was used to observe the characteristic morphology of the membranes. Activated partial thromboplastin time, prothrombin time, and thrombin time were detected to evaluate the antithrombotic property of the modified membrane.

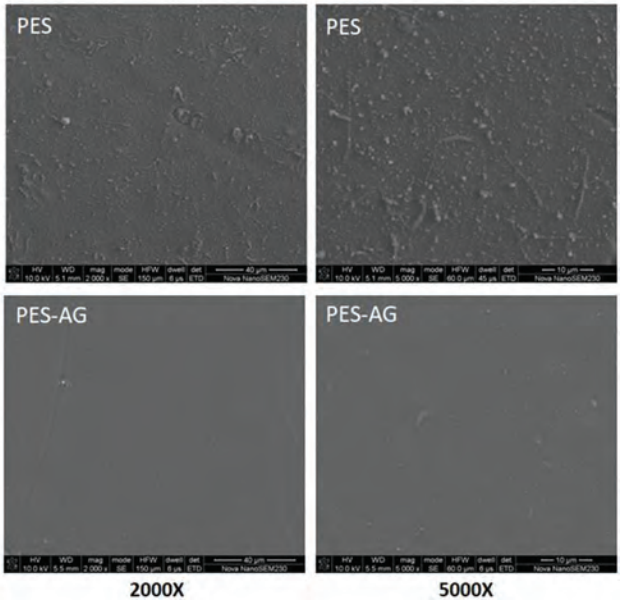
Results: FTIR indicated that argatroban modified PES membranes(PES-AG) were successfully prepared. Compared with the PES membrane, the clotting time value of the PES-AG membrane was significantly prolonged, and the difference was statistically significant, which initially indicated that the PES-AG membrane had a better anticoagulant effect. SEM showed that the PES-AG membrane could decrease local thrombus formation.

Conclusions: Preparation of the argatroban modified PES membrane is feasible, and the anticoagulant performance is superior to the unmodified PES membrane.

Funding: Government Support - Non-U.S.



FTIR of PES and modified membranes



the surface local thrombus formation SEM micrographs of PES and modifiedmembranes

PO1128

Filter Operation Mode Affects the In Vivo Performance of a Synthetic Plasma Fractionation Membrane

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Background: The mode a dialyzer or fractionator is operated may affect the fouling processes of the filter membrane and, hence, may determine its patency and performance. Purpose of the present study was to assess such effects *in vivo*. To avoid the often varying treatment conditions in humans, a large animal model was used.

Methods: In a prospective, randomized, controlled, crossover trial, four sheep were subjected to double filtration plasmapheresis with a polyethersulfone plasma fractionation membrane intended for lipid apheresis (FractioPES® 200; 3M, Germany). Five different operation modes were tested in each animal: Low (30 mL/min), medium (36 mL/min) and high (42 mL/min) plasma flow rates as well as high flow rate at increased plasma temperature (38.5 °C; thermofiltration) and reversed plasma filtration flow direction (outside-in), respectively. The totally treated plasma volume was 1500 mL. Reduction ratios (RR) and sieving coefficients (S_K) at 300, 600, 900 and 1200 ml of treated plasma were determined for LDL cholesterol (2.500-3.000 kDa), HDL cholesterol (175-360 kDa), fibrinogen (305-385 kDa), immunoglobulin IgG (150 kDA) and albumin (67 kDa).

Results: Compared to the other modes (medium flow rate, 0.05±0.02 to, high flow rate, 0.08±0.01), S_K for LDL were significantly higher (P<0.001) in outside-in filtration at 300 mL (0.21±0.03). S_K for LDL were also significantly higher (P<0.001) in both outside-in (0.19±0.07) and at high flow (0.17±0.02) conditions at 600 mL. For IgG at 900 mL, S_K for low flow (0.57±0.32) was lower (P=0.049) compared to the high flow rate (1.05±0.07). For fibrinogen, S_K at 600 mL (0.23±0.03) was higher (P=0.001) in outside-in filtration compared to the other modes. At 900 mL, the S_K for fibrinogen determined in outside-in (0.37±0.12) was superior to the low and high plasma flow modes (0.08±0.08 and 0.13±0.01, resp.). Several significant differences in S_K were identified at different plasma volumes within the same operation mode. No significant differences in RR were determined between operation modes.

Conclusions: Compared to the other operation modes, outside-in filtration and, less pronounced, also high plasma flow rates increase the permeability of a synthetic fractionation membrane for larger proteins. The differences in S_K did not translate into different reduction ratios.

Funding: Commercial Support - 3M Deutschland GmbH

PO1129

Abstract Withdrawn

PO1130

Online High-Volume Hemodiafiltration Reduces Pre-Dialysis Levels of Indoxyl Sulfate Compared with High-Flux Hemodialysis: Results from the HDFit Multicentric Randomized Controlled Trial

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Background: Although HDF improves the clearance and pre-dialysis concentration of middle size molecules, little is known about its effect on concentration of protein-bound uremic toxins (PBUT) particularly in comparison to HD. Here, we investigated whether HDF impacts pre-dialysis plasma levels of the PBUTs indoxyl sulfate (IxS), *p*-cresyl sulfate (pCS) and indole 3-acetic acid (IAA) compared to HD.

Methods: This is *post-hoc* analysis of the multicentric randomized controlled trial studying the impact of HDF *versus* hf-HD on measured physical activity (HDFit - clinicalTrials.gov: NCT02787161), which included clinically stable HD patients with a vintage >3 to <24 months. Total plasma levels of IxS, pCS and IAA were determined by high performance liquid chromatography with fluorescence detection at baseline, 3 and 6 months. Mean difference in pre-dialysis PBUTs between HDF and hf-HD during the 6 months was estimated by linear mixed effect models.

Results: One hundred ninety-three patients (mean age 53 years old, 70% males and 60% white) were analyzed. There were no differences between HD and HDF groups regarding clinical and biochemical characteristics at the baseline. In the HDF group, 99% of patients achieved a convective volume higher than 22 L. The mean differences (95% CI) in concentrations over time for PBUTs among HDF and HD groups are shown in the Figure.

Conclusions: In this *post-hoc* analysis of the HDFit trial, high-volume HDF consistently reduced pre-dialysis concentration of IxS compared to hf-HD. These results demonstrate the sustained effect of mixed-diffuse convective methods in the removal of PBUTs compared to predominantly diffuse techniques.

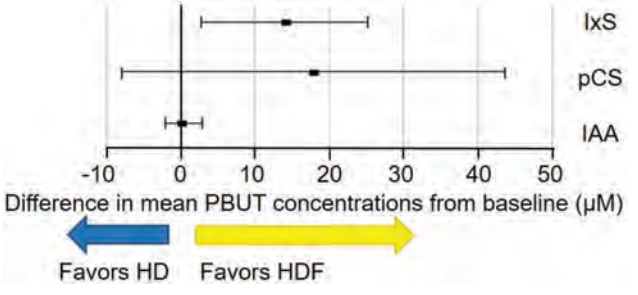

Figure - Mean differences between groups in the change from baseline along with 95% confidence intervals (CI). Results shown IxS favored by HDF compared to HD.

PO1131

Use of Cytokine Adsorbing Membranes in Patients with Acute Renal Failure in Intensive Care Units

Eva Jakopin, Martin Hren, Tina Stropnik Galuf, Masa Knehtl, Tadej Zorman, Nina Vodošek Hojs, Robert Ekart, Radovan Hojs, Sebastjan Bevc. *Univerzitetni Klinicni Center Maribor, Maribor, Slovenia.*

Background: Use of cytokine adsorbents has been proposed as a novel therapeutic approach in sepsis management. Our aim was to evaluate laboratory markers, clinical parameters and SOFA (Sequential Organ Failure Assessment) score in patients who were treated with cytokine adsorbing membrane (CytoSorb®, CytoSorbents Corp. New Jersey, USA) and continuous veno-venous haemodialysis.

Methods: We included adult patients with septic shock and acute renal failure. We retrospectively collected laboratory results (leukocytes, thrombocytes, C-reactive protein, procalcitonin, lactate, urea, creatinine, bilirubin, PaO_2), clinical parameters (mean arterial pressure (MAP), FiO2, residual diuresis), SOFA score and vasopressor use at the beginning and at the end of the procedure.

Results: We included 69 patients, 51 men, aged 56.6 ± 15 years. 51 patients had 1 procedure, 14 patients had 2 procedures, 3 patients had 3 procedures and 1 patient had 4 procedures. Median time from admission to initiation of procedure was 47 hours, median treatment time was 23.6 hours. We discovered significant improvement in procalcitonin (35.36 ± 37.33 ng/mL vs. 24.25 ± 31.18 ng/mL; p<0.001), creatinine (345.06 ± 174.65 μmol/L vs. 233.11 ± 108.82 μmol/L; p<0.0001), SOFA score (14.20 ± 2.64 vs. 12.69 ± 3.52; p<0.001) and FiO_2 (48.17 ± 21.17 % vs. 44.63 ± 21.45 %; p=0.020). Patients with more than 1 procedure showed statistically significant reduction in lactate level (5.40 ± 4.74 mmol/L vs. 2.46 ± 1.74 mmol/L; p=0.010) and vasopressin dose (1.26 ± 1.61 vs. 0.88 ± 3.2 IU/h; p=0.022).

Conclusions: We observed potential beneficial effect of adsorptive membrane use in septic patients. According to our results two or more procedures were associated with improved laboratory markers and lower vasopressor requirement.

PO1132

Clinical Safety of a New Hemodialyzer with the Surface Modifying Molecule Endexo™

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Background: The new Optiflux Enexa™ dialyzer (OED) contains a fluorinated polyurethane surface modifying macromolecule (Endexo™) blended in the membrane during manufacturing. Performance and safety of the dialyzer were assessed in a multi-center, open-label study (NCT# 03536663). This sub-analysis reports additional safety results for OED.

Methods: Subjects enrolled in the study underwent 12 HD treatments on the Optiflux® F160NR followed by 38 HD treatments (visits 13-50) with the OED. Safety was assessed by evaluating: 1) hematology tests and serum chemistry measured pre and post HD at the first use of OED and then measured pre HD for subsequent visits at approximately 2 weeks intervals; 2) Complement activation and serum albumin measured pre and post HD at the first use of OED; and 3) Adverse events recorded during the study.

Results: 23 subjects were enrolled in the study of which 18 subjects (safety population [SPOP]) had at least one HD treatment with the OED for a total of 664 OED treatments. SPOP median age was 63.5 years, female (77.78%) and white (66.67%). Table 1 reports SPOP (n=18) mean (SD) for chemistry and hematology. An increase in mean serum albumin level from 3.94 to 4.23 g/dL was observed. No overt complement activation was noticed. Thirty-two AEs (4.8%) and 3 SAEs were reported, none were device related. No deaths or AEs leading to study discontinuation occurred.

Conclusions: The novel Optiflux Enexa™ dialyzer was well tolerated in a clinical study including 664 HD treatments in ESRD patients.

Funding: Commercial Support - Fresenius Medical Care North America

Table 1. Mean (SD) of lab tests for SPOP (n=18)

Visit	13		22	34	46
Lab test	Pre HD	Post HD	Pre HD		
Chemistry					
K (mEq/L)	4.8 (0.4)	3.5 (0.7)	5.1 (0.3)	5.0 (0.5)	5.1 (0.6)
P (mg/dL)	5.1 (1.5)	1.7 (0.6)	4.7 (1.3)	4.6 (1.5)	4.2 (1.2)
Ca (mg/dL)	9.1 (0.7)	8.9 (0.7)	8.9 (0.5)	9.0 (0.4)	8.7 (0.6)
Mg (mEq/L)	2.1 (0.4)	1.7 (0.2)	2.1 (0.4)	2.1 (0.3)	2.0 (0.3)
Hematology					
Hb (g/dL)	10.6 (0.7)	11.1 (1)	10.9 (0.7)	10.6 (0.8)	10.2 (0.8)
Hct (%)	33.3 (2.2)	34.2 (3.8)	34.2 (2.9)	33 (2.7)	31.6 (2.6)
Platelet Count ($x10^3$/μL)	198.9 (55.9)	199.2 (45.0)	205 (61.4)	201.4 (62.0)	196.7 (50.8)

PO1133

Changes in Sensitivity Patterns of Gram-Negative Isolates in Bacteraemic Haemodialysis Patients

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Background: Gram-negative bacteraemias (GNBs) in haemodialysis (HD) patients are associated with significant morbidity and mortality. While there is a paucity of global data around the quantitative impact of drug resistant organisms, it is clear that they result in increased mortality, longer length of illness and higher costs of delivering appropriate treatment. We aimed to determine the sensitivity patterns of GNBs in our HD cohort.

Methods: Data were collected from clinical records, electronic records, and the microbiology database of all bacteraemias in HD patients between 2007 and 2018.

Results: 283 episodes of GNB occurred in 1361 patients over the 12-year period. *Escherichia Coli* and *Klebsiella Pneumoniae* were the dominant pathogens, accounting for 40.6% and 15.9% of bacteraemias isolated respectively. Sensitivity pattern analysis reveals that Meropenem was almost universally effective against gram negative isolates, with little change over the study period. Similarly, Gentamicin had sensitivity rates of >80% each year except 2010 (50%). Co-Amoxiclav had a variable sensitivity profile and the resistance appeared more prevalent over time – see Figure 1.

Conclusions: Judicious antimicrobial use is a World Health Organisation objective in the fight against antimicrobial resistance. Our local HD policy includes Vancomycin and Gentamicin as empiric therapy. The emergence of Vancomycin-resistant enterococci and more recently staphylococci will influence our future use of Vancomycin. In our population group, Gentamicin therapy remains effective. Carbapenem resistant organisms are a global health threat so whilst Meropenem is efficacious, it should be reserved for more resistant strains or treatment failures. Resistance is increasing at a rate far greater than production of novel antimicrobials so antimicrobial stewardship is paramount; particularly in HD populations with high rates of infection, morbidity and antibiotic exposure.

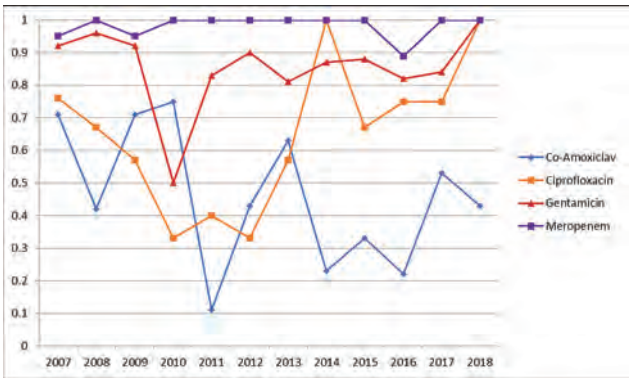

Figure 1: Sensitivity of gram negative isolates between 2007-2018

PO1134

Association Between Nrf2 and CDKN2A Expression in Patients with ESRD: A Pilot Study

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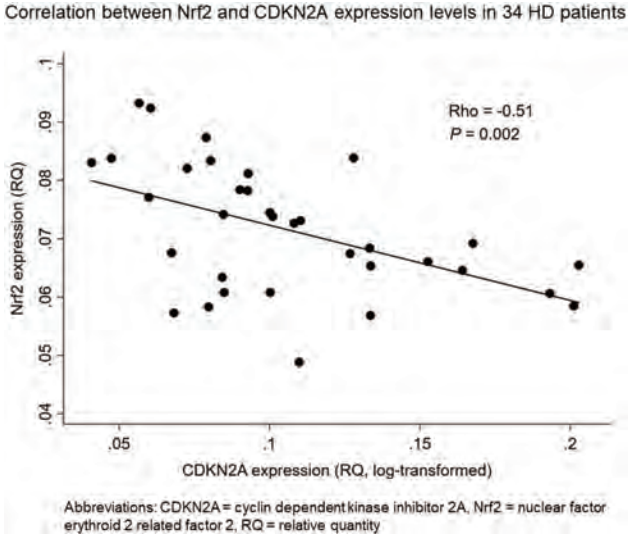
Background: Patients with ESRD display phenotypic features of premature biological aging, characterized by disproportionately high morbidity and mortality at a younger age. Nuclear factor erythroid 2-related factor 2 (Nrf2) activity, a master regulator of antioxidative responses, declines with age and is implicated in the pathogenesis of age-related disorders; however, little is known about the association between Nrf2 and premature biological aging in ESRD patients.

Methods: In a cross-sectional pilot cohort of 34 ESRD patients receiving maintenance hemodialysis, we measured the expression of Nrf2 and cyclin-dependent kinase inhibitor 2A (CDKN2A, or $p16^{INK4a}$, a biomarker of biological aging) genes in whole blood and examined the association of Nrf2 with CDKN2A expression and with chronological age, using Spearman's rank correlation and multivariable linear regression models with adjustment for chronological age, gender, race, and diabetes status.

Results: The mean (SD) age was 62.6 (9.8) years old; 52.9% of patients were male; 70.6% were African American; and 70.6% were diabetic. There was a significant negative correlation between Nrf2 and CDKN2A expression (rho=-0.51, *P*=0.002; **Figure**); while no significant correlation was found between Nrf2 expression and chronological age (rho=-0.02, *P*=0.91). After multivariable adjustment, Nrf2 expression remained significantly and negatively associated with CDKN2A expression (β coefficient=-0.0151, *P*=0.01).

Conclusions: Lower Nrf2 expression levels were significantly and negatively associated with higher CDKN2A expression levels in whole blood of patients with ESRD, independent of chronological age. Our findings suggest a potential contribution of Nrf2 dysfunction to the development of premature biological aging and its related morbidities in ESRD patients.



PO1135

Do Dialysis Facilities Improve Quality After Receiving a Penalty Under the ESRD Quality Incentive Program?

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Background: We examined whether quality measures improve at dialysis facilities penalized under the Centers' for Medicare and Medicaid (CMS) End-Stage Renal Disease Quality Incentive Program (ESRD QIP) after receipt of a penalty.

Methods: Using data from CMS public use files from payment years (PY) 2014-2017, Medicare claims, and CROWNWeb, we used a difference-in-differences analysis to compare patient level measures of dialysis quality at facilities that did and did not receive penalties before and after the performance period. We also used a regression discontinuity design to compare patient quality measures two years after the performance period at facilities just above and just below ESRD QIP's performance score penalty threshold.

Results: Patients at penalized facilities had improved dialysis adequacy after the performance periods associated with PY2014-2017 and improved vascular access after the performance period associated with PY2014, compared to patients at nonpenalized facilities. Changes in vascular access after the PY2015 – PY2017 performance periods were not statistically significant. In the 5 years after the performance period associated with PY2014, the percent of patient-months with a fistula in use and the percent of patient-months meeting adult HD Kt/V standard (HD Kt/V ≥1.2) increased by 2.2 percentage points (95% CI 0.9 to 3.4) and 2.9 percentage points (95% CI 1.4 to 4.4), respectively, while the percent of patient-months with a catheter in use decreased by 2.6 percentage points (95% CI -3.7 to -1.5) at penalized facilities compared to nonpenalized facilities. Compared to those at nonpenalized facilities with relatively similar quality scores, patients at penalized facilities had lower catheter use two years after the PY2014 performance period and higher fistula use two years after the PY2016 performance period. However, these estimates are sensitive to specification changes. Other estimates were not statistically significant.

Conclusions: Receiving an ESRD QIP penalty is associated with subsequent improvements in some measures of dialysis quality, though results differ across payment years and analytic method.

Funding: Other U.S. Government Support

PO1136

Predicting Dialysis Facilities at Risk of Low ICH-CAHPS Quality of Center Scores

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Background: Medicare administers biannual ICH-CAHPS surveys to capture patients' perceived experience of outpatient hemodialysis (HD) care. Recent operations efforts at a national dialysis provider aimed to develop prediction models to identify HD facilities at risk of low ICH-CAHPS rating in the subsequent survey period.

Methods: We used retrospective data from HD facilities at a national dialysis provider during 2018-2019. Two models were built to predict HD facilities that continued to have (Model 1) or decreased below (Model 2) a <60% top box ICH-CAHPS rating on the dialysis center staff, care, and operations subdomain in the spring 2019 survey period. Facility variables in 2018 included were: fall and spring ICH-CAHPS ratings; patient/employee net promoter (NPS) scores; employee retention rate; center quality Five Star rating; years of certification; facility size; composite clinical quality score; and % of HD non-adherence. Predictor variable importance was evaluated, and the performance of various modeling methods was assessed using several machine learning algorithms. We randomly selected derivation (70%) and validation (30%) datasets.

Results: We found the highest performance using GLM and GAM methods for both Models (**Figure 1**). The assessment of performance via the area under curve (AUC) showed use of GLM modeling correctly predicted true/false positives in 73% of facilities that continued to have (Model 1) and 70% of facilities that decreased below (Model 2) a <60% top box ICH-CAHPS rating.

Conclusions: The developed prediction models may be used as a tool in identifying HD facilities at risk of low patient ICH-CAHPS ratings. Prospective use in quality improvement efforts appears warranted.

Funding: Commercial Support - Fresenius Medical Care

Figure 1A: Assessment of variable importance

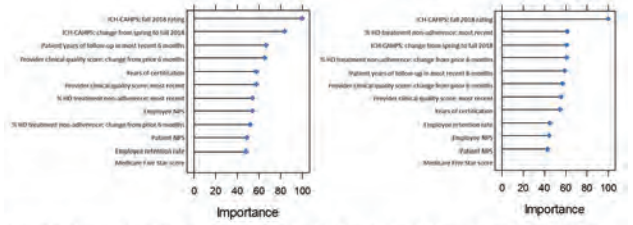
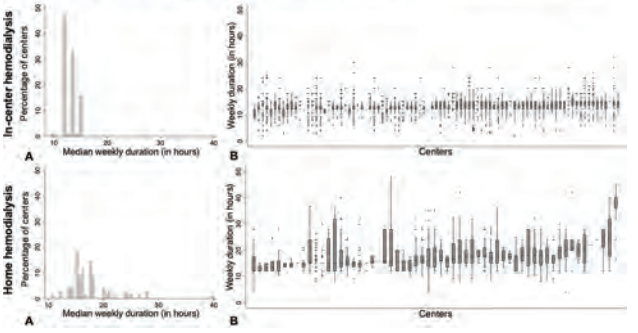


Figure 1B: Performance of prediction models of dialysis facilities that continued to have (Model 1) or decreased below (Model 2) a <60% top box ICH-CAHPS rating on the dialysis center staff, care, and operations subdomain in spring 2019

Prediction Modeling Method	Model 1 AUCs for facilities prior rating <60% top box	Model 2 AUCs for facilities prior rating ≥60%
Generalized linear model (GLM)	0.733	0.699
Generalized additive model (GAM)	0.714	0.693
Random forest	0.663	0.594
XGBoost	0.711	0.600

Figure 1. Distribution of median weekly duration [A] and variability of weekly duration [B] across centers on in-center and home hemodialysis. *Note: Two outlier values (weekly duration of 56 and 70 hours) are not shown on the home hemodialysis figure B for better visualisation of the overall values.*



PO1137

Variability and Trends over Time and Across Centers in Hemodialysis Weekly Duration in Australia and New Zealand

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Background: Hemodialysis treatment prescription varies widely around the world. This study explored patient- and center-level characteristics associated with weekly haemodialysis hours.

Methods: Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry data was analyzed. Characteristics associated with weekly duration were evaluated using mixed-effects linear regression models with patient- and center-level covariates as fixed effects, and dialysis center and state as random effects using the 2017 prevalent in-centre hemodialysis (ICHD) and home hemodialysis (HHD) cohorts. Evaluation of patterns of weekly duration over time analyzed the 2000 to 2017 incident ICHD and HHD cohorts.

Results: Overall, 12,494 ICHD and 1,493 HHD prevalent patients in 2017 were included. Median weekly treatment duration was 13.5 (interquartile range (IQR) 12-15) hours for ICHD and 16 (IQR 15-20) hours for HHD. Male sex, younger age, higher body mass index, arteriovenous fistula/graft use, Aboriginal and Torres Strait Islander ethnicity and longer dialysis vintage were associated with longer weekly duration for both ICHD and HHD. No center characteristics were associated with weekly duration. Variability in duration across centers was very limited in ICHD compared to HHD, with variation in HHD being associated with state. Duration did not vary significantly over time for ICHD, whereas longer weekly HHD treatments were reported between 2006 and 2012 compared to before and after this period.

Conclusions: This study in the Australian and New Zealand hemodialysis population showed that weekly treatment duration was primarily associated with patient characteristics. No center effect was demonstrated. Practice patterns seemed to differ across states/countries, with more variability in HHD than in ICHD.

Funding: Government Support - Non-U.S.

PO1138

Clinical Outcomes Among Dual-Eligible Medicare and Medicaid Dialysis Patients in the United States

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Background: Dual Medicare-Medicaid eligible beneficiaries generally live in poverty and account for approximately 28% of the US end-stage kidney disease (ESKD) population, but their clinical outcomes are largely unknown. We compared individual- and dialysis-facility level clinical quality measures and survival between dual-eligible and Medicare-only incident dialysis patients.

Methods: In this retrospective cohort study using the United States Renal Data System, we identified 52,863 patients who had Medicare as the primary payer, initiated on dialysis from January 1, 2016 through December 31, 2016, and followed until June 1, 2018. We incorporated data from the Consolidated Renal Operations in a Web-Enabled Network (CROWNWeb) and the Centers for Medicare & Medicaid Services (CMS) Dialysis Facility Compare files. We excluded those who were <18 years, transplanted or died within 90 days of dialysis initiation. We conducted multivariable Cox regression with death as the outcome, adjusted for demographic and clinical factors.

Results: The Medicare-primary cohort consisted of 19,819 (37.5%) dual eligible and 33,044 (62.5%) Medicare-only beneficiaries, with median follow-up of 1.8 years. Dual eligibles were more likely to be female, Black, Hispanic and younger than their Medicare-only counterparts (59 ± 15 vs. 66 ± 14 years, p<0.001). At 12 months after dialysis initiation, individual-level quality measures such as hemodialysis treatment time, KT/V, hemoglobin, albumin, calcium, and phosphorus were similar between the 2 groups. However, a slightly greater proportion of dual eligibles were dialyzed via catheter at 12 months compared with Medicare-only patients (47.2 vs. 43.0%, p<0.001). At a facility level, mortality rates, hospitalization rates, standardized infection ratios for bloodstream infection, and total performance scores were similar between the 2 groups. Adjusted analyses demonstrated higher risk of death in dual eligibles compared to Medicare-only patients (hazard ratio 1.29 (95% CI 1.23-1.34, p<0.001).

Conclusions: The Medicare-Medicaid dual eligibility status, as an indicator of poverty, was independently associated with higher mortality, despite similar individual- and facility-level performance measures. Further studies to delineate factors associated with death in this large segment of the ESKD population are needed.

PO1139

The Implementation of a Clinical Pharmacist in a Hemodialysis Center

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Background: Hemodialysis (HD) patients have complicated disease states placing them at a higher risk for drug related problems (DRPs), medication discrepancies, and non-adherence. The objective of the study is to evaluate the impact of a clinical pharmacist in a HD center by assessing the efficacy of medication reconciliation (MR) in HD patients and evaluating the potential impact on the health system.

Methods: This is a retrospective study conducted in Greenfield Health Systems, a division of Henry Ford Health System that operates 14 dialysis centers throughout southeast Michigan. West Pavilion outpatient dialysis clinic, one of the centers in Detroit, Michigan consisting of an interprofessional team. Patients included in the study had at minimum four visits from the clinical pharmacist or pharmacy interns from August 2017 to October 2018. Study aim was to evaluate the impact of a clinical pharmacist in a HD center by assessing the efficacy of MR in HD patients and evaluating the potential impact on the health system. Descriptive statistics were used to collect DRPs and classified based on the modified Hepler-Strand approach.

Results: A total of 1403 DRPs with an average of 8.94 DRPs per patient were found with an average number of 7 visits per patient. Adherence was the most common DRP (31%). The most common drug class the pharmacist made interventions on was for medications used to treat blood pressure (37%) followed by vitamin D analogs/ calcimimetics (29%). A projected total of $447,355 was saved.

Conclusions: Pharmacists in HD clinics has a positive influence on HD patients through medication management and cost savings.

PO1140

Dietary Potassium Intake and All-Cause Mortality in Adults Undergoing Hemodialysis: The DIET-HD Cohort Study

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Background: Dietary modification to reduce the risk of hyperkalemia in people undergoing maintenance hemodialysis is standard practice and is commonly recommended in guidelines despite a lack of evidence. A low potassium diet may impair quality of life and nutritional status. We aimed to assess the association between dietary potassium intake and mortality and whether hyperkalemia mediates this association.

Methods: 9690 adults undergoing maintenance hemodialysis in Europe and South America were recruited in the DIET-HD study, of which 1647 were excluded for lack of data-linkage identifier or incomplete or implausible dietary assessment. We measured baseline potassium intake from the GA²LEN food frequency questionnaire and performed time-to-event and mediation analyses.

Results: The median dietary potassium intake at baseline was 3.5 g/day (IQR 2.5 to 5.0). During a median follow-up of 3.97 years (25,890 person-years), we observed 2921 (36%) deaths including 1316 (45%) from cardiovascular causes. After adjusting for baseline characteristics including presence of cardiac disease and food groups, dietary potassium intake was not associated with all-cause mortality (hazard ratio [HR] 1.00 95% confidence interval [CI] 0.95 to 1.05). A mediation analysis showed no association of potassium intake with mortality either through or independent of serum potassium (HR 0.999, 95% CI 0.996 to 1.002 and 1.000, 95% CI 0.999 to 1.002, respectively). Higher potassium intake was not associated with higher serum potassium (B=0.04 mEq/L 95% CI 0.00 to 0.09) or the prevalence of hyperkalemia (≥ 6.0mEq/L) at baseline (OR=1.08, 95% CI 0.93 to 1.24). Hyperkalemia was associated with cardiovascular death (HR=1.23 95% CI 1.03 to 1.48).

Conclusions: Higher dietary intake of potassium is not associated with hyperkalemia or death in patients treated with maintenance hemodialysis.

Funding: Government Support - Non-U.S.

PO1141

Serum-to-Dialysate Calcium Gradient and Its Association with Mortality in Incident Hemodialysis Patients

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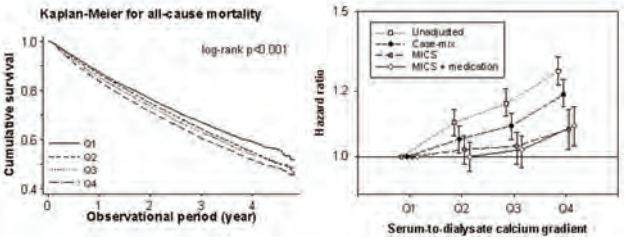
Background: A high serum-to-dialysate calcium gradient at start of hemodialysis leads to rapid lowering of serum calcium and was associated with higher risk of witnessed cardiac arrests. However, the association of serum-to-dialysate calcium gradient with mortality remains unclear. The objective of this study was to evaluate the serum-to-dialysate calcium gradient associated with a greater risk of adverse events in incident hemodialysis patients.

Methods: We retrospectively examined 96,339 in-center hemodialysis patients who initiated dialysis treatment between January 1, 2007, and December 31, 2011 in a large United States dialysis organization. Cox proportional hazards model was used to assess the multivariable association between serum-to-dialysate calcium gradient and patient survival.

Results: Higher serum-to-dialysate calcium gradient was associated with older age, higher proportion of hypertension, lower blood pressure in post dialysis, and worse nutritional indices. Adjusting for patients differences, there was a dose-response relationship between higher serum-to-dialysate calcium gradient and greater risk of all-cause mortality [adjusted hazard ratios: 1.00 (95% confidence interval [CI]: 0.96–1.04), 1.02 (95% CI: 0.97–1.06), and 1.09 (95% CI: 1.05–1.15) for subjects in the second, third, and fourth quartiles (reference: first quartile group)]. Similar trends were observed for cardiovascular and sudden cardiac mortalities.

Conclusions: Higher serum-to-dialysate calcium gradient is independently associated with greater risk of all-cause, cardiovascular, and sudden cardiac mortalities in hemodialysis patients.



PO1142

Pharmacokinetics, Pharmacodynamics (PK-PD), and Exposure-Efficacy Evaluation from CaLIPSO, a Phase 2B Study to Assess the Effect of SNF472 on Progression of Cardiovascular Calcification in Patients on Hemodialysis

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Background: Cardiovascular calcification (CVC) is a major contributor to increased morbidity and mortality in end stage kidney disease (ESKD) patients on dialysis. SNF472, a selective calcification inhibitor that interferes in the formation and growth of ectopic hydroxyapatite (HAP), has showed a significant reduction in CVC progression in CaLIPSO, a randomized, double-blind, placebo-controlled phase 2b trial. The drug is also currently in Phase 3 trial for the treatment of calciphylaxis. Our aim was to perform PK-PD and exposure-response analyses from the CaLIPSO trial.

Methods: PK and PD were assessed at weeks 1, 10, 22 and 52, following intravenous administration thrice weekly over 52 weeks. Efficacy was assessed as % change in coronary artery calcification score by volume (CACv) over 52 weeks. The relationship between PK (C_{max}) - PD (ex-vivo inhibition of HAP crystallization in plasma), PK-efficacy and PD-efficacy was evaluated using linear and E_{max} models.

Results: The analyses included data from 56 patients. C_{max} values and PD responses per group were similar over the 52 weeks of treatment, indicating no accumulation of SNF472. Mean plasma C_{max}, mean PD effect and % change in CACs over 52 weeks per group are shown in the table. An E_{max} model described well the relationship between PK-PD (E_0=8.8%, E_{max}=75.9%, EC_{50}=5.5 μM); and PK-efficacy (E_0=16.9%, E_{max}=-14.5%, EC_{50}=12.2 μM). The PD-efficacy relationship was better described by a linear model.

Conclusions: SNF472's PK showed no accumulation and PD remained constant over 52 weeks of treatment. E_{max} models showed a robust relationship between SNF472's C_{max} and both the ex-vivo inhibition of HAP crystallization and clinical efficacy measured by % change in CACv over 52 weeks. Higher SNF472 exposure and inhibition of HAP crystallization correlated with a reduction in CVC progression in ESKD patients on dialysis.

Funding: Commercial Support - Sanifit Therapeutics

Parameter	Group		
	Placebo	300 mg	600 mg
PK (C_{max}, μM)	Undetectable (<0.76)	15	45
PD effect (%)	17	60	75
% change CACv	14	9	-2

CACv: Coronary artery calcification score by volume

PO1143

Associations of Dialysis Facility Clinical Performance with Patient Outcomes in the Medicare ESRD Quality Incentive Program (QIP)

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Background: In CY2017, CMS implemented the Meaningful Measures Initiative, which aimed to reduce data reporting burden and costs for health care providers and to focus improvement efforts on the most meaningful outcomes for patients. To assure the ESRD QIP is aligned with this initiative and is achieving CMS goals, we assessed whether facility clinical measure performance is associated with improved patient outcomes.

Methods: Patient outcomes at the facility level were evaluated using the CY17 standardized mortality ratio (SMR) and standardized hospitalization ratio (SHR) from Dialysis Facility Compare, and the ESRD QIP CY17 In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH-CAHPS) scores. Facility-level performance in CY17 on ESRD QIP measures for hypercalcemia, fistula, long-term catheter, comprehensive Kt/V, NHSN bloodstream infection (BSI) standardized infection ratio (SIR), and standardized transfusion ratio (STrR) was assessed using tertiles. Associations between facility measure performance and outcomes were tested using Poisson models for SMR and SHR and Analysis of Variance (ANOVA) models for ICH-CAHPS scores.

Results: For all ESRD QIP clinical measures, lower levels of performance were associated with higher relative risks (RR) for SMR and SHR (p<.05; Table). For all clinical measures except STrR and NHSN BSI SIR, lower levels of performance were also associated with lower ICH-CAHPS QIP scores (p<.05; Table).

Conclusions: The observed associations of facility performance on individual ESRD QIP clinical measures with mortality, hospitalization, and patient experience with care indicate that the program is incentivizing improvements in care that are related to important patient outcomes.

Funding: Other U.S. Government Support

Table: Associations between facility measure rate/ratio tertiles and SMR, SHR, and ICH CAHPS (CY 2017)

Measure Tertiles		SMR RR (95% CI)	SHR RR (95% CI)	ICH CAHPS Score (95% CI)
Hypercalcemia Rate	0%	0.91 (0.89, 0.94)	0.93 (0.92, 0.94)	5.30 (5.17, 5.43)
	1%	0.95 (0.93, 0.97)	0.96 (0.94, 0.97)	5.18 (5.04, 5.32)
	2%-48%	1	1	4.56
Fistula Rate	3%-61%	1.09 (1.06, 1.11)	1.07 (1.05, 1.08)	4.68 (4.53, 4.84)
	62%-71%	1.02 (1.00, 1.05)	1.02 (1.01, 1.04)	5.17 (5.03, 5.32)
	72%-100%	1	1	5.60
Catheter Rate	0%-6%	0.93 (0.91, 0.95)	0.94 (0.92, 0.95)	5.42 (5.26, 5.58)
	7%-11%	0.95 (0.94, 0.97)	0.98 (0.96, 0.99)	5.14 (5.00, 5.28)
	12%-60%	1	1	4.89
Comp Kt/V Rate	0%-95%	1.15 (1.13, 1.18)	1.13 (1.12, 1.15)	4.54 (4.37, 4.71)
	96%-97%	1.1 (1.08, 1.12)	1.08 (1.06, 1.09)	5.01 (4.86, 5.16)
	98%-100%	1	1	5.65
NHSN BSI SIR	0-0.42	0.96 (0.94, 0.98)	0.97 (0.95, 0.98)	5.00 (4.83, 5.17)
	0.43-0.96	0.97 (0.95, 0.99)	0.99 (0.97, 1.00)	5.25 (5.10, 5.39)
	0.97-7.12	1	1	5.20
STrR	0-0.7	0.84 (0.83, 0.86)	0.80 (0.79, 0.81)	5.37 (5.21, 5.54)
	0.71-1.09	0.92 (0.90, 0.94)	0.89 (0.88, 0.90)	5.06 (4.92, 5.20)
	1.1-5.35	1	1	5.08

PO1144

Types of Incidents (Patient Safety) Managed at Two Different Medical Levels in a Large Multinational Renal Services Provider Network

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Background: Patient safety programs need a well-structured organization to facilitate proactive and fair reporting, prompt evaluation analysis and timely feedback followed by measure implementation and auditing. **Objectives** To analyze all types of incidents in our network during 2019 by two different levels (Corporate and Country) of medical management alert.

Methods: Our institution has tracked all incidents under a structured process program for the last 10 years, according to 4 incident types (Patient related, Staff-visitors, Products and Equipment) and 54 subcodes. Incidents are considered as serious when they may be life-threatening or result in death, impaired body function/structure and/or are deemed serious based on appropriate medical judgment. Communication to Health Authorities applies in accordance with local country regulations. "Serious incidents" are immediately notified to the Corporate Office and to each Country Medical lead, whilst different codes may generate alerts into Corporate or Country.

Results: 92.923 incidents (2.7 incident/patient/year) were reported during 2019. Total incidents/1000 treatments were 17.2 (12.2 were patients related incidents). Causes for alerts at Corporate level (n=81) were cardiorespiratory arrest (26%); unexpected death (19%); seroconversion (9%); wrong disposable/dialyzer (9%); hemolysis (7%); severe hypotension (5%) and different mix codes (25%). Reported incidents at country level (n=831) were more than half ascribed to equipment [water supply, power failure and flooding (53%)], medication errors (35%), venous needle dislodgment (20%) and staff-visitors Injuries (4%).

Conclusions: Tracking of incidents have potential to increase quality of care and patients outcomes. Despite continuous efforts to get better results, there is room for improvement on better staff compliance with our standard operating procedures especially regarding medications and venous needle dislodgment risk assessment.

PO1145

Roxadustat in Treating Anemia in Dialysis Patients (ROAD): Short-Term Impact on Serum Triglyceride

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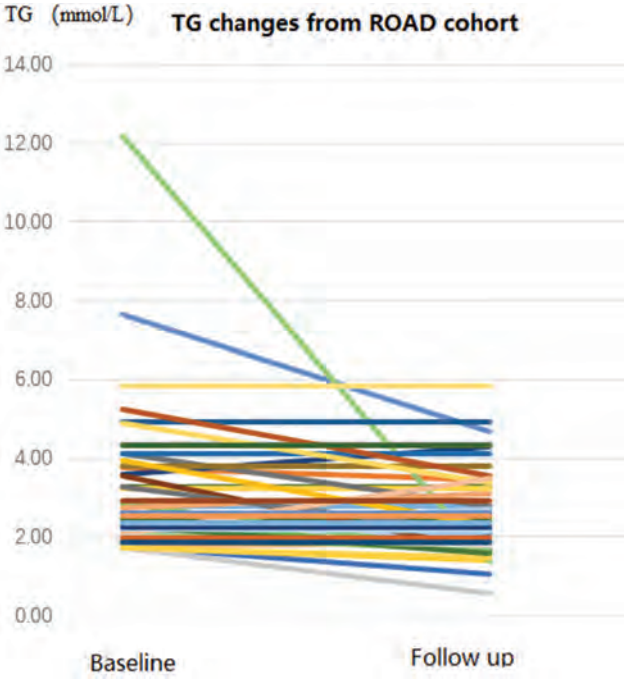
Background: Roxadustat has been shown effective in lowering serum cholesterol in treating patients with anemia due to chronic kidney disease. However, its effect on serum triglyceride (TG), especially in dialysis patients that have high prevalence of hypertriglyceridemia remains unknow. This analysis is to provide clinical data of Roxadustat on serum TG in a real-world prospective observational cohort.

Methods: This is a multicenter, prospective, longitudinal observational cohort study assessing if Roxadustat improves prognosis in at least 250 dialysis patients with renal anemia. Primary outcomes will be major cardiovascular events. The current analysis was done in the enrolled 144 patients to compare the changes of serum TG from baseline to current follow up. The analysis was done in the whole cohort and subgroups according to baseline serum TG level.

Results: Till May 20, 2020. 144 dialysis participants (76 male, mean age 52+/-15 years) were enrolled from 11 sites of the study with a follow up of 8 (0~12) weeks. The primary disease of kidney failure was predominantly primary glomerulonephritis (67 cases, 46.5 %) and diabetes (28 cases, 19.4%). The serum TG at baseline and at the last follow up was 2.06+/-1.58 mmol/L (range from 0.14 to 12.04 mmol/L) and 1.90+/-1.09mmol/L respectively (p=0.162). In patients with TG greater than 1.7mmol/L, serum TG decreased significantly (n=53, 2.59+/-1.06 *vs.* 3.09+/-1.75 mmol/L, p=0.028) after Roxadustat treatment with -0.50mmol/L (95%CI: -0.05, 0.95mmol/L).

Conclusions: Hypertriglyceridemia is prevalent in ROAD cohort. Roxadustat could alter serum TG, especially lowering its level in dialysis anemia patients with hypertriglyceridemia which should be confirmed in future studies.



TG changes from ROAD cohort.

PO1146

Roxadustat in Treating Anemia in Dialysis Patients (ROAD): Short-Term Impact on Serum Iron Markers

Daqing Hong,[1] Guangyi Zheng,[4] Yang Zou,[1] Yanrong Cai,[2] Jingdong He,[3] Hen Xue,[4] Qiang He,[1] Guisen Li.[1] *[1]Department of Nephrology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China; [2]Gao Xin Boli Hospital, Chengdu, China; [3]The Second Affiliated Hospital of Chengdu Medical College, Chengdu, China; [4]Department of Nephrology, Ya'an People's Hospital, Chengdu, China.*

Background: This analysis is to provide clinical data of Roxadustat on iron markers in a real-world prospective observational cohort.

Methods: This is a multicenter, prospective, longitudinal observational cohort study assessing if Roxadustat improves prognosis in at least 250 dialysis patients with renal anemia. Primary outcomes will be major cardiovascular events. The current analysis was done in the enrolled 144 patients to compare the changes of iron markers from baseline to present.

Results: Till May 20, 2020. 144 dialysis participants (76 male, mean age 52+/-15 years) were enrolled from 11 sites of the study with a follow up of 8 (0~12) weeks. Hemoglobin increased by 8.5g/L (95%CI:6.1 to 10.8 g/L, p<0.001) significantly from baseline to last follow up. The serum ferritin at baseline and at the last follow up was 639.13+/-530.18 pg/ml and 473.52+/-520.34 pg/ml respectively (p<0.001). TSAT remained stable from baseline to last follow up (36.8+/-20.5% *vs.* 36.7+/-22.7%, p=0.93). In patients with ferritin greater than 500 pg/ml or 800 pg/ml, changes of ferritin were 245 pg/ml (95%CI:117.62 to 373.46, p<0.001) and 362.01 pg/ml (95%CI: 99.34 to 580.30, p=0.008). In patients with low responsiveness to ESA, according to ESA dosage (greater than 300U/Kg/Week, 199.41pg/ml, 95%CI: 37.69 to 361.12, p=0.019) or by investigators' judgement (143.83pg/ml, 95%CI:55.99 to 231.67 pg/ml, p=0.002), the results were similar and significant. TSAT did not change significantly among the whole cohort and in the subgroup analysis.

Conclusions: Roxadustat could increase hemoglobin in dialysis patients in ROAD cohort. It could decrease serum ferritin in dialysis patients, regardless of the high ferritin or responsiveness of ESA treatment and maintains stable TSAT. These might indicate that Roxadustat partially increase hemoglobin by alter iron status even in patients have low responsiveness to ESA treatment.

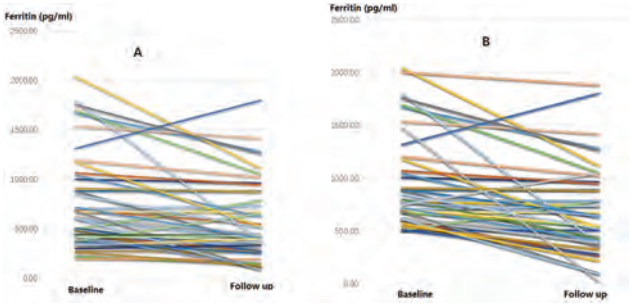


Figure 1 Ferritin changes from ROAD cohort.

A. patients with hyperresponsiveness to ESA

B. patients with baseline ferritin greater than 500 pg/ml.

PO1147

Relationship Between Fluid Overload (FO) and Hemoglobin Concentration (Hgb) in Hemodialysis (HD) Patients (Pts)

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Background: FO is common in HD pts and the BCM (Fresenius Medical Care, Germany)allows the assessment of fluid volumes and FO. We studied the association between FO and Hgb concentration in a cross-sectional study in four urban US dialysis clinics and tested the effects of inflammation and erythropoiesis-stimulating agents (ESA).

Methods: We conducted BCM measurements in participating HD pts, and obtained Hgb, neutrophil-to-lymphocyte ratio (NLR) and ESA usage from the EMR. The association between FO (stratified into tertiles) and Hgb and NLR, resp., was tested using ANOVA and that between FO and ESA usage using Chi-Square Test. We further employed linear regression, stratified by ESA usage (yes/no), to test associations of FO with Hgb and NLR.

Results: We studied 170 pts (40% female, 52.9% black, 28.2% Hispanic, 61.3±14.4 years, FO 2.2±2.4 L, Hgb 10.9±1.3 g/dL, NLR 3.5±1.9). Greater FO associated with higher NLR (Figure 1a) and lower Hgb (Figure 1b) and also with ESA use (P<0. 001). Hgb negatively correlated with NLR (r=0.1, P=0.10) and FO (r=0.3, P<0. 01). The association between Hgb and FO remained after adjustment for NLR (Beta -0.17, P<0. 01). When the same association was tested separately for pts on ESA and those not on ESA, Hgb was inversely correlated with FO only in patients not on ESA (Beta -0.22, P<0.01), whereas its inverse relationship with NLR remained significant in both subgroups.

Conclusions: FO and inflammation inversely associates to Hgb and deserves consideration in anemia management. BIA can help the clinician assess whether FO may be contributing to low Hgb values. As such, it is a valuable diagnostic tool that should find its way into routine care for US HD pts.

Figure 1a

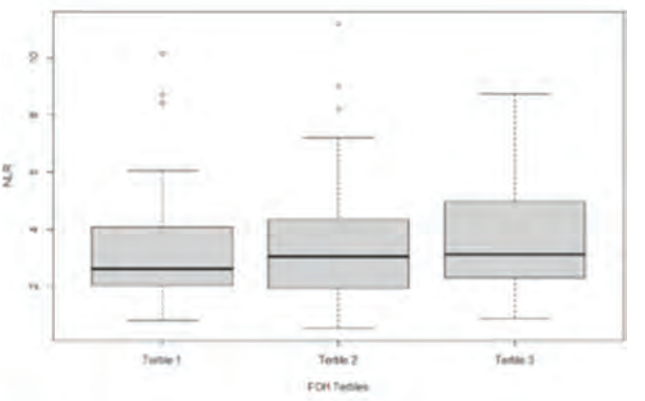
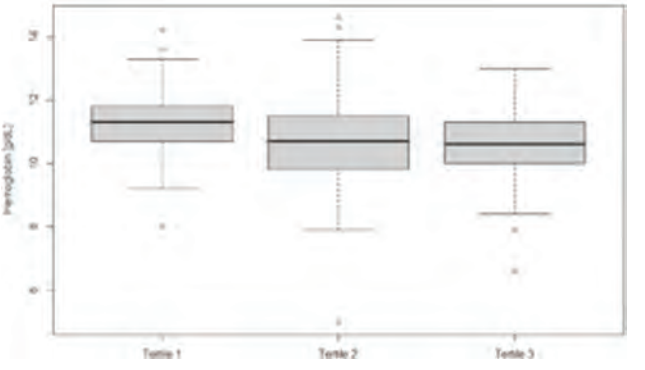


Figure 1b



PO1148

Automated Early Detection of Hyponatremia in Hemodialysis Patients Derived from Online Conductivity Measurement

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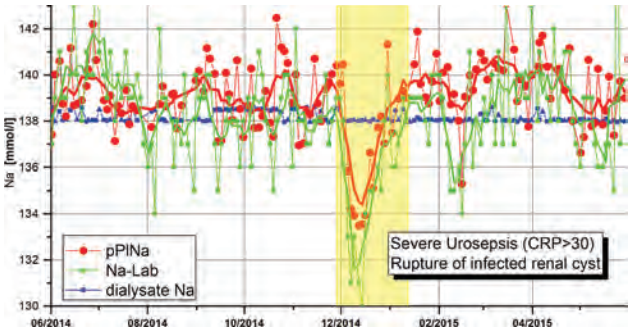
Background: Hyponatremia in dialysis patients is a strong indicator of poor outcome that requires early detection to facilitate clinical workup and management. However, plasma sodium concentration as determined by lab methods (*Na-Lab*) is measured at the best monthly in clinical practice. Recently, online monitoring of predialytic plasma Na (*pPlNa*) as estimated from dialysate conductivity using an electrolyte model has become available at every hemodialysis session, thus providing an unprecedented close and almost continuous monitoring of this crucial indicator. This could be used as diagnostic tool to earlier alert the physician of underying clinical illnesses.

Methods: In a monocentric retrospective clinical study in 114 patients on maintenance hemodialysis (>90% online postdilution HDF) for whom online *pPlNa* was available for a period of at least 12 months at least once a week, kinetics of *pPlNa* were analyzed. For 11 patients with hyponatremic episodes as manifested in *pPlNa*, the agreement between time course of *pPlNa* and *Na-Lab* and the correlation to the manifestation of clinical findings was explored.

Results: Time course of *pPlNa* and *Na-Lab* showed very good agreement. In addition, in each case the onset of hyponatremia was linked to a subacute illness development (i.e., sepsis, congestive heart failure, …) underpinned by various degrees of fluid overload. Correction of the underlying pathology and fluid overload by dry weight adjustement permitted to improve clinical outcome.

Conclusions: The clinical examples show that due to the good agreement of the time course of *pPlNa* and *Na-Lab*, *pPlNa* can be used as adjuvant diagnostic tool for the early detection of onset and progression of morbid events. This online tool will support physicians in decision making for improving dialysis patient management and likely outcome. Further studies are deserved to confirm the clinical value of this tool.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH



Example for the agreement between the time course of *pPlNa* and *Na-Lab*, and to clinically manifested illness during a period of hyponatremia

PO1149

Prevalence of Fluid Overload in a US Dialysis Population

Ulrich Moissl,[2] Lemuel Rivera Fuentes,[1] Mohamad I. Hakim,[1] Laura Rosales,[1] Fansan Zhu,[1] Dewangi A. Kothari,[1] Jochen G. Raimann,[1] Stephan Thijssen,[1] Peter Kotanko.[1] *[1]Renal Research Institute, New York, NY; [2]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany.*

Background: Hypervolemia remains one of the main reasons for increased cardiovascular (CV) morbidity and mortality in chronic hemodialysis (HD) patients. Quantification of fluid status using bioimpedance spectroscopy (BIS) has become routine in many countries outside the United States (US). Due to previous unavailability of FDA-cleared BIS devices, no cross-sectional appraisal of fluid status in HD patients has yet been done in the US. The aim of this study was to perform the first assessment of fluid status in a US dialysis population using a BIS device

Methods: Fluid overload (FO) was measured in 170 chronic HD patients from four clinics in New York City using the BCM Body Composition Monitor (Fresenius Medical Care) which provides the amount of excess extracellular water (ECW) in liters. Measurements were performed before dialysis; post-dialysis fluid status was estimated by subtracting the removed fluid from pre-dialysis FO

Results: Pre- and post-dialysis FO were found to be 2.2L ± 2.4 L and -0.2 ± 2.7 L (mean ± SD), respectively. Before the start of HD, 42.9% of patients were fluid overloaded (criterion: FO/ECW > 15% in males, and >13% in females), 53.5 % were normally hydrated, and 3.5% were fluid depleted (FO/ECW <-7%).

Conclusions: The prevalence of pre-HD fluid overload was significantly higher in this US population (42.9%) than in a previously published large European cohort (29.6%). This suggests the need for more adequate assessment of fluid status to support the clinicians in identifying and treating fluid overload in HD patients

Funding: Private Foundation Support

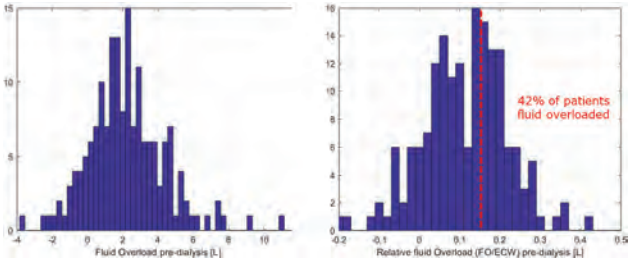


Figure 1: a) distribution of pre-dialysis FO in liters, b) relative FO

PO1150

The Use of Loop Diuretics in Newly Initiated Hemodialysis Patients: The Clinician's Perspective

Tripta Kaur, Steven G. Coca, Girish N. Nadkarni, Lili Chan. *Icahn School of Medicine at Mount Sinai, New York, NY.*

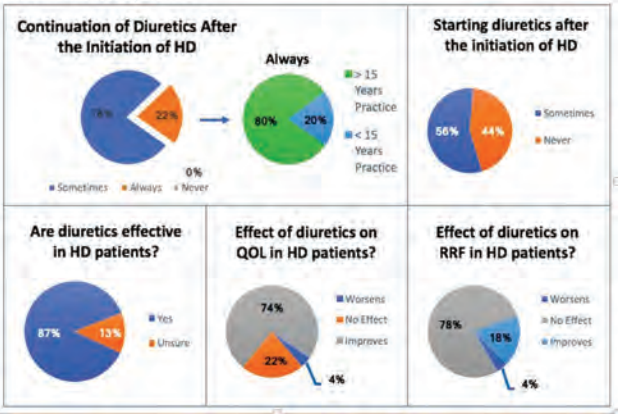
Background: ESRD patients newly initiated on HD have varying levels of residual renal function (RRF). The loss of RRF is associated with increased cardiovascular and all-cause mortality and decreased quality of life (QOL). There are no studies reported to date that have explored in detail the physicians' clinical opinion and approach to the use of diuretics after the initiation of HD.

Methods: A one-time anonymous electronic survey was created to explore the clinicians' opinion and practice pattern of diuretic use in new-start HD patients. 50 nephrologists associated with the Mount Sinai Health System were included.

Results: 23 (46%) completed the survey and 8 (35%) have practiced nephrology for > 15-years. 16 (70%) assess RRF monthly. The level of urine output per day (UOP/d) considered adequate for diuretic use was 200-250 mL by 7 (30%) and 400-500 mL by 12 (52%). While 20 (87%) and 18 (78%) of the physicians felt that diuretics are effective in HD patients and improve quality of life (QOL), respectively, only 5 (22%) always continue diuretics and 13 (57%) sometimes start diuretics after initiation of HD (Fig 1). Physicians with >15 years in practice were more likely to continue diuretics than physicians with less experience (50% vs. 7%, P=0.03). Volume status (70%) and the ineffectiveness of diuretics (64%) were considered more important factors in the decision to use diuretics. Only 5 (26%) routinely use furosemide > 240 mg/day, but only 10 (43%) were influenced by ototoxicity.

Conclusions: While a majority of physicians believe that diuretics are effective and improve patient QOL, few consistently continued diuretics and only half started diuretics "sometimes". The factors that were considered more important in decisions to continue or start diuretics were volume status and the opinion that diuretics can be ineffective in HD patients.

Figure 1. Diuretic use after the initiation of HD and the physician's opinion on the role of diuretics in HD patients.



PO1151

Assessment of Estimated Dry Weight in Dialysis Patients Undertaking Kidney Transplantation by Evaluating Post-Transplant Weight: The Kidney Knows Best

Spencer Hodgins,[1] Bikash Chapagain,[1] Twara K. Tarasaria,[1] Yossi Chait,[2] Michael J. Germain,[1] Barbara A. Greco.[1] *[1]Baystate Medical Center, Springfield, MA; [2]University of Massachusetts System, Boston, MA.*

Background: The consequences of volume overload include recurrent hospitalizations and increased mortality in dialysis patients. Dry weight (EDW) is estimated in dialysis patients to provide a target for ultrafiltration and to prevent the consequences of volume overload. New kidney transplant recipients with good allograft function provide a unique opportunity to evaluate the accuracy of EDW. With the assumption that a good functioning kidney allograft would return the patient to their optimal dry weight (ODW), we compared the differences between EDW and ODW in a cohort at our center.

Methods: We retrospectively reviewed 138 adult kidney transplant recipients at Baystate Medical Center between June 2015 and October 2019. Patients were excluded on the basis of not achieving a serum creatinine of ≤1.5 mg/dl at 2 weeks post-transplant. ODW was defined as the weight at 2 weeks in a patient with good allograft function. Patients with EDW in the range +3% and -1% of ODW were considered to be euvolemic pre-transplant. Patients with EDW below and above that range were considered hypovolemic and hypervolemic, respectively. 35 patients met criteria and were included in the analysis.

Results: The mean (SD) age was 54.3 (12.7) years with 52% male. 31.4% of patients had live donors. Based on pre-transplant EDW values, 23% were above (hypovolemia), 17% within, and 60% below (hypervolemia) the range of euvolemia (Figure 1).

Conclusions: We conclude that many dialysis patients (83%) may not be at their ODW. This illustrates the importance of finding novel tools to help achieve accurate dry weight patient undertaking dialysis in order to reduce hospitalizations and improve mortality.

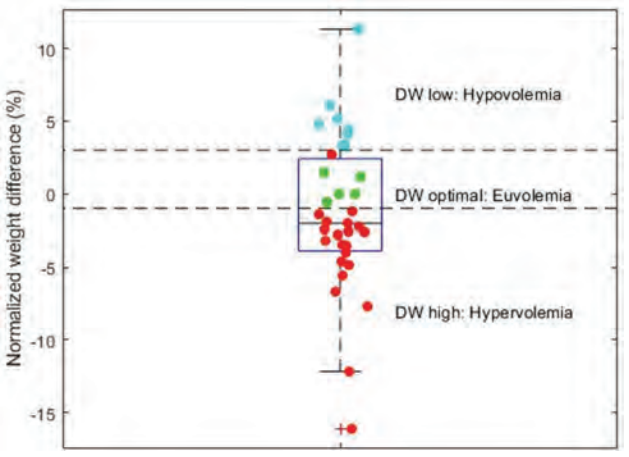


Figure 1. Box Plot Showing the normalized weight differeince in %.

PO1152

Novel Ultrafiltration Rate Feedback Controller for Attainment of Relative Blood Volume Targets During Hemodialysis

Lemuel Rivera Fuentes,[1] Mirell Tapia,[1] Sabrina Rogg,[2] Stephan Thijssen,[1] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Preciado et al. have identified half-hourly relative blood volume (RBV) targets during a hemodialysis (HD) session that are associated with significantly improved patient survival. Attainment of these RBV targets would require incessant empiric adjustments to the ultrafiltration rate (UFR) by the dialysis nurse. We developed a novel proportional-integral controller that takes RBV data from the commercially available CLiC® device as an input and provides UFR suggestions to guide the RBV curve into the desired targets. The clinician specifies the desired UF goal with the maximum allowed upward/downward deviation from this goal, and the UFR Feedback Controller then optimizes the RBV trajectory within the limits of the prescription. The present study aimed to characterize the behavior of this feedback controller

Methods: We conducted a single-arm, prospective, interventional pilot study in subjects on chronic HD at 3 dialysis centers in NYC. RBV was measured with the CLiC® device. CLiC® and HD machine data were fed into a research laptop running the UFR Feedback Controller software. The UFR recommendations (generated every 10 min) were evaluated by dialysis nurses who then either implemented or disregarded them as they deemed clinically appropriate

Results: 15 subjects (58.9 ± 15.3 years, 53% black, weight gain 2.6 ± 0.8 L, HD time 222 ± 28 min) were studied (63 study visits, 4.2 ± 1.9 visits/subject). Of 300 analyzed RBV target timepoints, 63% had RBVs within the desired target range, 33% of the RBVs were above and 4% were below target. Stratified by timepoint, the on-target percentage increased from 37% at 30 min to 73% at 3h into HD. The rate of intradialytic morbid events did not appear to be increased. In subjects with at least 4 complete study visits (N=8), on average 71.8% of subjects were within the desired RBV target at 3h into HD

Conclusions: The UFR Feedback Controller behaved as expected, steering the patients' RBV curves toward the predefined target ranges while strictly observing the prescribed UF goal. Preciado et al. had reported a third of patients within the favorable RBV target range at 3h into conventional HD. In contrast, with the use of this novel UFR Feedback Controller, approx. 72% of subjects were within the desired RBV target range at 3h

Funding: Private Foundation Support

PO1153

A Novel Algorithm to Identify Presumably Fluid Overloaded Hemodialysis Patients

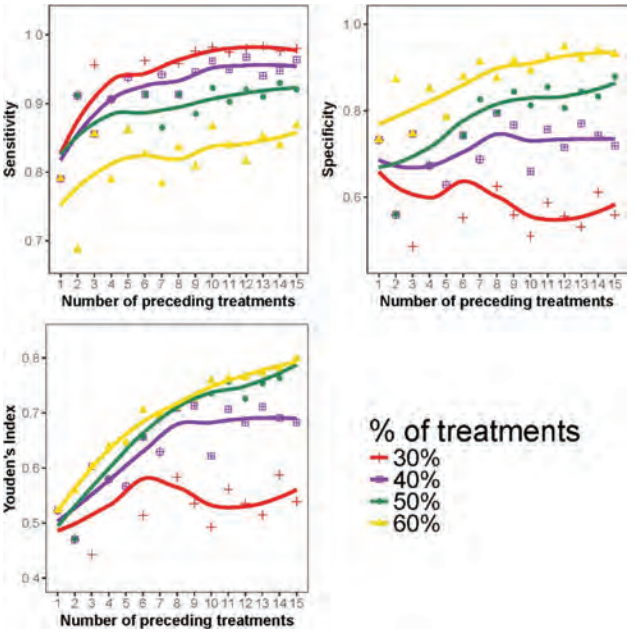
Priscila Preciado,[1] Hanjie Zhang,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Mount Sinai Health System, New York, NY.*

Background: Adequate volume control is a major challenge in hemodialysis (HD) patients. Relative blood volume (RBV) monitoring evidence suggests that flat RBV slopes indicate fluid overload. We aim to develop an algorithm to identify presumably fluid overloaded HD patients based on a small number of consecutive RBV recordings

Methods: We based our analysis on the 842 prevalent HD patients in our previously published study, RBV was assessed over a 6-month baseline period and all-cause mortality recorded;an RBV between 86 and 92% three hours into treatment was associated with significantly better survival. Our goal was to develop an algorithm that would require a much shorter observation period with clinically meaningful sensitivity and specificity to identify (presumably FO) patients with flat RBV profiles (RBV >92% at 3 hours). We categorized patients as either positive (mean RBV >92%) or negative. We computed sensitivities and specificities relative to the positive and negative cases for 1-15 HD sessions and various rates of treatments with flat RBV curves

Results: Sensitivities, specificities, and Youden's indices (=sensitivity+specificity–1) for 1-15 treatments and across the different rates of positive RBV curves are shown. We found a sensitivity of 92%, specificity of 80%, and Youden's index of 73% when >=50% of 10 preceding treatments were positive

Conclusions: Our algorithm requires only a small number of RBV readings to identify presumably fluid overloaded patients with a clinically acceptable sensitivity and specificity. It would be of interest to compare the performance of this algorithm with volume status as determined by bioimpedance;however, bioimpedance has not yet been approved for use in HD patients in the U.S.



Sensitivity, specificity & Youden's index as a function of HD treatments and rate of treatments with flat RBV curves.

PO1154

Peak Oxygen Capacity in Patients on Dialysis: The Role of Fluid Overload

Vanessa O. Gomes, Marília P. Viana, Lizbeth C. Benavides, Marcelo P. Menezes filho, Jose Mariano S. Pantoja, Luana R. Soares, Jukelson B. Silva, Valkercyo A. Feitosa, Rosa M. Moyses, Rosilene M. Elias. *Universidade de Sao Paulo Hospital das Clinicas, São Paulo, Brazil.*

Background: Exercise capacity is predictive of cardiovascular disease and mortality in patients with chronic kidney disease on dialysis. Fluid overload, a common feature in these patients, may play a role in this pathophysiology.

Methods: The Duke Activity Status Index (DASI) questionnaire was administered to 27 patients on peritoneal dialysis (PD) and 82 patients on hemodialysis (HD). Results were expressed as peak oxygen uptake (Vo2peak, ml/kg/min). Electrical bioimpedance was applied to assess body composition. Fluid overload was assessed as the ratio of extracellular water/total body water (ECW/TBW).

Results: The patients on HD and PD have no difference in age (44 ± 15 vs. 49 ± 18 years, p=0.224) and body mass index (25.0 ± 4.9 vs. 26.3 ± 4.9kg/m2, p=0.245), with similar gender distribution (p=0.870), prevalence of diabetes (p=0.404) and smoking habit (p=0.223). Vo2peak was lower among patients on PD than HD (21.4 ± 7.5 vs. 25.3 ± 7.6ml/kg/min, respectively, p=0.023). Vo2peak correlated with ECW/TBW (r=-0.436, p=0.0001) and age (r=-0.483, p=0.0001) in both groups and within each group. Vo2peak correlated with interdialytic weight gain in patients on HD (r=-0.236, p=0.031).

Conclusions: Patients on dialysis present reduced exercise capacity, which is even more pronounced for patients on PD. Volume overload seems to be involved in this reduction and might be a target for interventional therapies.

PO1155

Simplifying the 28-Zone Lung Ultrasound Protocol

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Background: Lung ultrasound (LUS) using a 28-zone quantitative B-line score (BLS) is a reliable marker of fluid overload (FO) among patients with end-stage kidney disease (ESKD) on hemodialysis (HD), outperforming physical exam and correlating well with cardiovascular outcomes. A trial comparing BLS-guided dry weight probing to usual care showed improved blood pressure and echocardiographic parameters. However, 28-zone BLS study is criticized as impractical for clinical practice. Using a machine learning algorithm we determined whether accurate assessment of FO can be determined using just 4, 6, and 8 scanning zones.

Methods: We analyzed an existing dataset of 28-zone BLS scores obtained from 100 HD patients presenting to acute care at our center for a total of 2800 scored LUS clips. Using linear correlation and discriminant analysis, we fit models that allowed us to approximate the 28-zone BLS based on 4, 6, or 8 zone protocols. We next applied linear discriminant analysis to study whether we could predict FO severity (low: BLS <15, moderate: BLS 15 to 30; high BLS>30) based on the limited zones. Finally, we tested whether we could achieve better diagnostic performance with subsets of scan-zones that had not previously been reported. Final outcome measures were reported as correlation coefficients and Cohen's kappa.

Results: We found that the BLS of the 4, 6, and 8-zone scan correlated strongly and linearly with the BLS of the full 28-zone scan with Pearson correlations of 0.95, 0.92, and 0.92, respectively. In determining FO severity based on the limited scanning zones, the model produced resultant Cohen's Kappa values of 0.74, 0.76, and 0.71 for the 4, 6, and 8-zone scans, respectively. We identified an undescribed 4-zone scan that produced a Kappa of 0.82. We found that equal linear weighting of all zones gave the best accuracy.

Conclusions: We found that 4, 6, and 8 zone BLS scores perform similarly to the 28-zone BLS. We identified a subset of 4 zones that gave better accuracy than existing 4, 6, or 8-zone scans. These findings support that a limited number of scanning zones can be used to reliably determine FO. Further work is needed on a larger dataset to validate these findings and to explore the physiological mechanism to support the novel 4-zone scan.

PO1156

Incidence and Outcomes of Gram-Negative Bacteraemias in Haemodialysis Patients: 12-Year Single-Centre Experience

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Background: Patients on haemodialysis (HD) are at increased risk of contracting infections. Gram-negative bacteraemia in HD patients is associated with early mortality. In our HD population, we looked at the incidence and clinical outcomes of gram-negative bacteraemias over 12 years.

Methods: Data were collected from clinical records and the hospital's microbiology database of all confirmed bacteraemias in HD patients between 2007 and 2018.

Results: 283 episodes of gram-negative bacteraemia occurred in 1361 patients over the study period. 166 (58.7%) were male. The median age was 71 years (range 26-95). The proportion of gram-negative bacteraemias fell significantly between 2007 and 2010 and has plateaued since then. 90 (31.8%) had arteriovenous fistulae (AVF) or grafts, the remainder had dialysis lines, of which 41 (21.2%) had dual access (AVF or graft + line), with the AVF/graft not yet in use. The bacteraemias were deemed to be access related in 89 events (31.4%). Of these, 73 (82.0%) were related to dialysis lines, 16 (18.0%) were related to AVF/graft. 190 (67.1%) were from other sources including urinary tract 18.4% (n=52), hepatobiliary 7.8% (n=22), chest 7.8% (n=22), gastro-intestinal 6.0% (n=17) and skin/soft tissue in 4.9% (n=14). There was no information on 4 patients (1.5%). Complications of the bacteraemias included: discitis (6, 2.1%); osteomyelitis (5, 1.8%); endocarditis (2, 0.7%); septic arthritis (2, 0.7%); and death (34, 12.0%).

Conclusions: The incidence of gram-negative bacteraemias in our cohort appears to have plateaued, with bacteraemias originating from other sources such as the urinary tract and intra-abdominal accounting for a greater proportion of gram-negative bacteraemias in our cohort - a trend reflected in other similar observational studies in HD populations. Dialysis lines remain a significant risk factor for bacteraemia, lending further weight to the importance of establishing early definitive vascular access. The increased incidence of pathogens from non-access related sources however, highlights that HD populations are exposed to both community and healthcare associated infections, and ongoing surveillance and strategies to reduce the burden of infections in this at-risk cohort remains imperative not just in dialysis centres, but also in the community

PO1157

New Polymeric Dialysis Membrane with Endexo™ Surface Modifying Macromolecule

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Background: Surface-modifying macromolecules (SMM) may improve the hemocompatibility of hemodialyzers. We report the i*n vitro* characterization of a new Optiflux® Enexa™ dialyzer containing a membrane with a fluorinated polyurethane SMM (Endexo™).

Methods: Hollow fiber membranes were manufactured by mixing polysulfone (PS), polyvinylpyrrolidone (PVP), and the Endexo™ SMM. Contact angle and zeta potential were used to characterize the surface of the membrane compared to hollow fiber membranes from Optiflux® F160 dialyzers without Endexo™ SMM. *In vitro* hemocompatibility was assessed using freshly collected heparinized human blood. An *in vitro* simulation model was used to mimic the clinical frequency of blood contact with the dialyzer, and to evaluate platelet and complement activations as well as coagulation factors. Comprehensive biocompatibility evaluations and toxicological risk assessment were performed on Endexo™ SMM and the dialyzer, based on ISO 10993 guidelines.

Results: Surface characterization of the membrane revealed a slight increase in hydrophobicity in the inner lumen and up to 40% increase in the outer lumen, and a lower zeta potential on the blood side (-1.9 meV) compared to the control membrane (-12.9 meV). *In vitro* simulations with the Optiflux® Enexa™ dialyzer showed 58% and 67% lower platelet count reduction and platelet activation than observed with Optiflux® dialyzer. Extractable/leachable testing using 17.2% and 39.1% ethanol on the Optiflux® Enexa™ dialyzer resulted in margin of safety (MOS) values of > 1. Biological tests received passing/acceptable results.

Conclusions: Improved membrane surface characteristics and hemocompatibility performance were observed *in vitro* using a new dialyzer containing the Endexo™ fluorinated polyurethane surface modifying molecule. Based on the biocompatibility data, and toxicological assessment of exposure to chemicals from the device, the weight-of-evidence suggests that the concern for adverse effects following the intended use of the Dialyzer with Endexo™ is minimal.

PO1158

Procalcitonin Is a Biomarker for Inflammation in Outpatient Hemodialysis Patients

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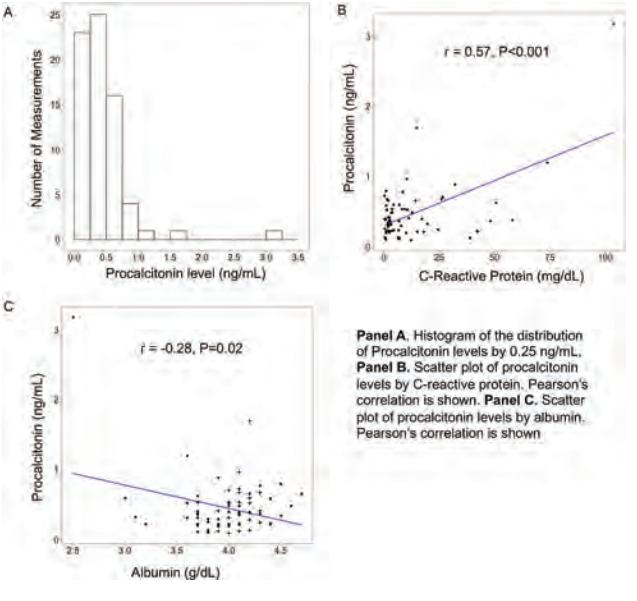
Background: Procalcitonin is a widely used test to distinguish bacterial infections from viral infections, but its level is influenced by kidney function. The normal range of procalcitonin levels in end-stage renal disease (ESRD) patients on hemodialysis (HD) is not well established. In this study, we evaluated the relationship between Procalcitonin and inflammatory markers and outcomes in ESRD outpatients on HD.

Methods: We recruited 71 ESRD outpatients on HD from October 1st 2019 to December 15th 2019 and measured their procalcitonin levels prior to dialysis. We evaluated whether procalcitonin levels were associated with clinical characteristics, laboratory parameters, and future hospitalizations and infections.

Results: In this cohort, the median procalcitonin level was 0.38 ng/mL with an interquartile range of 0.23 ng/mL and 0.54 ng/mL. The distribution of procalcitonin values are found in Fig. 1A. African Americans had a significantly higher procalcitonin level than non-African Americans (P=0.02, Wilcoxon rank sum test). ESRD outpatients who had hypertension, diabetes mellitus, or HIV did not have significantly higher procalcitonin levels than those who did not (P> 0.05). Procalcitonin levels were positively correlated with CRP (r=0.57, P<0.001) (Fig. 1B) and negatively correlated with albumin (r=-0.28, P=0.02) (Fig. 1C). Procalcitonin levels were not correlated with Kt/V, white blood cell count, and ferritin levels (P>0.05). ESRD outpatients who developed infections or who were hospitalized did not have significantly higher initial procalcitonin levels than those who did not (P>0.05).

Conclusions: Procalcitonin levels are correlated with inflammatory markers such as CRP and albumin, suggesting its potential use to identify ESRD on HD at high risk for complications, especially in the era of COVID-19.

Funding: Private Foundation Support



Panel A. Histogram of the distribution of Procalcitonin levels by 0.25 ng/mL. **Panel B.** Scatter plot of procalcitonin levels by C-reactive protein. Pearson's correlation is shown. **Panel C.** Scatter plot of procalcitonin levels by albumin. Pearson's correlation is shown

PO1159

Prolactin and Inflammatory Cytokines in Hemodialysis Patients: A Cross-Sectional Study

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Background: Cardiovascular disease (CV) is the main cause of mortality in patients with chronic kidney disease. Non-traditional CV risk factors such as hyperphosphatemia, inflammation and microalbuminuria are important in these patients. Among these, hyperprolactinemia emerges as a potential non-traditional risk factor because it

accumulates with loss of renal function and is associated with increased mortality. Initially described as a lactation hormone, today it is known that prolactin (PRL) has several actions, from pro-inflammatory effects to accelerated atherosclerosis. The aim of our study was to correlate serum levels of inflammatory cytokines in hemodialysis (HD) patients with normal and elevated PRL

Methods: Single-center cross-sectional study evaluating all patients regularly enrolled in HD program in September 2019. Patients over the age of 18, on HD for at least 6 months, using an arteriovenous fistula for dialysis access were included. Those with active viral or bacterial infections, active cancer, inadequate KtV, use of medication or disease known to elevate PRL(hypothyroidism, chronic liver disease, macroadenoma), pregnant women and using immunosuppressants were excluded. Clinical, biochemicals and inflammatory cytokines [interleukin (IL)-2,-4,-6,-10,-17A, TNF-α and gamma interferon] were evaluated and compared between HD patients with elevated and normal PRL

Results: Of the 360 regular HD patients, 249 were excluded: 110 temporary access, 87 active infection (viral or bacterial), 23 on drugs, 12 on immunosuppression, 5 cirrhosis, 4 inadequate KtV, 4 cancer, 3 less than 6 months on HD, 1 macroadenoma. Comparing data between patients with high(61) and normal(50) PRL, no statistical difference was seen in terms of age, sex, BMI, etiology, time on HD, cholesterol, albumin, calcium, phosphorus, PTH, glycated hemoglobin, hemoglobin, IL-2, IL-4, IL-17A, TNF-α,gIFN. There was a positive PRL correlation with serum levels of IL-6($p<0.0001$,$R=0.44$); between PRL and IL-10, the correlation was negative and also statistically significant($p<0.046$,$R=0.2$)

Conclusions: HD patients with elevated PRL have been shown to have higher levels of IL-6 and lower levels of IL-10

Funding: Commercial Support - Siemens Healthcare Diagnósticos Ltda, Private Foundation Support

Laboratory parameters of patients with high and normal Prolactin

Variables	Elevated Prolactin	Normal Prolactin	p-valor
Interleukin-6	8.18±7.09 (0.72-35.36)	3.23 ± 4.9 (0-28.46)	< 0.0001
Interleukin-10	1.4 ± 5.74 (0-43.66)	2.78 ± 18.04 (0-126.45)	0.046

PO1160

Biphasic Dynamics of Inflammatory Biomarkers Following Dialysis Initiation: Results from the MONDO Initiative

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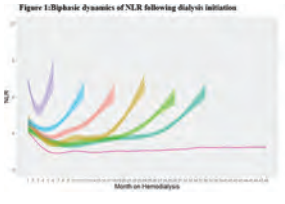
[1]Renal Research Institute, New York, NY; [2]Fresenius Medical Care AG und Co KGaA, Waltham, MA; [3]Fresenius Medical Care AG und Co KGaA, Bad Homburg, Germany; [4]Fresenius SE & Co KGaA, Buenos Aires, Argentina; [5]Maastricht University Medical Center, Maastricht, Netherlands.

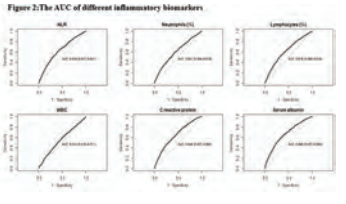
Background: Inflammation is highly prevalent among patients (pts) with end stage kidney disease and is associated with adverse outcomes. We aimed to investigate in a large diverse international cohort of incident hemodialysis (HD) pts firstly the dynamics of inflammatory indicators, namely white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), serum albumin (lab) and C-reactive protein (CRP), following initiation of HD. Secondly their predictive power over all-cause of death.

Methods: We included all incident in-center adult HD pts treated 01/2000 to 12/2012 with ≥ 1 neutrophils, lymphocytes, WBC, and CRP values within the study periods. Following HD initiation, pts were stratified into 7 subgroups: 6 semi-annual groups according to the dialysis vintage at the time of the pts' death (0 to 6; 7 to 12; 13 to 18; 19 to 24; 25 to 30; 31 to 36 months) and a survivor group (pts who survived ≥37 months). Cubic smoothing spline functions were applied to study the trends of each marker. Receiver Operating Characteristic Curve (ROC) Analyses were performed to evaluate the predictive power of each of the markers with 1st year as the baseline and the following 1 year as the follow-up.

Results: In total, 18,276 incident pts who were treated in 25 countries were included. WBC, NLR (Figure 1), and CRP declined sharply after HD initiation and increased before death, while started & remained low in the survivors. In general, WBC, NLR, and CRP were highest at HD initiation and prior to death in non-survivors. Alb levels increased after HD initiation and remained high in the survivor cohort. In contrast, lab levels dropped significantly before death. Alb (AUC: 0.66), CRP (AUC: 0.64), and NLR (AUC: 0.62) all show stronger predictive power than WBC (AUC: 0.55) (Figure 2).

Conclusions: In non-survivors, NLR, WBC, and CRP showed a similar trend after HD initiation and before death. As CRP is not a routinely used marker in many regions of the world and NLR has near comparable predictive power, this marker could be used as an alternative indicator of inflammation in resource-limited areas.





PO1161

Accumulation in Hemodialysis Patients of Solutes Secreted by the Native Kidneys

Seolhyun Lee,[1,2] Christian G. Bolanos,[1,2] Robert Mair,[1,2] Natalie Plummer,[1,2] Timothy W. Meyer,[1,2] Tammy L. Sirich.[1,2] *[1]Stanford Medicine, Stanford, CA; [2]US Department of Veterans Affairs, Palo Alto, CA.*

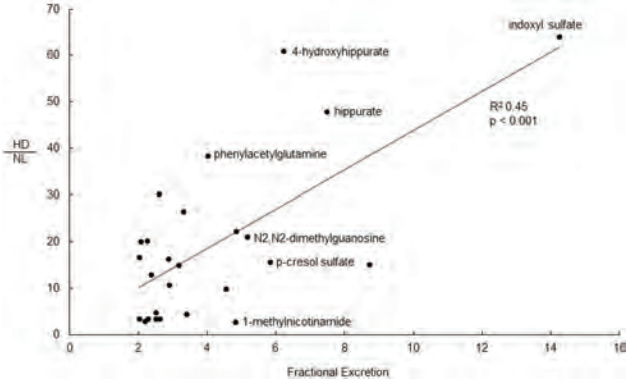
Background: The native kidneys rapidly clear numerous solutes by tubular secretion, a function not replicated by hemodialysis (HD). We examined whether solutes which are normally cleared by secretion accumulate to high levels in the plasma when kidney function is replaced by HD.

Methods: Metabolomic analysis was performed on plasma ultrafiltrate (UF) and urine from 16 control subjects (NL) and on plasma UF from 36 HD patients using an established platform (Metabolon). The fractional excretion (FE) for each solute was calculated as its urine to UF ratio relative to that of creatinine. The extent of accumulation in HD patients was calculated as the ratio of the average UF peak area for each solute in HD relative to NL subjects (HD/NL). An FE > 2 was considered evidence of secretion and only solutes detected in samples from all 16 NL subjects and 36 HD patients were analyzed.

Results: 26 solutes had FE greater than 2 (mean 4.1±2.7, range 2.0 to 14.2). HD/NL ratios were significantly higher for solutes with greater FE values as shown in the Figure (R^2 0.45, $p < 0.001$). HD/NL ratios varied however among individual solutes with similar FE values.

Conclusions: Uremic solutes that are rapidly cleared by the kidneys tend to accumulate to high levels in HD patients. Non-renal clearance and differences in generation rate and distribution volumes may result in variable HD/NL ratios for solutes with similar secretory clearances in the native kidney.

Funding: Veterans Affairs Support



PO1162

The Accumulation of Various Uremic Retention Solutes Is Associated with Early Mortality After Starting Hemodialysis

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Background: Uremic retention solutes (URS) generally accumulate in patients with end-stage renal disease (ESRD). Many of these URS have been shown to exert unfavorable biological activity resulting in poor prognosis. Although some kinds of URS before starting hemodialysis (HD) has been proven to be a risk factor for early mortality after starting HD, it remains unknown whether excess accumulation of various URS is associated with further worse prognosis after starting HD according to the degree.

Methods: We conducted a retrospective cohort study to investigate the association between the accumulation of various URS and early mortality after starting HD. The cohort consisted of adult patients who started HD for ESRD at the National Center for Global Health and Medicine from 2010 to 2019. To evaluate the accumulation of various URS, the uremic score was specifically defined as a total number of measurable variables related with uremia in clinical practice; blood urea nitrogen (BUN) >100 mg/dl, change in anion gap corrected for albumin (ΔAG) >5 mmol/l and β2-microglobulin (β2MG) >20 mg/l before starting HD. The primary outcome was death within a year of the start of HD. The hazard ratio for one score increase in the uremic score was calculated using Cox proportional hazard models with adjustments for baseline characteristics. Moreover, we investigated underlying characteristics related with these variables using logistic regression.

Results: We enrolled 206 patients (males, 76%). During a mean follow-up of 344 days, the primary outcome was observed in 16 patients. The uremic score was significantly associated with the primary outcome (hazard ratio: 1.97, 95% confidence interval 1.19-3.27; adjusted hazard ratio: 4.82, 95% confidence interval 1.97-11.7). Patients with high

BUN had a lower frequency of cardiovascular disease. High ΔAG and β2MG were associated with hypoalbuminemia respectively. Moreover, patients with high ΔAG were relatively young and had a lower frequency of diabetes.

Conclusions: The accumulation of various URS is associated with early mortality after starting HD.

PO1163

Routinely Measured Cardiac Troponin I and NT-ProBNP as Predictors of Mortality in Japanese Hemodialysis Patients: The Dialysis Outcomes and Practice Patterns Study

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Background: Due to the interplay of chronic kidney disease and the heart, it is common for myocardial damage and strain to be present in hemodialysis (HD) patients. The cardiac troponin I (cTnI) and NT-proBNP are widely used as cardiac biomarkers to evaluate the patients at high risk for cardiovascular disease (CVD). However international The Dialysis Outcomes and Practice Patterns Study (DOPPS) data indicate that these cardiac biomarkers are measured in fewer than 2% of HD patients in real-world practice.

Methods: Pre-dialysis levels of cTnI and NT-proBNP at study enrollment were measured in 1176 prevalent Japanese HD patients (DOPPS phase 5). Cox regression was used to test the association of the cardiac biomarkers with all-cause mortality, adjusting for potential confounders. Subgroup analyses were performed to assess potential effect modification of clinical characteristics: age, systolic blood pressure, HD vintage, diabetes mellitus, CVD, and heart failure.

Results: Median [IQR] cTnI (99th percentile; 0.04 ng/mL) and NT-proBNP levels were 0.018 [0.005, 0.04] ng/mL and 3432 [1580, 8017] pg/mL, respectively. There were 175 deaths during a median [IQR] follow-up of 2.8 [2.3, 2.9] years. Higher levels of both cardiac biomarkers were incrementally associated with mortality after adjustment for potential confounders. Even after adjustment for the alternative cardiac biomarker, the HRs of death for cTnI >0.04 and NT-proBNP >8000 pg/mL versus those references (cTnI <0.01 and NT-proBNP <2000) were 2.67 (95% CI 1.47-4.87) and 2.05 (95% CI 1.10-3.84), respectively and still remained significant. Subgroup analyses showed the associations of both cardiac biomarkers with mortality were consistent between stratified groups. (the p values for interaction were >0.10 for all stratified models).

Conclusions: Routinely measured NT-proBNP and cTnI are strongly associated with mortality among prevalent Japanese HD patients. These associations were still significant even after adjustment for the alternative biomarker, suggesting that cTnI and NT-proBNP may reflect different pathologic aspects for cardiac abnormalities.

PO1164

Efficacy of Double Filtration Plasmapheresis Therapy on Patients with Lipoprotein Glomerulopathy

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Background: To Retrospectively observe the clinical efficacy of double fltration plasmapheresis(DFPP) in patients with lipoprotein glomerulopathy(LPG).

Methods: 17 Patients with biopsy-proven LPG in our center who received DFPP treatment from 2010 to 2016 were involved, clinical parameters before and after DFPP treatment were recorded and analyzed.

Results: 15 of the patients underwent 3-10 courses of DFPP, and 2 patients were unable to tolerate DFPP due to allergic reactions. All patients received fenofibrate or statins and other relevant symptomatic treatments. After short-term DFPP treatments, serum creatinine(Scr, 1.76±0.87mg/dl vs 1.55±0.83mg/dl,P<0.01), plasma apolipoprotein E(7.94±1.87mg/dl vs 3.58±1.32mg/dl,P<0.01)and proteinuria (4.68±2.50g/24h vs 2.70±2.20g/24h,P<0.01),were relieved significantly. 1 patient (6.7%) achieved complete remission of proteinuria, and 5 patients (33.3%) achieved partial remission of proteinuria. Four patients underwent repeated renal biopsy after DFPP treatment, and 2 of them who received 10 courses of DFPP were observed disappearment of intraglomerular lipoprotein thrombi, and negative ApoE staining. While 2 patients who underwent only 3 and 4 courses of DFPP respectively showed no significant pathological improvement. After a median follow-up of 7 month(IQR 31.5-1), all patients had elevated ApoE level, 4 patients showed an elevation trend of Scr. 3 of the 4 patients who had got partially or completely remission of proteinuria after DFPP tend to be stable after 12 months' follow-up.

Conclusions: Short-term efficacy of DFPP in patients with LPG was definite. However, Scr and ApoE levels rebounded in some patients during long-term follow-up

PO1165

Disease Course of Hyperkalemia in Patients on Hemodialysis

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Background: Hyperkalemia (HK) preceding hemodialysis (HD) is associated with increased risk of mortality and hospitalization. Longitudinal data on serum potassium (sK^+) in this population is sparse. This *post-hoc* analysis of data from the placebo (PBO) arm of DIALIZE (NCT03303521) explored the course of HK in HD pts.

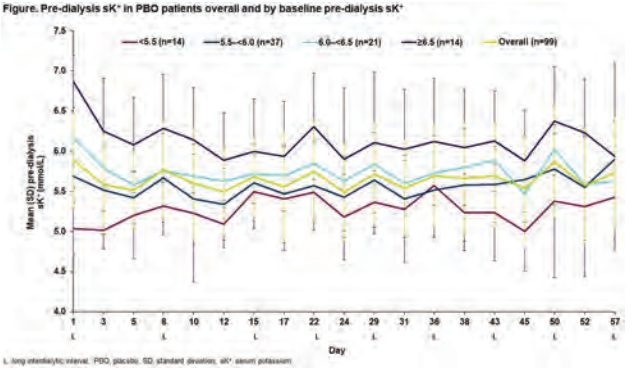
Methods: In DIALIZE, 196 pts were randomized 1:1 to PBO (n=99) or sodium zirconium cyclosilicate (SZC) (n=97) 5 g starting dose once daily on non-dialysis days for 8 weeks (8w), comprising a 4-week SZC dose-titration phase (max 15 g) to achieve target pre-dialysis sK^+ 4.0–5.0 mmol/L, and a 4-week stable-dose evaluation phase. All pts received HD TIW and dietary counselling. *Post-hoc* analysis of PBO pts by baseline (BL) pre-dialysis sK^+ included mean pre- and post-dialysis sK^+ by visit, and proportions of pts who had mean pre-dialysis sK^+ of 4.0–5.0 and 4.0–5.5 mmol/L by visit (including pts receiving rescue therapy).

Results: Mean pre-dialysis sK^+ after the long interdialytic interval was 5.9 mmol/L at BL (Day 1) and 5.7 mmol/L at end of treatment (EOT; Day 57) (**Figure**). Across all BL pt strata, mean pre-dialysis sK^+ remained ≥5.0 mmol/L for all study visits (**Figure**). For pts with BL pre-dialysis sK^+ <5.5, 5.5–<6.0, 6.0–<6.5, and ≥6.5 mmol/L, mean pre-dialysis sK^+ at EOT was 5.4, 5.9, 5.6, and 5.9 mmol/L, respectively (**Figure**). Over 8w, only 7.0–23.1% and 31.1–60.6% of PBO pts had a pre-dialysis sK^+ of 4.0–5.0 and 4.0–5.5 mmol/L, respectively, at any study visit. Mean post-dialysis sK^+ was 3.9 mmol/L at BL and at EOT.

Conclusions: In pts receiving PBO and counselling following a HK event, mean sK^+ remains high over 8w. Most pts remain hyperkalemic over this period and are therefore at continued risk of adverse outcomes.

Funding: Commercial Support - AstraZeneca

Figure. Pre-dialysis sK^+ in PBO patients overall and by baseline pre-dialysis sK^+



L: long interdialytic interval; PBO: placebo; SD: standard deviation; sK+: serum potassium

PO1166

A USRDS Database Study on the Use of Pegloticase in Patients Undergoing Dialysis

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Background: Gout is a common co-morbidity of chronic kidney disease, but prevalence in dialysis patients is not precisely known. Oral urate-lowering therapy use is limited in patients with advanced renal disease, particularly end-stage. Pegloticase (PEGylated uricase) rapidly lowers serum uric acid, but phase 3 trials did not include dialysis patients. However, a phase 1 trial in non-gout patients showed that pegloticase efficacy and pharmacokinetics are not affected by dialysis. Beyond this, pegloticase use in dialysis-dependent patients is not reported in the literature. This United States Renal Data System (USRDS) study sought to better quantify and understand real-world use of pegloticase in patients undergoing dialysis.

Methods: Patients with advanced renal disease, who are dialysis-dependent, or who have undergone renal transplant are in the USRDS. USRDS patients who were administered pegloticase and undergoing dialysis were identified in 2012-2017 Standard Analytical Files. Parameters examined included demographics, comorbidities, dialysis type, number of pegloticase infusions, and time between pegloticase infusions.

Results: 58 dialysis centers reported on 136 patients. Pegloticase was most prescribed by rheumatologists (68%) and internal medicine physicians (7%). The majority of patients were white (61%) and male (73%) and patient age averaged 56.9 ± 16.8 years; all adult age groups were represented (18-44 years: 27%, 45-64 years: 35%, ≥65 years: 39%). Hypertension (74%) and diabetes (46%) were the most reported comorbidities. 9 patients (7%) were donor kidney recipients. More patients were undergoing hemodialysis (108 patients [79%]) than peritoneal dialysis (23 [17%]). Patients received 13.4 ± 19.1

pegloticase infusions (median: 7, 46 [34%] patients ≥12) and median time between doses was 14 days (mean: 21 days). This treatment schedule reflected that of pegloticase labeling (biweekly infusions).

Conclusions: The literature contains few reports of pegloticase use in dialysis patients. Our real-world data suggest that pegloticase is well-tolerated in dialysis patients, as indicated by a median of 7 infusions per patient and the expected treatment schedule. Further research is needed to verify these findings.

Funding: Commercial Support - Horizon Therapeutics

PO1167

Feasibility Study of Wrist-Based Wearable Activity Trackers in Hemodialysis Patients

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Background: Wearable activity trackers allow physicians to access patient's physical activity (PA) outside the dialysis clinic. Hemodialysis (HD) population have an increased cardiovascular mortality and they are less active than their healthy counterparts. We aim to assess the feasibility of use of a wearable trackers in a HD population.

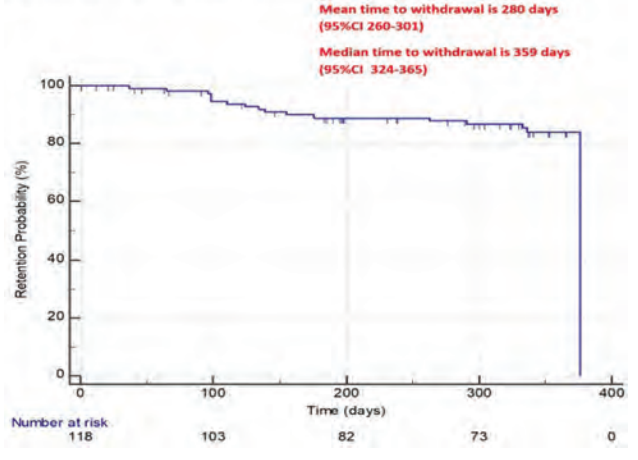
Methods: HD patients from 4 NYC clinics were enrolled in the study starting from June 2018, followed up to 1 year. Patients ≥18 years on maintenance HD, able to walk, owning a smartphone, tablet or PC were included. Each patient received a wrist-based monitoring device (Fitbit Charge 2) to wear for a year. They were trained how to use and sync data. A stepwise intervention was created. After 3 in-person visits are completed, patients were deemed non-adherent and withdrawn. Events such as device failure or broken band were not counted as an in-person visit. We used Kaplan-Meier analysis to study time to withdrawal for non-adherence and predictors of time to withdrawal were assessed by univariate Cox Regression. The end of the observation period was May 8, 2020.

Results: 118 patients were studied. Patients were 54±12 years old with a HD vintage of 5.2±5.1 years, 37% lived alone, 59% unemployed, 57% were African American, and 42% had an education level of some college or higher. Seventeen patients were withdrawn due to non-adherence. Mean and median time to withdrawal were 280 days (95%CI 260-301) and 359 days (95%CI 324-365). The probability of retention is shown in Fig.1. There was no association found between age, gender, race, living status, and education and time to withdraw due to non-adherence.

Conclusions: Only a small number of patients were withdrawn due to non-adherence, and the average time to withdraw was 9 months. We believe that the use of a wrist-based wearable device for remote patient monitoring, at least up to one year, is feasible in the HD population.

Funding: Private Foundation Support

Fig.1 Kaplan-Meier curve of time to withdrawal



PO1168

Evaluation of Biomarkers in Chronic Hemodialysis (HD) Patients Dialyzed with Optiflux High-Flux Dialyzers

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Background: Optiflux® (OPTI) dialyzers are single-use, high-flux dialyzers available in the following sizes: F160NR (1.5 m^2), F180NR (1.7 m^2), F200NR (1.9 m^2), and F250NR (2.5 m^2). They are designed to enhance small and middle molecule clearance without increasing albumin loss. Epidemiologic data has shown low serum albumin (sALB) to be a marker of increased mortality risk in dialysis patients (pts). Thus, loss of albumin should be avoided especially in pts with low sALB. This retrospective study aimed to assess changes in biomarkers in pts dialyzed with Optiflux dialyzers for 6 months, including a subset of pts with low sALB levels at baseline.

Methods: 976 in-center HD pts treated exclusively with Optiflux dialyzers for 6 months without liver disease, cancer, HIV, or history of drug abuse were analyzed in this study. Pre-HD labs at the first month of data collection (M1) and Month 6 (M6) were compared using paired t-test. A sub-analysis of pts with hypoalbuminemia (sALB ≤3.5mg/dL) at M1 was conducted. All analyses were performed separately for each dialyzer. Pts dialyzed with F200NR and F250NR were combined into 1 group.

Results: Mean biomarker levels during M1 and M6 are presented for the dialyzer groups (table). Most notably, significant increases of mean sALB and hemoglobin were observed in all groups. In the sub-analysis of pts with hypoalbuminemia at M1 (n=156), 87% of pts had increases in sALB by M6 (48/59=81.4% in F160NR, 82/92=89.1% in F180NR, and 5/5=100% in F200NR and F250NR) and 53.8% (84/156) achieved sALB >3.5 g/dL at M6.

Conclusions: During a 6-month follow-up, HD patients dialyzed with Optiflux dialyzers showed increases in serum albumin and hemoglobin while maintaining dialysis adequacy.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

		Serum albumin (g/dL)	Hgb (g/dL)	spnPCR (g/kg/day)	UFV (L)	spKt/V
F160NR (n=310)	M1	3.80	10.66	1.03	2.13	1.80
	M6	3.89	11.05	1.07	2.20	1.81
	Difference	0.09	0.39	0.04	0.06	0.02
	p-value	<0.0001	<0.0001	0.01	0.08	0.36
F180NR (n=634)	M1	3.86	10.82	1.03	2.56	1.64
	M6	3.91	11.08	1.07	2.62	1.69
	Difference	0.05	0.26	0.04	0.06	0.05
	p-value	<0.0001	<0.0001	0.0006	0.03	0.002
F200NR and F250NR (n=32)	M1	3.82	10.91	1.10	3.65	1.54
	M6	3.93	11.28	1.05	3.56	1.54
	Difference	0.11	0.37	-0.06	-0.09	-0.005
	p-value	0.02	0.03	0.05	0.40	0.87

Sp= single pool; nPCR = normalized protein catabolic rate; UFV= ultrafiltration volume

PO1169

Postoperative Outcomes After Bariatric Surgery in Chronic Dialysis Patients: A Meta-Analysis and Systematic Review

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Background: Renal transplantation improves longevity and quality of life for patients on chronic dialysis. However, obesity is a growing surgical contraindication in this group such that bariatric surgery is increasingly being considered as a bridge to transplantation. The risks and benefits of bariatric surgery in the dialysis population have not been synthesized.

Methods: Authors performed a systematic review of observational studies indexed in Embase, MEDLINE and CENTRAL till April 2020 that reported postoperative outcomes in chronic dialysis and non-dialysis patients undergoing bariatric surgery. Summary level data on patient demographics and comorbidity were extracted. The primary outcome was death (30-day or in-hospital mortality); secondary outcomes were myocardial infarction, surgical site infection, pneumonia, unplanned return to theatre, sepsis, and rates of kidney transplantation. Random effects meta-analysis was performed to derive summary risk estimates.

Results: Four cohort studies involving 4,096 chronic dialysis and 732,204 non-dialysis patients undergoing bariatric surgery were included. Sleeve gastrectomy (34%), and roux-en-Y gastric bypass (24%) were the most common procedures performed followed by gastric band or biliopancreatic diversion. There were increased odds of postoperative mortality(0.4-0.5% vs 0.1%; OR 4.7, 95%CI 2.2-9.9,$I^2$0%), myocardial infarction(0.0-0.5% vs 0.1%, OR 3.4, 95%CI 2.0-5.9,$I^2$0%) and pneumonia(0.3-0.9% vs 0.2-0.4%, OR 2.3, 95%CI 1.1-4.5,$I^2$50%) in dialysis patients compared to non-dialysis patients. Patients on dialysis also had increased odds of return to theatre compared to non-dialysis patients (3.2-3.4% vs 1.4-2.0%, OR 2.2, 95%CI 1.7-3.0). There were no differences in the odds of surgical site infections, bleeding, or thromboembolic complications. Rates of renal transplant wait-listing among dialysis patients undergoing bariatric surgery were not reported in any of the studies.

Conclusions: Chronic dialysis patients have substantially increased odds of postoperative mortality and myocardial infarction. However, the absolute rates of complications are low and may not be prohibitive if they facilitate successful renal transplantation. Systematic reporting of both the benefits and risks of bariatric surgery in dialysis patients are needed.

Funding: Private Foundation Support

PO1170

Peridialytic Serum Cytokine Levels and Their Relationship with Postdialysis Fatigue and Recovery in Patients on Chronic Hemodialysis

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Background: The etiology of postdialysis fatigue (PDF), an intermittent but debilitating fatigue occurring in 40-80% of chronic hemodialysis (HD) patients after HD treatment, is still unclear. In other illnesses, such as inflammatory diseases, mounting

evidence points toward the involvement of the immune system in the development of fatigue symptoms. Altered serum levels of inflammatory cytokines have also been shown in chronic HD patients and positive associations between interleukin-6 (IL-6) and fatigue symptoms in general in this patient population have been recently reported. Therefore, we investigated whether fatigue specifically occurring after HD (PDF) or the time needed to recover from HD treatment (TIRD) were related to pre- and postdialysis serum levels of pro- and anti-inflammatory cytokines (i.e. IL-1β, IL-6, TNF-α and IL-10) or their intradialytic changes (if any).

Methods: Serum levels of IL-1β, IL-6, TNF-α and IL-10 were measured immediately before and after HD in 45 chronic HD patients using commercially available kits on an ELLA™ automated immunoassay system. The presence and severity of PDF as well as TIRD duration were assessed by self-report measures.

Results: Thirty-three patients (74%) reported PDF, with a median PDF severity index of 3.30 [IQR: 3.00-4.30] on a scale from 1 to 5. Median TIRD was 120 min [IQR: 60-480]. PDF severity correlated strongly with TIRD, r_s=0.85, p<0.001. Only predialysis IL-10 serum levels significantly and positively correlated with PDF severity (r_s=0.43, p=0.003). Postdialysis cytokine levels and their intradialytic changes were not significantly related to PDF or TIRD.

Conclusions: The present study does not support the hypothesis that the immune system may be involved in the development of PDF or TIRD. The positive, but counterintuitive relation between predialysis anti-inflammatory IL-10 levels and PDF severity warrants further research. However, the present findings do not necessarily undermine the previously found positive relationship between IL-6 levels and chronically fatigue experience in HD patients, as fatigue as response to treatment may have other determinants than a more chronically fatigue.

PO1171

Tryptophan Removal in ESRD Patients Treated with High-Flux and Medium Cut-Off Dialyzers During Hemodialysis and Hemodiafiltration

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Background: Tryptophan (Trp) loss in kidney failure patients is likely to be associated with poor nutritional status and depletion due to dialysis. However, Trp removal with medium cutoff (MCO) membranes has not been investigated. Here, we compared Trp reduction ratios (RR) between an MCO dialyzer and a high-flux polysulfone (HFPS) dialyzer

Methods: Clinically stable, anuric hemodialysis patients on thrice-weekly HD were enrolled. Over the course of 4 weeks, each subject traversed through the following combinations (with 2 study treatments per week, 4 hours per HD session): post-dilution hemodiafiltration (HDF) with FX120 (Fresenius Medical Care), HD with FX120, HDF with Theranova 400 (Baxter), HD with Theranova 400 (Fig. 1). All subjects exercised using stationary bicycles during HD. Blood samples were collected before dialysis (B0) and at 230 min (B230) upstream of the dialyzer. Trp in plasma was analyzed by liquid chromatography–mass spectrometry. RR was calculated using signal intensities for Trp according to RR=(B0-B230)/B0, with correction for hemoconcentration using hemoglobin levels (Schneditz, ASAIO 2012)

Results: Twelve subjects completed the study (50% female, 43.8±18.5 years old). With HD, RR was comparable between the MCO dialyzer and the larger HFPS dialyzer (median RR 0.29 for MCO, 0.33 for HFPS; surface areas 1.7 m^2 vs. 2.5 m^2, respectively). In HDF, our data suggest somewhat greater Trp loss with the MCO dialyzer despite its smaller surface area compared to the HFPS dialyzer

Conclusions: Use of an MCO dialyzer may result in similar or greater Trp loss as use of an HFPS dialyzer with a much larger surface area. When considering the use of MCO dialyzers, clinicians should consider the potential impact on removal of salutary substances (incl. protein-bound substances), an area that deserves further research

Funding: Private Foundation Support

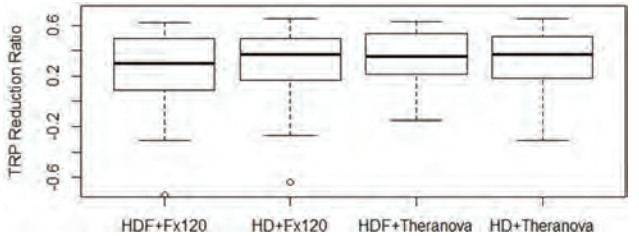

Figure 2. Box-Whisker plot of Trp RR.

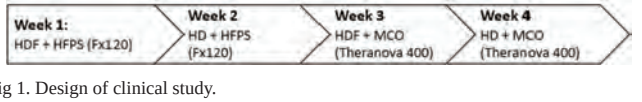

Fig 1. Design of clinical study.

PO1172

Effect of Hemodiafiltration with Medium Cut-Off Dialyzer on Uremic Toxins Removal

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Background: To our knowledge no study has ever evaluated the use of middle cut-off membranes (MCO) with online hemodiafiltration (OL-HDF). This study aims to show if the combination of OL-HDF with MCO can achieve a higher reduction ratio of some uremic toxins in comparison to regular OL-HDF

Methods: Patients from our hemodialysis unit were treated twice with four different modalities, namely combinations of post-dilutional OL-HDF or hemodialysis (HD) with a high-flux dialyzer (CordiaxFX120, area 2.5 m^2) or the MCO (Theranova 400; area 1.7 m^2), respectively. We analyzed the reduction ratios (RR) of erythropoietin, beta2-microglobulin (B2M), phosphate, and urea.

Results: Twelve anuric patients were studied (6 females; mean age 43.818.5 years; HD vintage 35.2 ± 27.8 months.) Mean blood flow (Qb) was 367 23 ml / min, dialysate flow (Qd) was 493 57 ml / min, ultrafiltration volume was 2382 5683 ml. B2M RR of HDF+HiFlux was higher than HD+MCO (**p=0.003),** and HDF+MCO vs. HD+MCO **(p=0.029**). There was no difference in EPO, phosphate, and urea RR between any of the four groups.

Conclusions: Adding a medium cut-off (MCO) dialyzer to HDF does not add benefit. The B2M RR with HiFlux exceeds the one of a MCO dialyzer. HDF provides benefit over HD regarding the B2M RR regardless of the dialyzer used.

Funding: Commercial Support - Fresenius

Reduction (%)	HDF + HiFlux	HD + HiFlux	p*	HDF + MCO	HD + MCO	p*	p value +
EPO[a]	15 (-44-60)	36 (-10 to 48)	0.95	40 (-16 to 53)	10 (1 to 35)	0.52	0.91
B2M[a]	92 (89-93)	88 (86 to 90)	0.018	90 (88 to 92)	85 (77 to 89)	0.005	**0.002‡**
B2M[b]	89 (86-92)	82 (82 to 86)	0.015	88 (83 to 90)	81 (79 to 89)	0.042	**0.023•**
Phos	57 (43-65)	55 (44 to 62)	0.6	53 (36 to 58)	58 (33 to 66)	0.57	0.7
Urea	81 (76-83)	81 (78 to 84)	0.68	83 (78 to 84)	81 (75 to 85)	0.71	0.9

Medians (interquartile ranges) [a]Adjusted to plasma volume [b]Adjusted to body weight * = Kruskal Wallis test ‡ Dunns comparison test (HDF+HiFlux vs. HD + MCO (p=0.003), HDF+ MCO vs. HD+MCO (p=0.029) • Dunns comparison test HDF+HiFlux vs. HD + MCO (p=0.046)

PO1173

pH-Dependent Protein Binding Properties of Uremic Toxins In Vitro

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Background: Patients with chronic kidney disease undergoing dialysis treatment have worse clinical outcomes. One cause is the interactions between various uremic toxins and organ/tissues. Protein-bound uremic toxins (PBUTs), such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS), are difficult to remove by conventional dialysis treatment owing to their high protein binding property. A possible treatment strategy is to weaken the protein binding of PBUTs. Acidic and alkaline pH change the conformation of proteins, which may be associated with the binding of uremic toxins. We examined the influence of pH on the protein binding properties of PBUTs *in vitro*.

Methods: Albumin conformation at pH 2 to 13 was analyzed using circular dichroism. Albumin reacted with IS at pH 4 to 11. The protein binding behavior was examined using isothermal titration calorimetry and free IS concentration was measured by mass spectrometry. Bovine serum with IS, PCS, indole acetic acid (IAA), or phenyl sulfate (PhS), as well as serum from hemodialysis patients, were adjusted to a pH of 4 to 11, and the concentration of the free form of PBUTs was measured.

Results: Albumin partially unfolded at pH <4 or >12. Calorimetric analyses revealed weakened interaction between IS and albumin at pH <5 or >10. The concentration of free IS in the presence of albumin was significantly increased at pH 4 (89.49±1.38 μg/dL) and pH 11 (22.45±1.38 μg/dL) compared to pH 7 (17.20±0.87 μg/dL) (both $p<0.01$). Addition of bovine serum to IS, PCS, IAA, or PhS at the physiological concentration of uremic patients and adjustment of pH from 4 to 11 resulted in increased concentrations of the free form of the solutes at acidic and alkaline pH, compared with the concentrations at neutral pH. Adjustment of serum from 19 hemodialysis patients from pH 4 to 11 resulted in increased concentrations of the free forms of IS, PCS, PhS, and IAA at acidic and alkaline pH. (e.g., IS: pH 4, 152.5±77.6 μg/dL; pH 11, 153.8±135.5 μg/dL vs pH 8, 38.8±33.4 μg/dL; $p<0.01$, respectively)

Conclusions: Acidic and alkaline pH changed albumin conformation and weakened protein binding property of PBUTs *in vitro*. The findings could inform strategies to increase the removal of PBUTs with convection/diffusion in hemodialysis treatment.

PO1174

Associations Between Prelude eGFR Category and Trajectories of Uric Acid and eGFR Prior to Dialysis Transition Among US Veterans

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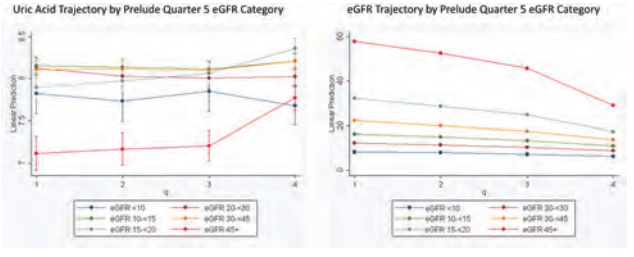
Background: Prior studies have demonstrated that elevated uric acid is associated with declining kidney function. However, how uric acid and estimated glomerular filtration rate (eGFR) levels change with progression towards end stage renal disease have not yet been fully characterized. We sought to examine trajectories of eGFR and uric acid 1 year prior to ESRD transition across strata of eGFR 5 quarters prior to transition.

Methods: From a cohort of US veterans who transitioned to dialysis between 10/2007-03/2015, we identified 15,725 patients with a pre-dialysis eGFR measurement 5 quarters prelude (15 months) before transitioning to ESRD and at least 1 uric acid measurement prior to ESRD. Trajectories were modeled across eGFR strata using mixed effects model with random slope and random intercept.

Results: The mean age of the cohort was 67±11 years old and included 2% females and 35% African American. In addition, the mean prelude quarter 5 uric acid level was 8±2 mg/dL and the median eGFR was 21 ml/min/1.73m^2. While the trajectories of uric acid were relatively stable for most strata, eGFR steadily declined across all strata. However, in the final 3 months prior to ESRD transition (PQ2 to PQ1), those in the highest PQ5 eGFR category (>=45 ml/min/1.73m^2) showed a sharp decrease in eGFR and corresponding sharp increase in uric acid, while there were less notable trends for other strata. [Figure]

Conclusions: Patients with the most rapid renal function decline also had a sharp increase in uric acid 3 months prior to transition to ESRD. The mechanism behind this relationship is currently unknown, and should be investigated in future studies. Future studies should also examine the clinical implications of elevated uric acid in patients transitioning to dialysis earlier due to a rapid renal function decline.



PO1175

Insulin Resistance and Hemodialysis

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Background: Insulin resistance is an important risk factor in Chronic Kidney disease (CKD) patients. We analysed insulin resistance indices in hemodialysis (HD).

Methods: Subjects with CKDV not on dialysis (CKD), and on HD (HD) were included. Age, gender, Body mass index (BMI), Wasit:Hip ratio (WHR) were noted. Fasting blood glucose, fasting insulin (Ins), C-peptide (Cp), bicarbonate (HCO3), calcium (Ca), phosphorus (Pi), Vitamin D (Vit D), parathyroid hormone (PTH), Albumin (Alb), Ferritin, C-reactive protein (CRP) were measured. HOMA-insulin resistance using Ins (IR-Ins) and Cp (IR-Cp), Insulin sensitivity and Beta cell function using Ins (IS-Ins, BF-Ins) and Cp (IS-Cp, BF-Cp) and C-peptide resistance index (CRI) were calculated.

Results: 20 patients with CKD, 22 on HD were analysed. In HD, IR-Cp had significant positive correlation with eGFR, and CRI with HCO3, Vit D, Ca, Pi, IR-Cp and negatively with PTH,CRP,eGFR. In CKD, IR-Cp had significant positive correlation with PTH,eGFR and negatively with HCO3,Ca. CRI had significant positive correlation with HCO3, Vit D, Ca, Pi, negatively with PTH, IR-Cp. Between groups, IR-Ins, IR-CP, IS-Ins, IS-Cp and BF-Ins had significant difference (Table 1)

Conclusions: IR-Ins, BF-Ins, IS-Cp, CRI were higher in HD, while IR-Cp,IS-Ins were higher in CKD. Cp based indices could be better markers of IR.

Comparison between groups

	CKD	HD	P value
Age	56.8	57.0	0.978
BMI	25.0	21.7	0.004
WHR	0.9	1.0	<0.001
Insulin	139.4	269.0	<0.001
C-peptide	4.2	2.5	0.103
HCO3	20.7	19.0	0.417
Ca	8.8	8.1	0.031
Pi	5.0	5.3	0.633
Vit D	19.4	25.9	0.198
PTH	168.0	319.3	0.049
Alb	3.5	3.5	0.734
Ferritin	393.7	651.4	0.126
CRP	1.4	1.0	0.247
eGFR	10.1	8.0	0.020
IR-Ins	2.7	4.6	<0.001
IR-Cp	9.4	5.2	0.002
IS-Ins	36.7	26.0	<0.001
IS-Cp	15.5	23.2	0.018
BF-Ins	124.4	354.0	0.001
BF-Cp	294.3	399.2	0.188
CRI	1.7	2.1	0.337

PO1176

Effect of Citrasate Dialysate on Intact Parathyroid Hormone (iPTH) in Prevalent Hemodialysis (HD) Patients: A Matched Retrospective Cohort Study

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Background: Citrate-acidified dialysate (CAD) has anti-coagulation properties compared to acetate-acidified dialysate (AAD), due to its binding of calcium. PTH regulates the calcium concentration through its actions on bone and kidney. The objective of this study is to assess any long-term changes in iPTH levels when patients (pts) are switched from AAD to CAD.

Methods: A retrospective cohort study of 3 clinics converting from AAD to CAD during 2009 to 2011 matched to 12 geographically proximate AAD clinics, on the same month as CAD conversion. Clinics were selected before year of 2013, so that the follow-up did not include time when the management of mineral bone disease changed at large dialysis organizations (LDOs). In-center HD pts included in the analysis received HD treatment for at least 6 months before (baseline, BL) and 6 months after (follow up, FU) CAD conversion. BL and 6-month FU average values of clinical measures were compared within and between CAD and AAD clinics. Measures included pre-dialysis iPTH and serum calcium (sCa), prescribed (Rx) dialysate calcium (dCa), Rx calcium-based phosphate binders (Ca-based PB), Cinacalcet and IV Vitamin D (VitD).

Results: Changes in iPTH and sCa were not significantly different from BL to FU between CAD and AAD clinics (Table). Mean iPTH decreased by 17 pg/mL (4.1%, p=0.49) in CAD clinics and increased by 13 pg/mL (3.8%, p=0.13) in AAD clinics. However, Rx dCa increased in CAD clinics, but not in AAD clinics. Increases of Ca-based PB and Cinacalcet prescriptions were greater in AAD clinics. No significant differences were observed in changes of VitD over time between CAD and AAD clinics.

Conclusions: Similar trends in iPTH and sCa were observed in clinics switched from AAD to CAD and geographically-matched clinics with continuous use of AAD.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	CAD clinics (142 pts)			AAD clinics (671 pts)			P (CAD vs AAD clinics) +
Measures	BL	FU	Δ (FU- BL)	BL	FU	Δ (FU- BL)	
iPTH, pg/mL	411	394	-17	338	351	13	0.24
sCa, mg/dL	8.93	9.00	0.07	9.03	9.08	0.05*	0.61
dCa, mEq/L	2.33	2.52	0.19*	2.42	2.43	0.01	<.0001
Ca-based PB, %	20.4%	27.5%	7.1%*	27.7%	46.4%	18.7%*	0.01
Cinacalcet, %	17.6%	17.6%	0	11.0%	16.5%	5.5%*	0.01
VitD, %	86.6%	93.0%	6.4%*	83.9%	87.6%	4.6%*	0.26

*p<0.05 from paired t or McNemar's test

+2 sample t test and repeated measures logistic regression for continuous and categorical variables

PO1177

High-Volume Hemodiafiltration Reduces Pre-Dialysis Beta-2 Microglobulin Concentration Compared with High-Flux Hemodialysis: A Post Hoc Analysis of the HDFit Trial

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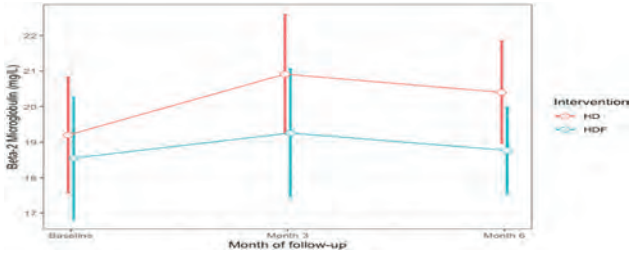
Background: High-volume hemodiafiltration (HDF) is a diffusive-convective modality that provides higher clearance of middle-size uremic toxins, such as beta-2 microglobulin (β2M), compared to predominantly diffusive high-flux hemodialysis (HD). Previous studies have shown HDF may reduce circulating pre-dialysis concentrations of β2M compared to low-flux HD. We studied to which extent HDF reduces pre-dialysis β2M concentrations compared to high-flux HD.

Methods: HDFit randomized patients with a permanent vascular access time on HD between 3 and 24 months to either high flux HD or high volume HDF (convective volume (CV) target of 22L/session) / treatment). Patients were followed for 6 months. Measurements of circulating pre-dialysis β2M levels were made at baseline, 3 and 6 months during mid-week session. Linear mixed effects models were used to estimate the mean difference (95% confidence interval (CI)) in β2M levels between HDF and HD.

Results: A total of 195 patients (mean age 53±15 years, albumin 4±0.4 g/dL) were randomized (HDF n=97, HD n=98). Patient characteristics were balanced across intervention groups. Median treatment time was 235 min in both groups. Monthly mean CV ranged from 27.1 to 27.5L/treatment; the target CV was achieved in 96 out of 97 patients. Compared to HDF, in the HD arm monthly mean pre-dialysis β2M levels were 1.57 mg/L (95% CI 0.02 to 3.12) higher. In other words, HDF reduced mean circulating β2M levels over time compared to HD. (Figure).

Conclusions: In this *post-hoc* analysis of the HDFit trial, we describe for the first time that high-volume HDF sustainably reduces pre-dialysis β2M concentration compared to high-flux HD. High convective volume was easily achieved with online HDF. Our findings suggest that HDF can be readily implemented and that this treatment modality yields a sustained higher control of middle-size uremic toxins.

Funding: Commercial Support - Fresenius Medical Care



PO1178

Hand Grip and Leg Muscle Strength in Hemodialysis Patients and Its Determinants

Ran-hui Cha. *National Medical Center, Seoul, Seoul, Republic of Korea.*

Background: Chronic kidney disease is associated with chronic inflammation and progressive loss of peripheral muscle strength and the ability to exercise, and these changes are more pronounced in patients on hemodialysis (HD). We evaluated the hand grip and leg muscle strength in patients receiving HD and tried to find factors associated with muscle strength.

Methods: We screened hand grip (opposite to fistula side) and leg muscle strength (both sides) at single center (n=112) by using digital hand and leg dynamometer (T.K.K.5401 and 5710e/5715, Takei scientific instruments Co. Ltd., Niigata, Japan).

Results: Mean age was 62.6 years, and 73.2% of patients were men. Diabetes was the cause of kidney failure in 50% of patients and median HD vintage was 34 months. 77.7% of patients answered 'yes' to regular home exercise and 33% of patients regularly participated in the hospital based latex-band exercise. Hand grip strength (HGS) and leg muscle strength (LMS) showed good correlation (r = 0.715, p < 0.001). HGS (25.1 vs. 17.0 kg) and LMS (30.1 vs. 20.4 kg) were better in men (p < 0.001 and p < 0.001, respectively). Older patients (≥ 60 years) showed decreased LMS than others in men and women (p = 0.01 and p = 0.04, respectively), but HGS was not different by age. Patients doing regular home or hospital based exercise showed higher HGS (24.2 vs. 18.6 kg, p = 0.01) but LMS did not show statistical significance (29.3 vs. 23.6 kg, p = 0.19). Serum albumin and creatinine showed positive correlation with HGS and LMS, and hs-CRP was negatively correlated only with HGS. Multiple linear regression analysis proved male sex, younger age, and any type of exercise were factors associated with better HGS and LMS.

Conclusions: Sex, age, and exercise were the most important determinants of muscle strength in HD patients. We need to encourage patients to do regular home or group exercise and introduce new feasible form of exercise for HD patients.

Table 3. Multiple linear regression analysis of the factors related with hand grip and leg muscle strength

	Hand grip strength		Leg muscle strength	
	Standardized coefficient	p-value	Standardized coefficient	p-value
Constant	21.80	0.001	28.92	0.008
Sex (female)	-0.489	< 0.001	-0.449	< 0.001
Age (year)	-0.271	0.003	-0.352	< 0.001
BMI (kg/m2)	0.069	0.41	0.125	0.15
Exercise, home- or hospital-based (yes)	0.335	< 0.001	0.227	0.01
Serum albumin (g/dl)	0.024	0.78	0.02	0.82
Serum creatinine (mg/dl)	0.141	0.11	0.104	0.26
hs-CRP (mg/dl)	-0.035	0.70		

BMI, body mass index, hs-CRP, highly sensitive C-reactive protein

PO1179

Effect of Intradialytic Exercise on the Removal of Tissue Sodium During Hemodialysis

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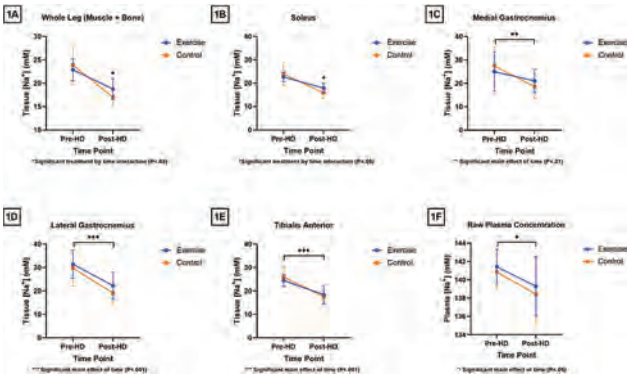
Background: Emerging evidence using ^{23}Na-MRI shows that sodium can be stored in the skin and muscle. Hemodialysis (HD) patients appear to have higher tissue sodium concentration ([Na^+]) compared to healthy controls, though tissue [Na^+] appears to be partially reduced during HD. In this study, we thus aimed to determine whether intradialytic cycling (IDC) potentiates the removal of tissue [Na^+] during HD.

Methods: Seven HD patients (sex: 57% male; age: 60±12 y; BMI: 36±10 kg/m^2; spKt/V: 1.4±.32; dialysate [Na^+]: 136±1.90 mEq/L; UFR: 7.7±3.4 mL/kg/hr; thrice-weekly HD) underwent ^{23}Na-MRI scans (3T system) before and after HD, on both a control (CON) and exercise (EX) day. Patients performed 30 minutes of IDC during the first hour of HD on the EX day and received standard care on the CON day. [Na^+] of the medial (MG) and lateral (LG) gastrocnemius, soleus (Sol), tibialis anterior (TA), and the whole lower leg (WL) were quantified from MRI images by trend analysis. Plasma [Na^+] was also assessed by a colorimetric enzymatic assay (Piccolo). Repeated measures ANOVA was used to examine changes in muscle and plasma [Na^+] between the EX and CON treatments from pre to post HD.

Results: There was a significant treatment by time interaction for [Na^+] in WL (P=.036) and Sol (P=.016), with the EX treatment attenuating the drop in [Na^+] during HD compared to the CON condition in both WL and Sol (Figure1A-B). [Na^+] of MG (P=.002), LG (P<.001),TA (P<.001), and plasma (P=.042) were reduced during HD, but these changes did not differ by treatment (treatment x time interaction P = N.S. for all; Figure1C-F).

Conclusions: Contrary to our hypothesis, it appears that IDC may attenuate, instead of potentiate, the magnitude of tissue [Na^+] removed during HD. However, this was not a consistent finding across all muscle beds analyzed. More studies are needed to examine if this result is a manifestation of the timing of MRI, the limited sample size, or other factors.

Funding: Private Foundation Support



PO1180

Exercise Training to Improve Patient-Important Outcomes in Adults Undergoing Maintenance Dialysis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Background: Multiple trials have assessed the potential for exercise training to improve outcomes in adults undergoing dialysis. However, uncertainties exist in its relevance and sustainable benefits for patient-important outcomes.

Methods: We conducted a systematic search of the Cochrane Kidney and Transplant Specialised Register for randomised controlled trials of structured exercise programs of eight weeks or more in adults undergoing maintenance dialysis (hemodialysis or peritoneal dialysis) compared to no exercise or sham exercise. Two authors independently assessed the trials for eligibility, extracted the data and assessed the risk of bias. We conducted random-effects meta-analyses.

Results: We identified 93 studies involving 4634 participants and 71 studies involving 3973 participants contributed to the meta-analyses. The interventions lasted from 8 weeks to 2 years and most often took place thrice weekly during hemodialysis treatments. Overall, the quality of the included studies was low. In adults undergoing dialysis, compared with no or sham exercise, exercise training may improve fatigue, the physical component of health-related quality of life (HR-QoL)(MD 4.5, 95% CI 2.2 to 6.8 points/100: low certainty evidence), depressive symptoms (SMD 0.73, 95% CI 0.39 to 1.07: moderate certainty evidence), pain (MD 6.1 95% CI 0.5 to 11.7 points on a 100-points scale: low certainty evidence), functional capacity measured in terms of the 6 Minutes-Walk Test (MD 49.9 meters, 95% CI 37.2 to 62.6; moderate certainty evidence) and the Sit-To-Stand test (MD 2.4 cycles, 95% CI 1.8 to 3.1; moderate certainty evidence). The impact on depression was greatest for those who had maintained exercise beyond 4 months (SMD 1.26, 95% CI 0.72 to 1.80). We could not draw conclusions for all-cause mortality, cardiovascular events, the mental component of HR-QoL, blood pressure and the safety of exercise training for adults undergoing maintenance dialysis due to the very low quality of the evidence.

Conclusions: In adults undergoing maintenance dialysis, exercise training is likely to improve depressive symptoms and functional capacity and may improve fatigue, the physical component of quality of life and pain.

Funding: Government Support - Non-U.S.

PO1181

Comparative Risk of Fall-Related Fractures Among Hemodialysis Patients Newly Initiating Zolpidem vs. Trazodone Therapy

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Background: Zolpidem, a non-benzodiazepine hypnotic, and trazodone, a sedating antidepressant, are the most common medications used to treat insomnia in the United States. Both drugs have side effects (e.g. drowsiness, dizziness, cognitive and motor impairment) that can increase the risk of falls and resultant fracture events. Despite widespread zolpidem and trazodone use, little is known about the comparative safety of these medications in hemodialysis patients, a vulnerable population with an exceedingly high fracture rate.

Methods: We conducted a retrospective cohort study using an active comparator new-user design to investigate the association between zolpidem vs. trazodone initiation and the 30-day risk of hospitalized fall-related fractures among Medicare-enrolled hemodialysis patients in the United States Renal Data System Registry (2013 – 2016). We used an intention-to-treat analytic approach and propensity score weighted survival models, adjusted for numerous demographic and clinical covariates, to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs). Death was treated as a competing event.

Results: A total of 31,055 hemodialysis patients were included in the study, 18,941 zolpidem initiators (61%) and 12,114 trazodone initiators (39%). Newly initiating zolpidem vs. trazodone therapy was associated with a higher risk of hospitalized fall-related fractures, HR [95% CI] = 1.71 [1.11, 2.63]. The association was more pronounced among individuals prescribed higher zolpidem doses (1.92 [1.14, 3.21]) and in subgroups with fall-related risk factors, such as older and frailer patients (1.89 [1.14, 3.09] and 2.49 [1.31, 4.73], respectively) and individuals using other medications with central nervous system activity (2.04 [1.14, 3.67]). Sensitivity analyses using longer follow-up durations, evaluating a broader outcome (hospitalized fracture), and employing an on-treatment analytic approach yielded similar results (data not shown).

Conclusions: Hemodialysis patients newly initiating zolpidem had a higher risk of hospitalized fall-related fracture compared to patients initiating trazodone, suggesting that trazodone may be a safer pharmacologic treatment option for the management of insomnia in this vulnerable population.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO1182

Relationship of Peripheral Nerve Function with Mobility in ESKD

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Background: Mobility limitation is widely prevalent in patients undergoing dialysis and is associated with frailty, disability, hospitalizations and mortality. Motor and sensory nerve impairments are reported in ESKD but their relationship with mobility is poorly studied. We tested the hypothesis that objective measures of nerve function in the lower extremity are associated with mobility limitation.

Methods: Twenty-five subjects with ESKD underwent nerve testing after their routine dialysis session. Nerve testing was done using the Natus Viking Quest NSC system and vibration detection threshold (VDT) was measures with a Medoc VSA-3000 analyzer. Predictors were nerve action potentials (amplitude) and nerve conduction velocity (NCV) in motor (peroneal) and sensory (sural) nerves as well as VDT quantitatively measured at the pulp of the big toe. Gait speed (mobility outcome) was measured over 4 meters and the better of 2 attempts used. Leg extensor strength, a covariate was measured by a dynamometer. Patient symptoms were assessed using the Neuropathic Pain Questionnaire.

Results: Subjects were 23-74 y, 14 male, 23 black, 14 diabetic, median dialysis vintage 4.5 yrs. Median gait speed was 0.70 m/s (IQR 0.61-0.86). Neuropathic pain was noted in ~57% patients, but did not correlate with objective measures of nerve function or gait speed. Median vibration detection threshold was 51μ (IQR 26-104) and showed significant negative correlation with gait speed ($p < 0.01$). Higher sensory (sural) nerve onset and peak latency and lower sensory conduction velocity were correlated with lower gait speed (all $p < 0.01$). Higher peroneal motor nerve amplitude was positively correlated with gait speed ($p < 0.05$). Higher VDT remained significantly associated with gait speed in multivariable regression model adjusted for demographics, diabetes, dialysis vintage and muscle strength (model R^2=0.74).

Conclusions: In patients with ESKD, objective measures of nerve function are associated with mobility dysfunction regardless of diabetes, muscle strength and dialysis vintage. In contrast, subjective assessment of neuropathy is not associated with mobility dysfunction. These results demonstrate that the neuropathy of ESKD is a contributing factor to the widespread impairment in mobility observed in patients undergoing dialysis and that objective testing is required for diagnosis.

Funding: Private Foundation Support

PO1183

Native Hawaiian/Pacific Islander Data in the USRDS

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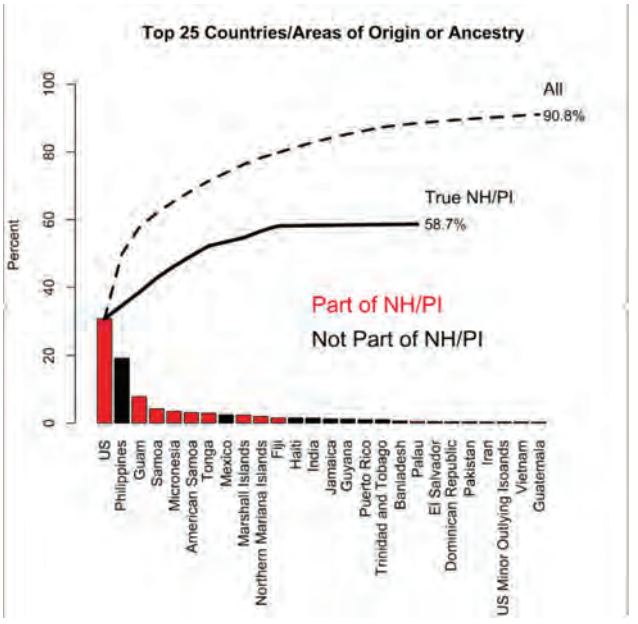
Background: The United States Renal Data System (USRDS) has reported very high ESRD incidence and prevalence rates among patients designated as Native Hawaiian or Other Pacific Islander (NH/PI) race. Xiang et al. (2019 NKF Spring Clinical Meeting) reported a "denominator problem," caused by a large percentage of NH/PI individuals reporting multiple races in the US census. By counting only single-race individuals, resulting dominators are too small, leading to rates that appear to be too large. We sought to assess whether reporting of race is accurate for these individuals by examining reported country of origin on the CMS 2728 Medical Evidence (ME) form.

Methods: Using data from the ME form for patients initiating dialysis in 2016, we examined the accuracy of the country/area of origin field, which is required to be filled out only when NH/PI race is chosen. We assumed all those reporting the US as the country of origin were correct.

Results: The figure displays country/area of origin or ancestry for the 1578 patients who reported NH/PI race, for the top 25 countries, which accounts for 90.8% of all NH/PI patients. Only 58.7% of them came from countries that are actually part of the census definition of NH/PI. The largest misclassified countries were Philippines (19.2%) and Mexico (2.5%).

Conclusions: The apparently high rates of ESRD among NH/PI individuals have gained increasing attention. Our finding of inaccurate understanding of the US census definition of NH/PI leading to numerators of rates that are too large, combined with the already important problem of the US census single vs. multiple race denominator, makes it difficult and perhaps even impossible to calculate accurate incidence and prevalence rates for this race group. Improvements in capturing accurate race information at the time of ESRD initiation are needed.

Funding: NIDDK Support



PO1184

Workforce Capacity for ESKD Care: An Analysis from the Global Kidney Health Atlas Study

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Background: Despite the rising burden of chronic kidney disease, recent surveys reveal a global shortage of nephrologists and other kidney healthcare professionals. The objective of the second iteration of the International Society of Nephrology's (ISN) Global Kidney Health Atlas was to assess inter- and intra-national variability in the capacity for end-stage kidney disease (ESKD) care.

Methods: Data were collected in two steps: desk research and a cross-sectional survey. Desk research used data from online sources, such as the Central Intelligence Agency World Factbook and the World Health Organization Global Observatory. The survey was administered online to key stakeholders worldwide, and all country-level data were analyzed by ISN region and World Bank income classification.

Results: The results of desk research showed that the general healthcare workforce density varied by income level: high income countries had more healthcare workers per 10,000 population (30.30 physicians; 79.21 nursing personnel; 7.20 pharmacists; 3.47 surgeons) than low income countries (0.85 physicians; 5.02 nursing personnel; 0.10 pharmacists; 0.03 surgeons). A total of 182 countries responded to the survey, with 160 (88%) countries responding to questions pertaining to the ESKD workforce. Nephrologists were primarily responsible for providing care to ESKD patients in 92% of countries. Global nephrologist density was 9.95 per million population (pmp) and nephrology trainee density was 1.42 pmp. High income countries reported the highest densities of nephrologists and nephrology trainees (23.15 pmp and 3.83 pmp, respectively), whereas low income countries reported the lowest densities (0.24 pmp and 0.11 pmp, respectively). Compared to higher income countries, more low income countries reported shortages of all types of ESKD healthcare providers, including nephrologists, transplant surgeons, peritoneal and hemodialysis access surgeons, and peritoneal and hemodialysis access interventional radiologists.

Conclusions: In this global survey, a significant trend was demonstrated in workforce capacity and distribution for ESKD care across countries. There was limited capacity in low income compared to high income countries. National and international policies are required to build a workforce that can effectively address the growing burden of ESKD.

PO1185

Patient Activation in Prevalent Hemodialysis Patients in the United States

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Background: Patient activation (PA) is the product of knowledge, skills and confidence that enable a person to manage their health and care. PA is associated with healthy behaviors, disease management and hospitalization rates. This study aimed to investigate the status and correlates of PA among prevalent HD patients in the US.

Methods: We surveyed patients from 10 HD centers using the Patient Activation Measure 13-item instrument (PAM-13), which reports a score out of 100 and is categorized into four levels (higher scores or levels denoting higher activation). We described the distribution of PA status, and investigated associations with demographics, vintage, education level and HD center.

Results: 925 respondents completed the survey out of 1374 patients (response rate 67%). Mean age 62 ± 14 years, 40% female, and median vintage 41 months (IQR 19-77). Mean PAM score was 56 ± 13, and 14%, 50%, 25%, and 10% were in levels 1 to 4 respectively. Mean PAM scores were higher in younger patients (<55yrs: 59 ± 14, 55 to <65yrs: 55 ± 14, 65 to < 75: 55 ±12, >75 yrs:54 ± 12; p<0.001). Higher PAM scores were observed with higher education (College: 60 ± 14, High School: 57 ± 14, <High School: 51 ± 10; p<0.001) and in blacks (58 ± 15) compared to non-blacks (55 ± 13; p=0.008). Mean PAM scores varied significantly across centers ranging between 52 and 61 (p=0.004). In regression analysis, there were lower odds of having high activation (levels 3 or 4 vs levels 1 or 2) in association with age (for every 10 years: aOR 0.79 [95% CI: 0.71 – 0.87]) and male sex (0.72 [0.53 – 0.96]). Compared to having less than high school diploma, high school diploma and college were associated with high activation (2.36 [1.60 – 3.47], and 3.52 [2.25 – 5.54] respectively). HD center differences remained significant after adjustment. However, vintage, race, and ethnicity did not have a significant association with activation in the adjusted model.

Conclusions: Patient activation is low in a high proportion of HD patients. Older age, less education and male gender were associated with lower activation. This study is the first to report activation status among individuals on HD in the US, identifying an opportunity to direct resources to high-risk groups and develop programs to improve activation.

PO1186

Analysis of Psychological Detachment of Primary Caregivers of Maintenance Hemodialysis Patients

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Background: Long term care for maintenance hemodialysis patients will bring physical, mental and economic burden to the caregivers. If the caregivers cannot detach during non working hours, it will affect their physical and mental health. The goal was to Analysis the psychological detachment level of primary caregivers of maintenance hemodialysis patients and its influencing factors.

Methods: By convenient sampling method,240 caregivers of maintenance hemodialysis patients in our hospital from June to September 2019 were selected and investigated by using Psychological Detachment Scale, Zarit Burden Inventory Scale, and Warwick-Edinburgh Mental Well-being Scale.

Results: The total score of psychological detachment of caregivers in maintenance hemodialysis patients was 12.02 ± 3.31, which was negatively correlated with the burden of caregivers (P < 0.01), and positively correlated with the total score of Warwick Edinburgh positive mental health(P<0.01) and psychological detachment level was high at 53.2% and low at 46.8%.The main influencing factors of caregiver's psychological detachment were time of care, type of character, burden of care, positive mental health, duration of dialysis and types of complications(P<0.01).

Conclusions: Medical staff should pay attention to the psychological status of caregivers and take positive measures to improve the level of psychological detachment and promote their physical and mental health.

PO1187

Factors Contributing to Primary Care Provider (PCP) Use in ESKD Patients After Starting Hemodialysis (HD)

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Background: While the importance of primary care is well-recognized, PCP use among HD patients has not been well-characterized and factors contributing to PCP use are unknown.

Methods: We characterized change in PCP use (≥1 PCP visit) 1 year before and 1 year after dialysis start among adults ≥67 years old with Medicare coverage initiating in-center HD between 2008-2014 (data from the United States Renal Data System). We used multivariable logistic models adjusting for demographics, clinical characteristics, and pre-ESKD nephrology care to identify factors associated with continuity of PCP care (defined as PCP use pre- and post-HD start) and new initiation of PCP care post-HD start.

Results: Among 111,424 older HD patients, 34% did not use PCP care post-HD start. Among patients with PCP use pre-ESKD, 15% did not continue to use PCP care post-HD start. Among patients without PCP use pre-ESKD, 70% did not initiate PCP care post-HD start. Black race, Medicaid insurance, impaired functional status, and residence in less urban or higher poverty neighborhoods were associated with lower odds of continuity of PCP care or initiating PCP care after HD start. (Table)

Conclusions: Among older incident HD patients, continuity of PCP care and initiation of PCP care were lower among patients who were black, of lower socioeconomic status,

from more rural areas, or had functional impairments. Research to understand the barriers to PCP use may inform interventions to improve delivery of primary care for these vulnerable populations.

Funding: Private Foundation Support

Factors Associated with Continuity of PCP Care and Initiation of PCP Care after Starting HD

Patient Characteristics	Continuity of PCP care after starting HD (n=74253) OR* (95% CI)	Initiation of PCP care after starting HD (n=37171) OR* (95% CI)
Medicaid enrollment	0.75 (0.71-0.79)	0.73 (0.68-0.77)
Non-Hispanic Black (vs. Non-Hispanic White)	0.83 (0.78-0.88)	0.71 (0.66-0.75)
Functional impairment	0.65 (0.61-0.68)	0.90 (0.85-0.96)
% neighborhood-level poverty (tertiles)		
Medium (vs. low)	0.89 (0.84-0.94)	0.88 (0.83-0.93)
High (vs. low)	0.85 (0.81-0.90)	0.82 (0.77-0.87)
% neighborhood urban (tertiles)		
Medium (vs. low)	1.28 (1.21-1.34)	1.38 (1.30-1.46)
High (vs. low)	1.20 (1.13-1.27)	1.41 (1.32-1.50)

*Adjusted for variables in Table and age, sex, employment, co-morbid conditions (hypertension, diabetes, CVD, CHF, COPD, and cancer), US region, and pre-ESKD nephrology care

PO1188

Status and Trajectory of Patient Activation Among Incident Dialysis Patients in the United States

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Background: Patient activation (PA), a measure of knowledge, skills and confidence in managing one's health, is associated with healthy behaviors, better disease management and improved health outcomes. We investigated the status and correlates of PA among end-stage kidney disease (ESKD) patients at dialysis initiation, and changes in PA after the first 3 months of dialysis.

Methods: Adult ESKD patients commencing dialysis at 25 in-center hemodialysis (ICHD) and 12 home dialysis facilities completed the Patient Activation Measure 13-item instrument (PAM-13) at dialysis initiation (t0) and month 4 (t1). Logistic regression was used to examine factors associated with high PA levels at t0 (PAM levels 3 and 4). Paired t-test was used to examine changes in PAM scores from t0 to t1.

Results: 227 patients completed the survey at t0 between Jun – Nov 2019; 166 (73%) on ICHD and 61 (27%) on home dialysis, mean age 60 ± 15 years. At t0, mean PAM scores were 65.1 ± 16.8; and 44% of patients had low activation. Mean PAM scores were 63.7 ± 17.3 and 69.4 ± 14.5 in ICHD and home patients respectively. In the adjusted model, higher education level and longer pre-ESRD nephrology care were associated with high PA at t0, while increased age was associated with lower odds of high activation – Figure 1. There was no significant change in PA scores among 182 participants who completed the survey at t1 (mean 64.8 ± 17.8, mean change: -0.3 ± 17.3, p = 0.80).

Conclusions: Low activation is common among incident dialysis patients and is more common among those on ICHD. Patient activation does not seem to improve over the first 3 months of dialysis with current practice.

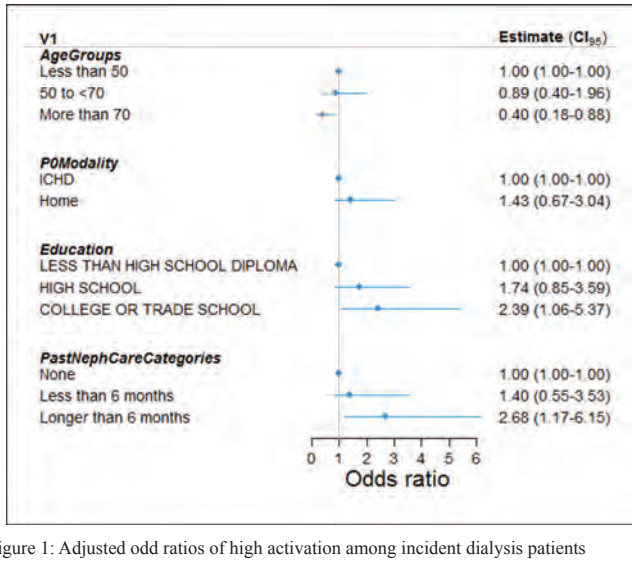

Figure 1: Adjusted odd ratios of high activation among incident dialysis patients

PO1189

Fully Immersive Virtual Reality-Based Mindfulness Intervention in Hemodialysis Patients: A Pilot Study Assessing Safety and Utility

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Background: Virtual reality (VR) is an evolving technology that is becoming a more common treatment for pain management and psychological phobias. While non-immersive VR (i.e., Nintendo Wii) has been used in trials involving hemodialysis (HD) patients, no studies to date have used fully immersive VR as a tool for intervention delivery. Because HD treatment and fully immersive VR have similar potential adverse side effects (e.g., fatigue, nausea), the current pilot trial tests the initial safety and utility of fully immersive VR during maintenance HD treatment sessions.

Methods: HD patients (n=20) were enrolled in a single-arm pre-post pilot study. Participants were exposed to our fully immersive VR program, Joviality™, which delivered mindfulness training and guided meditation using the Oculus Rift head-mounted display. Participants experienced our 25-minute program on two separate occasions during HD treatment sessions. Participants recorded their level of HD treatment and/or motion-related symptoms prior to VR exposure and then again immediately following each VR exposure using the Simulator Sickness Questionnaire (SSQ). Validated utility measures included participant's ability to be fully immersed in the virtual environment, interact with virtual objects, and find our VR program user-friendly.

Results: Mean age was 55.3 (±13.1) years; 80% male; 60% African American; and mean dialysis vintage was 3.56 (±3.75) years. The SSQ displayed significant decreases in total composite symptom score following VR Exposure 1 (22.6 vs. 11.2; p=0.03). Decreases were evident after Exposure 2, though these were non-significant (11.97 vs 7.29; p= 0.18). Participants reported high levels of spatial presence in the VR world with an average of 5.03/7.0 and they rated our VR program as easy to operate, with average System Usability Scores of 82.8/100.

Conclusions: HD patients routinely suffer from fatigue, nausea, and dizziness during HD, and we hypothesized that fully immersive VR may exacerbate these symptoms. By contrast, we saw a significant reduction in severity of symptoms on at least one of the two exposure days. Fully immersive VR may be a safe mode of intervention delivery during HD.

PO1190

Skim the Fat: PLEX for Hypertriglyceridemia-Induced CRRT Clotting

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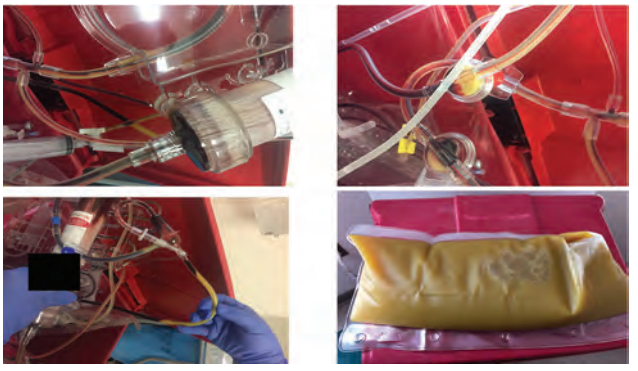
Introduction: CRRT filter clotting remains a significant barrier to providing adequate dialysis in critically ill patients. Clotting leads to reduced clearance and volume removal, blood loss in the circuit, and increased nursing workload. Elevated triglycerides have been reported to result in filter clotting. Here, we present a case of CRRT circuit clotting in a patient with familial hypertriglyceridemia-induced pancreatitis.

Case Description: A 46-year-old man with obesity, hyperlipidemia, recurrent pancreatitis secondary to hypertriglyceridemia, and DMII presents with 2 days of abdominal pain. CT abdomen showed pancreatic necrosis and stranding prompting admission for pancreatitis. Hospital course was complicated by hypoxic respiratory failure requiring intubation, shock, and oliguric AKI requiring initiation of CVVHDF. Shortly after initiation of CVVHDF, the filter and tubing clotted with a milky yellow substance. This recurred after circuit exchange and use of regional anticoagulation with Citrate Dextrose 3%. Triglyceride level returned at 3,668 mg/dL (reference range: <150 mg/dL). Given the severe hypertriglyceridemia and inability to effectively provide RRT, he underwent one session of therapeutic plasma exchange (PLEX) with subsequent fall in triglyceride levels to 433 mg/dL. Further CRRT was then effectively provided with typical filter and circuit life.

Discussion: This case highlights the impact of elevated triglyceride levels on CRRT filter life. Prior case reports have described clotting and shortened filter life in the setting of lipid infusion and propofol-induced hypertriglyceridemia despite regional Citrate anticoagulation. Triglyceride levels fell and clotting resolved with cessation of the infusions in both situations. In the setting of a non-iatrogenic etiology of elevated triglycerides, we suggest consideration of anticipatory plasma exchange to avoid CRRT filter clotting and to be able to provide more effective dialysis.



Milky Substance Noted Throughout CRRT Circuit and PLEX Effluent

PO1191

Mariachi Madness: A Unique Presentation of Acyclovir Toxicity

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Introduction: Acyclovir and valacyclovir (pro-drug) are often prescribed for treatment of infections caused by herpes viruses. Neurological toxicity consisting of hallucinations, seizures, and coma are rare reported side effects occurring predominantly in renal failure as a result of the renal clearance of the drug.

Case Description: A 71-year-old woman with end stage renal disease from amyloidosis on maintenance hemodialysis presented with recent onset of confusion, slurred speech, weakness, and intractable auditory hallucinations described as "mariachi music." She had been recently treated for herpes keratitis four days prior to presentation. On exam she was noted to be inattentive with disorganized thought-processes, diffuse hyporeflexia, generalized myoclonus, and up-beating nystagmus with superior gaze. A medication reconciliation revealed that she had been prescribed valacyclovir at a dose of 1,000 mg three times daily. She had additionally continued previously-prescribed prophylactic acyclovir at a dose of 200 mg twice daily. Urgent hemodialysis was performed for presumed acyclovir toxicity. An acyclovir level drawn 2 hours after initiation was elevated at 2.6 mcg/mL (typical therapeutic level 0.14 – 1.2 mcg/mL). After a four-hour session of hemodialysis her mental status improved, and her movement symptoms resolved. The following morning a repeat acyclovir level was 1.1 mcg/mL. An additional session of hemodialysis was performed due to persistent altered mentation with subsequent resolution to baseline. She was transitioned to topical ganciclovir for her keratitis and discharged home.

Discussion: This case describes the rare yet potentially underrecognized syndrome of acyclovir neurotoxicity, manifesting as delirium with prominent auditory hallucinations and myoclonus. Such toxicity is more likely to present in patients with acute or chronic renal failure given the drug's pharmacokinetics. Both acyclovir and valacyclovir are dialyzable (30-60% drug removal in a four-hour session). Given these medications are commonly prescribed, as well as the severity of neurotoxicity and the rapid improvement with hemodialysis, it is critical to maintain a high index of suspicion and begin treatment promptly. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

PO1192

The New Face of Dialysis Disequilibrium Syndrome: A Case Report, Systematic Literature Review, and Suggested Management Guidelines

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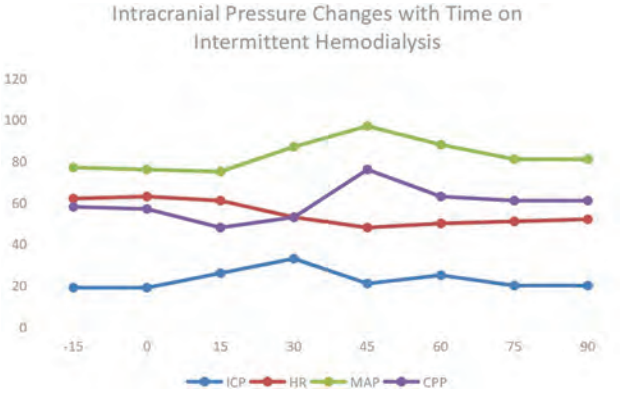
Introduction: After implementation of standard protocols for new start dialysis, Dialysis Disequilibrium syndrome has become rare. Patients with preexisting neurologic damage, head trauma or stroke are more vulnerable to this complication. We present a case report of a patient who had a "near miss" safety event after starting intermittent hemodialysis in the setting of a traumatic brain injury (TBI). His deterioration on dialysis is not fully explained by the current leading theory on the pathogenesis of this syndrome (theory of "reverse urea effect") implying that either a multifactorial etiology is implicated or that impaired cerebral autoregulation may play a more significant role than previously believed.

Case Description: A 70 year old male was hospitalized after being involved in a motor vehicle accident. He suffered multiple injuries including cardiac arrest from which he was revived, TBI and acute kidney injury (AKI) requiring initiation of hemodialysis using the new start protocol. Trends of intracranial pressure (ICP), cerebral perfusion pressure (CPP) and heart rate (HR) before, during and after intermittent hemodialysis showed clear worsening of these parameters after beginning dialysis with subsequent improvement after discontinuing dialysis (Figure).

Discussion: This case points toward a change in the pattern of presentation of DDS, requiring new guidelines focusing on dialyzing vulnerable TBI patients. These guidelines include early initiation of dialysis, selection of CVVH as preferred modality given reduced dialysis dependency in AKI patients, adjusting dialysis settings to minimize urea clearance per unit time, utilizing ICP monitoring when available, using hypertonic saline to maintain serum sodium > 155 mmol/L and avoiding central lines on contralateral side to an internal jugular dialysis catheter to preserve cerebral venous return. The establishment of these guidelines may help reduce the risk of poor outcomes in this population.



PO1193

Rescue Hemodialysis for Paroxysmal Hyperammonemic Encephalopathy Sans Cirrhosis

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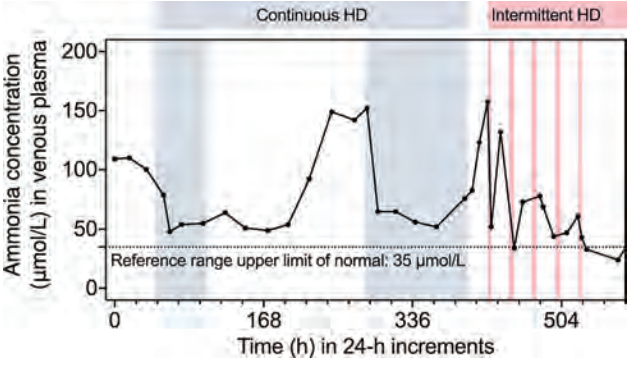
Introduction: Ammonia is a product of protein catabolism that is converted to less toxic urea before excretion by the kidneys in urine. Hyperammonemia can be associated with coma, cerebral edema, and herniation. Ammonia levels do not correlate linearly with encephalopathy, especially in patients with chronic hyperammonemia.

Case Description: A 63-year-old female with a history of Roux-en-Y gastric bypass surgery > 20 years ago and malnutrition presented with three weeks of encephalopathy. Initial workup, including head CT and EEG, was negative. She was noted to have normal liver function and an elevated ammonia level of 110 µmol/L which was not responsive to conventional therapies. Continuous veno-venous hemodialysis (CVVHD) was successfully employed to prevent neurologic catastrophe. After discontinuation of CVVHD, she experienced recurrence of hyperammonemic encephalopathy prompting the use of hemodialysis (HD) intermittently throughout the hospital stay. We believe this patient's paroxysmal hyperammonemic encephalopathy is a consequence of progressive metabolic disarray following gastric bypass surgery coupled with an exceptionally poor diet.

Discussion: There is historical precedent for extracorporeal blood purification in hyperammonemic states, typically related to pediatric inborn errors of nitrogen metabolism or fulminant liver failure with hyperammonemic encephalopathy. Recurrent hyperammonemic encephalopathy in the absence of liver failure has been described after bariatric surgery. Ammonia, a small, water-soluble molecule without significant protein binding, is cleared well with dialysis. Due to a large volume of distribution, ammonia levels frequently rebound after discontinuation of HD. Intermittent HD allows for the highest rate of reduction of ammonia, though CVVHD may be superior in severe encephalopathy. This patient's ongoing need for HD, either chronically or episodically during decompensations, remains to be determined.



PO1194

A Case of Polysulfone Membrane-Induced Thrombocytopenia

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Introduction: The development of biocompatible hemodialysis membranes has been a major advance in the treatment of renal failure. Newer, synthetic membranes such as polysulfone are considered to be more biocompatible than the older cuprophane or cellulose membranes. However, polysulfone dialyzers can interact with and thereby

reduce platelet counts. A few isolated case reports have observed thrombocytopenia in patients following hemodialysis with polysulfone membranes.

Case Description: We report a case of an 82 year old man with a history of hypertension, an abdominal aortic aneurysm Stage 5 chronic kidney disease and AV malformations admitted to with recurrent GI bleeding and acute kidney injury. Admission laboratory values were significant for Hgb 4.9, Plt 209, HCT 16.0, BUN 166, Cr 19.23, K 5.7, Bicarbonate 7 and Phosphorous 7.5. The bleeding site was found to be the transverse colon, which was ligated with resolution of the bleeding. Intermittent hemodialysis was initiated thrice weekly using an F180NR polysulfone hemodialysis membrane. On admission, the patient's platelet count was 233,000. However, each morning after a hemodialysis treatment, his platelet count was ~40% lower than that of the previous day, but then increased until the next dialysis session. Over the course of the admission, his platelet count therefore progressively fell, reaching a nadir of 37,000 on hospital day 38. The patient was anticoagulated with citrate and did not receive heparin. His heparin-induced thrombocytopenia panel (HIT) was negative. On hospital day 38, the dialysis membrane was changed to *Cellentia-H* cellulose triacetate single-use, hollow-fiber, high-flux hemodialyzer. Over the following week he underwent 3 additional dialysis treatments, over which time his platelet count rose to 120,000 and the post-dialysis drop in platelet count was no longer observed.

Discussion: Dialyzer membrane-associated thrombocytopenia was suspected by the platelet count decline observed the morning after a dialysis treatment, and by eliminating other possible causes. We observed significant improvement in platelet count when the membrane was changed to modified cellulose membrane (cellulose triacetate). In patients that develop thrombocytopenia following the initiation of dialysis with a polysulfone membrane, consideration should be given to a trial of an alternative membrane, such as cellulose triacetate.

PO1195

Drug Confusion: A Case of Valacyclovir-Induced Neurotoxicity

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Introduction: Medication dose adjustment in ESRD is paramount to avoid serious adverse effects. Valacyclovir(VA) is >90% renally excreted after conversion to acyclovir, & if not adjusted can cause life threatening valacyclovir induced neurotoxicity(VAN). Prompt recognition and treatment(dialysis) to reduce mortality is crucial. We present a case of VAN in ESRD.

Case Description: 69-year-old male with ESRD on hemodialysis(HD),DM, HTN,CAD, prostate cancer presented with 1 day of confusion, weakness, flight of ideas, auditory/visual hallucinations & persecutory delusions. 3 days prior he was given VA 500mg bid after telemedicine encounter for a rash. On exam, BP 238/106, heart rate 71,T97.8F, he was oriented to person, time & place, had atomic aphasia, impaired short term memory & confabulation. There was no skin rash. Labs noted Hb 11g/dl,WBC 10.2,PLT 170,Na136,K5.6,BUN 70, creatinine 9.2 & calcium 10. Head CT showed no abnormalities. He underwent emergent HD for acute encephalopathy due to VA use & during HD, his confusion & confabulation improved. The morning after HD he returned to baseline mental status & was counseled on the importance of discussing new medications with his nephrologist so dosage adjustments can be made appropriately.

Discussion: VA is a prodrug of Acyclovir & is >90% renally excreted. Appropriate dose adjustment based on CrCl must be considered in CKD/ESRD to prevent serious adverse events such as VAN and reduce mortality. It may be difficult to differentiate VAN from Herpes encephalitis. Prompt recognition & urgent dialysis is needed in the former. The mechanism of VAN is poorly understood but postulated to be acyclovir inhibition of mitochondrial DNA polymerase & altering mitochondrial function. Half-life of acyclovir in ESRD is ~14 hours, which compounds the neurotoxicity if not emergently dialyzed. Our patient had typical symptoms of confusion/hallucinations with recent use of VA, but had no evidence of Zoster on exam, with rapid return to baseline after urgent dialysis. Recognition of the need for dosing adjustment in ESRD of medications such as VA is important to prevent & monitor for life-threatening adverse effects. Entertaining VAN as a differential in ESRD patients with acute encephalopathy & background use of VA is paramount in early recognition and treatment to prevent further morbidity and mortality.

PO1196

A Case of a Yellow Dialyzer in a Hemodialysis Patient

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Introduction: Yellowish discoloration of a dialyzer during hemodialysis (HD) can have various diagnostic and therapeutic implications, however its recognition must be made in a timely manner. Here we present a case of a patient whose dialyzer color was noted to be yellow after his HD session.

Case Description: A 65-year-old African American male with ESKD secondary to hypertension and diabetes mellitus, on intermittent hemodialysis for 9 years was noted to have a yellow dialyzer post hemodialysis. His only complaint during dialysis was severe itching for two days. On exam, he had no scleral or palatal icterus. Stat outpatient laboratory testing revealed a total bilirubin of 13.1 mg/dL with a direct bilirubin of > 10.0 mg/dL which led to his hospital admission. Further laboratory testing revealed an AST of 188 U/L, ALT of 188 U/L, alkaline phosphatase of 587 U/L, a normal amylase and lipase, and negative viral testing for hepatitis A, B, C, CMV, and EBV. Autoimmune workup revealed a normal ANA, anti-mitochondrial, and anti-smooth muscle antibody. An abdominal ultrasound showed mildly thickened gallbladder, without stones, sludge or ductal dilatation. Doppler showed no portal or hepatic vein thrombosis. A CT scan of his abdomen showed no discernable liver or gallbladder issues. He denied herbal medications or rifampin use. Although etiology was entirely unclear, there was suspicion for drug induced liver injury caused by hydralazine and high dose statin. Patient had a planned liver biopsy however he decompensated rapidly, and had a cardiac arrest which led to his demise.

Discussion: Although yellow dialyzers have been described they are still quite a rare entity. In this case, the presence of a yellow dialyzer was one of the only two presenting symptoms for this patient, the other being itching. Itching, which occurs in dialysis patients could have easily been disregarded if it were not for the dialyzer discoloration. We highly stress that close attention to dialyzer color is needed in patients who present with itching, in the absence of any other symptoms. Recognition of a yellow dialyzer in a timely manner can assist in discerning if the etiology is medication related or hyperbilirubinemia related where the yellow color is thought to be due to entrapment of unfiltered bilirubin-albumin complexes by the dialysis membrane. Hopefully this recognition can improve outcome.

PO1197

Life Finds a Way: Two Successful Pregnancies in a Woman Without Kidneys

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Introduction: Bilateral nephrectomy is a controversial and rarely used approach to control refractory hypertension in patients with anuric end-stage renal disease (ESRD) who require dialysis. This extreme measure results in complete dependence on dialysis to maintain metabolic homeostasis. This procedure has become rare due to advances in anti-hypertensive pharmacotherapy. Given the rarity of this approach, there is a paucity of literature regarding how the absence of kidneys after bilateral nephrectomy impacts childbearing. We present the first known case of successful pregnancy in a woman on intermittent hemodialysis (iHD) without kidneys due to bilateral nephrectomy.

Case Description: The patient was a 31-year-old female who had ESRD secondary to hypertension and atypical hemolytic uremic syndrome (aHUS). She was diagnosed with aHUS condition during her first pregnancy and was initiated on biweekly infusions of eculizumab after delivery. Seven months after delivery, she underwent bilateral nephrectomy to control her hypertension. Two years following nephrectomy, she presented to the Emergency Department (ED) with dyspnea. Her urine β-HCG was positive and ultrasonography confirmed an intrauterine pregnancy. Throughout this pregnancy, she required iHD six days weekly. She delivered at 27 weeks gestation and after a short stay in the neonatal intensive care unit (NICU) her baby was discharged home in healthy condition. Two years later, the patient presented to the ED and was again found to be pregnant. She was managed with HD six days weekly. This child was born at 23 weeks gestation and was discharged home after several weeks in the NICU.

Discussion: Theoretically, bilateral nephrectomy can curtail regulatory mechanisms leading to hypertension. This approach has fallen out of favor given advancements in pharmacotherapy. There is almost no known scientific literature regarding how the absence of kidneys after bilateral nephrectomy impacts childbearing. On an extensive review of the literature regarding bilateral nephrectomy and pregnancy, only one case report was identified. This article details a Saudi Arabian woman receiving intermittent peritoneal dialysis who successfully carried a pregnancy to 29 weeks, with the birth of a healthy child. This report highlights the lack of literature regarding managing pregnant patients on iHD, especially those without kidneys.

PO1198

First Report of Simultaneous HBsAg and Anti-HBs Reactivity in a Hemodialysis Patient

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Introduction: Of great concern to dialysis units is the presence of bloodborne pathogens. The incidence of HBV infection is quite low in the United States, however outbreaks of hepatitis B in hemodialysis units have occurred. CDC guidelines recommend hemodialysis patients be screened for HBV surface antigen (HBsAg) surface antibody (anti-HBs) and core antibody (anti-HBc) on admission to the dialysis unit. We present an usual case of a patient with both HBsAg and anti-HBs positive who required hemodialysis (HD).

Case Description: A 78-year-old Chinese female with past medical history of CKD stage V, Type 2 DM, hypertension, chronic HBV with no prior treatment, presented to the ED with signs of fluid overload. In the ED she was hypertensive to 170/107. Labs showed a creatinine of 5.7 (baseline) and a serum sodium of 116. Liver enzymes were mildly elevated with no associated jaundice. Physical exam showed +2 peripheral edema and bilateral crackles, neither abdominal tenderness nor scleral icterus was present. No neurological deficits appreciated. Acute coronary syndrome was excluded. She was admitted and scheduled for hemodialysis. Admission labs showed anti-HBc positive, HBsAg positive, as well as anti-HBs positivity. Confirmatory HBV quantitative PCR testing resulted at 28 IU/ml.

Discussion: Classically, anti-HBs antibodies neutralize and clear HBsAg from peripheral blood. Therefore, the presence of anti-HBs is considered an indicator of immunity from ongoing HBV infection. The typical serological feature of chronic HBV infection is circulating HBsAg and lack of anti-HBs. However, the coexistence of HBsAg and anti-HBs has been reported to be as high as 8% of chronic HBV patients. The coexistence of HBsAg and anti-HBs has been explained by the phenomenon of "escape variation". Point mutations or deletions in the pre-S/ S gene of HBsAg may give rise to

mutant surface proteins. The detectable HBsAg is thus a mixture of wild type and variants, whereas the detectable anti-HBs are only against wild type viruses. These patients are still in the chronic HBV infection category as they typically do not progress to active disease, however acute infection is possible. Given our patient's low HBV DNA (< 10,000 IU/ ml) and mild transaminitis, she fits the chronic, inactive carrier state. Appropriate infection control precautions for HD were taken as established for chronic HBV infection patients.

PO1199

Dialysis Disequilibrium Syndrome and Cerebellar Herniation with Successful Reversal Using Mannitol

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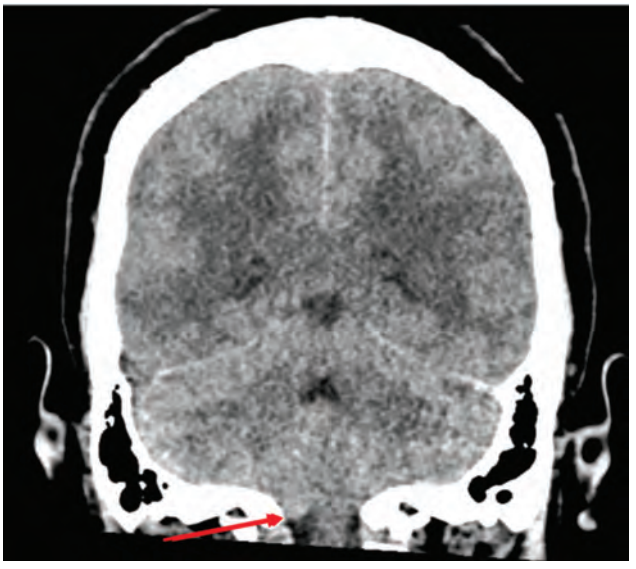
Introduction: Dialysis disequilibrium syndrome (DDS) is a complication of hemodialysis. Symptoms can include headaches, seizures, and even death. An extensive literature review yielded thirteen documented reports of patients suffering from cerebral herniation secondary to DDS with poor outcomes.

Case Description: 47-year-old male with hypertension presented to the emergency department (ED) with complaints of abdominal pain. Initial laboratory studies were concerning for thrombocytopenia and acute renal failure. The patient was urgently admitted to the Intensive Care Unit (ICU) and hemodialysis was initiated. Approximately 20 minutes into the hemodialysis session, the patient became unresponsive. A right eye gaze deviation and right-sided fasciculations of the upper and lower extremities were observed. Hemodialysis was discontinued and a head CT was obtained. Imaging revealed pontine edema with mass effect and cerebellar tonsillar herniation (Figure 1). Intravenous mannitol was initiated. Within 30 minutes of initiation of the mannitol infusion, the patient regained consciousness. Follow-up neurological exam showed resolution of the right-sided fasciculations and gaze palsy. The follow-up head magnetic resonance imaging (MRI) showed resolution of the midline shift and tonsillar herniation.

Discussion: Historically, even with swift intervention, cerebral herniation due to DDS carries a grim prognosis. Current guidelines stress the importance of preventative measures and the use of IV mannitol if cerebral herniation is suspected. The case reported herein is the first documented account of reversal of the clinical and imaging findings of tonsillar herniation secondary to DDS using intravenous mannitol.



PO1200

Gross and Microscopic Evidence of Platelet Clumping in the Extracorporeal Circuit Causing Thrombocytopenia in a Patient on Continuous Renal Replacement Therapy

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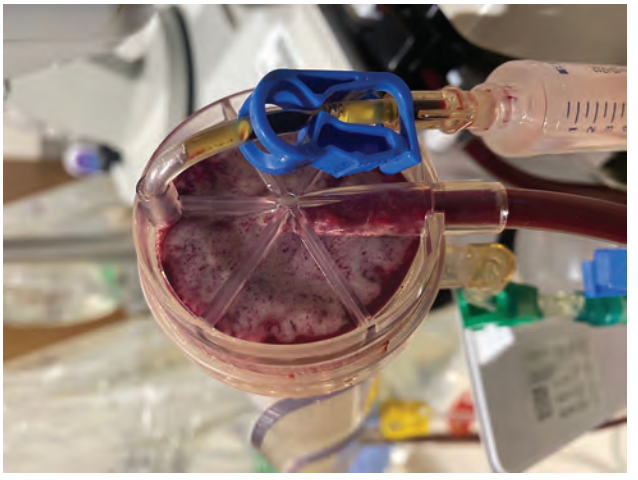
Introduction: Thrombocytopenia has been reported coincident with continuous renal replacement therapy (CRRT). We present a patient who developed thrombocytopenia on CRRT with gross and microscopic evidence of platelet clumping in the extracorporeal circuit.

Case Description: An 83 year old female with atrial fibrillation developed acute kidney injury requiring CRRT in the setting of ischemic bowel. Heparin was started due to suspicion of embolic phenomena. CRRT with citrate anticoagulation was begun using the NxStage System One (Purema H) without immediate issues. However, coincident with a progressive thrombocytopenia to a nadir of 75 $x10^3$/uL, the care team noticed a white substance at the venous header of the dialyzer (Figure 1). Heparin was stopped due to concern for heparin-induced thrombocytopenia. CRRT was stopped and the dialyzer was sent to Pathology for evaluation. The white substance was found to be composed of many platelets with entrapped white blood cells and red cells, consistent with platelet clot. CRRT was withheld for 2 days with improvement of platelet count from 75 to 140 $x10^3$/uL before the patient was restarted on CRRT due to clinical need; platelets subsequently decreased to 79 $x10^3$/uL with reappearance of the white substance in the dialyzer. HIT testing was negative. The patient expired several days later when her family requested comfort care.

Discussion: Thrombocytopenia is frequently seen in critically ill patients, and it is often difficult to pinpoint a specific cause. In our case, gross and microscopic evidence of platelet clumping were seen in the CRRT filter coincident with thrombocytopenia, which remitted when off and then recurred when restarted on CRRT. Care teams should examine the dialyzer carefully when there is unexplained thrombocytopenia, as platelet activation and trapping within the circuit may be responsible.



Venous header of dialyzer with representative white film

PO1201

Doctor, There Is a Blood Leak!

Deepthi C. Malepati, Sindhura Bobba, Monika Aggarwal (Gupta). *Hunter Holmes McGuire VA Medical Center, Richmond, VA.*

Introduction: Blood leak detector detects blood in the dialysate that is confirmed with a blood leak test strip. We report a case of false blood leak alarm due to hydroxocobalamin that was initially treated as a true positive blood leak due to the incorrect use of blood leak test strip, and required switching from hemodialysis (HD) to continuous veno-venous hemodialysis (CVVHD).

Case Description: 67 year old male with alcohol abuse presented with shortness of breath. Exam significant for tachycardia, confusion and respiratory distress. Laboratory data remarkable for serum potassium 3.1 meq/L, bicarbonate 6 meq/L, anion gap 45, serum osmolality 351 mosm/L, and osmolar gap 61. Serum creatinine was 2.5 mg/dl. Fomepizole and Hydroxocobalamin were given. HD with Fresenius 2008T was terminated after 2 minutes due to a blood leak alarm. Blood leak test strip (Serim Guardian) was read positive for blood. HD was reinitiated with a new setup, again triggering blood leak alarm. Effluent was pink (Figure 1.) and repeat blood leak test strip was negative at 60 seconds. Patient was successfully switched to CVVHD (Nxstage) without further blood leak alarms.

Discussion: False positive blood leak alarm was triggered due to change in the color of the effluent by hydroxocobalamin. Fresenius 2008T dialysis machine blood leak detector uses red and green light. Green light was absorbed due to the discoloration of the effluent, triggering blood leak alarm. Blood leak alarm was not triggered on NxStage, as it uses infrared wavelength, allowing continuation of dialysis. Initial blood leak test strip was read positive due to reading beyond recommended 60 seconds (subsequent test strip was negative). Correct use of blood leak test strip would have avoided second setup of HD and would have correctly identified false blood leak alarm due to hydroxocobalamin requiring switching to CVVHD.

Figure 1.

PO1202

Tailoring the Dialysis Prescription in Patients at Risk for Dialysis Disequilibrium Syndrome

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Introduction: The dialysis disequilibrium syndrome (DDS) is a potentially fatal, preventable syndrome in uremic patients treated with dialysis. Urea kinetics can be used to tailor the dialysis prescription to a goal urea reduction ratio (URR) of less than 40%.

Case Description: A 22-year-old female patient presented to the emergency department with severe renal failure and a failing transplant secondary to noncompliance with medications for 1 year. Serum creatinine was 32 mg/dl, blood urea nitrogen (BUN) 226 mg/dl, potassium 9.2 meq/l and serum total carbon dioxide content 6 meq/l. Intermittent hemodialysis was started using a dialyzer with a mass transfer coefficient (koA) of 1200 ml/min, a blood flow rate of 250 ml/min, a dialysate flow rate of 500 ml/min and zero ultrafiltration. She was given 12.5 g of mannitol to reduce the risk of DDS. Her weight was 60 kg. After 1.5 hours of dialysis, the patient developed generalized seizures secondary to brain edema. BUN 6 hours after dialysis was 137 mg/dl. She was declared brain dead 4 days later.

Discussion: The dialysis disequilibrium syndrome results from osmotic shifts between the blood and the brain compartments. Rapid changes in BUN are known to contribute, but other osmotic substances may contribute to the development of DDS as well. Patients at risk for DDS include those with very elevated BUN, concomitant hypernatremia, metabolic acidosis, and those with low total body water volumes. There is no absolute cut off value for URR that is guaranteed to prevent DDS. However, a URR of 40-45% over 2 hours and a total decrease in serum osmolality no more than 24 mosm/kg per 24 hours are recommended. A simplified relation between Kt/V and URR is provided by the equation: kt/V= -ln (1-URR). A URR of 40% is roughly equivalent to a kt/V of 0.5. Thus, targeting a kt/V of 0.5 is a reasonable goal for the initial treatment. k can be plotted on the nomogram in figure 1 (used with permission) for a given dialyzer koA and blood flow rate. Using a 400 koA dialyzer at a blood flow rate of 200 ml/min for 120 minutes in a patient with a V of 30 l, the estimated kt/V is 0.45 and the estimated URR is <40%. When low-efficiency dialyzers are not available, other measures to lower clearance such as reversing dialysis lines or CRRT need to be considered. Sodium modeling and mannitol may also mitigate rapid changes in osmolality.

PO1203

Association Between Serum Alkaline Phosphatase Levels and Stroke Risk in Patients Receiving Maintenance Hemodialysis: The Q-Cohort Study

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Background: Elevated serum alkaline phosphatase (ALP) levels have been associated with increased risks of all-cause and cardiovascular mortality in patients receiving hemodialysis (HD). However, little is known about the impacts of serum ALP levels on the occurrence of stroke, including brain hemorrhage and brain infarction. This study aimed to explore the association between serum ALP levels and brain hemorrhage or brain infarction separately in HD patients.

Methods: A total of 3,497 maintenance HD patients registered in the Q-Cohort Study, a multicenter observational cohort study in Japan, were examined. The primary outcomes were the first-ever incidence of either brain hemorrhage or brain infarction during the follow-up period. The covariate of interest was serum ALP levels. Patients were divided into tertiles based on the serum ALP levels at baseline [ALP (U/L): T1, <69.3; T2, 69.3–98.4; T3, >98.4]. The risks for brain hemorrhage or brain infarction were estimated using a Cox proportional hazards model and a Fine-Gray proportional subdistribution hazards model with all-cause death as a competing risk. The restricted cubic spline model was used to plot the multivariable-adjusted association between serum ALP levels and hazard ratios (HRs) and 95% confidence intervals (CIs) for brain hemorrhage or brain infarction.

Results: During the follow-up period of four years, 89 patients developed brain hemorrhage and 195 patients developed brain infarction. The risk of brain hemorrhage in the highest tertile (T3) was significantly higher than that in the lowest tertile (T1): multivariable-adjusted HR [95% CI], 1.93 [1.15–3.35], subdistribution HR, 1.91 [1.10–3.30]. Furthermore, restricted cubic spline curves showed that higher serum ALP levels were significantly and incrementally associated with an increased risk for brain hemorrhage. In contrast, no significant association was identified between serum ALP levels and the risk of brain infarction.

Conclusions: Higher serum ALP levels were associated with an increased risk of brain hemorrhage in patients receiving maintenance HD. Our results suggest that ALP might play some roles in the pathogenesis of brain hemorrhage in HD patients.

Funding: Private Foundation Support

PO1204

Effects of Improvements in Nutritional and Physical Conditions on Life Prognosis in Elderly Hemodialysis Patients in Japan

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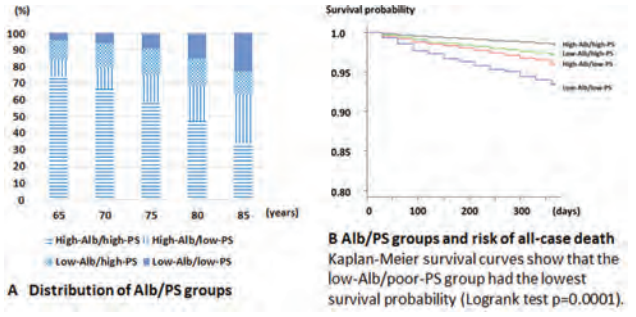
Background: The increase in the number of elderly dialysis patients is an urgent worldwide issue. Among these patients, malnutrition and physical-function decline are often observed. Therefore, we conducted a nationwide cohort study using the elderly hemodialysis patient database (n=38227) of the Japanese Society for Dialysis Therapy to investigate the relationship of their nutritional and physical conditions with their risk of one-year death.

Methods: Malnutrition and poor performance status (PS) were defined as being indicated by low serum albumin levels, and high scores of the modified Eastern Cooperative Oncology Group PS, respectively. After a one-year follow-up of changes in these factors, the relationships between the changes in these factors and the risk of one-year death were evaluated using Cox proportional hazards models adjusted for baseline characteristics.

Results: Among the patients examined, 57.9% were males; age, 73.2±6.0 years; diabetes mellitus, 33.7%; serum albumin level, 3.7±0.3 g/dL. The prevalence of patients in the low-albumin/poor-PS group tended to increase with age: 65 to 69 years, 1.4%; 85 years or older, 22.7% (Figure A). The low-albumin/poor-PS group showed a higher risk of all-cause of death than the high-albumin/good-PS group: adjusted hazard ratio (aHR), 2.77 (95% CI, 2.24, 3.44) (Figure B). The 0.1 g/dL improvements in serum albumin levels and 1 point improvement in PS scores were independently associated with better life prognosis; aHR 0.93 (0.92, 0.95); aHR 0.76 (0.71, 0.81). These results were confirmed in subgroups categorized on the basis of age, and the presence of DM.

Conclusions: Malnutrition and PS decline are risk factors for death in elderly hemodialysis patients, and should be evaluated and treated simultaneously. It is expected that the treatments of patients with these factors will improve their life prognosis independent of their baseline characteristics.



A Distribution of Alb/PS groups

B Alb/PS groups and risk of all-case death
Kaplan-Meier survival curves show that the low-Alb/poor-PS group had the lowest survival probability (Logrank test p=0.0001).

PO1205

Ultrafiltration Accuracy of the Tablo® Hemodialysis System During 24-Hour Therapy

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Background: Ultrafiltration (UF) accuracy is vital to ICU management of patients with kidney failure. Renal replacement options include intermittent hemodialysis, continuous renal replacement therapy and slow low efficiency dialysis. Regardless of therapy, clinicians need confidence that the dialysis device chosen will accurately remove volume to achieve the prescribed goal. The Tablo Hemodialysis System is an all-in-one system with on demand water purification and dialysate production indicated for use in clinic, hospital, and home settings. Prior reports have demonstrated UF accuracy over a wide range of conditions up to 12 hours. The objective was to report on the accuracy of Tablo's unique flow balancing technology over 24 hours of continuous therapy utilizing HD, isolated ultrafiltration, or a sequential therapy modes.

Methods: Bench testing was conducted to evaluate UF accuracy across clinically relevant parameters during a simulated 24-hour treatment with a single cartridge. Ten distinct treatment conditions were created. Effluent was weighed and compared to the prescribed goal at treatment completion. Treatment conditions included: mode (HD, UF-Only, and Sequential therapy (HD→UF only, UF only→HD), blood flow rates (Qb) from 150-400 ml/min, dialysate flow rates (Qd) from 50-300 ml/min, UF goals from 0 to 1.9 L/hr, and low to high venous and arterial pressure.

Results: Thirty simulated treatments were performed. Twenty-four treatments were performed with Qb from 150-250ml/min and 6 were performed with Qb 300 or greater. Twenty-seven treatments had fluid removal goals between 250ml/hr to 2000ml/hr and 3 treatments were performed with a UF goal of 0ml/hr. Ninety-three percent of treatments were within 20ml/hr of accuracy (< 480ml of total error). Sixty-seven percent of treatments were within 10ml/hr of the prescribed UF goal (< 240ml of total error). Blood flow and UF rate showed correlation to UF accuracy with minimum error between Qb 200-300ml/min and UF rate between 0-1000ml/hr. There was no impact to UF accuracy from treatment mode or dialysate flow rate.

Conclusions: Tablo's proprietary flow balancing technology maintains a high level of UF accuracy across a wide range of 24-hour treatment prescriptions. Optimal accuracy was noted at parameters typically prescribed in continuous renal replacement therapy.

Funding: Commercial Support - Outset Medical, Inc.

PO1206

Unfavorable Vintage: Dialysis-Related Amyloidosis Discovered at Transplant

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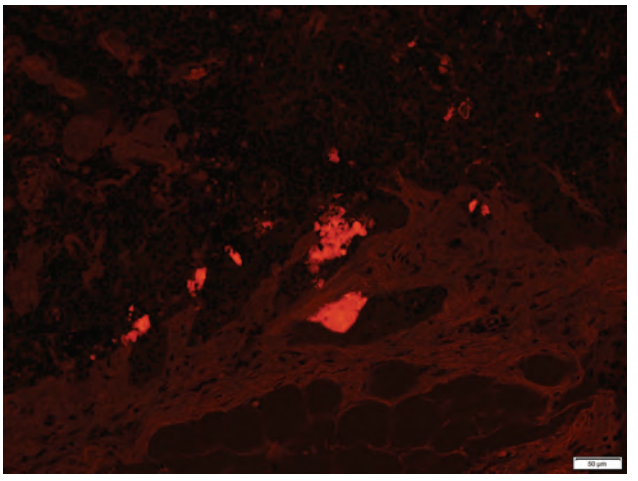
Introduction: Despite its life-sustaining potential, prolonged dialysis and inadequate clearance of middle molecules can have untoward consequences. Largely underdiagnosed, dialysis-related amyloidosis (DRA) is an effect of prolonged dialysis vintage. We present a case of DRA in a patient with nearly 25 years of dialysis-dependence, diagnosed histologically at time of transplant.

Case Description: A 60-year-old man with hypertension, on dialysis since 1996, presented for renal transplant evaluation. Hematology labs showed normal serum protein electrophoresis but elevated free kappa (κ) to lambda (λ) light chain ratio of 10.9. Bone marrow biopsy was normal but patient was found to have elevated serum β_2 microglobulin (β_2-m) at 23.6 μg/mL. He was listed and immediately received a diseased donor transplant. Intraoperatively, biopsy of a large iliac lymph node was submitted which showed Congo Red positive staining by light microscopy for amyloid but was negative for serum amyloid A (AA) and κ light chain and λ light chain (AL). Further testing identified the amyloid protein as β_2-m. Retrospective history revealed he had suffered years of joint pain, especially in his shoulders, and had bilateral carpal tunnel surgery. He was chronically dependent on hydrocodone but since transplant he no longer experienced pain. Nadir serum creatinine was 1.3 mg/dL and repeat β_2-m level decreased to 4.1 μg/mL.

Discussion: Present on all cell surfaces, β_2-m is freely filtered then reabsorbed and catabolized in proximal tubules. Prolonged reduction in glomerular filtration leads to accumulation and deposition of amyloid fibrils particularly in periarticular structures, leading to debilitating arthritis. Although no precise treatment for DRA exists, transplantation leads to renewed clearance and dramatic improvement in symptoms. This case reiterates the importance of remaining alert for such diseases in patients with prolonged dialysis vintage.



Congo Red Staining in Vessel Wall Demonstrates Amyloid Deposition

PO1207

Baclofen Pump Causing Electroencephalography Seizures

Niraj K. Yadav, Janame J. Kottey, Josephine Abraham. *University of Utah Health, Salt Lake City, UT.*

Introduction: Baclofen is a centrally acting muscle relaxant that inhibits monosynaptic and polysynaptic reflexes at the spinal cord level resulting in relief of muscle spasticity. Baclofen is commonly used orally and intrathecally. We present the case of a patient on intrathecal baclofen through a pump presenting with respiratory failure and seizures.

Case Description: A 59 year old male with Atrial fibrillation, right MCA stroke and resultant left hemiparesis was under treatment with intrathecal baclofen through a pump. He underwent fluoroscopy guided pump refill and was found unresponsive later that night. EMS was called and he was intubated en route to the ED. He was hypotensive with recorded blood pressures 48/26-84/45 mm Hg. He had two seizures in ED and received IV lorazepam. Initial labs showed lactate 11.9 mmol/l, PCO2 80 mm hg, pH 6.9 and creatinine 2.0 mg/dl. Urine was positive for opiates and benzodiazepines. CT head did not show acute changes and was consistent with previously seen right cerebral encephalomalacia. He received intravenous fluids and creatinine improved to 0.9 mg/dl with resolving oliguria. Electroencephalography(EEG) was concerning for status epilepticus and he was transferred to our center for further management. Baclofen level was 0.13 mcg/ml. The acute encephalopathy, status epilepticus and respiratory failure were attributed to baclofen toxicity and nephrology was consulted for emergent dialysis. He underwent a 4 hour hemodialysis session using a Nipro 17H filter and maximum blood flow with dialysate flow at 600 ml/min. A post hemodialysis baclofen level was undetectable. Continuous EEG on the day after the hemodialysis session had improved.

Discussion: Role of hemodialysis in life threatening baclofen toxicity in a patient with AKI and improved renal function is not well described. Baclofen is small molecule with a molecular weight of 213g/mol that is primarily excreted unchanged by the kidneys with an apparent volume of distribution of 59 liters and is 30 percent protein bound. A single hemodialysis session may be adequate to clear baclofen in patients without advanced CKD. It is pertinent to recognize baclofen as possible cause of encephalopathy and seizures and consider hemodialysis in severe cases.

PO1208

Hep B or Not Hep B: The Mystery of Hepatitis B Serology in a Dialysis Patient

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Introduction: Dialysis patients are susceptible to viral infections due to impaired cellular immunity. HepB remains a major problem in these patients. Hemodialysis, transfusions, frequent admissions and surgery, all increase risk of infections. While the introduction of vaccines and infection control measures have limited the spread of hepatitis infection within dialysis facilities, outbreaks occur and prevalence remains high. Serology testing is used to screen and identify infected patients. Interpretation of these serologies, as in our case, can be challenging.

Case Description: 83 y/o female with HTN, DM and ESRD on HD. Admitted from a NH with viral prodrome and tested +ve for COVID-19. Nephrology consult was requested for maintenance HD. She had HBsAg assay which came back positive. Full Hep B panel showed HBsAb +ve, HBcAB +ve (IgM), HepB DNA PCR –ve, HBeAg & Ab-ve. Surprisingly, old records showed HBsAg positivity 6 months prior to admission and the rest of the serology was identical to this admission. Within the last 6 months, she have had multiple HBsAg tests that all came back -ve. Up to this point, she wasnt receiving HD in dedicated HepB machines. Decision was to apply segregation and to contact the health department to trach down all patients that were dialyzed with the same machines.

Discussion: The prevalence of HepB in dialysis patients is 1%. Cirrhosis, which can result from HepB, is associated with a 35% increased mortality in dialysis patients. To prevent transmission, measures include barrier procedures, routine screening, disinfection and vaccination. Failure to use dedicated machines may increase incidence of HepB. Serology can identify infected patients. Screening consists of HBsAg, anti-HBs, and anti-HBc. Our patient's serology was unique. Her Anti-HBs was always positive. Due to anti-HBc positivity, we believe that she was infected in the past. Interestingly, the HBc-IgM was always +ve and DNA was always -ve. The occasionally positive HBsAg is bizarre. This can be seen in patients receiving vaccination but it doesn't apply to our patient. We don't have an explanation for positive HBsAg in the absence of DNA and there are no recommendations to guide clinicians in such cases. In our patient, we decided to consider her a chronic HepB patient for the purpose of dialysis segregation, however, she does not meet criteria for chronic HepB and will unlikely require treatment.

PO1209

Temporal Change in Formula-Derived Creatinine Index as a Surrogate for Lean Muscle Mass Correlates Well with Change in Post-Hemodialysis Weight but Not with the Volume of Urea Distribution

Xiao Ling, Andrew I. Chin. *University of California Davis, Sacramento, CA.*

Background: In hemodialysis (HD) patients, creatinine kinetic modeling to derive a Creatinine Index (CI) is a measure of lean muscle mass. Loss of lean muscle mass is associated with poor outcomes. This modeling process is complex and not routinely performed. A simplified formula for CI was developed in a previous study. We sought to determine if temporal change in the calculated CI using the simplified formula correlated with more commonly available data used in routine clinical care of HD patients.

Methods: We retrospectively queried long-term HD patients without residual function who had available serologic, urea kinetic, and clinical care data at least 18 months over a 24 month span. We used the simplified formula previously published for creatinine index: CI (mg/kg/day) = 16.21 + 1.12 x [1 if male, 0 if female] - 0.06 x age (yrs) – 0.08 x spKt/Vurea + 0.009 x Creat (pre-dialysis). Regression lines were created for each parameter over the 24 months. Slopes in the change of CI, post-HD wt, urea generation rate (G) and kinetic modeled distribution of urea (V) were compared by paired t-tests.

Results: We included 455 long-term HD patients without residual renal function (we measure this routinely) with at least 18 out of 24 months of complete data. Mean HD vintage was 40 months. We found the slope of CI to be poorly correlated to V or G, but did compare favorably to change over time slopes for V and post-HD weight.

Conclusions: In this retrospective analysis in HD patients, the temporal *change* of calculated Creatinine Index as an indicator of lean muscle mass compared best with *change* in post-HD weight. While the volume of urea distribution is related to body composition, the change V over time surprisingly did not mirror that of calculated CI. We also compared the slope of V to that of post-HD weight and found a strong association. The simplified equation for CI, applied to our population in Northern California, may correlate poorly with lean muscle mass.

Funding: Clinical Revenue Support

Comparisons of slope of regression lines for stated factors

	P-value of pair-wise t-test
Creatinine index (CI) to urea generation rate (G)	0.99
CI to urea distribution volume (V)	0.69
CI to post-HD weight	0.0005
V to post-HD weight	0.001

PO1210

Crit-Line Blood Volume Monitoring in a Community Hemodialysis Unit

Carl E. Dukes. *Carl E. Dukes, MD PA, San Antonio, TX.*

Background: A quality improvement (QI) project on fluid management using Crit-Line Blood Volume Monitors (CLM) was conducted by a nephrologist in one community hemodialysis unit in Texas. A goal of the QI project was to decrease the blood pressure medication burden to facilitate better ultrafiltration during treatment. This analysis examines the changes in blood pressure (BP) medication (Med) and associated changes in post-dialysis weight and systolic BP.

Methods: Chronic HD patients of the nephrologist leading the QI project, receiving care during baseline (month before QI project) and the first month of QI project follow-up were included in this analysis. Time was divided into 1-month Baseline, 3-month training period, and 7-month follow-up. The physician reviewed each Crit-Line session and directed the staff to challenge the patient's weight based on a positive refill curve. In order to facilitate further fluid removal, the vasodilating anti-hypertensive medications were discontinued. Thereafter, the other anti-hypertensive medications such as beta-blockers and RAASi agents were reduced or discontinued.

Results: Patients (n=43) were on average 63 years old, with a HD vintage of 5 years and had a fistula for vascular access (77%). 58% of patients identified as black/African American and 40% identified as Hispanic/Latino. Most patients (74%) had pre-HD systolic BP at baseline in the hypertensive range. 41 patients had BP Med information. During follow-up, 16.7% of patients discontinued BP med, 28.6% reduced BP med pills/day, 4.8% increased BP med pills/day, and the remaining had unchanged BP med. Changes in post and pre HD systolic BP and post-HD weight are presented in the table.

Conclusions: In a single-center QI project addressing fluid management through relative blood volume monitoring, 46% of patient were able to reduce (28.6%) or discontinue (16.7%) blood pressure medication. Patients able to discontinue the medications, had the largest decrease in post-HD weight.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Change from baseline to last month of QIP	Unchanged BPM (n=19)	Reduced BPM (n=12)	Discontinued all BPM (n=7)	Increased BPM (n=2)
Post-HD Weight (kg)	-1.37 ± 4.57	-0.78 ± 6.77	-2.19 ± 4.44	0.18 ± 7.97
Pre-HD Systolic BP (mmHg)	0.18 + 14.5	1.8 ± 17.5	-2.7 ± 25.0	-19.4 ± 34.3
Post-HD Systolic BP (mmHg)	3.0 ± 14.2	-0.11 ± 18.2	-4.5 ± 25.4	-7.5 ± 18.2

PO1211

Effects of Combined Expanded Hemodialysis (HDx) and Hemoadsorption (HA) in Hemodialysis (HD) Patients: A Single Center's Experience

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Background: HDx appears to achieve a better removal performance of middle and large molecules due to the cut-off pores and the internal architecture of the membranes while recent studies have indicated the effective role of HA in reducing uremic symptoms in HD patients. The aim of our study was to assess the impact of the appliance of these two new modalities on several clinical parameters in chronic HD.

Methods: 15 HD patients (mean age=53.5 years, BMI= 26.5 kg/m^2, years on dialysis=5.5) were included. All subjects were already treated with HDx (Baxter Theranova) for 6 months. After this period, patients received combined HDx with HA (Jafron HA-130) weekly for 4 weeks and an additional combined treatment in week 12. The HA was applied in the middle-week day session for 2.5 hours. No change in their current medication was done during this period of time. Serum biomarkers were measured at baseline, at week 1, 12 and 16 (follow-up period) and included measurement of hemoglobin, platelet count, white blood cells, albumin, lipids, calcium, phosphorus, β2-microglobulin and Parathormone levels. Monthly kt/v was calculated appropriately.

Results: No statistically significantly differences were observed before and after the appliance of the combined treatment in respect of hemoglobin, white blood cells, platelets, phosphorus, Parathormone, HDL, triglycerides, albumin levels and the dialysis efficiency expressed by the monthly kt/v. However, a statistically significantly decrease of calcium levels were found between baseline levels and levels measured at the follow-up period (9.08±0.77mg/dl vs 8.37±0.66 mg/dl, p=0.005). Furthermore, LDL levels appeared to show a statistically significantly decrease until week 12 (110.33±28.99 mg/dl vs 103.00±27.19 mg/dl, p=0.048) and then a statistically significantly increase at the follow-up period (103.00±27.19 mg/dl vs 109.83±30.60 mg/dl, p=0.030). No adverse events were reported.

Conclusions: A combination of HDx and HA seems to show a potential effect in modifying lipid abnormalities in dialysis patients. These results can improve the outcome, especially in cardiovascular disease patients. However, the frequency of applying sorbent-based therapies for maintaining the desired results, needs to be evaluated and standardized in larger studies.

PO1212

Merits of Using mHealth Experience Sampling Methodology to Assess Fatigue in Chronic Hemodialysis Patients

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Background: Understanding the development of fatigue and related behavioral, social and psychological factors in hemodialysis (HD) patients is crucial for the development of effective treatment. However, conventional fatigue measures provide limited insight in diurnal variations in fatigue and related factors in daily life and are prone to memory bias. The Experience Sampling Methodology (ESM) overcomes these limitations by repeatedly assessing 'real-time' symptoms in patients' natural environments. We aimed to gain in-depth understanding of HD patients' diurnal fatigue patterns and related variables using a mobile Health ESM application (*mHealth* app) and to investigate how retrospective fatigue reports correspond to real-time symptom experiences.

Methods: Forty HD patients used the *mHealth* app for seven days to assess real-time fatigue and potentially related variables, including daily activities, social company, location and mood. In addition, they retrospectively evaluated their experienced fatigue over the preceding week on an end-of-week questionnaire and the conventional Fatigue Severity Scale (FSS).

Results: Analyses of momentary observations (N=1778) revealed that fatigue as well as mood varied *between* and *within* individuals. Real-time fatigue significantly related to concurrent type of daily activity and mood. Interestingly, time-lagged analyses showed that HD treatment predicted more fatigue later in time (β=.22, p=.013), and that higher fatigue levels predicted lower mood later in time (β=.05, p=.019). Retrospective fatigue evaluation was significantly higher than the mean of real-time fatigue score, t(38)=3.54, p=.001. FSS-scores correlated moderately with mean real-time fatigue score, r=.63.

Conclusions: This study demonstrates that fatigue in chronic HD patients varies over time and increases after HD treatment, corroborating the occurrence of post-dialysis fatigue. Furthermore, our findings suggest that depressed mood may be secondary to fatigue in HD patients. Finally, retrospective fatigue evaluation overestimated real-time assessments, suggesting memory bias when using conventional fatigue measurement instruments. ESM provides novel insights and personalized information about fatigue symptoms in patients daily life, paving the way toward personalized interventions.

PO1213

Use of Triferic and Outcomes of Hemodialysis-Dependent Patients: Initial Analysis Using 2016-2017 USRDS

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Background: Use of iron oxide nanoparticles (IONP) to replace iron losses in CKD-HD patients has been associated with increased risk of infections. We have examined patient outcomes with ferric pyrophosphate citrate (FPC; Triferic®), a novel iron compound delivered via the hemodialysate, relative to the general U.S. hemodialysis patient population receiving IONPs in US Renal Data System (USRDS). A single outpatient free-standing hemodialysis center with ~57 adult CKD-HD patients between 2016 and 2017, converted to FPC in January 2017. Unadjusted all-cause and infection related hospitalizations and mortality were examined pre-FPC and post-FPC and compared with the general USRDS data during the same period.

Methods: USRS methods were utilized for calculation of the crude hospitalization and mortality rates. For each calendar study year, the period at risk begins at the later date of either January 1 or day 91 of ESRD, and censoring occurs at death, or December 31.

Results: Consistent with findings from USRDS, unadjusted all-cause hospital and mortality rates for the *general ESRD population* in 2016 were 2.12 hospital admissions, 16.0 hospital days, 0.35 infection-related admissions, 3.05 infectious hospitalization days per patient year, and 164 deaths per 1,000 patient years. Notably, patients in 2017 exhibited similar rates compared to 2016. In contrast, patients treated in the facility using Triferic experienced a reduction in both mortality and infection-related hospitalizations. Specifically, mortality rates reduced 58% from 101 per 1,000 patient-years in 2016 to 42 in 2017; infectious hospital admission reduced 73% from 0.49 admissions per patient-year in 2016 to 0.13 admissions in 2017. Furthermore, infection-related hospital days reduced 82% from 3.86 days per patient-year in 2016 to 0.71 in 2017.

Conclusions: This observational cohort study suggests that use of ferric pyrophosphate citrate as an iron replacement therapy is associated with reduction in all cause and infection-related hospitalizations and mortality. Further analysis is needed to confirm the findings from this initial analysis after controlling a variety of patient case-mix factors and dialysis center characteristics with a larger sample size.

Funding: Commercial Support - Rockwell

PO1214

Association of Geriatric Nutritional Risk Index with Decline in Residual Kidney Function in Incident Hemodialysis Patients

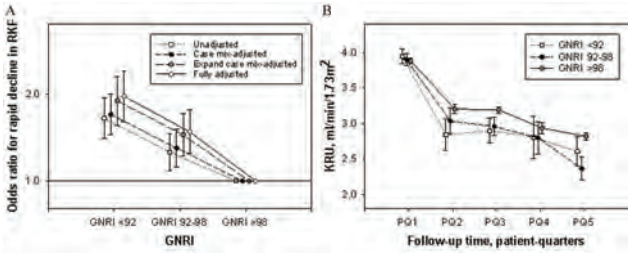
Hiroshi Kimura,[1] Cachet Wenziger,[1] Jui-Ting Hsiung,[1] Connie Rhee,[1] Elani Streja,[1] Csaba P. Kovesdy,[2,3] Kamyar Kalantar-Zadeh.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]Memphis VA Medical Center, Memphis, TN.*

Background: Malnutrition is highly prevalent and is a significant contributor to adverse outcomes among hemodialysis patients. Residual kidney function (RKF) provides effective and continuous clearance of both small and middle molecules, plays an important role in nutritional status. However, the impact of malnutrition on the decline of RKF has not been well studied. The objective of this study was to investigate the association of baseline Geriatric Nutritional Risk Index (GNRI) with a decline in RKF over 1 year after dialysis initiation among hemodialysis patients.

Methods: We included 6,649 hemodialysis patients who initiated dialysis treatment in a large United States dialysis organization between January 1, 2007, and December 31, 2011. Rapid decline in RKF was defined as the percent change in residual urea creatinine (KRU) greater than 50% per year. The associations of GNRI with decline in RKF were retrospectively examined across three strata of GNRI [low (GNRI <92), middle (GNRI 92-98), high (GNRI >98) GNRI group] using logistic regression models adjusted for clinical characteristics and laboratory valuables. Then, we used the linear mixed-effects model allowing for a random intercept and slope using unstructured covariance matrices to estimate the magnitude and decline of RKF over 1 year according to the GNRI groups

Results: The median GNRI and baseline KRU were 107.7 and 3.4 ml/min/1.73m^2, respectively. Lower GNRI was associated with a smaller proportion of diabetes, lower baseline KRU, BMI, nPCR, and serum albumin. Adjusting for patient's differences, there was an inverse relationship between lower GNRI and a higher odds of rapid decline in RKF [adjusted odds ratio: 1.97 (1.61–2.41) and 1.48 (1.25-1.76) for low and middle GNRI groups, (reference: high GNRI group]. KRU trajectories showed greater KRU decline over time in lower GNRI.

Conclusions: Lower GNRI was associated with a rapid decline in RKF, especially in the first 3 months after transitioning to hemodialysis.



PO1215

Prognostic Nutritional Index and Mortality Among Maintenance Hemodialysis Patients

Yoshikazu Miyasato,[1] Cachet Wenziger,[1] Jui-Ting Hsiung,[1] Elani Streja,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2,3] Kamyar Kalantar-Zadeh.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]Memphis VA Medical Center, Memphis, TN.*

Background: Malnutrition and inflammation are associated with the mortality of dialysis patients. Prognostic Nutritional Index (PNI), which is composed of serum albumin levels and total lymphocyte count, has been suggested as a simple and useful prognostic marker in postoperative cancer patients. We evaluated the usefulness of PNI for predicting mortality in hemodialysis patients.

Methods: This retrospective cohort study included the patients who started hemodialysis in a large U.S. dialysis organization from 2007 to 2011. We examined the association between the quartiles of PNI and mortality using Cox regression model. Besides, we compared the mortality predictability of PNI and its components (serum albumin levels and total lymphocyte count) using the receiver operating characteristic curve (AUROC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: The mean age (and standard deviation) of total 101,616 patients was 63±15 years, and 26,622 died during the median follow-up period of 1.4 years. Higher quartiles of PNI were associated with lower mortality; case-mix adjusted hazard ratios (95%CI) were 0.66 (0.64-0.68), 0.49 (0.48-0.51), 0.35 (0.34-0.37) among patients with PNI 39.5-<43.1, 43.1-<46.6, and 46.6-< (reference: PNI <39.5). PNI showed higher mortality predictability than serum albumin levels and total lymphocyte count; AUROC (95%CI); 0.746 (0.742-0.750), 0.743 (0.739-0.748), 0.711 (0.706-0.716), NRI (95%CI); 0.436 (0.418-0.454), 0.410 (0.392-0.429), 0.174 (0.156-0.192), IDI (95%CI);0.034 (0.032-0.035), 0.032 (0.030-0.033), 0.003 (0.003-0.004), respectively. The difference in the AUROC was statistically significant between PNI and its components. In subgroup analysis PNI well predicted mortality in younger than 75 year-old patients.

Conclusions: Higher PNI was associated with lower mortality in hemodialysis patients. Compared with serum albumin levels and total lymphocyte count, PNI seems to be a useful predicting marker of mortality.

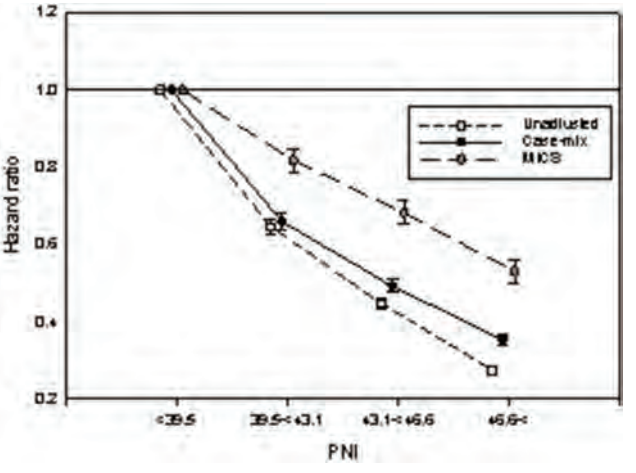


Figure: Mortality risk associated with PNI

PO1216

Hemodialysis-Assisted Management of Severe Hypoglycemia

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Introduction: Many medications are cleared by hemodialysis (HD)but the effectiveness of clearance depends on drug characteristics including molecular weight, protein binding, volume of distribution and water solubility. The effectiveness of HD in clearing endogenous insulin has not been well studied. We present a case of refractory hypoglycemia in a patient with ESRD, which was likely due to ciprofloxacin (cipro)-induced insulin release that was successfully managed with HD.

Case Description: A 77 year old man with ESRD receiving chronic HD and no previous history of diabetes, was admitted for management after he pulled out his tunneled HD catheter. The patient had HCV-induced cirrhosis and had been receiving outpatient cipro for spontaneous bacterial peritonitis prophylaxis. Initial electrolytes did not warrant urgent HD so was admitted to medical floor pending new HD catheter placement. During first several days after admission, the patient had persistently low blood glucose (BG) despite not receiving any hypoglycemic medications and receiving continuous infusion of dextrose solution and repeated boluses of 50% dextrose. Prior to receiving HD, serum insulin was elevated at 42 miU/ml and 148 miU/ml despite hypoglycemia and c-peptide was >40ng/ml consistent with excessive endogenous insulin secretion. The patient was suspected to have cipro-induced hyperinsulinemia. Emergently HD was performed to

increase clearance of cipro and insulin. After 1 HD session, insulin level decreased to 14.6 with improved BG levels. The patient was subsequently managed on octreotide with stable BG levels without further IV dextrose administration.

Discussion: Fluoroquinolones have been associated with hypoglycemia in diabetic and non-diabetic persons. Animal studies have suggested fluoroquinolones can block the ATP sensitive K+ channels in B-cells and increase the insulin secretion. Although our patient received his chronic dose of cipro (250mg daily), it is possible that lack dialysis for several days may have led to accumulation of cipro. The effect of HD on immune reactive insulin (IRI) was evaluated by Masanori et-al, in diabetic and non-diabetic patients. Analysis of pre and post-dialyzer samples revealed evidence of significant HD clearance of endogenous insulin. It is therefore likely that HD reduced insulin in our patient by reducing cipro-induced endogenous insulin secretion and via clearance of insulin.

PO1217

Low-Sodium Home-Delivered Meals Reduce Thirst and Xerostomia in Patients on Hemodialysis

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Background: Hemodialysis (HD) patients are often advised to restrict dietary sodium and fluid. Thirst and xerostomia contribute to non-adherence with fluid restricted diets resulting in fluid retention and chronic volume overload. Dietary sodium restriction may reduce thirst and xerostomia, which may, in turn, reduce fluid intake and retention. The purpose of the study was to determine if 4-weeks of low-sodium home-delivered meals reduces HD patient's subjective thirst and xerostomia.

Methods: Twelve HD patients had 3 low sodium meals/day (Mom Meals, Inc) delivered to their homes for 4 weeks. On average they were on 17 medicines among which 7 (Mean) had prior evidence to induce xerostomia. Subjective thirst and xerostomia were measured at three time points: baseline (BL), after 4 weeks of low sodium meals (INT), and 4 weeks post-meals (POST[SAA1]). Thirst was measured using the dialysis thirst inventory scale (DTI) that had 7 domains describing thirst, and numerical rating scale for thirst (NRS-T) while xerostomia was measured with a numerical rating scale for dry mouth (NRS-X) and the xerostomia inventory scale (XI) that had 11 domains describing dry mouth symptoms.

Results: Participant's mean thirst during the day, thirst after HD, thirst's influence on social life, dry mouth feeling, total XI, NRS-T, NRS-X scores were significantly lower during INT compared to BL (Mean±SD scores from BL to INT: 3.1±1 to 2±1; 3.5±1 to 2.2±1; 2±2 to 1.3±0.9; 2.9±1 to 1.9±0.8 on the scale of 1-5; 28.5±12 to 19.3± 9 on the scale of 1-55; 6±3 to 2.8±2 and 5.5±3 to 3.1±2 on the scale of 0-10, respectfully; $p<0.05$). The score of thirst's influence on social life and NRS-T were significantly higher in POST compared to INT (Mean±SD scores from INT to POST: 1.3±0.9 to 1.7±1; 2.8±2 to 4.5±2.6; $p<0.05$). NRS-T is significantly lower in POST compared to BL (Mean±SD scores from BL to POST: 6±3 to 4.5±2.6; $p<0.05$)

Conclusions: Multiple domains of subjective thirst and xerostomia decreased after 4 weeks of home-delivered low sodium meal consumption but generally returned close to baseline 4 weeks after cessation of the meal delivery. The feasibility and efficacy of long-term meal provision for reducing thirst, xerostomia, and chronic volume overload need to be further evaluated in future studies.

PO1218

Survival Outcomes in Patients with Advanced CKD Who Opt for Dialysis Treatment or Conservative Care: A Systematic Review and Meta-Analysis

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Background: Non-dialytic conservative care (CC) has been proposed as a viable treatment option for end-stage kidney disease, alternate to dialysis. This systematic review aims to compare survival outcomes on survival in dialysis and conservative care treatment pathways.

Methods: PubMed, Embase, Cochrane, CINAHL Plus and PsycINFO were searched from origin up to October 1st 2019 for studies comparing survival outcomes among patients choosing dialysis treatment or CC. Unadjusted survival for patients choosing dialysis versus CC was derived from Kaplan Meier curves. Meta-analysis was performed on outcomes of studies with limited clinical heterogeneity.

Results: From 6,126 citations, 21 observational cohort studies were included covering 20,212 adult patients. Studies varied in study design, target group, inclusion criteria (e.g. varying age groups), and starting point of survival analysis, and were receptive for selection bias and confounding. Patients opting for CC were in general older and had more comorbid conditions than patients who chose for dialysis treatment. Unadjusted median survival (reported in 16 studies) ranged from 8-67 months among patients who chose for dialysis and from 6-31 months in the CC group. Unadjusted one year survival (N=18 studies) ranged from 72% to 100% in patients choosing dialysis, and from 31% to 88% in patients choosing CC. Meta-analysis of studies (N=12) reporting survival adjusted for age, sex, and/or comorbid conditions, showed a pooled adjusted hazard ratio for death of 0.49 (95% CI 0.40-0.58) for patients choosing dialysis compared to CC. Survival benefit in patients choosing dialysis with severe comorbidities was highly reduced.

Conclusions: Observational studies, whilst heterogenous, suggest that patients who choose dialysis live twice as long as patients who opt for CC. Severe comorbidity is suggested to substantially reduce the survival benefit of dialysis compared to CC. Due to (high risk of) confounding, results should be interpreted cautiously and cannot be translated to individual patients. Future prospective data, using clear definitions and stratified for subpopulations, are critical to estimate relative survival benefit in clinical practice.

Funding: Private Foundation Support

PO1219

End-of-Life Care Experiences and Beliefs Among African American Hemodialysis Patients

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Background: Prior work has shown that African Americans with end-stage renal disease (ESRD) are less likely than their White counterparts to have discussed end-of-life (EOL) care preferences with their providers, and more likely to prefer life-extending treatments. We sought to determine what demographic and institutional factors are associated with African American ESRD patients' experiences and beliefs on EOL care

Methods: Self-identifying African American adults receiving hemodialysis at three university-affiliated dialysis units completed surveys about their prior EOL care planning and preferences in various EOL situations. We used bivariable and multivariable logistic regression to analyze the association between EOL care views and several covariates including age, gender, education level, income, insurance, and previous experiences with EOL care discussions.

Results: From June to September 2019, 101 patients completed the study. The mean age was 58.7 years, 52% identified as female, and 42% have been on dialysis for >5 years. Almost 69% of patients reported they had never discussed EOL care with any healthcare provider; 95% (64/69) reported their providers never initiated EOL care conversations with them, though 37% desired them. There was no association between having past EOL care discussions and any clinical or demographic covariates. The proportion agreeing that at the EOL if was wrong to "withhold treatments," 2) "withdraw treatments," and 3) "to withhold nutrition and fluids" were 78%, 71%, and 63%, respectively. Previous experience with EOL care discussions with either family or healthcare providers was significantly associated with a decreased likelihood to prefer life-extending treatments at EOL ($p<0.05$).

Conclusions: A majority of African American patients with ESRD reported never having any EOL care discussions. Most of these patients are open to speaking about EOL care with their healthcare providers but are unwilling to initiate discussions. Furthermore, past experience with EOL care discussions with either family or medical team is associated with a decreased preference for aggressive life-extending care. Despite provider and patient discomfort with EOL care discussions, healthcare providers should address EOL care with African American patients with ESRD to identity how medical care at EOL can be more congruent with their values and needs.

Funding: Private Foundation Support

PO1220

Impact of a Palliative Hemodialysis on Quality Standards and Hospice Utilization

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Background: Minimal data exists regarding effect of palliative dialysis on clinical outcomes and quality measure. Frail, elderly patients may find thrice weekly, 3-5 hour hemodialysis treatments burdensome. Numerous barriers exist to providing palliative dialysis, including quality standards set by the ESRD Quality Incentive Program (QIP). This study shows the impact of reduction in dialysis frequency and time on quality standards and hospice utilization in the seriously ill elderly.

Methods: A retrospective chart review was performed on four deceased patients who received palliative dialysis in one ambulatory dialysis center. Quality standards reviewed included: dialysis adequacy (Kt/V), metabolic control, nutrition, hemoglobin and ultrafiltration rate. Clinical outcomes were also reviewed.

Results: All four patients were elderly with reduced functionality, heavy symptom burden and difficulty tolerating regular hemodialysis sessions. Patients were decreased to three hour hemodialysis sessions twice weekly. Despite decreased treatment time and frequency, most quality measures did not differ from baseline. Duration of palliative dialysis ranged from 2-11 weeks. Most patients tolerated palliative dialysis, remained free of hospitalization, successfully transitioned to hospice and did not experience serious clinical issues. Lack of negative impact on quality measurements were attributed to patients poor oral intake, loss of body mass and minimal weight gains between dialysis sessions. Patients were observed to have a better quality of life and better utilization of time with family.

Conclusions: Palliative care, incorporating the patient and family, appears to be a good option for patients and families who are not ready to withdraw from dialysis. Palliative dialysis allows patients a slower transition to end-of-life care with more support and proper preparation in line with patients' wishes. In addition, with our recent experiences with covid 19 infections, this practice might be a possible option for someone with serious illness, hoping to avoid unwanted hospitalization and aggressive medical treatment. Goals of care conversation, timely plan of care for transition of care and close monitoring of patients are essential for palliative dialysis.

PO1221

Surprise Question: A Mortality Predictor in Hemodialysis Patients?

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Background: Surprise question (SQ), used in Palliative Care (PC) and Oncology, has already been tested to assess prognosis in several chronic diseases. In Portugal, as worldwide, an elderly and fragile hemodialysis (HD) population has been emerging. Tools to screen patients who might benefit from end of life care would be useful. The present study aims to test SQ mortality prediction value in a Portuguese cohort of HD patients, answered by nephrologists and nurses. The study ran between November 2018 and November 2019.

Methods: We design an observational prospective study. All patients on regular HD for more than 3 months were included. Experienced nephrologists and dialysis nurses, but without PC training, answered SQ at the beginning of the follow-up. We collected demographic, clinical and analytical data. At the end of follow-up, we analyzed evolution during follow-up and survival status.

Results: We included 194 patients, median age of 69.9 y-o. Median age-adjusted Charlson Comorbidity Index (aCCI) was 6 (5-8). Table 1. After one year of follow-up 22 (11.3%) patients have died. Nephrologist and nurse SQ were both good predictors for mortality within one year, with an OR 7.44 (IC95% 2.92-20.74) and 8.47 (IC95% 3.00-30.34) respectively (both with a p-value <0.001). Institutionalization, aCCI, albuminemia and hospital admissions during follow-up also seems to be important predictors. Table 2. With multivariate analysis, SQ for nephrologists and nurses are no longer statistically significant: OR 1.25 (IC95% 0.31-5.11) and 3.09 (IC95% 0.81-11.86), respectively.

Conclusions: Our results showed that SQ answered by nephrologist and nurse are not good mortality predictors, reflecting this method subjectivity and the lack of PC training. Probably, SQ should be reserved to professionals with PC training, a profound gap in nephrologists training in Portugal.

Characteristic		Total patients (n=194)
	Age (years)	69.9 (58.4-77.8)
	Male Gender	122 (62.9%)
Race	Caucasian	177 (91.2%)
	Black	12 (6.2%)
	Other	5 (2.6%)
	Institutionalization	17 (8.8%)
Social support	Household	133 (68.6%)
	Single-handed	44 (22.7%)
	Elderly home	17 (8.8%)
Education	Compulsory education	156 (80.4%)
	Illiterate	21 (10.8%)
	High	17 (8.8%)
Kidney disease etiology	Indeterminate	37 (19.1%)
	Diabetes *Mellitus*	35 (18.0%)
	Tubulo-interstitial disease	29 (14.9%)
	Hypertension	26 (13.4%)
	Glomerular disease	21 (10.8%)
	Hereditary cystic disease	20 (10.3%)
	Others	26 (13.5%)
	aCCI	6 (5-8)
	Peripheric arterial disease	68 (35.1%)
	Diabetes Mellitus	67 (34.5%)
	Total RRT time (months)	117 (51.6-272.4)
	Candidate to kidney transplant	24 (12.4%)
	Albumin (g/dL)	4.1 (3.8-4.3)
	PTHi (ng/dL)	380.5 (200.1-668.1)
	Hemoglobin (g/dL)	11.1 ±1.3
	Ferritine (ug/L)	514.6 (368.1-648.5)
	Kt/V	1.7 ± 0.3
	Dry weight (Kg)	65.2 (57.6-75.0)
	HD adherence	183 (94.8%)
	Catheter (beginning of follow-up)	18 (9.3%)
	Need for VA interventions (during follow-up)	57 (29.4%)
	Hospital admissions (during follow-up)	38 (19.6%)

PO1222

Code Status Variability in a Regional Hemodialysis Program

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Background: Patients with end stage kidney disease (ESKD) treated with hemodialysis (HD) have poor life expectancy and may not benefit from aggressive measures at the end of life. Previous studies suggest variability in Do Not Resuscitate (DNR) orders in patients treatd with HD but they are limited by missing code statuses and inability to adjust for demographics. In our regional HD program, with complete code status ascertainment that is updated annually, our objective was to examine DNR variability while accounting for demographic factors.

Methods: We conducted a cross-sectional study of DNR prevalence in October 2019 in patients treated with in-centre HD in a regional program, which consists of a main centre and six smaller centers. Patients are transferred to smaller centres based on location. Each centre has an attending nephrologist who reviews code status yearly with every patient. Unadjusted DNR prevalance are compared using the Chi-square test and multiple logistic regression is used to control for covariates (age, sex, race, dialysis vintage, HD unit).

Results: We included 374 patients, 193 (52%) from the main centre and 181 (48%) from its satelite units. Mean age of patients is 67.2±14.3 years, 52% male, 87% Caucasian, and dialysis vintage 5.2±5.5 years. Code status was full code in 78% and DNR in 22% with significant variation across sites (range of 9% to 44%, p = 0.02) (Figure 1). Variation remained significant (p = 0.03) after controlling for covariates.

Conclusions: Variability in code status at different HD centres in our regional program persisted despite accounting for differences in patient age, sex, race, and HD vintage. This finding suggests factors related to the HD centre may affect code status decisions, such as local culture, question phrasing, and views of the treating nephrologist. Future studies are planned to determine if a standardized approach to discussing code status would normalize rates.

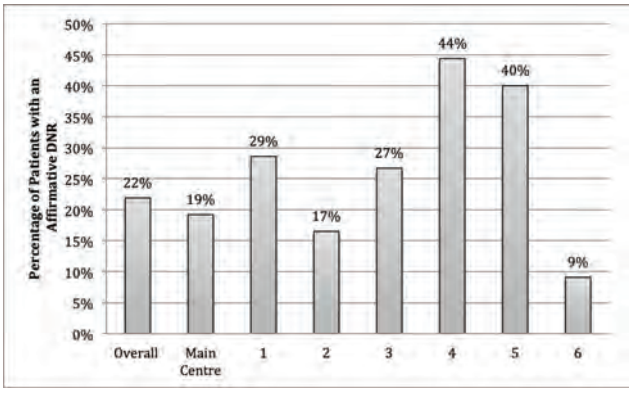


Figure 1: Unadjusted DNR prevalence in hemodialysis units across a regional dialysis program.

PO1223

Polypharmacy and Frailty Among Hemodialysis Patients

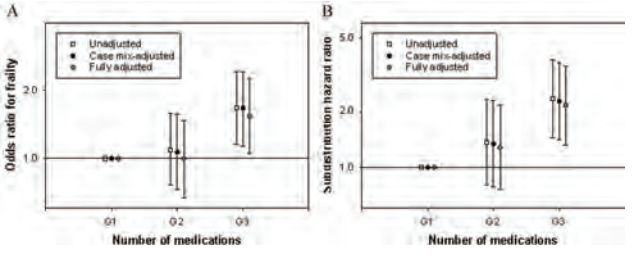
Hiroshi Kimura, John Sy, Connie Rhee, Elani Streja, Kamyar Kalantar-Zadeh. *Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA.*

Background: Most patients undergoing maintenance dialysis have multiple comorbidities, most of which require long term medication management and can inevitably lead to polypharmacy. Frailty is also highly prevalent among dialysis patients and has been associated with poor outcomes. With higher frailty and comorbidity rates among dialysis patients, it remains unclear if polypharmacy is still associated with the incidence of frailty among dialysis patients. The aim of this study was to examine the independent association between polypharmacy and frailty among hemodialysis patients.

Methods: We examined 337 patients enrolled in the ACTIVE/ADIPOSE dialysis cohort study. The number of prescribed medications and frailty were assessed at baseline, 12, and 24 months. We used logistic regression with generalized estimating equations to model the association of the number of medications and frailty over time; competing-risks regression to assess incidence of frailty.

Results: The mean number of medications was 10 ± 5, and 94 patients (28%) were frail at baseline. Patients taking greater than 11 medications showed higher odds for frailty as compared with patients taking less than 8 medications (OR 1.54, 95% CI 1.05-2.26). During two years of follow-up, 87 patients developed frailty among the non-frail patients at baseline. Compared with patients taking less than 8 medications, the incidence of frailty was approximately 2-fold in those taking greater than 11 medications (sub-distribution hazard ratio [SHR] 2.15, 95% CI 1.32-3.48).

Conclusions: Using a higher number of medications was associated with frailty and the incidence of frailty among hemodialysis patients. Minimizing polypharmacy may reduce the incidence and prevalence of frailty among dialysis patients.



PO1224

Optimal Patient Positioning for Chest Compressions in Dialysis Clinics: A Randomized Cross-Over Simulation Study

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Background: Sudden cardiac arrest is the leading cause of death for hemodialysis patients, and often occurs during treatment in hemodialysis units. Resuscitation guidelines emphasize the need for rapid delivery of effective chest compressions to improve survival. How different methods of patient positioning (in the dialysis chair or on the floor) affects chest compression quality is unknown.

Methods: This was a prospective randomized cross-over study to assess the quality of chest compressions performed on a simulation manikin(Laerdal SimMan3G). Dialysis staff were recruited from a single center and asked to perform 2 minutes of compressions on the manikin positioned: 1) on a gurney with a code-cart backboard (baseline); 2) on the floor; 3) in a reclined dialysis chair; and 4) in a reclined dialysis chair with a backboard placed underneath. The sequence of manikin positions was randomized to reduce carryover effects and assessments were conducted ≥48 hours apart to reduce participant fatigue. Mean compression depth, %compressions at appropriate depth, %compressions fully released and %compressions at adequate rate were assessed for each position and for each participant. Paired sample T-tests were performed to assess the mean differences in compression measures between positions and baseline.

Results: 13 dialysis staff members including 7 RNs, 3 MITs and 3 providers participated in the study. Compared to baseline, mean compression depth (-6.5 mm) and % compressions fully released (-26%) were significantly worse for compressions performed in the dialysis chair, and quality reductions persisted even when a backboard was utilized in the dialysis chair (see Figure 1). No significant differences in compression quality measures were observed with manikin positioning on the floor compared to baseline.

Conclusions: Performing CPR in a reclining dialysis chair results in significant reductions in CPR quality. This should be considered in developing dialysis-specific CPR protocols, and further studies should investigate the relative merits of different patient positioning options for optimal CPR delivery.

Funding: NIDDK Support

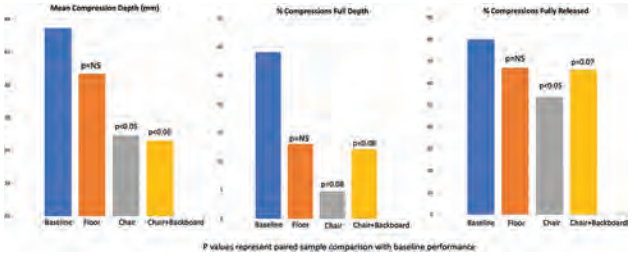

Figure 1: Summary of Results

PO1225

The Plasma Factor Beta-2 Microglobulin Drives Cognitive Impairment in ESRD

Eva Czirr, David Le, Cindy F. Yang, Shreya Chand, Jyotasana Gulati, Scott C. Lohr, Sakura Minami. *Alkahest Inc, San Carlos, CA.*

Background: Our goal is to decode changes in the plasma proteome in age and disease to identify novel therapeutic targets. We and others have shown that administration of aged human plasma in young immunodeficient mice results in impaired neurogenesis and cognition. We are now extending these findings to plasma from end-stage renal disease (ESRD) subjects undergoing hemodialysis (HD). The prevalence of chronic kidney disease increases with age, and hemodialysis patients have a high incidence of cognitive impairment. The causes for this cognitive impairment are not fully understood and we hypothesize that plasma proteins, specifically beta-2 microglobulin (b2M) are a contributing factor. B2M has been identified as a detrimental pro-aging factor in mice, however aging increases b2M levels moderately by about 1.5 – 2-fold, while they are elevated up to 80-fold in ESRD-HD.

Methods: Plasma was collected from healthy controls and matched ESRD-HD subjects. HD plasma was depleted of b2M by AKST1210, a b2M removal device. Proteomic analysis was performed using affinity-based and mass spectrometry platforms. Plasma was administered IV into young immunodeficient NSG (NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ) mice, followed by behavioral testing, and histological and molecular analysis. B2M was administered IP to wild-type (WT; C57BL/6) mice, followed by similar analyses.

Results: Injection of ESRD-HD plasma into young NSG mice resulted in cognitive impairment and molecular changes in the brain. Proteomic analysis of the plasma revealed many changes, with b2M as one of the most elevated proteins. We found that peripheral b2M injections lead to concentration dependent changes in cognition, neurogenesis, and synapse density. When we depleted plasma from ESRD-HD subjects using AKST1210 b2M levels were highly reduced and the proteomic profile was shifted towards healthy control plasma. Injection of depleted plasma into young NSG mice rescued some of the detrimental changes caused by undepleted plasma suggesting that removal of b2M has beneficial effects.

Conclusions: Taken together, our data shows that plasma-derived factors can impact cognition and suggests that accumulation of detrimental factors such as b2M contributes to the high incidence of cognitive deficits in ESRD-HD subjects.

Funding: Commercial Support - Alkahest Inc.

PO1226

Association Among Iron, Coronary Artery Calcification, and Mortality in Hemodialysis Patients

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Background: Coronary artery calcification (CAC) is recognized as one of the main causes of cardiovascular disease and death in hemodialysis (HD) patients. It had been suggested that iron may be related to vascular calcification (Balla et al. Pharmaceuticals. 2019;12:96). This study aimed to investigate the association among iron, CAC, and mortality in HD patients.

Methods: This study included 173 HD patients. Clinical data and Agatston's coronary artery calcification score (CACS) were obtained at baseline. Two groups comprised patients with CACS ≥400 (n=109) and patients with CACS <400 (n=64). Logistic regression analyses for CACS ≥400 and Kaplan-Meier survival and Cox proportional hazard analyses were conducted.

Results: The median (interquartile range) age and dialysis vintage among all subjects were 67 (60–75) years and 73 (37–138) months, respectively. Serum iron (Fe) and transferrin saturation (TSAT) levels were significantly lower, but age, dialysis vintage, C-reactive protein (CRP), and albumin-adjusted serum calcium (Ca) levels were significantly higher in patients with CACS ≥400 than in patients with CACS <400 ($P<0.05$). No significant differences in the dosage of phosphate binders, active vitamin D, cinacalcet, and iron were observed. In the univariate logistic regression analysis, CACS ≥400 had a significant association with TSAT ≥20%, Fe ≥80 μg/dL, age, and dialysis vintage ($P<0.05$). In the subsequent multivariate analysis, including all variables that showed significance in the univariate analysis, excluding Fe ≥80 μg/dL, and well-known risk factors for coronary artery calcification in HD patients (diabetes mellitus, Ca, phosphate, and CRP), TSAT ≥20% remained independently and significantly associated with CACS ≥400 (odds ratio 0.44, $P<0.05$). HD patients with Fe ≥80 μg/dL showed significantly higher 5-year survival. However, patients with serum ferritin ≥36.6 ng/mL (median ferritin value in this study) showed significantly lower 5-year survival than patients with ferritin <36.6 ng/mL, and ferritin ≥36.6 ng/mL was a significant predictor of 5-year all-cause mortality in HD patients (hazard ratio: 2.71, $P<0.05$).

Conclusions: In HD patients, there is an association among iron, CAC, and mortality, and TSAT ≥20% was found to be an independent and significant factor in the prevention of CACS ≥400.

Funding: Private Foundation Support

PO1227

Valvular Heart Disease in Prevalent Haemodialysis Patients

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Background: Valvular heart disease is observed in patients with Chronic Kidney Disease. Previous large studies found a prevalence rate of 14%-16% of valvular heart disease (VHD) in haemodialysis patients *(2018 USRDS; Hickson et al., 2016)*. KDIGO consensus group identified several evidence gaps where research is necessary in order to improve our understanding of diagnosis and management of VHD. The aim of our study is to assess the burden of VHD in a haemodialysis cohort in one center in the UK.

Methods: A single-center; retrospective, cross-sectional study of echocardiographic findings in prevalent haemodialysis patients. Patients were considered to have VHD if they had significant aortic or mitral valve disease (AVD, MVD) based on standard echocardiographic criteria. Medical records were reviewed for clinical information.

Results: This study included 425 haemodialysis recipients. Mean age was 61 years, (*SD: 14.96*). The cohort was predominantly male (*59.3%*). The mean BMI was 27.69 (*SD: 5.99*). 37.1% had a history of smoking. The median renal replacement therapy vintage was 3.19 years [*IQR: 1.99, 6.33*], with median haemodialysis vintage of 2.93 years [*IQR: 1.76, 5*]. 83% of patients had hypertension, 41% had diabetes, 29% had coronary artery disease (CAD) and 13% had a history of congestive cardiac failure (CCF). Atrial Fibrillation (AF) was present in 11.5%. 34% (n=143) had evidence of VHD. 18% had evidence of AVD (n=78); Aortic Regurgitation in 11%, and Aortic Stenosis in 7% of patients. 20% of patients (n=85) had MVD with Mitral Regurgitation in 18% of patients and Mitral Stenosis in 0.7% (n=3). 5% of patients had cardiothoracic intervention (n=21) for VHD. Compared to patients who had no evidence of VHD, those with VHD were significantly older ($p<0.001$), had lower relative BMI ($p=0.001$), and had co-existing AF, CAD and CCF ($p<0.05$). These patients had a significantly longer dialysis vintage ($p=0.001$). Patients, who had VHD, had a tendency to higher serum calcium, although this did not reach statistical significance ($p=0.057$). Similarly, diabetes was also higher in the non-VHD cohort (*44.3% vs 34.3%, $p=0.059$*).

Conclusions: 34% of patients had significant VHD, higher than the previously published figures. The lower prevalence of diabetes in the VHD cohort makes the metabolic milieu an additional important risk factor in VHD. Timely echocardiographic studies are essential to identify patients with significant VHD.

PO1228

The Effect of Intradialytic Potassium and Magnesium Fluctuations on Cardiovascular Functioning in ESRD Patients Undergoing In-Center Hemodialysis

Andy Chuu,[1] Gonzalo Matzumura Umemoto,[1] Michael I. Rauchman,[2,1] Frank J. O Brien.[1] *[1]Washington University in Saint Louis, Saint Louis, MO; [2]Saint Louis VA Medical Center John Cochran Division, Saint Louis, MO.*

Background: Patients with ESRD receiving in-center hemodialysis (HD) have an age-adjusted rate of mortality 4 times the general population. Increased mortality has been attributed to fatal arrhythmias. Mechanisms and risk factors for this are unknown. It has been postulated that changes in serum levels of Potassium(K)/Magnesium(Mg) with HD contribute to arrhythmia generation. Limited data is available to guide personalization of K prescription of HD to reduce this risk. No data exists describing the serum changes in Mg pre-, intra-, and post-HD. We examine the correlation between electrolyte fluctuations, arrhythmia generation, and heart rate variability (HRV) in ESRD patients undergoing in-center HD.

Methods: Single center, prospective, cross-sectional pilot study. 25 patients enrolled to achieve an 80% power. Demographic data, dialysis vintage, and HD prescription were recorded. Arrhythmia data was collected by placement of Holter monitor prior to 1st weekly HD session and recorded continuously for 5 days ending at completion of 3rd weekly HD session. Serum samples were obtained at time intervals 30, 60, 90, and 120 minutes during 1st weekly HD session for electrolytes. Pre and Post HD serum electrolyte analysis occurred during all 3 treatments. Associations were examined by count regression utilizing Poisson or negative binomial methods.

Results: 25 patients were included in data analysis. Mean age 63 and primarily African American (73%). 73% of individuals were dialyzed utilizing 2mmol/L. Ectopy data and serum potassium / magnesium data are summarized in Table 1.

Conclusions: There is a trend towards increased ectopy (particularly on HD day 1) and decreased HRV on HD days. There is a trend towards hypo-K post-HD after HD sessions 2 and 3. Serum Mg levels remained stable pre and post HD throughout all HD sessions. Data derived in this study will be utilized to guide a larger future study with the goal towards personalized HD treatments.

Results

	# Hypokalemia (n)	Mean Pre K (mmol/L)(std)	Mean Post K (mmol/L)(std)	Mean Pre Mg (mmol/L)(std)	Mean Post Mg (mmol/L)(std)
HD Session 1	7	4.7 (0.6)	3.4 (0.3)	2.3 (0.3)	1.9 (0.2)
HD Session 2	10	4.7 (0.4)	3.3 (0.3)	2.3 (0.2)	1.9 (0.2)
HD Session 3	10	4.7 (0.5)	3.4 (0.3)	2.3 (0.2)	1.9 (0.2)
			HD Session 1	Interdialytic Days	HD Session 2 & 3 (mean)
Mean Daily Ectopic Beats			5781	2346	3630

PO1229

Human Factors Testing of the Quanta SC+ Haemodialysis System: Demonstrating Ease of Use with Minimal Upfront Training in Health Care Practitioners and Patients

Paul Komenda, John Milad, Kathryn Compton. *Quanta Dialysis Technologies, Alcester, United Kingdom.*

Background: Quanta Dialysis Technologies has developed a compact, powerful personal haemodialysis system intended for home and self-care use designed in collaboration with patients and healthcare practitioners. Human factors testing is necessary to demonstrate ease of use with minimal up-front training.

Methods: In compliance with FDA guidance and EU standards, the user interface of the system was evaluated through human factors testing to assess the safe and effective use of SC+. This included a series of user-based tasks whereby representative users independently setup SC+ into a simulated treatment, managed alarms to resolution and external SC+ cleaning/disinfection. All participants received an introduction to SC+ and completed a competency sign off at the end of training. 15 healthcare professionals (6 renal nurses, 8 dialysis technicians, 1 patient care technician) received up to 4 hours of structured training followed by a 1-day learning decay period. In addition, 10 lay users (8 dialysis patients, 2 caregivers) received between 5.5 and 7.5 hours training followed by a 2-day learning decay period.

Results: Between the two user groups, there were a total of 8,110 opportunities for use errors to occur. Despite minimal training and representative learning decay, only 4 significant use events were observed requiring some user manual enhancements. Other use errors captured were minor or could not be mitigated further due to clinical practices and shared inherent risks across all haemodialysis systems.

Conclusions: The results of the human factors testing demonstrated that healthcare practitioners, patients and caregivers successfully operated SC+ independently with a high level of use safety, despite minimal training and learning decay. The SC+ user interface is optimised for safe and effective use under FDA guidance and EU standards.

Funding: Commercial Support - Quanta Dialysis Technologies

PO1230

Inpatient Dialysis Provider Type and Duration of Hospital Admissions of Dialysis Patients

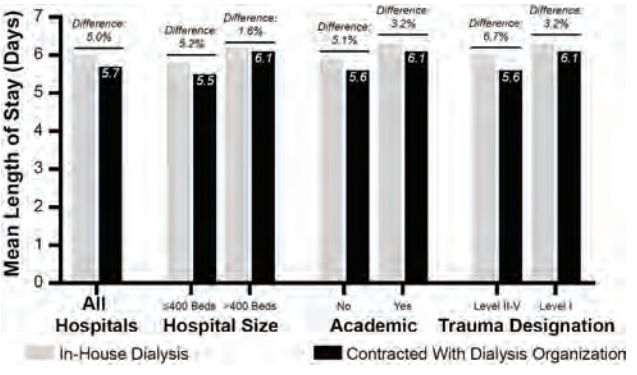
Joshua W. Morrison, Daniel Liu, David L. Mahoney, Jeffrey A. Giullian. *DaVita Inc, Denver, CO.*

Background: Inpatient dialysis treatments may be performed by hospital staff or by a contracted dialysis provider. In this study, we compared duration of hospitalizations of dialysis patients who were admitted to hospitals performing in-house dialysis to that of patients who were admitted to hospitals contracting with a dialysis provider.

Methods: Data for this analysis were derived from the electronic medical records of a large dialysis organization. We identified patients who were hospitalized between Jan 2017 and Sept 2019. Length of stay was compared for patients who were admitted to hospitals performing dialysis in-house versus patients who were admitted to hospitals that contracted with the dialysis organization.

Results: During the study period, we identified 155,458 hospitalizations among 64,662 patients at 572 hospitals in which dialysis was performed by in-house staff. There were 226,059 hospitalizations among 87,213 patients at 797 hospitals in which dialysis was performed by the dialysis organization. There were no meaningful differences in patient characteristics or reasons for admission among patients admitted to hospitals performing dialysis in-house compared to those of patients admitted to hospitals contracting with the dialysis organization. The mean length of stay for patients admitted to hospitals providing dialysis in-house was 6.0 days versus 5.7 days for patients admitted to hospitals contracting with the dialysis organization, a difference of 5.0%. We made similar observations for hospitals with ≤400 beds, hospitals that were not affiliated with an academic medical center, and hospitals designated trauma levels II to V. These differences were attenuated at hospitals with >400 beds, academic medical centers, and level I trauma hospitals.

Conclusions: These results suggest that use of a contracted dialysis organization may shorten the length of stay for patients who require dialysis during hospital admissions and this trend was more pronounced in smaller, non–university-affiliated hospitals.



PO1231

The Impact of CRRT Modality on Filter Life

Lewis Mann, Iiro Honkanen, Rebecca L. Hegeman, Chou-Long Huang, Prerna Kumar, Swe Zin Mar Winhtutoo, Christie P. Thomas, Melissa L. Swee, Benjamin R. Griffin. *University of Iowa, Iowa City, IA.*

Background: Increasing CRRT filter lifespan would save money, decrease iatrogenic blood loss, increase the time CRRT is actively running, and waste less nursing time. Filter clotting is a common reason for filter loss that can potentially be reduced. CRRT can be performed using convective clearance as in CVVH or diffusive clearance as in CVVHD. Whether convection or diffusion prolongs filter life over the other is unknown, but there are plausible arguments for both. CVVHD has no significant hemoconcentration within the circuit, whereas CVVH is subject to hemoconcentration as fluid is removed across the filter. However, pre-filter CVVH results in hemodilution prior to entering the filter that may mitigate the effects of the filter hemoconcentration. We hypothesize that filter life is longer in patients treated with CVVHD than CVVH.

Methods: In this unblinded prospective randomized trial, patients are assigned to either pre-filter CVVH or CVVHD. The standard treatment protocol at the University of Iowa is to use citrate anticoagulation with a blood flow rate of 200 mL/min and a dose of 25 mL/kg/hr. Using a power of 0.8 and an alpha of 5%, and historical filter loss attributable to clotting of 60%, a total of 1,010 filters are needed to show a hazard ratio of at least 1.3 for filter loss. The primary outcome is average filter life, and secondary outcomes are mortality, intensive care unit LOS, hospital LOS, and renal recovery.

Results: Beginning March 25, 2020, we have enrolled 30 patients using a total of 90 filters (Table 1). The average filter life in CVVH filters is 36.8 ± 26.8, compared to 37.0 ± 31.9 hours in CVVHD filters (p=NS).

Conclusions: Data from 2 months of a planned 12-month prospective study comparing filter life in CVVH vs CVVHD shows no significant difference in filter life.

Table 1: Patient characteristics

	CVVH (n=15)	CVVHD (n=15)	p value
Age	58.7 +/- 16.5	54.3 +/- 14.8	0.45
Male (%)	9 (60%)	9 (60%)	1.00
Caucasian (%)	9 (60%)	9 (60%)	0.30
Hispanic (%)	4 (27%)	4 (27%)	0.30
Black (%)	2 (13%)	1 (6.7%)	0.30
SOFA	11.5 +/- 2.12	9.1 +/- 2.67	0.011
COVID Positive (%)	3 (20%)	4 (27%)	0.66
Diabetes (%)	7 (47%)	9 (60%)	0.48
CAD / HF (%)	5 (33%)	3 (20%)	0.43

PO1232

Acute Dialysis in a High-Dependency Unit: A New Service with a Long-Term Legacy

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Background: Continuous Renal Replacement Therapy (CRRT) in the intensive care unit (ICU) was stretched to the limit during the COVID-19 pandemic. COVID-19 was commonly associated with dialysis requiring Acute Kidney Injury (AKI) in patients admitted to ICU, in addition to chronic dialysis patients with COVID-19 requiring ICU admission. During the peak of COVID-19 there was a critical national shortage of consumables and dialysis fluids In the United Kingdom (UK) required for CRRT in ICU. The ICU service at Queens hospital, Romford, UK was no exception with the need to develop a viable urgent alternative therapy. A modified prolonged intermittent haemodialysis treatment 4-8 hours every day in selected patients was set up in the high dependency unit. This method required the installation of additional equipment and staff training.

Methods: During the peak of the COVID-19 pandemic, 5 beds in HDU were created with mobile reverse osmosis (RO) units to provide acute dialysis. Within 10 days of service approval, the dedicated area in HDU was equipped with all necessary plumbing work, machines and consumables. In the interim nursing training was provided by the senior dialysis nurse from the satellite dialysis unit based in the hospital who also supervised all sessions of dialysis 6 days a week. Patients selected were relatively stable with or without the need for assisted ventilation and inotrope requirement with Noradrenaline up to 0.6mcg/kg/min. Dialysis treatmeant was provided 6 days week for 4-8 hours per session.

Results: 12 COVID-19 patients received haemodialysis in the newly established HDU dialysis unit between 30th April to 30th May 2020. 5 had AKI associated with COVID-19 and 7 COVID-19 patients were on chronic dialysis. Total 72 sessions were provided (range 1- 19 sessions per patient). Of the 12 patients 4 died, of whom 2 with AKI and 2 were on chronic dialysis. Of remaining 8, 5 patients were on chronic haemodialysis while 2 AKI patients continue to require haemodialysis and one became dialysis independent.

Conclusions: Prolonged intermittent renal replacement therapy in HDU was a viable alternative during the COVID-19 pandemic. The process was safe and manageable. The resources acquired during COVID-19 pandemic can be utilised in managing AKI and acutely ill chronic dialysis patients in a hospital where this service was not available before the pandemic.

PO1233

Predictors of 30-Day Hospital Readmission Among Minority ESRD Patients Receiving Maintenance Hemodialysis

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Background: End-stage renal disease (ESRD) is one of the most prominent disparities as racial/ethnic minorities are 1.5-4 times more likely than others to develop ESRD. Among patients with ESRD receiving hemodialysis, more than 1/3 of hospital discharges are followed by a readmission within 30 days. These subsequent readmissions are associated with increased healthcare costs and poor health outcomes. Therefore, knowing the incidence and risk factors for readmission are crucial steps needed for necessary prevention. This retrospective study aims to identify predictors within inpatient and outpatient care that contribute to 30-day hospital readmissions among minority ESRD patients receiving maintenance hemodialysis within an outpatient dialysis center located in the District of Columbia.

Methods: Data from electronic medical records were taken for patients who have had an unplanned hospital admission between January 1, 2017 and August 31, 2019. Descriptive statistical analysis was conducted for all study variables. Univariate and multivariable logistic regression analyses with 30-day readmission as the dependent outcome were conducted to identify and assess predictors of 30-day readmissions.

Results: A total of 96 patients were included in the study. Among these patients, 49 (51%) had 30-day hospital readmission. Overall, patients were predominantly African American (86.5%), age between the age of 60-69 (29.2%), and with a diagnosis of hypertension (89.6%). A diagnosis of secondary hyperparathyroidism, serum calcium < 8.5mg/dL at time of discharge, and serum PTH < 150pg/mL at time of discharge were significantly associated with higher readmission rates in multivariable analyses ($p < 0.05$). Gender, race, a weekend discharge, and serum phosphate at time of discharge were not associated with 30-day readmission.

Conclusions: Overall, the study findings provide some insight into risk factors associated with 30-day readmissions in minority patients receiving maintenance hemodialysis. These findings suggest that secondary hyperparathyroidism and chronic kidney disease mineral bone disorder (CKD-MBD) markers predict readmissions. Identifying inpatient and outpatient strategies to mitigate risks and prevent readmissions may improve outcomes among this high-risk ESRD population.

PO1234

Role of Lung Ultrasonography to Predict Intradialytic Hypotension in ICU Patients

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Background: Lung ultrasonography has emerged as a valuable tool in the assessment of volume status in hemodialysis (HD) patients. A-line profile noted on lung ultrasonography denotes low wedge pressure while B-line profile is associated with hypervolemia. We hypothesized that patients with A-line profile are more likely to experience intradialytic hypotension (IDH).

Methods: We identified all patients admitted to the Medical ICU at two tertiary care facilities in the Northwell Health system between Jan 1st, 2016 and Sep 23rd, 2019 in whom hemodialysis was performed and a lung ultrasound was documented the same day. We manually reviewed clinician documentation and included patients whose lung ultrasound findings demonstrated A-line profile or B-line profile. Patients with other lung ultrasound findings were excluded. IDH was defined as a decrease in systolic BP by ≥20 mmHg with a failure to meet UF goal or increase in pressor requirement during HD or associated symptoms of hypotension. In total 105 dialysis treatments were reviewed, 78 were included for analysis. Northwell IRB exempted the study for full IRB review.

Results: There were 55 treatments with A-line profile and 23 treatments with B-line profile on POCUS. The incidence of IDH in a HD treatment with A-line and B-line profile was 50.9% and 21.7% respectively. 13 HD treatments with A-line profile and 1 with B-line profile had an increase in pressor requirement.

Conclusions: Lung ultrasonography provides a quick and effective means of assessing volume status. Our data suggest that IDH occurs more frequently in patients with A-line profile compared to those with B-line profile. Further research should focus on describing the relationship between lung ultrasound and IDH.

Lung US Finding	Number of treatments	Intradialytic Hypotension (%)	Mean Pre-HD Blood Pressure	Mean Dialysate Temperature (C)	Na Modeling (%)
A-Line Profile	55	50.9	133/67	36.5	7.3
B-Line Profile	23	21.7	142/68	36.4	13

PO1235

Relationship Between Cardiac Output (CO) and Estimated Upper Body Blood Flow (eUBBF) During Hemodialysis (HD)

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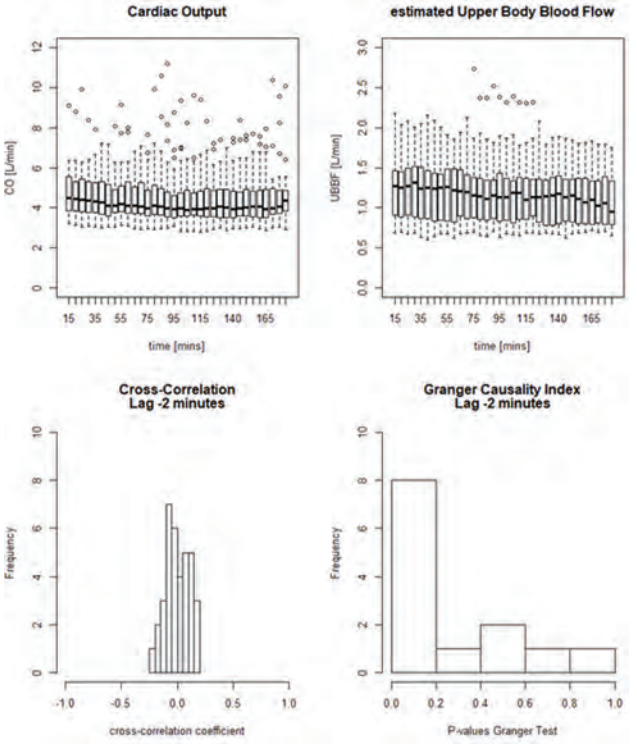
Background: Cardiopulmonary monitoring during HD could improve outcomes. Upper body oxygen consumption, arterial and central-venous oxygen saturation and hemoglobin concentration allows the calculation of eUBBF (Rosales 2019). We studied the association between eUBBF and CO during HD.

Methods: In patients with central-venous catheter we measured central-venous oxygen saturation and hemoglobin levels during HD using the Crit-Line Monitor (Fresenius Medical Care North America, Waltham, USA). We measured CO using the Task Force Monitor (CNSystems, Graz, Austria). We tested the time series for stationarity using the Dickey-Fuller test, employed differencing to make the time series stationary, analyzed the association between the time series using cross-correlations and Granger Causality test.

Results: We studied 13 patients (59±14 years, 5 (38%) male, 93±22 kg pre-dialysis weight 170±7 cm tall) during 34 hemodialyses. Averaged across all treatments, CO and UBBF were 4.7±1.0 and 1.3±0.4 L/min, respectively. CO showed a weak downward trend during hemodialysis. Cross-correlations showed no meaningful relationship between CO and eUBBF; Granger causality index was less than 20% in 8 treatments, albeit without clearly discernible patterns.

Conclusions: CO and eUBBF remained considerably stable during HD. Cross-correlations showed no significant relationships and Granger causality test suggests some form of a relationship which requires some further investigation. The clinical usefulness of eUBBF and future investigations will need to take additional parameters and dynamic relationships into account. **Figure 1:** Dynamic of CO and eUBBF flow during 34 HD; correlation coefficient from cross-correlations and Granger Causality index at a lag of -2 minutes.



PO1236

Point-of-Care Ultrasound Findings Among Dialysis Patients with COVID-19

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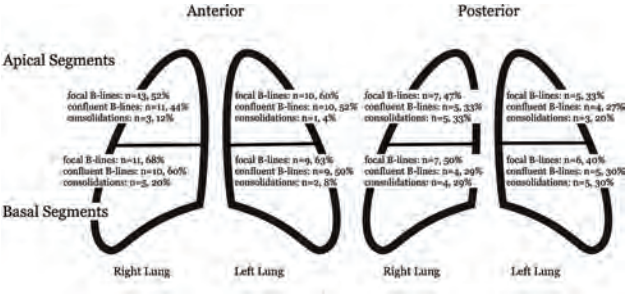
Background: Dialysis patients are vulnerable in the COVID-19 pandemic due to advanced age, comorbidities, and obligate travel with frequent healthcare contacts. Point-of-care cardiac and lung ultrasound (US) has been used to enhance the physical exam in dialysis patients and is a potent tool for assessment COVID-19, comparing favorably to computed tomography. Here we report findings of focused cardiac and lung US among dialysis patients in an acute care setting.

Methods: This is a cohort of dialysis patients who presented to our institution in Spring of 2020 with COVID-19. All patients started dialysis prior to the index acute care visit. Focused 5-view cardiac assessment and 12-zone lung US were obtained according to published protocols.

Results: 25 patients were included. 88% were African American. 64% were female. Mean age was 61.96 and body mass index was 25.8 kg/m^2. 56% had history of heart failure, 28% lung disease. 15 (60%) were discharged with mean length of stay 10 days. 36% required invasive mechanical ventilation and 56% intensive care unit admission. 23 patients had cardiac US. 17 had an ejection fraction (EF) >55%, 3 had EF 30-55%, 1 had EF <30%. 23 had inferior vena cava (IVC) assessment, 18 had a normal or collapsed IVC, and 5 had a full, non-collapsing IVC. 3 had pericardial effusion. 4 had right-ventricular dysfunction. 25 completed anterior lung US zones and 12 also had posterior lung US. In at least 1 lung zone 16 (64%) had confluent B-lines, 16 (64%) consolidations, 16 (64%) isolated B-lines, and 17 (68%) pleural thickening. 8 had pleural effusions (3 bilateral). **Figure 1 details lung US findings across anatomical zones.**

Conclusions: We showed a high prevalence of thickened pleural lines, subpleural consolidations, and multifocal or confluent B-lines among dialysis patients with COVID-19. Most had a normal or collapsed IVC and intact cardiac function. Pleural and pericardial effusions were uncommon. More study is needed to determine whether US findings can help guide fluid management in dialysis patients.



PO1237

Accelerated Renal Replacement Therapy: Single-Institution Experience in Calculating Delivered Clearance During the COVID-19 Pandemic

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Introduction: Continuous renal replacement therapy (CRRT) is commonly used in the intensive care unit (ICU) setting. A minimum delivered dose 20 ml/kg/hr is associated with improved survival. Previous studies have revealed significant discrepancy between prescribed and delivered CRRT dosing. Before the COVID 19 pandemic, CRRT was the main modality used at our medical center. But to accommodate the increase need for RRT and our limited resources, accelerated renal replacement therapy (ARRT), providing the same total CRRT clearance but in half the time, was used. To ensure that the delivered dose was appropriate given the reduction in time, we calculated delivered clearance.

Case Description: ARRT prescribed dose was based on patient's weight and time on therapy to achieve the equivalent 20cc/kg/hr over 24 hours. Delivered clearance (k) was calculated using the following formula K= Qd + Qr +Quf x FUN/BUN / weight/ 24 hours Qd =spent dialysate Qr= replacement fluid rate and Quf = net fluid removal rate. FUN = effluent urea nitrogen BUN= blood urea nitrogen. Hourly flowsheet with total time, Quf, Qd, and Qr were recorded during treatment by bedside nurse and reviewed to calculate the delivered clearance. 8 patients underwent 14 uninterrupted AVVHDF treatments. Total treatment time ranged from 8-10.5 hours. FUN/BUN ratio ranged from 0.5 to 1.05. The ratio between delivered clearance to prescribed clearance ranged from 0.83-1.08. Only 6 treatments (43%) achieved goal clearance.

Discussion: ARRT delivered clearance was only achieved 43% of time. While ARRT is a feasible modality when resources are limited, close monitoring of achieved clearance is needed to ensure that adequate dialysis is being delivered. Careful patient selection is important as delivered dose may be more difficult to achieve in obese patients. Although ARRT may be a practical alternative, continuous therapy would be ideal in the critical setting.

PO1238

Can COVID-19 Personal Hygiene and Social Distancing Reduce Bacteremia and Peritonitis Rates in Dialysis Patients

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Background: During COVID-19 pandemic affecting United Kingdom(UK) from March till May 2020 with social distancing guidelines in place (hand washing 5 times a day, 2 meter separation) and shielding in high risk individuals (including renal replacement therapy patients) and strict personal protective equipment (PPE) use in dialysis units we proposed the hypothesis that it may have positive impact on bacteremia in heamodialysis(HD) and peritonitis in peritoneal dialysis(PD) patients.

Methods: We compared Staphylococus Aureus (SA) bacteremia in HD patients and PD peritonitis rates over three months March, April and May 2020 and compared the results with similar duration during 2019. We also viewed SA colonization rate in a satellite unit during this period.

Results: Quarterly Staph. Aureus bacteremia results showed yearly rate on 31 May 2019, 31 August 2019, 30 November 2019, 28 February 2020 and 31 May 2020 as 0.014, 0.021, 0.039, 0.038 and 0.024 respectively. However yearly PD peritonitis rates were significantly down from 0.386 to 0.238 from January 2019 to April 2020. MRSA colonisation data from one satellite unit showed 2 out of 105 patients colonised in January 2019, of whom one decolonized by April 2020 while 16 patients in the same unit had MSSA colonization in January 2019 which was 15 out of 103 patients in February 2020 suggesting no significant difference in SA colonisation rate.

Conclusions: Improvement in peritonitis rates is indicative of personal behavioural change with regards to common sense hygienic principles being very important in PD. However, in HD patients it had no impact on bacteremia at similar time one year ago indicating that possibly colonisation with MSSA/MRSA are important and strategies to decolonisation of HD patients may help reduce episodes of bacteremia. There was some reduction in bacteremia rate from preceding quarter ending February 2020 to quarter ending May 2020 although not to May 2019 level. It will be difficult to say at this stage if this trend will be sustained in coming months.

PO1239

Effect of Lockdown to Stop Spread of COVID-19 on Physical Activity Levels of Hemodialysis Patients

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Background: On March 20, 2020, to stop the spread of the COVID-19, the New York State Governor issued a strict stay at home order for all tasks that were deemed as "non-essential" starting March 22 at 8PM. We would like to determine what change, if any, in physical activity levels (PAL) took place because of the lockdown order in HD patients.

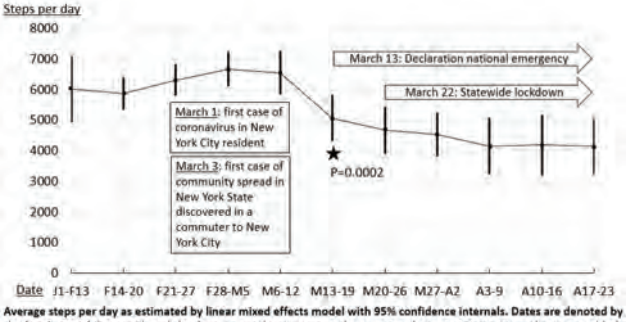
Methods: HD patients were enrolled from 4 clinics in New York City starting in May 2018 and followed for a period of up to 1 year. Patients ≥18 years, on HD ≥3 months, able to walk, and owning a smartphone were enrolled. PAL was defined by steps taken per day measured by with a wrist-based monitoring device (Fitbit Charge 2). Patients still in the study as of March 22, 2020 were included in the study cohort. Average steps per day was calculated for Jan 1-Feb 13, 2020 and the five weeks prior to and after the lockdown went into place. A linear mixed-effect model was used to estimate the average steps per day and 95% confidence intervals. Socioeconomic parameters such as age, race, employment status, and education level were taken at the beginning of the study.

Results: 42 patients were included in this analysis. At enrollment patients were 55±11 years old with a dialysis vintage of 4.5±4.4 years, and a BMI of 28.9±8.6 kg/m^2. 33% lived alone, 48% were single, 50% unemployed, 69% were African American, and 50% had an education level of some college or higher. Results on average steps per day are presented in Figure 1. Steps per day decreased significantly after the lockdown order with the most significant drop when the COVID-19 pandemic was declared a national emergency

Conclusions: There was a decrease in PAL due to the mandated lockdown. As sedentary behavior is a risk factor for negative outcomes in the HD population, we must implement interventions to promote PAL, such as intradialytic exercise.

Funding: Commercial Support - Fresenius Medical Care

Figure 1.



Average steps per day as estimated by linear mixed effects model with 95% confidence internals. Dates are denoted by the first letter of the month and the date. To put data in context, key events relating to COVID-19 pandemic are added.

PO1240

Affecting Factors on Circuit Lifespan in Continuous Renal Replacement Therapy

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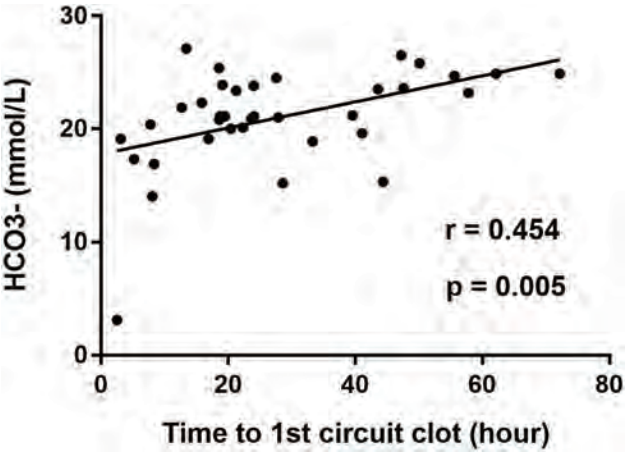
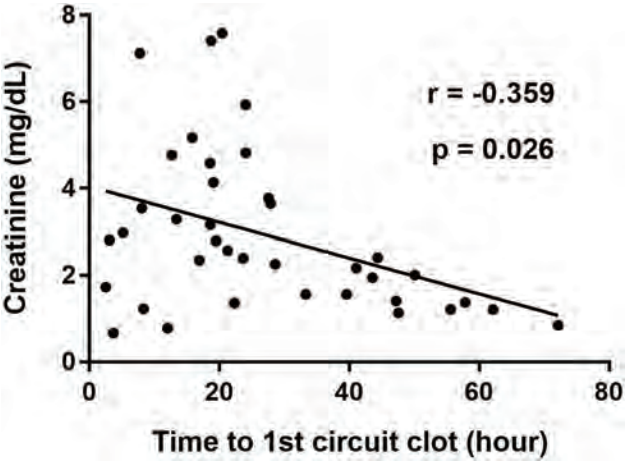
Background: CRRT is a useful dialysis modality in hemodynamically unstable patients. But despite use of anticoagulants, clotting of circuit frequently occurs, which reduces efficiency of dialysis and causes the consumption of RBC, platelets, and coagulation factors. Especially, the more severe patient is, the lower blood flow into circuit due to hypotension can lead to decrease circuit lifespan. This study aims to investigate the factors that affects CRRT circuit lifespan.

Methods: This is a retrospective observational study. From January 2018 to December 2019, 38 patients who underwent CRRT in the ICU were enrolled. Outcomes were defined as the time of first clotting in circuit from CRRT initiation and the number of clotting during total application period. We statistically analyzed association of circuit lifespan with patient's clinical characteristics.

Results: The results showed that first circuit clotting was significantly related to serum bicarbonate (r=0.454, p=0.005) and creatinine levels (r=-0.359, p=0.026). The total number of circuit clotting were related to RBC and platelet transfusion respectively (r=0.779, p<0.001 / r=0.652, p<0.001). Blood pressure, infection, blood flow of circuit showed no relationships with circuit lifespan. The use of heparin and nafamostat increased circuit lifespan compared to non-anticoagulant.

Conclusions: Circuit lifespan in CRRT is shorter in more serious metabolic acidosis and renal failure. Transfusion of RBC and platelet also reduces the circuit lifespan.





PO1241

Home Hemodialysis Patient Loss: A Quality Improvement Initiative to Review Technique Failure in Alberta Kidney Care - South

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Background: The number of dialysis patients has increased 15% over 5 years in Alberta Kidney Care South (AKC-S) with most patients pursuing in-centre hemodialysis. Although home hemodialysis (HHD) offers advantages of improved quality of life for patients and cost savings for programs it has grown at a slower rate. To increase the number of HHD patients, programs need to promote more patients to start on HHD and reduce the number of patients leaving HHD. Understanding the reasons for exit from HHD may lead to strategies to reduce patient loss.

Methods: A retrospective cohort study of adult HHD patients who entered training for HHD between January 1 2013 to December 31 2018 in AKC-S, followed until exit/study end date. Reasons for technique failure (TF) identified, with KM estimates used to determine technique survival, and Cox proportional hazard model used to determine risk factors for TF.

Results: 147 patients entered the HHD program-48(33%) women; 44(30%) DM, 38(25.9%) CAD, 14(9.5%) CVD, mean age of 54(13) years. 12(8.1%) did not complete training. Overall time in program 28 +/- 20 months, average training time 6.7 +/- 3.3 weeks. Reasons for exit include transplant 24(48%), death 6(4.5%), TF 32(24%). TF reasons include medical 9(39.1%), psychiatric 2(8.7%), social 3(13.0%), safety 4(17.4%), patient request 4(17.45%), change to PD 1(4.3%). Technique survival at 1, 2, and 5 years 91%, 85%, and 63%. Risk factors for TF include DM 2.36(1.06, 5.28) p= 0.036, CVD 4.34(1.8, 10.5) p=0.001 and a longer training time 1.18(1.07, 1.30) p=0.001.

Conclusions: We found a high HHD turnover rate with technique survival rates decreasing with time. Risk factors for TF include patients with DM, CVD, longer training time. Improved identification of and education for potential HHD patients could reduce training failure rates. Interventions to provide better support for patients at risk of TF could help keep patients at home longer.

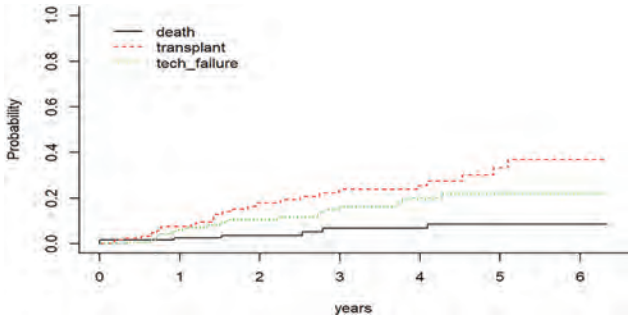

Figure 1. Cumulative Incidence of Competing Risks.

PO1242

Home Dialysis and Kidney Transplant Assessments in the ESRD Treatment Choices Payment Model

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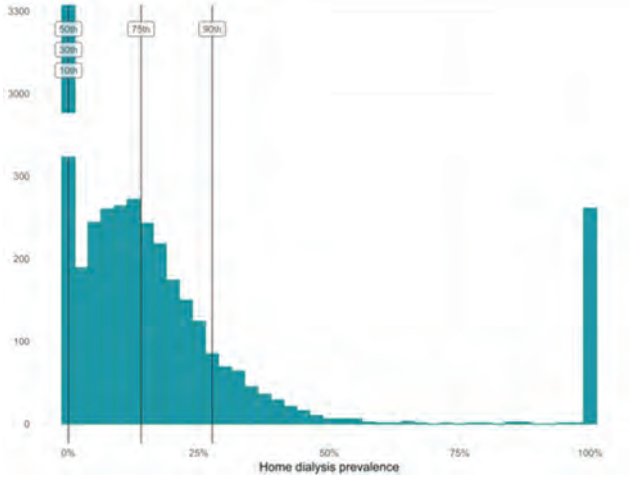
Background: The End Stage Renal Disease (ESRD) Treatment Choices (ETC) Model is a proposed mandatory payment model that assigns financial bonuses and penalties to dialysis facilities as a function of home dialysis prevalence and kidney transplant incidence among patients with Medicare fee-for-service coverage. We used claims data to estimate distributions of facility-level home dialysis prevalence and kidney transplant incidence.

Methods: Using Medicare Limited Data Sets, we identified all Part B claims for outpatient dialysis for the treatment of ESRD in 2017. In each dialysis facility with ≥132 adult patient-months, we estimated the percentage of patient-months with any home dialysis treatment. Using Part A claims in 2017, we also estimated the number of kidney transplants among dialysis patients in the facility.

Results: We identified 6263 dialysis facilities and 3,645,655 dialysis patient-months. Overall home dialysis prevalence was 10.8%. The distribution of facility-level home dialysis prevalence exhibited three features, as displayed: (1) over 54% of facilities with exactly 0% home dialysis prevalence; (2) among facilities with any home dialysis utilization, a unimodal distribution with peak prevalence near 12%; and (3) a small subset of facilities (4%) with home dialysis prevalence >90%. Regarding kidney transplant incidence, over half of facilities had ≤1 transplant. The 75th and 90th percentiles of transplant count were 2 and 4, respectively.

Conclusions: In patients with Medicare fee-for-service coverage, facility-level home dialysis prevalence exhibits a nonnormal distribution, while kidney transplant incidence typically manifests few (or no) events per year. Both patterns will complicate statistical analysis of performance in the ETC model. Alternative methodology should consider assessments in regional clusters of facilities.

Funding: Commercial Support - Fresenius Medical Care



PO1243

Identifying Barriers to Implementing an Assisted Home Hemodialysis Program in Canada

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Background: Policy changes such as the Advancing American Kidney Health Initiative and the impact of the COVID-19 pandemic will accelerate the trend for more home dialysis. Expanding the pool of patients eligible for HHD will require health care practitioner assisted models to be developed and deployed. We hypothesize that many barriers to delivering assisted HHD (aHHD) exist and implementation of a successful program would require meaningful input from frontline home dialysis nurses. Our primary objective of this study is to survey these key stakeholders to identify these barriers.

Methods: We conducted a semi-structured focus group of leaders within our large Canadian home dialysis program to anticipate key aspects of implementing aHHD, including gauging local demand, identifying eligible patients, and recognizing essential operational components. From this, we constructed questionnaires for frontline nursing staff within HHD, peritoneal dialysis (PD) and assisted PD (aPD) programs. We performed a qualitative analysis to identify common themes and implementation barriers.

Results: Twenty-six responses from three sites were received. 20/21 PD nurses reported existing aPD programs expanded the eligible pool of PD patients. 5/5 HHD nurses felt an aHHD program would keep more patients on the modality and prevent technique failure. Only 2/5 felt aHHD should be offered as a transition to HHD. While 18/21 PD nurses reported they could easily identify patients for aPD, only 2/5 HHD nurses agreed. Patients with sensory deficits, functional impairments, and limited support networks were felt to benefit most from aHHD. Lack of confidence and phobias were not agreed upon. Behavioral and safety issues, clinical instability, and inability to manage emergencies may be barriers to aHHD. Machine set-up, take-down, and establishing access were thought to be essential services. PD nurses felt clinical assessments should be routine. Few nurses felt complete assistance was necessary.

Conclusions: Our findings suggest there is a strong local demand for aHHD provided there is a clear criterion for enrollment and operational plans are well established. Frontline nurses have identified several important barriers to implementation which we will acknowledge and address when deploying our assisted home program over the upcoming year.

PO1244

Timed Repetitive Controlled Rotations of the CAR-170-C NXSTAGE Chronic Cartridge Hemodialysis Filter: An Original Newfangled Maneuver to Enable Heparin-Free Frequent Daily Home Hemodialysis

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Introduction: Heparin-free hemodialysis is usually obligatory in immediate post-operative states, bleeding diathesis and in critically ill patients. Conventionally, this is achieved through normal saline flushes, and regional citrate anticoagulation.

Case Description: An 87-yo white male with ESRD and atrial fibrillation on Warfarin, on maintenance daily Home Hemodialysis (HHD) with a NxStage machine, developed intra-abdominal abscess and sepsis following an urgent laparoscopic appendicectomy. He required emergent pericardiocentesis for cardiogenic shock from hemorrhagic pericardial effusion. Upon discharge, he was to continue heparin-free HHD. Despite the use of increasing volumes of normal saline flushes, his system clotted every day during HHD, therefore compromising his ability to carry out HHD. Our HD Senior Technician, had astutely observed that by a controlled timed manual and repeated to and fro rotation of the horizontally aligned CAR-170-C NXSTAGE Chronic cartridge, 60 degrees back and forth clockwise and counterclockwise, along the long axis of the filter, every 15 minutes, the filter stopped clotting. He has since then not needed saline flushes for smooth heparin-free HHD for several months.

Discussion: This is the first such report in the English literature. More studies are justified. We have hypothesized a mechanism and have named this the 'Adam Locke_ Onuigbo Maneuver'. If confirmed by subsequent research, we propose that a miniaturized motor set-up that would be programmed to mimic these timed controlled partial rotations of the horizontally aligned CAR-170-C NXSTAGE Chronic cartridge could translate to a commercial success with major clinical benefits to patients needing heparin-free hemodialysis in all settings.

PO1245

The Use of Etelcalcetide in a Special Cohort of Home Hemodialysis Patients with Severe Secondary Hyperparathyroidism

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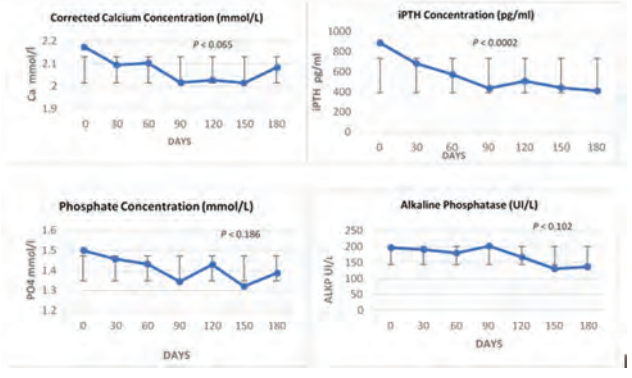
Background: Secondary hyperparathyroidism (sHPT), a is common complication of chronic kidney disease. Its clinical consequences include extraskeletal vascular and valvular calcifications, changes in bone metabolism resulting in renal osteodystrophy, and an increased risk of cardiovascular morbidity and mortality. Etelcalcetide is an intravenous calcimimetic that increases sensitivity of the calcium-sensing receptor to calcium and decreases PTH, so it's indicated for the treatment of secondary hyperparathyroidism (SHPT) in dialysis patients. In this observational study we are reporting our experience in treating SHPT by Etelcalcetide, in a very special cohort of sick, highly co-morbid, bed, and home bound hemodialysis patients, at home with the assistance of a hemodialysis nurse, we called the program as Nurse Assisted Home Hemodialysis (NAHHD).

Methods: This is a retrospective observational sixth months study. Thirty home HD patients, managed by NAHHD program, were included in this study, average age 59.6 (26-87year, 60% female. Etiology of ESRD was DM in 63%, 53% of them have hypertension. Vascular access AVF & AVG 60%, CVC 37%. Average comorbidities 9.4 (6-16). Patients were either naïve (30%) or switched from cinacalcet to Etelcalcetide due to non-compliance 50%, PTH resistance 31%, and bad tolerance of Cinacalcet 19%.

Results: The medication was well tolerated, two patients had GI side effects (6.5%), only with high dose of Etelcalcitide. The results of treating secondary hyperparathyroidism by Etelcalcetide in a special cohort of the patients for 6 consecutive months are illustrated in the graph.

Conclusions: This study showed that Etelcalcetide is efficient and well tolerated in this special group of sick, highly comorbid, bed and home bound home hemodialysis patients. The drug was well tolerated with minimal GI side effects.

Funding: Government Support - Non-U.S.



PO1246

Clinical Characteristics, Practice Pattern, and Outcome of Home Hemodialysis in India

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Background: Maintenance hemodialyis is growing steadily and is the dominant renal replacement modality and Home HD has been in recent times. But, the profile, treatment charactestics could be different from the western context but it remains unknown.

Methods: Prevalent patients on HD between Aug 2019 and Jan 2020 were reviewed for geographical location, age, gender, comorbidity, functional status, type of access, HD frequency, Hemoglobin, adequacy, S Albumin, S Calcium and S. phosphorus and survival. Descriptive statistics are presented to summarize data.

Results: n = 30. Mean age: 70.4 + 8.72, 15 males and 15 females. 26 were from large metropolitan cities. All patients underwent HHD with a help of HD technician deputed from a designated centre. 1388 sessions were done; total follow up:10610 patient days. 25 (83%) were diabetics, 21(70%) were Htn, 6(20%) had cardiovascular disease and 17(57%) were functionally dependant. 20(66.3%) patients had av fistula and 10(33.6%) had tunneled catheter. They reside at a distance of 13.85 + 8.76km from the HD centre. Range of HD frequency was from 1 to 3 per week. Mean Hb 9.80 + 1.34 g%. Kt/v: 1.50 + 016, S. Albumin: 3.52 + 0.44. Compliance for S. Ca testing was at 50% and S. Ca; 8.8 + 0.72, S Ph was 4.92 + 0.75 mg%. 3 patiens died during follow up after mean HD durtaion of 10.67 months

Conclusions: HHD patients in India are elderly with high prevalence of poor functional status, comorbidites, tunelled catheter and it is solely provider driven. Payer type was entirely out of pocket. HD outcomes are reasonable but long term survival remains unclear. Thus, HHD patient characteristics and practice pattern are distinctly different from developed countries

PO1247

A Pilot Evaluation of Thiol Metabolome in Peritoneal Dialysate as an Indicator of Peritoneal Fibrosis

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Background: The peritoneal dialysate is a precious source to find out markers for a better management of intraperitoneal dialysis (IPD). Low molecular weight thiols have been implied in the epithelial to mesenchymal transition, a process known to occur in peritoneal fibrosis. This study aimed to evaluate thiol metabolome in peritoneal dialysate and its relationship with peritoneal fibrosis. Thiol metabolome definition: total, free and protein bound fractions of glutathione, cysteine, cysteinylglycine and glutamylcysteine.

Methods: Peritoneal fibrosis was evaluated in biopsy specimen, performed during the placement of Tenkhoff catheter. Histological analysis were performed according to standard methods. Thiol related metabolome in peritoneal dialysate was assessed by high performance liquid chromatography+fluorescence detection. The relation thiol metabolome/fibrosis were assessed by multivariate analysis including principal component analysis (PCA) and partial least squared discriminanting analysis (PLS-DA).

Results: 42 patients (26 males), fibrosis in 26%, 16 Diabetic Age, diabetes, body max index, residual diuresis, Kt/v,nPCR, D/P, GFR residual, peritoneal Ca125, did not influence the thiol metabolome, that differed among those with and without fibrosis (fig). PLS-DA (p=8.09x10-7) identified that among the several thiol fractions obtained, cysteine fractions mainly contributed to this difference.

Conclusions: There is a thiol metabolome profile that can be measured in intraperitoneal dialysate fluid, that is related to fibrosis and rich in oxidized cysteine. This pilot analyses shows the potential contribution of thiol metabolome profile for precision prescription in IPD and stratification of patients according to fibrosis risk. This preliminary data might also support the existence of cysteine-dependent mechanisms of intraperitoneal fibrosis.

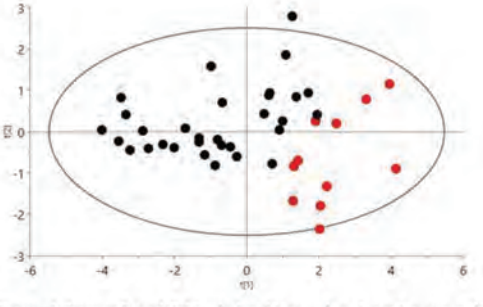

Figure 1 Score plot of PCA of the 42 samples. Samples are colored according to fibrosis at baseline (black: no, red: yes).

PO1248

Binding of TonEBP and ß-Catenin to the E-Cadherin Promoter Is a Key Process of Hypertonicity-Induced Phenotype Transition of Peritoneal Mesothelial Cells (MCs)

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Background: Epithelial-to-mesenchymal transition (EMT) of MCs is considered as an early mechanism of peritoneal fibrosis. Tonicity-responsive enhancer binding protein (TonEBP) is a transcriptional factor that enables cellular adaptation to hypertonic osmotic

stress. Recent data demonstrated the role of TonEBP in EMT of cancer cells, however the exact mechanisms how TonEBP regulated cell phenotype were not known. The aim of this study is to investigate the role of TonEBP in hypertonicity-induced EMT of MCs and its mechanism.

Methods: The expressions of TonEBP and other osmotic stress-related genes including sodium-myoinositol cotransporter (SMIT), betaine/γ-aminobutyric acid transporter (BGT1) and aldose reductase (AR) were evaluated. EMT was evaluated by morphological changes of MCs and the expressions of E-cadherin and α-smooth muscle actin (α-SMA) after stimulation of high glucose (HG, 30-120 mM) and mannitol (30-120 mM). E-cadherin promoter activity was confirmed by luciferase assay. Binding of TonEBP- or β-catenin to E-cadherin promotor was identified by chromatin immunoprecipitation (ChIP) assay. The interaction between TonEBP and β-catenin was analyzed by immunoprecipitation.

Results: Both HG or mannitol enhanced the expression of TonEBP as well as SMIT, BGT1 and AR from the concentration of 30 mM. HG induced EMT of MCs with a decrease in E-cadherin promotor activity, however mannitol did not induce EMT. HG (>30 mM) induced nuclear translocation of TonEBP which was associated with an enhanced binding to β-catenin. Mannitol also promoted nuclear translocation of TonEBP only at the highest concentration we tested (120 mM), however it was not associated with nuclear binding of TonEBP to β-catenin. In addition, mannitol induced a transient increase in nuclear β-catenin only with the highest concentration (120 mM) whereas HG showed a persistent increase in nuclear β-catenin.

Conclusions: This is study demonstrated the role of TonEBP in peritoneal EMT for the first time. Not the increased expression of TonEBP per se but binding of TonEBP and β-catenin to the E-cadherin promoter is a key mechanism by which TonEBP induced EMT of MCs.

PO1249

CD4⁺ ICOS-Expressing T Cells Contribute to Peritoneal Fibrosis in Patients Receiving Peritoneal Dialysis

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Background: Long-term peritoneal dialysis (LPD) can affect the morphology and function of the peritoneum, which causes peritoneal fibrosis one of the major causes of peritoneal dialysis (PD) failure. Reliable treatment strategies that successfully prevent progressive peritoneal fibrosis are still lacking. We performed single-cell RNA sequencing (scRNA-seq) on PD fluid from patients at different stages.

Methods: Firstly, PD fluid from patients with short-term peritoneal dialysis (SPD) (< 6 months) and LPD (>4 years) were collected for scRNA-seq analysis, and genomic expression differences of each sample were observed and analyzed. Secondly, peritoneum of PD patients and healthy inpatients were collected, and the expression of ICOS on $CD4^+$ T cells and ICOSL, COL1A1, COL1A2, FN, CDH, IL6 on peritoneal mesothelial cells (MSC) was detected by qPCR, ELISA, flow cytometry and immunofluorescence. Thirdly, $ICOS^+CD4^+$T cells and $ICOS^-CD4^+$ T cells in PD fluid were co-cultured with MSC cell lines, then stimulated with anti-ICOS monoclonal antibody. Lastly, we used gene pathway analysis and KEGG analysis to find out the possible mechanism pathway.

Results: A total of 13,167 T cells and 6,096 MSC from 8 PD fluid biopsies were included. Through scRNA-seq analysis, we found that under the stimulation of high glucose and other components in PD fluid, compared with SPD patients, the proportion of $ICOS^+CD4^+$ T cells within T cells and $ICOSL^+$ MSC within MSC from LPD patients was respectively increased by multiple of 0.58 and 0.29. Furthermore, the expression of COL1A1, COL1A2, FN, IL6 also increased in PD fluid and peritoneum from LPD patients. $CD4^+$ ICOS-expressing T cells interact with MSC by increasing the expression of profibrogenic proteins through ICOS/ICOSL pathway, then accelerate the progress of peritoneal fibrosis, anti-ICOS antibody can terminate these processes.

Conclusions: $CD4^+$ ICOS-expressing T cells contribute to peritoneal fibrosis, the anti-ICOS antibody can alleviate peritoneal fibrogenesis by interfering with the interaction between MSC and $ICOS^+CD4^+$ T cells, providing a new therapeutic target for progressive peritoneal fibrosis.

ICOS expression in T cells from SPD and LPD patients

PO1250

Geographic Variation of Home Dialysis Utilization in the United States

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Background: Increasing home dialysis utilization is an aim of the Advancing American Kidney Health Initiative. We estimated geographic variation in home dialysis utilization in a contemporary population of end stage kidney disease (ESKD) patients. We also assessed the extent to which race and payers—possible systemic barriers to home dialysis—account for this variation.

Methods: Using USRDS Standard Analysis Files, we identified all prevalent ESKD patients on December 31, 2017 and ascertained the dialysis modality—in-facility hemodialysis, home hemodialysis (HHD), or peritoneal dialysis (PD)—of each patient on that date. We categorized patients into 306 Hospital Referral Regions (HRRs), according to ZIP code of the dialysis facility. We estimated the standardized home dialysis ratio (SHDR) in each HRR, with expected home dialysis utilization as a logistic regression of age, sex, primary cause of ESKD, and ESKD duration. Subsequently, we added race and payer to the regression.

Results: The cohort comprised 513,669 patients. Home dialysis utilization was 12.0% (1.8% HHD, 10.2% PD). Among HRRs, 5th and 95th percentiles of observed utilization were 5.3% and 23.2%, respectively, whereas 5th and 95th percentiles of SHDR were 0.43 and 1.82, as displayed. There were 87 HRRs (28%) with SHDR significantly <1.0 ($P < 0.05$) and 116 (38%) with SHDR significantly >1.0. Of the 10 HRRs with largest patient counts, seven—Los Angeles, Houston, Manhattan, Dallas, East Long Island, Philadelphia, and San Antonio—had SHDR significantly <1.0. The addition of race and payer improved the discrimination of logistic regression, with black race and concurrent Medicaid enrollment as negative predictors of home dialysis utilization. However, the distribution of SHDR did not greatly compress. There were 29 HRRs (9%) with SHDR that was revised from significant to non-significant and 22 (7%) with SHDR that was revised from non-significant to significant.

Conclusions: Large geographic variation in home dialysis utilization exists. Race and payer are associated with utilization, but adjustment for these factors does not alter variation in SHDR.

Funding: NIDDK Support

Standardized Home Dialysis Ratio

	Percentiles						
	1st	5th	25th	50th	75th	95th	99th
SHDR	0.26	0.43	0.80	1.06	1.33	1.82	2.40
SHDR (revised)	0.24	0.42	0.79	1.05	1.30	1.73	2.29

In the revised SHDR, expected home dialysis utilization also reflects race and payer.

PO1251

Cost Savings Associated with Extending Patient Time on Peritoneal Dialysis

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Background: Only 7.1% of end-stage kidney disease (ESKD) patients receive peritoneal dialysis (PD) (USRDS, 2019). This number is expected to increase dramatically because of a 2019 U.S. presidential executive order which set the goal for 80% of patients to receive treatment at home or a transplant by 2025. To achieve this goal, providers and payers will not only need to encourage the use of PD but also will need to mitigate PD technique failure (TF). McGill et al. (AJKD, 2019) found that 6 out of 7 patients who start treatment with PD experience TF and will switch to hemodialysis (HD) within five years. Of patients who switch, Jaar et al. (BMC Nephrology, 2009) found that 20% did so by 6 months. Improving PD treatment time is important for patient quality of life and reducing healthcare costs. The goal of this study was to model Medicare cost savings associated with extending patient time on PD.

Methods: Using USRDS data, we calculated total Medicare spending per patient per day to be $226.71 for PD and $266.26 for HD, respectively. We estimated potential savings if treatment with PD could be extended each month up to 1 year using a base case of an incident ESKD patient who transitions to HD after receiving PD for 6 months. We assumed that during this year patients neither had a transplant nor died and that patients received HD once they stopped PD.

Results: Extending PD beyond 6 months for incident patients could result in potential savings to payers. Extending PD by 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months could save $1,203.05, $2,406.10, $3,609.15, $4,812.20, $6,015.25, or $7,218.30, respectively per patient. We found that if a patient could avoid TF, $14,436.59 could be saved annually.

Conclusions: Extending the PD treatment time beyond 6 months has the potential to reduce treatment costs by $1,203.05-$7,218.30 for patients staying on PD 1 month to 6 months longer, respectively. Annually, avoiding TF could result in savings of $14,436.59. Multiple risk factors are associated with TF. Focusing on identifying and addressing modifiable conditions may help to keep more patients dialyzing at home.

Funding: Commercial Support - Fresenius Medical Care North America Renal Therapies Group

PO1252

Higher Utilization of Peritoneal Dialysis Following the Executive Order on Advancing American Kidney Health

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Background: On July 10, 2019, the president of the United States issued an Executive Order on Advancing American Kidney Health (AAKH). As part of the order, the Centers for Medicare and Medicaid Services (CMS) issued a proposed rule regarding the End Stage Renal Disease Treatment Choices (ETC) Model, which would employ payment mechanisms in Medicare Part B to incentivize home dialysis and kidney transplantation.

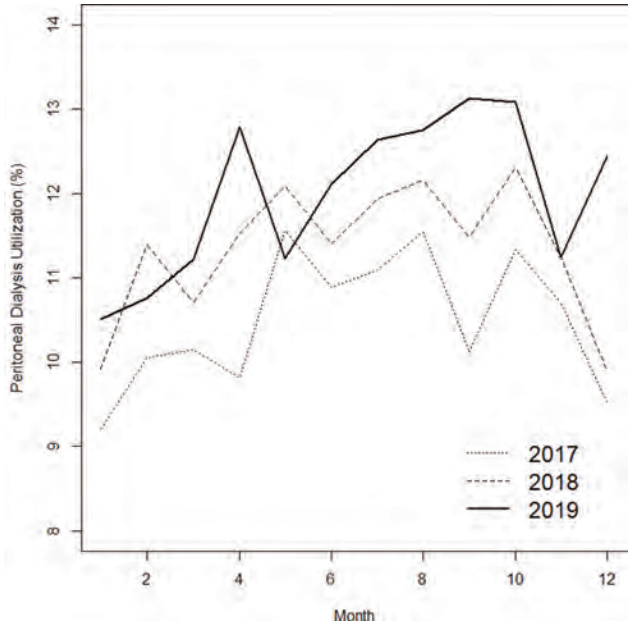
We assessed whether the period following the Executive Order was characterized by an increase in peritoneal dialysis (PD) utilization in incident end-stage kidney disease (ESKD) patients undergoing dialysis.

Methods: We analyzed submissions of form CMS-2728 ("ESRD Medical Evidence Report") among patients with dialysis initiation in 2017-2019, according to an April 2020 extract from the Renal Management Information System. For each calendar month in 2017-2019, we estimated the percentage of patients whose primary type of dialysis was PD. We used logistic regression to assess whether PD utilization during each quarter of 2019 exceeded corresponding norms in 2017-2018, with adjustment for age, race, and sex.

Results: The cohort comprised 375,815 incident ESKD patients undergoing dialysis. PD utilization increased each year, to an apex of 12.0% in 2019. In September and October 2019, PD utilization exceeded 13.0%, as displayed. Relative to corresponding quarters in 2017-2018, adjusted odds ratios of PD utilization in 2019 were 1.06 (95% confidence interval, 1.02-1.11) during January-March, 1.08 (1.04-1.13) during April-June, 1.16 (1.11-1.21) during July-September, and 1.16 (1.16-1.21) during October-December.

Conclusions: The Executive Order on AAKH and the proposed ETC Model together marked the advent of a period of significantly higher PD utilization among incident ESKD patients.

Funding: NIDDK Support



PO1253

Challenging Assumptions of Outcomes and Costs Comparing Peritoneal and Hemodialysis

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Background: Policy makers have suggested that increasing peritoneal dialysis (PD) use would improve end-stage kidney disease (ESKD) outcomes and reduce Medicare spending.

Methods: Using Medicare claims, we exploited an idiosyncratic Medicare coverage rule to conduct an instrumental variable analysis comparing mortality, hospitalizations, and Medicare spending between PD and hemodialysis (HD) in uninsured adults with incident ESKD. Uninsured patients usually receive Medicare at dialysis month four; however, those starting with PD receive Medicare at dialysis start *and* retroactive pre-dialysis coverage for the entire calendar month of dialysis start. Because pre-dialysis coverage is essential for PD catheter placements, the rule encourages more PD use among patients starting at the end of the month by increasing pre-dialysis coverage. We used dialysis start day as an instrumental variable to mitigate selection bias when comparing outcomes and costs of the two modalities.

Results: Starting dialysis later in the calendar month was associated with an increased probability of using PD at day 1 (*absolute* increase of 1.0% for every 10 days later in the month, 95% CI: 0.8%, 1.3%) and at month 12 (*absolute* increase of 0.7% for every 10 days later in the month, 95% CI: 0.4%, 1.0%). We observed no significant *absolute* difference between PD and HD for all outcomes: 12-month mortality, –0.4% (–3.4%, 1.8%), hospitalizations during months 7-12, 0.01 (–0.16, 0.17) per patient, and Medicare spending during months 7-12, $2,803 (95% CI: –$6,355, $508) per patient. We assessed the potential role of selection bias in prior studies by repeating the same analyses using traditional regression methods. In contrast to the instrumental variable model, when using traditional regression methods, PD was associated with statistically significant decreases in mortality but significant increases in costs.

Conclusions: Using an instrumental variable analysis, PD did not result in improved outcomes or lower costs when compared to HD. We observed evidence of selection bias when using traditional study methods. Policy makers eager to promote home dialysis should temper expectations of improved outcomes and reduced spending.

Funding: NIDDK Support

PO1254

Disparities in Home Dialysis and Links to Kidney Transplantation: Inequities Among African American ESRD Patients in Detroit, Michigan

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Background: African Americans with ESRD continue to fare worse than their White counterparts for graft and patient survival after kidney transplantation. These disparities may partly reflect differential use of peritoneal dialysis (PD) and hemodialysis (HD) among African Americans who undertake maintenance renal replacement therapy – although PD and preemptive tranplants are linked to longer survival and better kidney transplantation outcomes, emerging studies suggest that African Americans less often receive PD than Whites. The current analysis sought to explore whether disparate use of PD would persist in the context of an inner-city hospital that serves a majority African American patient population, within a predominantly African American city.

Methods: We compiled electronic medical record data from 2012-2018 for African American (n = 1078) and White (n = 155) ESRD patients who initiated maintenance dialysis through either HD or PD. We also compiled data on successful kidney transplantation in these patients, as well as sociodemographic and health status data, including BMI, age, PRA peak, race, sex, diabetes, and hypertension.

Results: Fisher's exact tests showed that African American patients were 2.28 times more likely to receive HD than PD as compared to White patients (p = .004), and that patients receiving PD were 2.09 times more likely to be transplanted (p = .01). Although attenuated, a robust relationship between PD and kidney transplantation persisted in a logistic regression that controlled for sociodemographic and health status variables (OR = 1.60, p = .10).

Conclusions: Disparities in use of PD can be observed even in the context of an inner-city hospital serving a predominantly African American population. Aligned with the Advancing American Kidney Health initiative to achieve 80% home dialysis by 2025, future research must identify and intervene on patient and clinician factors that contribute to lower PD use among African Americans.

PO1255

Home-Based Dialysis Care Among Veterans Within the Veterans Affairs Health Care System, 1995-2014

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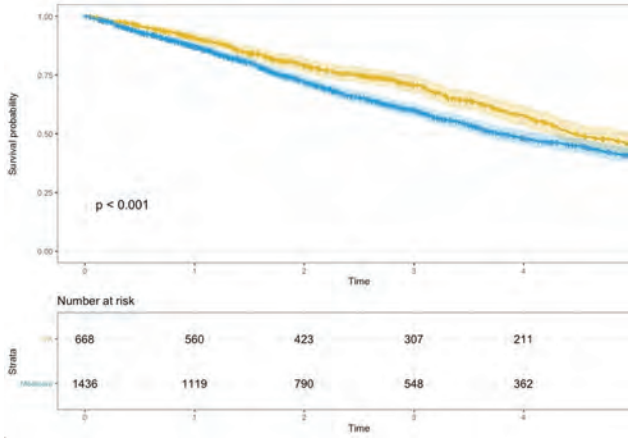
Background: Contemporary US policy is focused on proportionally increasing home-based dialysis care, however overall rates are lower in the US compared to other similarly developed countries. Use of peritoneal dialysis (PD), the most common home-based dialysis modality, is even lower among US Veterans. How the characteristics and rates of PD utilization among US Veterans vary by health system affiliation, is unknown.

Methods: Using United States Renal Data Systems (USRDS) combined with Medicare data for the years 1995-2014, we matched US Veterans initiating dialysis (*n* =14,904) to Veterans and Medicare non-Veterans receiving care in the community. Matching was performed in a 1:1 ratio according to year of dialysis initiation (+/- 2 years), age (+/- 2 years), gender, race, and reported cause of kidney disease. A total of 668 veterans initiated PD within the VA, compared to 890 Veterans and 1,436 non-Veterans in the community.

Results: After adjustment for patient age, gender, race, ethnicity, and region of residence, odds (AOR) of PD initiation within the VA was highest among those with diabetes mellitus (AOR 1.36; CI 1.18-1.57), tobacco use (AOR 1.59; CI 1.25-2.02), and a history of cancer (AOR 1.49; CI 1.10-2.02) and lowest for those of Hispanic ethnicity (AOR 0.73; CI 0.56-0.95), history of heart failure (AOR 0.74; CI 0.62-0.88). In 1995-1996, patients receiving Medicare coverage within the community were most likely to utilize PD compared to Veterans within the community and within the VA (18.9% vs. 9.6% and 8.2%, respectively), an observation that remained consistent over time. PD utilization among African-American Veterans was lower overall, although more closely approached estimates in white Veterans in more recent years. Veteran survival vs. Medicare controls is shown in **Figure 1**.

Conclusions: While PD utilization among Veterans is lower within the VA, the observed mortality benefit for care receipt within the VA was reassuring.



PO1256

Trends in Automated Peritoneal Dialysis (APD) Prescriptions in Adult Chronic Dialysis Patients at a Large Dialysis Organization from 2015 to 2019

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Background: Benefits of patients dialyzing at home have been well-reported. Peritoneal dialysis (PD) has grown in recent years and is expected to grow further due to the recent executive order encouraging home dialysis. Trends in APD prescriptions have not been well-described in the literature. This current retrospective analysis aims to describe trends in APD prescriptions from 2015-2019

Methods: All demographic, lab, and prescription data were retrospectively extracted and de-identified from a LDO's (Fresenius Kidney Care) electronic data warehouse. Patients included in the analysis were adults with chronic kidney disease on dialysis, incident to APD from Jan 1, 2015 to Dec 31, 2019, completed APD training, had at least one APD treatment recorded, and no data quality issues with their records. Patients were stratified by the year they started PD (2015, 2016, 2017, 2018, 2019) and patients' first APD prescription information was summarized.

Results: 16,047 patients were eligible for inclusion. The number of APD new starts eligible increased from 2,005 patients in 2015 to 4,751 patients in 2019, as did mean patient age (56.0 years in 2015 to 58.3 years in 2019, p<0.05). Few patients were prescribed daytime exchanges (7.6% in 2015 to 4.8% in 2019, p<0.05) and of those with daytime exchanges, the majority (>93% in all years) had 1 exchange. Table describes other prescription parameters by year.

Conclusions: Comparing 2019 to 2015 initial PD prescription patterns, there have been reductions in cycler volume, total number of exchanges, and prescriptions for daytime exchanges. These findings may support future studies on the current use of lower volumes with newer catheters (e.g. urgent starts) and accommodations made for patient lifestyle and choice

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Rx Parameters		2015	2016	2017	2018	2019	P-Value
Total cycler volume[a], L		9.0 ± 2.4	9.2 ± 2.5*	9.1 ± 2.5	9.0 ± 2.5	8.9 ± 2.4*	<0.001
Total cycler volume[a] per BSA, L/m²		4.6 ± 1.3	4.7 ± 1.4*	4.6 ± 1.2	4.6 ± 1.3	4.6 ± 1.3*	<0.001
Total prescribed volume[b], L		9.0 ± 2.5	9.2 ± 2.4*	9.0 ± 2.4	8.9 ± 2.4	8.8 ± 2.3*	<0.001
Total prescribed volume[b], L/m²		4.6 ± 1.3	4.7 ± 1.3*	4.6 ± 1.2	4.6 ± 1.3	4.5 ± 1.2*	<0.001
Total dwell time, minutes		480 ± 359	481 ± 370	452 ± 288*	464 ± 345*	471 ± 339	<0.001
Number of exchanges, mean		4.7 ± 0.9	4.6 ± 0.9	4.6 ± 0.9	4.5 ± 0.9**	4.4 ± 0.9**	<0.001
Number of exchanges, median		5 [4, 5]	5 [4, 5]	4 [4, 5]	4 [4, 5]**	4 [4, 5]**	<0.001
Number of exchanges, %							
	≤ 3	65 (3.2%)	110 (4.5%)	146 (4.8%)	239 (6.2%)*	295 (6.2%)*	<0.001
	4	863 (43%)	1043 (43.1%)	1463 (48%)	2025 (52.6%)*	2549 (53.7%)*	
	5	778 (38.8%)	938 (38.7%)	1063 (35.2%)	1421 (36.9%)	1583 (33.3%)	
	≥ 6	299 (14.9%)	331 (13.7%)	347 (11.5%)	166 (4.3%)	324 (6.8%)	
Night time dwell volume, L							
	< 2	529 (26.4%)	606 (25.6%)	715 (23.4%)	919 (23.9%)	1099 (23.1%)	0.02
	2 - 4	1449 (72.3%)	1765 (73.3%)	2299 (76.2%)*	2923 (75.9%)	3643 (76.7%)*	
	Missing	27 (1.3%)	51 (2.1%)	5 (0.2%)	8 (0.2%)	9 (0.2%)	

a (Night dwell volume * night dwell time) ; b (Day dwell volume * day dwell time) + (night dwell volume * night dwell time)
** P<0.001; * P <0.05

PO1257

Development of a Robust Peritoneal Dialysis Program

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Background: Despite ample evidence supporting the superior performance of Peritoneal Dialysis (PD) in a value-based heathcare system, this modality remains conspicuously underutilized in the USA. We implemented a multifaceted strategy to develop a high-performing PD facility in 28 months.

Methods: VIPKH, a private PD Center, was created through an affiliation with a five-doctor nephrology group in Florida and Medicare Certified 8/2017. Our physicians adopted an "upstream" approach to patient selection by promoting timely access to care for CKD 3b/4/5. KD education was mandatory. Social Media storytelling fostered a vibrant virtual CKD community. Patient vetting incorporated multidisciplinary evaluation of support systems and socio-economic and cultural determinants of health within their specific ecosystem. Expedited referral to an expert surgeon for laparoscopic catheter insertion was crucial. Home training and on-demand home visits were conducted routinely. 24/7 tele-access to clinicians and an open-door policy for non-routine care was instituted. Two satellite locations were available. FTE staff included an Administrator/ Population RN, two PDRN, Assistant Administrator and PTE RD and MSW.

Results: From 9/2017 through 12/2019 (28 months), 66 patients were admitted to VIPKH (Program Vintage 58 PD patient/years). Demographics: female 50%, 64.7 years (25-86), Caucasian 55%, African-american 23%, Hispanic 15%. Comorbidities: DM 47%, CHF 36%, DM/CHF 21%, Morbid Obesity 14%. As of 12/31/2019, 37 patients were on CCPD with good adequacy, 29 discharged: 1 Recovery, 7 Transplant, 3 Relocation, 4 Deceased, 1 Hospice, 13 Dropouts (5 peritonitis, 1 tunnel infection, 2 leaks, 1 inadequate dialysis, 3 disability, 1 burnout). Performance rates per 100 ESRD patient years (VIPKH vs Benchmarks): Peritonitis (10 vs 25), tunnel infection (2 vs 8), admissions (72.6 vs 170), hospitalization days (631 vs 1120), 30 day readmission (16.7% vs 37%), ED/Short-Stay (12.1 vs 350), transplant (12.9 vs 3.5), mortality (6.9 vs 22.5).

Conclusions: Our outcomes reflect the delivery of exceptional PD care. Our pragmatic approach to developing a successful PD program encompasses humble leadership which lays the foundation for building powerful relationships between all stakeholders through effective communication, education and collaboration, promotes shared decision-making and facilitates timely access to integrated, longitudinal, patient-centered care.

Funding: Clinical Revenue Support

PO1258

Acute Peritoneal Dialysis in Obese Patients During the COVID-19 Pandemic

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Background: Due to increased risk for infection, fluid leak, metabolic complications and poor uremic solute clearance, concerns have been raised in using peritoneal dialysis in obese patients. However, due to unprecedented need for renal replacement therapy (RRT) in New York City during the COVID-19 pandemic, acute peritoneal dialysis (APD) was initiated in patients regardless of body mass index (BMI).

Methods: 36 patients who received PD between April 8, 2020 and May 8,2020 were categorized into 3 groups based on BMI calculated using admission height and weight. Group 1 with BMI < 30, Group 2 with BMI 30-40 and Group 3 with BMI > 40 kg/m^2. Treatment goals included correction of hyperkalemia, hyperphosphatemia, acid-base abnormalities, reduction in blood urea nitrogen (BUN), creatinine and maintaining euvolemia. All patients were initially started on manual exchanges every 1-2 hours (Total volume 10-13L/24 hours) and eventually most were changed to automated PD (Total volume 18-20L/24 hours). We compared the frequency of treatment-related complications among the groups.

Results: Of the 36 patients, 13 had BMI < 30, 18 patients had BMI 30-40, and 5 had BMI > 40, one of whom had BMI > 50 kg/m^2. Patients showed improvement in serum creatinine, BUN, phosphorus, potassium, and bicarbonate. All had adequate ultrafiltration and improved volume status after optimization of PD prescription. No differences were observed between groups in achievement of treatment goals. No patients in any group required discontinuation of PD because of treatment-related complications or insufficient dialysis.

Conclusions: Acute PD was successfully performed in obese, and morbidly obese patients during the COVID-19 pandemic. Treatment goals were achieved based on relevant parameters and there were no increases of treatment related complications compared to non-obese patients. Acute PD should not be restricted based on elevated BMI.

PO1259

Comparing Mortality of Peritoneal and Hemodialysis Patients in an Era of Medicare Reform

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Background: Medicare's 2011 prospective payment system (PPS) encouraged the expansion of peritoneal dialysis (PD), which is preferred by many patients and less costly than in-center hemodialysis (HD). Prior studies have shown PD to be associated with lower or equivalent mortality to HD. Expansion of PD services after the PPS may change

the relative mortality of PD and HD if PD is increasingly used by sicker patients. This study revisits the comparative risk of mortality between PD and HD modalities in cohorts of patients spanning Medicare PPS.

Methods: From the US Renal Data System, we compared 2-year all-cause mortality in a cohort of incident dialysis patients in 2006-2013. Patients were censored at renal transplant or the end of the 2-year follow-up. Baseline characteristics of HD and PD patients were assessed via standardized differences and Kaplan-Meier curves. To compare HD and PD 2-year survival, a Cox proportional hazards model was fit using inverse probability of treatment weights (IPTW, generated from patient demographic and clinical characteristics) by incident year, adjusting for patient and dialysis market characteristics.

Results: PD use in the first 90 days increased from 9.5% of incident patients in 2006 to 13.6% in 2013. Crude 2-year mortality was 16.7% for PD and 27.6% for HD. There were no differences in patient characteristics between pre- and post-policy cohorts. In IPTW survival analysis across all incident year cohorts, no differences in 2-year mortality were found for those who attempted PD in the first 90-days of dialysis compared to patients receiving HD (example: HR, 0.93; 95% CI, 0.84 to1.04 for 2006 incident cohort). Mortality differences between PD and HD did not change over time (p=0.23).

Conclusions: Growth in PD initiation over time occurred without changing the patient mix towards sicker patients. After accounting for confounding, we found no evidence of mortality differences between PD and HD before and after payment reform. These findings suggest that Medicare PPS improved the value of dialysis care such that PD service use increased without adversely affecting patient mortality. Still, PD uptake in the US still lags that of many countries. Future policy initiatives may be needed to continue to increase clinically appropriate PD uptake.

Funding: NIDDK Support

PO1260

Duration of Serum Phosphorus Control Associated with Overall Mortality in Patients Undergoing Peritoneal Dialysis

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Background: Serum phosphorus (SP) level was closely associated with overall mortality and cardiovascular events, while the role of SP controlled duration was not fully recognized. Our study is to identify the relationships of SP controlled duration with clinical outcomes in patients undergoing peritoneal dialysis (PD).

Methods: This was a retrospective cohort study, including PD patients with regular follow-up in our center from Jan 1st, 2009 to Jun 30th, 2019. Clinical data were collected at baseline and at 3, 6, 9, 12, 18, 24, 30, 36, 48, 72, 96, and 120 months after dialysis. SP levels, changed degree of SP over baseline, and SP controlled duration were analyzed with overall mortality, PD withdrawal, and combined endpoint. Degree of SP change over baseline (%) = (SP level at following-up point - baseline SP level) × 100 / baseline SP level. Duration of SP control (months) = PD vintage when patients reached hyperphosphatemia - PD vintage when patients' SP decreased to less than 1.78 mmol/L after PD.

Results: 530 patients entered the analysis [the mean age was 45.4 ± 15.0-year-old, 57.2% were male, the median PD vintage were 32 (15-54) months]. 86.0% patients had hyperphosphatemia before dialysis, and the SP levels decreased soon after dialysis. Degree of SP change over baseline was the maximum at the 3rd month after dialysis (-31.0%), lower degree was associated with higher overall mortality [HR, 1.012(1.004-1.020); p=0.003]. The median SP controlled duration were 13 (5-28) months, the longer SP controlled duration, the lower overall mortality [HR, 0.968(0.956-0.981); p < 0.001], the lower incidence of PD withdrawal [HR, 0.964(0.954-0.973); p < 0.001] and combined endpoint [HR, 0.982(0.976-0.989); p < 0.001]. After categorized, patients whose SP never controlled had the maximum overall mortality (24.6%), the duration more than 12 months greatly improved the overall mortality [HR 0.197 (0.082-0.458); p < 0.001]. Phosphorus binders (PB) applying was significantly associated with overall mortality [HR 0.555(0.332-0.927); p=0.025] and PD withdrawal [HR, 0.523(0.391- 0.698); p < 0.001].

Conclusions: In PD patients, the level of SP and the degree of change after dialysis were tightly associated with overall mortality, PD withdrawal and combined endpoint. The longer SP controlled duration, the lower overall mortality. We should controll SP levels as early and as long as possible.

PO1261

Urgent-Start Peritoneal Dialysis and Outcomes

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Background: Many patients start dialysis without adequate pre-dialysis planning, and generally initiate hemodialysis using a central venous catheter (HD-CVC). A minority utilize urgent start peritoneal dialysis (USPD), where a peritoneal dialysis catheter is placed and used for dialysis initiation without the usual 2-4 week waiting period. Few analyses have compared outcomes between patients utilizing these two dialysis initiation routes.

Methods: All data for this retrospective study were derived from deidentified electronic health records. Patients who initiated dialysis via HD-CVC during 2018 were matched 1:1 to patients who initiated dialysis using USPD during the same period on the basis of insurance type, etiology of end-stage kidney disease, race, and presence of diabetes. Hospitalization, mortality, and scores on the Kidney Disease Quality of Life (KDQOL) survey were evaluated from dialysis initiation through the first of death, transplant, loss to follow-up, or study end (30 June 2019). Outcomes were compared across exposure groups using models adjusted for age and sex.

Results: A total of 717 USPD patients were matched to HD-CVC patients. During follow-up (mean 1.2 ± 0.6 years in both groups), USPD patients were hospitalized at a rate of 1.21 admissions/patient-year (pt-yr), vs. 1.51 admissions/pt-yr for HD-CVC patients. This corresponded to a 24% lower rate of hospitalization among USPD patients (adjusted incidence rate ratio 0.76, 95% confidence interval [CI] 0.65 – 0.88). Mortality rates were likewise lower among USPD patients compared to HD-CVC patients (0.08 vs 0.11 deaths/pt-yr) although this trend did not achieve statistical significance (adjusted hazard ratio 0.84, 95% CI 0.62, 1.15). No differences were observed with respect to KDQOL scores.

Conclusions: Among patients with little to no predialysis planning, use of USPD is associated with a lower subsequent hospitalization rate and a trend towards lower mortality rate, compared to HD-CVC. In areas where facilities and clinical expertise exist, more widespread adoption of USPD may lead to better outcomes among patients with limited pre-dialysis planning.

PO1262

Efficacy of Statin Use in Patients Undergoing Peritoneal Dialysis

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Background: The efficacy of statin uses in patients with PD have not been proven in large studies. Because most of studies included only HD patients or a small number of PD patients, there is lack of evidence whether statin have positive effect on PD patients or not. The aim of this study was to reveal the efficacy of statin uses in PD patients.

Methods: A total 612 incident PD patients between January 2006 and August 2019 were included in this study. The primary outcome was all-cause mortality and the main exposure of interest was a cumulative dose of statin. For defining the cumulative dose for statin, the definition of defined daily dose by World Health Organization was used. Patients who used statin for at least 28 cumulative defined daily doses (cDDD) after initiation of PD were defined as statin user.

Results: During a median follow-up duration of 33.0 months (IQR, 15.0-63.0), the primary outcome occurred in 124 (20.2%) patients. The mean age at initiation of PD was 53.6±14.5 years and 329 (53.8%) patients were men. The number of statin users was 390 (63.7%) and the number of patients who use statin before starting PD was 311 (50.8%). Statin use (≥28 cDDD) was associated with a lower risk of all-cause mortality (HR, 0.32; 95% CI, 0.20-0.52) after adjustment and this association was also consistent regardless of the use of statin before PD initiation. Adjusted hazard ratios for the all-cause mortality were 0.87 (95% CI, 0.53-1.43), 0.39 (95% CI, 0.20-0.75), 0.41 (95% CI, 0.18-0.91), and 0.13 (95% CI, 0.06-0.26) for the 28-365, 366-730, and 731-1095, respectively, compared with cDDD<28. The risk reduction of statin may be dose dependent.

Conclusions: Statin use was associated with a reduced risk of all-cause mortality in incident PD patients with or without statin use before dialysis.

PO1263

Mortality and Hospitalization in a Large International Peritoneal Dialysis Institution During 2018

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Background: With the exception of some national registries, data referred to mortality or hospitalization within a single large international peritoneal dialysis (PD) institution are seldom reported. **Objectives:** To study all-cause mortality, transplantation rate, hospitalizations and peritonitis rates in our large PD program during 2018.

Methods: Observational, prospective registry in 8 countries. The following variables were tracked: crude mortality rate and causes, hospitalization variables (number of hospitalization days per patient; number of hospitalization episodes per patient; number of days per hospitalization episode; causes of hospitalization), peritonitis rate (episodes/year at risk and patient months at risk to a peritonitis episode) and transplantation rate.

Results: By the end of December 2018, 1207 pt. were treated (11 countries) but only 8 countries submitted data. Evaluated population as "*patients treated at risk during the year*": AR (319.5), RO (173.5), DE (137), HU (103), PL (97), UR (69.5), CL (27), KZ (7). Crude mortality rate was 13.1%, same if first 90 days on therapy were excluded. Lowest mortality was seen in HU (9.9%) and highest in DE (19.3%). Causes of death: cardiac 32%, all type infections 22% [Sepsis 78%, PD related 11% (as 0.7% of total mortality), pulmonary 3.7%, others 7.4%], vascular 10%, gastrointestinal 3.3%, unknown 10.7% (highest in DE, 23%), other known causes 21.5%. Hospitalization rates: 0.55 episodes/per patient-year and 7.6 days of hospitalization per patient-year. N. of days per hospitalization episode was 13.7. Causes of hospitalization: PD related 38%, cardiovascular 17%, non-PD infection sepsis 10.7% (higher in LA, 16.6%), vascular access 2.1%, unknown 4.5%, others 23.3%. Global peritonitis rate was 0.18 episodes/pt-year at risk (1 episode every 66 m.). However, large differences were seen among countries. Transplantation rate was 6.5% (much higher in UR). PD was withdrawal in 35% of pt. Country specific data have been evaluated but are not shown here.

Conclusions: The use of a common registry in our institution increases quality and allows homogeneous comparisons across countries that if promptly addressed may increase patients' outcomes. Our series may bring light into the PD community as one of the ever largest tracked in a single institution.

PO1264

Association Between Peritoneal Dialysis (PD) Patient-Reported Family Member Assistance and Peritoneal Dialysis Modality Persistence

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Background: Increasing the number of dialysis patients who start and maintain home therapies is an urgent national priority. PD patients perform their own dialysis procedures at home. Family members may assist with moving dialysate bags, catheter care, dialysis machine set-up and connections, and medication administration. Understanding and supporting caregivers is an important driver of successful home dialysis, necessary to inform program content and activities. This study describes associations between patient reported family member assistance with healthcare tasks, and modality persistence.

Methods: Prospective, single site, cohort study of adults receiving PD for kidney failure. A baseline survey assessing family assistance with healthcare tasks at home was administered during a routine outpatient visit. Longitudinal data were tested using Chi-squared (SPSS) for associations between patient reported family member assistance, and PD modality persistence at six months.

Results: This sample of N=100 patients was 57% male, 31% African American, and 4% Hispanic/other. Average age was 52 +/- 16 years. Most patients reported a family member provided help at home (65%). Among those reporting family member assistance, 20% reported help administering insulin, 65% reported help with the PD procedure, 54% managed medications, and 59% provided wound care. Also, 16% reported help with one or two tasks, 28% help with three tasks, 25% help with five tasks. Patients who self-identified as Black/Hispanic/other reported less family member assistance than whites (51% vs. 71%, p=0.04). In the 74% of the initial sample who completed 6 month follow-up, for patients reporting any family assistance compared to those reporting none, there was a trend toward higher PD modality persistence (86.4% vs. 70.4%, p=0.092).

Conclusions: Optimizing family assistance may be a strategy to promote PD modality persistence. More work is needed to better characterize the caregiver role and its impact on health outcomes specific to home dialysis.

PO1265

Patient Outcomes of a Two-Exchange Assisted Continuous Ambulatory Peritoneal Dialysis (CAPD) Programme for Frail Older Patients

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Background: Recognising the burden that hospital haemodialysis (HD) places on frail people in terms of time away from home, transport and haemodynamic shifts, we developed a 2-exchange assisted CAPD (aCAPD) programme to enable this group to receive a home-based therapy. Eligible patients include frail, mostly elderly patients who are symptomatic from advanced kidney disease and have residual kidney function. The focus of the programme is to optimise patients' symptoms while avoiding a high treatment burden.

Methods: In this observational study, all 2-exchange aCAPD patients attending for routine review are approached for assessment. Frailty is assessed with the Edmonton Frail Scale (EFS), cognitive function with the Montreal Cognitive Assessment (MOCA), treatment satisfaction with the Renal Treatment Satisfaction Questionnaire (RTSQ) and symptoms with the Palliative Outcome Scale-Symptom Renal (POS-S Renal). Data was collected via patient interviews and chart review.

Results: Of the 17 patients currently receiving 2-exchange aCAPD, results have been collected from 47% (N=8) to date. Mean age is 82 years (77-90) and 50% are male. Mean number of co-morbidities was 4.4. Mean time on 2-exchange aCAPD was 9 months (0-24). 63% had at least mild frailty with an EFS of >8/17 (3-11). 75% had memory impairment with a MOCA <26/30 (8-30). Median number of hospital admissions was 1 (0-3). 38% have travelled outside of the UK (with family support) since commencing aCAPD. 85% reported high satisfaction with treatment with a RTSQ of >55/66 (median 62). Patients reported a low symptom score with a median POS-S Renal of 14.5 (7-27). Pain, lack of energy and poor mobility were the most commonly reported symptoms.

Conclusions: Our results demonstrate a frail, elderly population with multiple co-morbidities. Although our population number is small and they are not matched to the assisted PD and HD populations published in the FEPOD study they do compare favourably in terms of the RTSQ score; median of 60 vs 55 for assisted PD and 60 vs 51 for HD. Our population was comparable to both groups in terms of the POS-S Renal symptom scores; 14.5 vs 14 for assisted PD and 14.5 vs 16 for HD. This indicates that 2-exchange aCAPD could potentially become the dialysis modality of choice for the frail, older person requiring dialysis.

PO1266

A Snapshot for Peritoneal Dialysis Clinic Visits: Addressing Hospitalization Rates with a Checklist

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Background: Readmission rates are a component of quality metrics in home dialysis follow-up. Common causes of peritoneal dialysis (PD) related hospitalizations have been elucidated through National Readmission Database review. However, a systematic approach to identify individual risk factors leading to the index hospitalization and targeted interventions are not directly designed into clinic workflow. Often information regarding these specific risk factors are not exacted. We identified a need to standardize practice in our PD clinic by conceiving an action checklist for nephrologists and nurses to minimize index admissions.

Methods: Our quality improvement project sought to identify risk factors by analyzing the cause of admission from our cohort of 103 PD patients over 8 months. We divided reasons for admission into related and unrelated to PD. Based on these categories, we created a list of potential contributory risk-factors for admission. We also surveyed providers to determine key clinical components for a clinic checklist to encourage early recognition of the risk-factors.

Results: Of the 105 individual admission events identified from June 2018 to March 2019, 45% were identified as PD-related. Such admissions included peritonitis (34%), hypervolemia (19%), electrolyte derangement (13%), hypotension (13%), hypertension (10.6%) and catheter dysfunction (10.6%). 37 admissions (35%) were readmissions in the last 30 days, of which 60% were PD-related. From these results we designed a snapshot of trends of the prior 3 months' vital signs, electrolytes, weights, PET results, PD adequacy results, urine volume, peritonitis history and current medications for clinicians to review pre-visit.

Conclusions: We are currently implementing this checklist in our monthly PD clinic visits. Though the idea was conceived prior to the pandemic, we have increasingly seen the benefit of a clinical trends snapshot readily available as we transition to Telehealth visits to prevent patients' exposure to COVID-19. This method assists the clinician in triaging remotely. Ultimately, through utilization of this tool, we hope to unify our practice pattern in the clinic to reduce admission rates by prompting proactive, not reactive, interventions.

PO1267

Lung Comets and Hydration Status in Peritoneal Dialysis Patients

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Background: Multiple diagnostic options to determine hydration status in peritoneal dialysis (PD) patients are available. Multifrequency bioimpedance spectroscopy (MBIS) is a non-invasive method of estimating body composition, including total body water (TBW), extracellular water (ECW), intracellular water (ICW) and the ratio between both spaces (ECW/ICW). Lung ultrasonography (LUS) and lung B-lines (lung comets) can be used for the evaluation of extravascular lung water. Ultrasound evaluation of inferior vena cava (UIVC) provides a non-invasive assessment of a patient's hemodynamic and volume status. N-terminal pro-brain natriuretic peptide (NT-proBNP) is related to fluid status and fluid distribution. The aim of our study was to assess fluid status in PD patients comparing four different methods: MBIS,LUS,UIVC and NT-proBNP.

Methods: We performed a single-centre cohort study in 19 PD patients. The body composition was measured using the portable whole-body MBIS device, BCM(®) (Fresenius Medical Care, Germany), LUS with portable US device (VScan, GE Corporate),UIVC index with SonoSite US device. NT-proBNP was measured in a one-step sandwich chemiluminescent immunoassay (Siemens Healthcare Diagnostics, Newark, USA).

Results: The mean age of patients was 54±10 years, mean dialysis vintage 53 (10-194) months, 63% were men. Thirteen (68.4%) patients had fluid overload (FO)>1.1 L. Data of patients are presented in table 1. We found a statistically significant correlation between the number of lung comets and ECW/ICW ratio (r=0.496, P=0.031) and NT-proBNP (r=0.759, P<0.0001). In contrast, there was no significant correlation between the number of lung comets and UIVC (r=0.221, P<0.364).

Conclusions: According to our results, LUS with lung comets, MBIS with ECW/ICW ratio and NT-proBNP are useful and complementary methods for evaluation of fluid status in PD patients.

Descriptive data of the patients included in the study (N=19)

Variable	Mean ± SD
Lung comets (number;mean±SD)	1-87; 16±21
UIVC (mm/m2,mean±SD)	8.11±1.76
NT-proBNP (pmol/L)	1151±1077
MBIS: Total body water (L)	43.1±10.3
MBIS: Extracellular water (ECW) (L)	20.3±5
MBIS: Intracellular water (ICW) (L)	22.8±6.1
MBIS: ECW/ICW	0.9±0.14
MBIS: Overhydration (L)	2.45±3.05

PO1268

Outcomes of Urgent-Start Peritoneal Dialysis in a Retrospective Cohort

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Background: Peritoneal dialysis (PD) has shown to have early survival benefit and increased patient satisfaction when compared to in-center hemodialysis. Despite this, 87% of patients with End Stage Renal Disease (ESRD) start on hemodialysis, while only 10% of patients start RRT via peritoneal dialysis. The Advancing American Kidney Health Initiative was launched in July 2019, with the goal of having 80% of incident ESRD patients on a home modality or transplant by 2025. In this context, major changes will need to ensue so patients starting RRT can have increased access to home dialysis. Conventional start peritoneal dialysis requires the PD catheter to rest for several weeks

after insertion prior to use. This limits the use of PD for patients that need to start RRT urgently. An alternative is urgent start PD where dialysis can be started as soon as 1 day after catheter insertion. There is growing evidence that urgent start PD is a safe and effective alternative to urgent start hemodialysis.

Methods: A retrospective analysis of patients that underwent urgent start peritoneal dialysis from 2013 to 2019 at the Washington University Home Modalities Dialysis Clinic was conducted. Complications (including catheter leak, catheter malfunction, infections and bleeding episodes), hospital admissions in the first 30 days after catheter placement and time patients remained on PD after urgent start were examined.

Results: 41 patients were started on urgent PD during the study period. 12 patients (29%) were started as an inpatient and 29 patients (71%) as an outpatient. Median time from catheter placement to initiation of dialysis was 5 days. Major complications including peri-catheter leaks occurred in 3 patients (7.3%), catheter malfunction in 7 patients (17.1%), peritonitis within the first 4 weeks occurred in 3 patients (7.3%) and 2 patients (4.8%) developed an exit site infection. There was 1 patient that had a major bleeding event after catheter placement. 11 patients (27%) were admitted to the hospital within the first 30 days after urgent start PD. During the follow-up period, the median time patients were on PD after urgent start was 15.9 months, 16 patients (39.02%) transitioned to another form of RRT.

Conclusions: As has been demonstrated in previous studies urgent start PD remains a viable option for initiation of RRT and ensures increased access to home dialysis.

PO1269

Megaloblastic Anemia in a Patient on Peritoneal Dialysis Returning from Kenya

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Introduction: We describe a case of atovaquone-proguanil (A-P)-related toxicity in a patient treated with peritoneal dialysis (PD).

Case Description: A 40-year old man treated with PD presented 48 hours after return from Kenya with a diffuse erythematous rash, dysphagia, fever and weight loss. Clinical evaluation showed a maintained general status, diffuse non-palpable purpura and tonsillopharyngitis. Laboratory testing revealed an elevated c-reactive protein and pancytopenia. Malaria prophylaxis (A-P) had been prescribed by his general practitioner and accurately taken. Malaria infection was ruled out through blood smear analysis. Broad serologic testing was negative. Empiric antibiotics were administered for tonsillopharyngitis. Bone marrow examination showed a megaloblastic anemia. Besides, he developed a diffuse nonscarring hair loss within weeks.

Discussion: DNA synthesis requires the presence of thymidylate, a nucleotide present in cells in rate-limiting amounts. Both folate and vitamin B12 are crucial cofactors in the thymidylate metabolism. Vitamin B12/folate deficiency or drugs affecting the vitamin B12/folate metabolism will slow down DNA synthesis. Proguanil is a folate analogue and its metabolites inhibit dihydrofolate reductase (DHFR), disrupting the thymidylate synthesis. The use of a fixed dose combination of A-P for malaria prophylaxis is contra-indicated in chronic kidney disease (CKD) because of proguanil accumulation in patients with kidney disease. Inhibited DNA synthesis manifests as megaloblastic anemia or as hair loss because of altered regulation of hair follicle growth cycle. DHFR inhibition was corrected by discontinuing A-P and by stimulating thymidylate synthesis through the administration of folinic acid. Supportive care included administration of Granulocyte–Colony Stimulating Factors, platelet and red blood cells transfusion. PD was continued. There was no indication in switching the patient to hemodialysis since extracorporeal clearance of proguanil is limited due to high protein binding (75%) and very high distribution volume (42L/kg).

Key message: The use of A-P is contra-indicated in CKD, due to the risk of proguanil accumulation and consecutive hematologic toxicity. Treatment is based on discontinuing the drug, administration of folinic acid and supportive care. Data suggest proguanil is poorly dialyzable.

PO1270

Serum Uric Acid, Mortality, and Decline of Residual Kidney Function in Patients Undergoing Chronic Peritoneal Dialysis

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Background: Hyperuricemia is known to be associated with cardiovascular (CV) events and mortality in patients with chronic kidney disease (CKD). However, in the particular case of patients on chronic dialysis, the relationship between serum uric acid (UA) levels and adverse outcomes is less consistent. The aim of this study was to identify the correlation between UA, on one side, and all-cause mortality (primary endpoint) and the rate of decline of residual kidney function (RKF) (secondary endpoint), on the other, among patients undergoing chronic peritoneal dialysis (PD).

Methods: We conducted a single centre, retrospective, observational cohort study of 682 patients who started PD between 1990 and 2019. We recorded essential demographic, clinical and laboratory data at baseline, 6, 12 and 24 months. We categorized the study population according to the median of mean UA levels during the first 3 months on PD (hyperuricemic/nonhyperuricemic) and, on the other side, according to any of: mean UA above/below median and treatment with UA lowering agents (gouty/nongouty). Cox proportional hazard model was applied to investigate the primary endpoint, and logistic regression analysis was used to assess the secondary endpoint.

Results: The study population included 407 males and 275 females, with a mean age of 60.2±14.6 years. Diabetes was present in 30.9% (n=211) of the patients. Mean follow-up on PD was 31,4±25,6 months. In univariate analysis, hyperuricemic patients presented higher levels of albumin (p=0.001), phosphate (p=0.003) and haemoglobin (p=0.002), and lower levels of cholesterol (p<0.001) and ferritin (p=0.039). In multivariate analysis, hyperuricemia was not an independent predictor of the rate of decline of RKF (HR 1.069; 95% CI:0.695 -1.644; p=0.761) or mortality (HR 0.997; 95% CI:0.738 -1.345; p=0.983), after controlling for age, diabetes, comorbidity and baseline RKF. The same applied when the study population was categorized as gouty/nongouty patients.

Conclusions: Higher UA levels were not independent predictors of mortality or the rate of decline of RKF, in our patients on PD. Patients presenting higher UA levels display a better nutritional and inflammatory profile than those with lower UA levels, which may suggest a component of reverse epidemiology.

PO1271

Phase Angle and Extracellular Mass to Body Cell Mass Ratio in Peritoneal Dialysis

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Background: Extracellular mass to body cell mass ratio (ECM/BCMr) is an important marker of malnutrition and a described independent predictor of long-term survival in Peritoneal Dialysis (PD). Its potential as dual index of wasting-fluid overload has been explored in Hemodialysis (HD). Phase angle (PA) – a predictor of long-term survival in dialysis – also appears as a potential nutritional-evaluation tool, with some authors defining protein-energy wasting as PA <4.5°. Higher ECM/BCMr would indicate either lower muscle mass and/or fluid overload. Its adequate cut-off point in PD remains unclear. Reports in CKD/HD-patients suggest a cut-off point ≥1.20, which added to a PA value <6, would work as markers of poor cardiovascular prognosis. But, how could these markers work in our population?

Methods: A prospective study included patients' first simultaneous acquisition of bioelectrical impedance analysis (BIA) and peritoneal equilibration test (PET). Phase angle at 50 kHz was recorded. Spearman correlation and T-student analysis were used.

Results: Were included 67 patients, with a mean age of 54.1±17.3 years, 59.7% men, 95.5% Caucasian, 84.4% hypertensive and 31.3% diabetic. Mean ECM/BCMr was 0.57±0.03 and mean PA was 5.12±0.3°. ECM/BCMr is positively correlated with age (r=0.293, p=0.017), pulse pressure (r=0.334, p=0.006=), ECW/TBW (r=0.948, p<0.01) and TBW/FFM (r=0.678, p<0.01), and inversely with albumin (r=-0.477, p=<0.01), uric acid (r=-0.287, p=0.027) and GFR (r=-0.308, p=0.012). A higher ECM/BCMr was observed among diabetics (0.59 vs. 0.56, p=0.011). PA is directly correlated with albumin (r=0.364, p=0.013) and GFR (r=0.291, p=0.049). Inverse correlations are described with ECW/TBW (r=-0.888, p<0.01), TBW/FFM (r=-0.674, p<0.01), ECM/BCMr (r=-0.909, p<0.01), age (r=-0.323, p=0.029) and diabetes (r=-0.312, p=0.035).

Conclusions: ECM/BCM and PA correlate with several volume and nutrition markers and work "contrariwise". Our population is prone to a poorer cardiovascular prognosis and eventually malnutrition, considering these cut-offs. Since BIA is a non-invasive, easily and periodically applied method, we believe that approval of these markers as dual index could be applied to PD, although admitting that this population would probably require new cut-offs.

PO1272

Association of Ambulatory Blood Pressure with All-Cause Mortality and Cardiovascular Outcomes in Peritoneal Dialysis Patients

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Background: Ambulatory blood pressure monitoring (ABPM) is the gold standard for the diagnosis of hypertension, but its effects on all-cause mortality and cardiovascular outcomes in peritoneal dialysis (PD) patients remain uncertain. We aimed to investigate the association of ambulatory blood pressure and clinical outcomes in PD patients and to explain the underlying cause of the association.

Methods: A prospective, observational cohort study was conducted in PD patients enrolled from March 2001 to July 2018 and followed until October 2019. Blood pressure was evaluated using 24-hour ambulatory blood pressure monitoring. The endpoints included all-cause mortality, cardiovascular mortality and cardiovascular events. Multivariable Cox regression was used to identify the associations between ambulatory blood pressure and endpoints. Subsequently, multivariable logistic regression was conducted to identify factors associated with elevated pulse pressure.

Results: A total of 260 PD patients (154men, 59.2%) were recruited. The median follow-up duration was 40.7 months. Our studies revealed that pulse pressure was an independent predictor for all-cause mortality (HR, 1.018; 95%CI, 1.001-1.034; P=0.032), cardiovascular mortality (HR, 1.039; 95%CI, 1.017-1.061; P<0.001) and cardiovascular events (HR, 1.028; 95%CI, 1.011-1.046; P=0.001). Systolic blood pressure was an independent predictor of cardiovascular mortality (HR, 1.023; 95%CI, 1.007-1.040; P=0.005) and cardiovascular events (HR, 1.018; 95%CI, 1.006-1.030; P=0.003). The presence of vascular calcification (OR, 3.069; 95%CI, 1.632-5.772; P=0.001) and NT-proBNP (OR, 1.074; 95%CI, 1.026-1.124; P=0.002) were significantly associated with elevated pulse pressure.

Conclusions: 24-hour ambulatory pulse pressure is the most significant predictor of all blood pressure indicators for clinical outcomes in PD patients, and systolic blood pressure is an independent predictor for cardiovascular outcomes. Meanwhile, it suggests that the associations can be explained by vascular calcification and volume status in PD patients.

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PO1273

Differences in Protein Energy Wasting Indicators by Peritoneal Transport Type: A Cross-Sectional Study with Automated Peritoneal Dialysis Patients

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Background: In chronic kidney disease (CKD) population protein energy wasting syndrome (PEW) is a prevalent problem with a multifactorial etiology (uremia, low energy and protein intake, basal energy expenditure increased, inflammation, metabolic acidosis, nutrient loss during renal replacement therapy (RRT). In peritoneal dialysis, patients with high peritoneal transport tend to have enhanced clearance of small solutes and shows low ultrafiltration capacity and higher inflammatory state, that impacts negatively in nutritional status. We evaluate the differences in nutritional status indicators and the association of high type transporter peritoneal with protein energy wasting (PEW) syndrome.

Methods: Cross-sectional study of a cohort of 36 patients with CKD on automated peritoneal dialysis (APD) [18 men, 18 women; age, 35.1 ± 13.3 years; dialysis duration, 7 (2-24) months]. Peritoneal transport characteristics were classified after a peritoneal equilibration test (PET). The PET study reasons were: baseline study, low ultrafiltration, underdialysis and after an event of peritonitis. Patients were classified according to peritoneal characteristics as a low transporter (LT) [low/low average] and as high transporter (HT) [high/high average transporters]. Weight and height were measured using standard procedures and body composition was assessed by multifrequency bioelectrical impedance analysis.

Results: HT individuals have lower albumin concentrations than LT (3.3 ± 0.42 vs 3.7 ± 0.39, p=0.026). Higher glucose absorption from dialysis solution (p=0.036) and a trend toward in higher c reactive protein plasma concentrations (p=0.089) was observed in the HT group. Higher prevalence of PEW condition (50 vs 23%) was observed in HT group without statistical significance (p=0.144). Higher malnutrition status using malnutrition inflammation score and PEW criteria was observed in HT-PET, without statistical significance.

Conclusions: HT peritoneal membrane confers a risk for hypoalbuminemia and inflammatory state in CKD patients on automated peritoneal dialysis. HT patients are at an increased risk of PEW. Intervention studies to elucidate the best nutritional approach should be designed to improve nutritional status in this population.

PO1274

Monitoring for Early Signs of Peritonitis in Patients Undergoing Peritoneal Dialysis

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Background: In 2019 the U.S. Department of Health and Human Services (HHS) established the "*Advancing American Kidney Health*" initiative, with a goal of increasing home-based dialysis from 12% to over 50% by 2025. To meet this goal, healthcare providers must address the common complications of peritoneal dialysis (PD) that contribute to modality failure and reluctance to opt for PD when starting dialysis. A sharp increase in PD utilization will require new approaches to reducing peritonitis and infection-related hospitalization.

Methods: Current strategies to detect peritonitis rely on crude signs and symptoms – predominantly cloudy spent dialysate and abdominal pain – an insensitive and non-specific approach. With the CloudCath monitoring system, the intent is to automatically and quantitively monitor the turbidity of the effluent fluid. We evaluated the CloudCath monitoring device which includes a cloud-based algorithmic solution for early detection of the patient condition associated with peritonitis.

Results: The device and algorithm were tested in a proof of concept clinical study where we found a discernable change in monitoring status in 99% of samples from patients with peritonitis, while changes in monitoring status were present in only 2% of samples from dialysis sessions of otherwise healthy PD patients. In some cases, the device was able to provide indicators of impending peritonitis, before standard laboratory values met accepted diagnostic criteria peritonitis. The device (CloudCath, San Francisco, CA) remotely monitors the patient's effluent dialysis fluid and sends alerts via the cloud to healthcare providers as soon as abnormal fluid characteristics are detected.

Conclusions: Early detection of peritonitis can lead to earlier clinical intervention and a better clinical response, relative to the current standard of care. Studies are ongoing to test the ability of the device to reduce morbidity, reduce infection-driven hospitalizations, and maintain PD as the patient's preferred dialysis modality.

Funding: Commercial Support - CloudCath

PO1275

Patient-Reported Factors and Peritonitis Risk: Results from the Optimizing Prevention of Peritoneal Dialysis-Associated Peritonitis in the US Study (OPPUS)

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Background: Peritoneal dialysis (PD)-associated peritonitis has been found to be associated with depression in a single-center study (Troidle 2003). Using international multicenter PDOPPS data, we investigated the association of peritonitis with reported symptoms of depression via the Center for Epidemiologic Studies Depression Scale (CES-D) and quality of life (QoL) measures.

Methods: We used Peritoneal Dialysis Outcomes and Practice Patterns Study phase 1 (2014-2018) data from Australia and New Zealand (A/NZ), Canada (CA), Japan (JP), Thailand (TH), the UK and US in cause-specific recurring-event survival models on peritonitis outcomes, stratified by previous episodes. Patient QoL) was estimated using the SF-12 Physical and Mental Health Composite Scores (PCS, MCS), and CES-D. Analyses were adjusted for age, years on PD, serum albumin level, residual urine, black race, sex, heart disease, diabetes, GI bleed, country, and prior peritonitis events.

Results: Peritonitis risk was associated with higher CES-D scores (p=.05). Patients who reported CES-D scores ≧ 15 had 27% higher peritonitis risk compared to patients who reported scores < 10. While associations were weaker for MCS (p=.69) and PCS (p=.40), scores that indicated the lowest tertile of QoL in these areas were associated with 6-7% higher peritonitis risk than scores in the highest tertile (table).

Conclusions: While the association between poorer QoL and peritonitis risk was weak and non-significant, the association between having greater symptoms of depression (per CES-D) and future peritonitis risk warrants further investigation, as depression may be a modifiable risk factor.

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	HR (95% CI)
CESD <10 (n=2014)	1 (ref)
CESD 10-14 (n=722)	1.14 (0.95, 1.36)
CESD 15+ (n=480)	1.27 (1.04, 1.55)
MCS < 41 (n=983)	1.07 (0.89, 1.27)
MCS 41-51 (n=1060)	1.06 (0.91, 1.24)
MCS 52+ (n=1068)	1 (ref)
PCS < 34 (n=975)	1.06 (0.87, 1.30)
PCS 34-43 (n=1077)	0.94 (0.80, 1.12)
PCS 44+ (n=1059)	1 (ref)

Hazard ratio of peritonitis, adjusted for case mix. Higher CES-D=more symptoms of depression, higher PCS, MCS = better QoL.

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Image-Guided Percutaneous Peritoneal Dialysis Catheters: Greater Than the Sum of Their Parts

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Background: Peritoneal Dialysis (PD) is a favored treatment modality for patients with end stage kidney disease. PD initiation depends on adequate and timely insertion of PD catheter. Most centers rely on laparoscopic insertion of PD catheters for PD initiation. Small studies indicate that image guided percutaneous (IGP) PD catheter insertion by interventional radiology (IR) may be non-inferior to laparoscopic catheters. However, there are limited data to compare IGP PD catheters to those inserted with laparoscopic technique. Hence, there are no definitive evidence based recommendations to support which technique may be superior. We conducted a retrospective analysis to compare complication rates and catheter survival in laparoscopic versus IGP PD catheter insertions.

Methods: Patients who underwent laparoscopic or IGP PD catheter placement from Jan 2014 to Aug 2019 were included in the analysis. IGP catheter placement employed

both fluoroscopic and ultrasound guidance. Primary outcome was rate of mechanical complications. Secondary outcome was death and transplant censored complication free catheter survival at 1 year.

Results: 244 PD catheters were placed at our institution during the study time period - 56 by laparoscopic surgical technique and 188 by IGP technique. Baseline characters including age, gender, race and BMI were similar in both groups. Surgical group consisted of 60% of patients with prior abdominal surgery as compared to 24% in the IR group OR 4.62 (2.35 – 9.09), P <0.0001. Mechanical complication rates were higher in the surgical group 29.6 % (18.0 – 43.6) versus 13.4 % (8.9 – 19.2) in the IR group (p 0.02). Death and transplant censored complication free catheter survival rate at one year was 87.8% (79.6 – 93.5) in the IR group and 73.3% (54.1 – 87.7) in the surgical group, P 0.063. In the surgical group, patients with higher BMI (> 35) had higher rate of complications 83.3% versus 22.9% in the low BMI (<35) group, OR 16.82 (1.77 – 159.58) P 0.014. In the IR group, catheter complication rates were not different in high versus low BMI groups, 5.0% vs 14.6% respectively, OR 0.31 (0.04- 2.4) P 0.26.

Conclusions: Our findings suggest IGP PD catheter is an effective option for PD initiation even in patients with high BMI and offers several advantages including ease of placement and lower recovery time.

PO1277

Repeat Peritonitis: A New Reality After *Staphylococcus aureus* Carriage Surveillance Implementation

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Background: Peritonitis is one of the major peritoneal dialysis complications and an important cause of technique failure. Notably, repeat peritonitis (RP) have substantial risk of developing further infection episodes that perpetuate peritoneal membrane damage. As S*taphylococcus aureus* (SA) is a major causative of RP, strategies such as *staphylococcus aureus* carriage surveillance (SACS) were implemented to decolonization of carriers in order to decrease SA PD infections. This study aims to describe repeat peritonitis clinical behavior and SACS influence on repeat peritonitis.

Methods: We developed one center retrospective study from 1998 to 2019 that compared RP episodes with a control group in terms of causative microorganisms, cure rate, catheter removal and permanent and temporary transfer to hemodialysis. We also compared the same data in RP episodes before and after SACS.

Results: Overall, RP were caused by gram positive microorganisms and had a significantly higher cure rate (97,1% *versus 67,3%*, $p<0.001$) and lower rate of hospitalization (11,4% versus 30,8%) than control group. After SACS, global peritonitis rate decreased (0,54 versus 0,35 episodes per patient-year), and RP rate increased (37,5% versus 7,4% p<0,001) as *Streptococci* became more frequent (56,7% versus 0,0% p 0,007) and *SA* less frequent (3,3% versus 60,0% p=0,001). Also, RP cure rate increased (100 % versus 80,0%, p 0,013) and permanent transfer to hemodialysis decreased (6,7%, versus 40,0%, p=0,03).

Conclusions: RP Group have more favorable results than control group that presented higher gram-negative peritonitis rate. After *SACS, Streptococci* became more frequent than *SA* in repeat group, peritonitis outcomes became more favorable but repeat peritonitis rate increased. We believe that as measures to prevent *SA* infections are implemented more programs will face this reality.

Repeat Peritonitis Causative Micoorganisms

	Before SACS (n=5)	After SACS (n=30)	Univariate Analysis p value
Streptococci spp	0	17, 56,7%	0,007
Coagulase-negative Staphylococcus	2, 40,0%	7, 23,3%	0,48
Staphylococcus aureus	3, 60,0%	1, 3,3%	0,001
Gram negative	0	1, 3,3%	0,55

PO1278

Strategies to Prevent Infection-Related Losses in US Peritoneal Dialysis Programs by More Actionable Predictive Data Reporting

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Background: Peritoneal dialysis (PD)–associated peritonitis (PTN) accounts for a significant percentage of patients who transition to hemodialysis due to infection-related technique failure. Data reporting to individual PD home programs on PTN rates is designed to drive a proactive approach for optimizing infection rates in PD programs.

Methods: Between 2016 and 2020, a standardized reporting of PD-related PTN was carried out for 1487 affiliated PD programs across the United States (66,687 patients). Currently, PTN is reported on a 3-month rolling average for each program, with a current average PTN rate of 1 event/66 patient-months; 32% of PTN events fall into the hospitalization criterion bucket, with 3% already having cultures drawn prior to admission. Among all episodes with an associated hospitalization, 90% have an associated culture. For non-hospitalization events, 64% had an associated culture among other criteria for event diagnosis. Beginning in 2020, an effort to advance PTN preventive strategies with a more in-depth characterization of PTN events was implemented. These additional data included reporting rates as episodes/patient-year; PD catheter removal rate post PTN/infection; culture-negative PTN rate; organism-specific PTN reporting, with patient loss by organism; percentage of patients PTN-free (cumulative patient-months without an infection); percentage of patients with >1 episode/year; percentage of events occurring at <30 days or 30 to 90 days; PTN-associated hospitalization rates and length of stay; time at risk calculation (>day 1 training); and PTN-associated mortality rates.

Results: The table displays PTN from 2019 and preliminary results of the PTN additional data report from January through March 2020.

Conclusions: Reporting on PTN events with these additional metrics, on a program-by-program basis, could assist in aligning specific action steps critical to reducing infection related PD failure. These data could be incorporated into an early warning system to predict PD loss.

	2019	2020 (Jan - Mar)
Female, n (%)	1067 (41.9)	484 (42.5)
Observed PTN Events	3992	1140
PTN Rate Overall Annualized	1 per 5.9 patient years 0.17 per-patient per year	1 per 5.5 patient-years 0.18 per-patient per year
Patients with Culture-Negative PTN, n(%)	678 (17.0)	191 (16.8)
Gram-Positive PTN, n (%)	1448 (36.7)	450 (39.5)
PTN-Free Patients, n (%)	32,554 (90.8)	27,471 (96.3)
Fungal PTN, n (%)	79 (2.0)	25 (2.2)
Patients with Any Infection who Experience PD Failure within 30 Days, n (%)	905 (22.7)	200 (17.5)
Patients with Gram-Positive Infection who Experience PD Failure within 30 Days, n (%)	214 (14.8)	54 (12.0)

PO1279

Smoking Is a Risk Factor for Endogenous Peritonitis in Peritoneal Dialysis Patients

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Background: Peritonitis is one of the most common complications observed in patients who are undergoing peritoneal dialysis (PD). PD-related peritonitis is associated with total mortality and transfer from PD to hemodialysis. Therefore, the prediction and prevention of peritonitis are important in PD patients. Exit-site infection (ESI) is an important risk factor for peritonitis. Whereas, there exists peritonitis without ESI and technical failure such as endogenous peritonitis in patients on PD. However, it is unclear that the prevention and prediction of endogenous peritonitis. Therefore, we investigated the risk of endogenous peritonitis in PD patients in this study.

Methods: We investigated the patients who were undergoing PD at our hospital and attended our hospital regularly from April 2015 to March 2020. We treated 22 cases of peritonitis in these patients; there were 18 cases of endogenous peritonitis without ESI and technical failure. We considered older age, female sex, obesity, diabetes mellitus, diverticulosis, and constipation as the important risk factors for endogenous peritonitis in patients undergoing PD. Therefore, we added these six factors as confounding factors with current and previous smoking history in the univariate logistic regression models. P values < 0.05 were considered statistically significant.

Results: We used univariate logistic regression models for the above-mentioned seven factors. Then, we defined age > 65 years as older age and body mass index > 25 as obesity. We defined patients who received purgative medication as having constipation. We found that diabetes mellitus ($p = 0.0106$), former or current smoking ($p = 0.0065$), and constipation ($p = 0.0065$) were statistically significant risk factors of endogenous peritonitis. Moreover, smoking and constipation were the most significant independent risk factors for endogenous peritonitis ($p = 0.0036$) in our multivariate logistic regression model.

Conclusions: In conclusion, smoking and constipation are significant independent risk factors of endogenous peritonitis in PD patients. The management of constipation and discontinuation of smoking may lower the risk of endogenous peritonitis in PD patients.

PO1280

Impact of Performing Cultures of Peritoneal Fluid Correctly on the Reduction of False-Positive and False-Negative Culture Rates in Patients on Peritoneal Dialysis (PD) Presenting with Peritonitis

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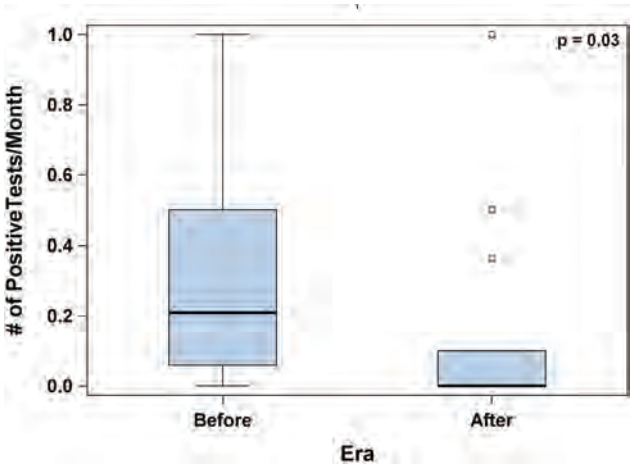
Background: Peritonitis is feared complication of PD and reason for loss of peritoneal membrane function. It negatively impacts the Quality metrics of home program performance. Preliminary observations in 2013 showed a high failure rate for treating culture negative peritonitis. Intervention based on our root cause analysis from 07/30/2013 to 12/31/2019 done to address disparities in performing proper culture techniques within hospital systems and outpatient home dialysis ambulatory clinics

Methods: Prior to 07/30/2013 (5-10 ml) of a cloudy PD fluid was injected into an aerobic and an anaerobic blood culture bottle. After 07/30/2013 we implemented a policy whereby 50 ml of PD effluent was used for centrifugation and the pellet was injected into culture bottles to preferentially concentrate the inoculum. We queried our EMR after 7 years as rates of peritonitis are low across programs. Data was extracted using diagnostic codes and laboratory request. Data was analyzed using student's 2 sample t test, Kruswall-Wallis and Wilcoxian analysis

Results: Total of 41 observations met our inclusion criteria for retrospective analysis. We had 26 observations before and 15 observations after the policy implementation. Mean number of tests ordered after 07/30/2013 declined. Number of false positive tests declined and number of true negative tests and true positive tests increased (p=0.02), indicating increasing specificity and a more targeted antibiotic regimen rescuing peritoneal membrane function early. No direct impact on survival nor any impact on technique failure was observed

Conclusions: A gap in proper collection of PD fluid was identified. We educated all residents, renal fellows, nursing staff and microbiology laboratory staff across the entire health care systems, and created an order sets within EMR systems to close this gap



PO1281

A Rare Cause of Peritoneal Dialysis-Associated Peritonitis

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Introduction: Peritoneal dialysis (PD)-associated peritonitis (PDaP) caused by the non-tuberculous mycobacterium (***M)*** species *Mycobacterium abscessus* (***MA***) is emerging as a severe infective complication of PD. ***MA*** causes disseminated infection in immunocompromised individuals and is resistant to classical anti-tuberculous drugs and antibiotics. Diagnosis of ***MA*** PDaP is often delayed, as it presents as a culture –ve peritonitis. Successful treatment requires a PD catheter (PDC) removal in addition to multiple anti-microbial therapies and results in a permanent switch to haemodiafiltration (HDF).

Case Description: A 50-yr-old ♂, presented with fever, abdominal pain and cloudy PD fluid (PF) after returning from a holiday. He was systemically well apart from a tender abdomen. PD exit site and tunnel appeared normal. CRP was 80.7 mg/L (0-5 mg/L) and WCC was 6.0 x 10^9/L. Empirical treatment for PDaP was commenced with intra-peritoneal Vancomycin + Gentamicin. Microscopy of the PF showed a WCC of 155/µL and –ve Gram stain. ***MA*** was cultured and confirmed by whole-genome sequencing. Clarithromycin, Amikacin, Imipenem + Cilastatin and Tigecycline were commenced. Emergency PDC removal with a peritoneal washout was performed. He was switched to HDF. Day16, Clarithromycin was stopped due to a prolonged QTc interval. Day26, he developed hepatopathy that resolved after cessation of Tigecycline. Amikacin + Imipenem was continued for 5 months and switched to Amikacin + Linezolid. He developed Amikacin-induced tinnitus despite therapeutic dose monitoring. He completed 20 weeks of therapy and remains free of infection.

Discussion: ***MA*** is an environmental ***M*** that is found in water, soil, dust and is related to ***M*** causing tuberculosis and leprosy. It is known to contaminate devices and medical products. It causes lung infections in the immunocompromised. Our patient had no such history. The duration between PDC insertion and this episode was 2 yrs, making this an unlikely cause. The history did not reveal any reason for contracting this organism. The optimum treatment duration and selection of anti-microbial therapy in the management of ***MA*** PDaP is unclear, primarily due to the paucity of confirmed cases and variability of the treatment regimens. PDC removal and peritoneal washout remain the mainstay of treatment. Our case highlights ***MA*** as an emerging organism in PDaP and physicians should be aware of it.

PO1282

A Unique Case of Encapsulated Peritoneal Sclerosis

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Introduction: Encapsulating peritoneal sclerosis (EPS) is a rare but devastating sequela of chronic inflammation in patients on peritoneal dialysis (PD). EPS is classically associated with filtration failure and can lead to recurrent abdominal pain and obstruction due to encasement of small and large bowel

Case Description: A 45 year-old Cambodian male with a past medical history of ESRD secondary to IgA nephropathy on PD for 10 years presented with loose stools and hypotension after dialysis. His medical history included CML complicated by spinal chloroma, paraplegia, neurogenic bladder and PVD with osteomyelitis resulting in bilateral AKA. He was previously admitted 14 days prior for culture negative (including fungal) peritonitis treated with intraperitoneal cefepime and C. difficile colitis treated with oral Vancomycin. Despite completing a course of antibiotics, he had persistent abdominal pain and inability to tolerate PO intake. Repeat diagnostic paracentesis on this presentation revealed a total cell count of 2519 with 98% PMN. But culture remained negative. CT of abdomen showed global thickening and calcification of his peritoneal membranes. Ex laparotomy was performed with biopsies confirming EPS. At the time of diagnosis, he did not exhibit signs or symptoms of dialysis failure with excellent ultrafiltration. Repeat microbiology studies showed fungal elements in the PD fluid, later identified as penicillium species mold. Patient was not started on Steroids and Tamoxifen due to underlying fungal peritonitis. He was transitioned to hemodialysis and treated with a prolonged course of amphotericin. Subsequent peritoneal studies showed increasing burden of mold despite intraperitoneal drains. His course was further complicated by recurrent upper GI bleed and inability to tolerate hemodialysis due to hypotension. Patient was eventually transitioned to comfort measures.

Discussion: The pathogenesis stilof EPS is poorly understood. Some of the risk factors include use of PD for > 5 yrs, high dialysate glucose concentrations, repeated episodes of peritonitis, which can cause structural and functional damage to the peritoneal membrane. Development of EPS is related to dialysis vintage and "second hits" like infection as demonstrated in this case. However, the case is unique in that he had no difficulty with his PD ultrafiltration, and we believe the fungal peritonitis was a late sequala of his EPS.

PO1283

Spontaneous Peritoneal Dialysis Catheter Expulsion: Our Experience

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Introduction: Mechanical complications of PD are a significant cause of technique failure. Amongst them, complete expulsion of the peritoneal catheter (PC) is rare.

Case Description: CASE1: 62-year-old woman with chronic kidney disease (CKD) secondary to unknown glomerulonephritis. PD was started after a failed transplant. She had two episodes of exit site infection (ESI) secondary to *Corynebacterium spp,* recovered. In 2001 she presented with pericatheter leak, solved after transient switch to hemodialysis for 2 months. In 2002 she was admitted with complete spontaneous PC extrusion (straight Tenckhoff PC 2 cuffs). She had no signs of ESI and denied using any topical medication. A contralateral PC was inserted with no complications. CASE2: 61-year-old woman with CKD due to anti-glomerular basement membrane disease. She received induction treatment with high-dose steroid therapy, with no response, so a straight Tenckhoff PC (2 cuffs) was placed and she started PD. 2 months later she presented a spontaneous PC expulsion with evidence of ESI with *Candida parapsylosis* that was adequately treated. After infection resolved, a contralateral PC was placed with no complications. CASE3: 68-year-old woman with CKD secondary to type 2 cardiorenal syndrome. She started on PD because of diuretic-resistant heart failure (straight Tenckhoff PC, 2 cuffs). She presented Pseudomonas aeruginosa relapsing peritonitis in 4 occasions, requiring taudolidine-urokinase PD catheter lock with good outcome. In 2018 she had an episode of ESI, again by *Pseudomonas aeruginosa* solved after a course of topical antibiotics as well as external cuff shaving. In 2019 she developed again ESI with *Pseudomonas areuginosa,* and despite topic treatment as per antibiogram exit site cultures remained positive. One month later she presented a spontaneous expulsion of the PC. A contralateral PC was placed without further infectious complications.

Discussion: We present an atypical complication in PD. Triggers for PC extrusion in our cases appear to be related to peritoneal leak in the first case, and to ESI in the remaining two cases. Steroids are likely disrupting exit site healing and fibrosis formation around the cuff, contributing to this infrequent complication. These risk factors should be identified and kept in mind to prevent the catheter extrusion.

PO1284

Polymicrobial Peritoneal Dialysis Peritonitis due to Eggerthella lenta, Parabacteroides Species, and Bacteroides distasonis

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Introduction: Peritionitis is a severe and common infectious complication among patients on peritoneal dialysis (PD). Most cases are due to Coagulase negative staphylococcus. Anaerobic bacteria constitute < 0.5% of the peritonitis in PD patients. This is a case of anaerobic polymicrobial PD peritonitis of rare pathogens without a clear intrabdominal source.

Case Description: 92 year old man with end stage renal disease who had a failed deceased donor renal transplant and was started on peritoneal dialysis 6 months ago was admitted for abdominal pain with cloudy peritoneal fluid for 3 days. Peritoneal fluid had cell count of 22,000 cells/ul. He was treated with intraperitoneal (IP) vancomycin and ceftazidime with improvement in abdominal pain and cell count downtrended to 2700/ul on Day four he was discharged with continued IP antibiotic administration. He was re-admitted in two days for worsening abdominal pain with a cell count of 14,000/ul. Patient had been correctly administering IP antibiotics with the assistance from his family members. CT abdomen pelvis with intravenous and oral contrast showed small bowel ileus likely due to the peritonitis. At this time the peritoneal dialysis catheter was removed and he was converted to hemodialysis. The peritoneal fluid cultures on Day 7 resulted Eggerthela Lenta and on Day 10 grew Parabacteroides species. Upon review his initial PD fluid culture prior to transfer from outside hospital was positive for Bacteroides Distastonis. Sensitivities were reported for only Eggerthela Lenta and Parabateroides species and they were both sensitive to metronidazole. Antibiotics were broadened to intravenous vancomycin, ceftazidime and metronidazole with clinical improvement in patient.

Discussion: To our knowledge, this is the first case of bacterial peritonitis from Parabacteroides species and Bacteroides Distastonis. There is only one case report of Eggerthela Lenta reported by Goupil et al. causing PD peritonitis. The PD fluid culture was slow growing and this highlights the potential need for anaerobic coverage in PD peritonitis without early pathogen isolation and/or failure of initial empiric treatment.

PO1285

A Rare Case of Trichoderma-Related Peritonitis in a Patient on Peritoneal Dialysis

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Introduction: Trichoderma spp are saprophytic fungi commonly found in the soil, decaying wood and humid environments. They are known to cause infections in immunocompromised hosts but rarely in peritoneal dialysis (PD) patients. Cases are infrequently reported in the literature and are associated with high morbidity and mortality.

Case Description: A 65yo white male with DM, HTN, HLD, ESRD on PD, was admitted with worsening abdominal pain for 4 weeks with low grade fever, chills, nausea and vomiting. His vitals were stable. Significant findings were a diffusely tender abdomen without guarding, rigidity or rebound tenderness. His PD effluent was cloudy. Labs were unremarkable. CT abdomen was negative for acute pathology. He was started on intraperitoneal vancomycin and ceftazidime as an outpatient as he had two earlier bacterial peritonitis episodes in the year. However, preliminary cultures from his clinic grew fungal elements. This prompted urgent PD catheter removal and conversion to hemodialysis. The fungus indentified was Trichoderma and he was started on IV Anidulafungin. Repeat PD cultures were negative and he was discharged on oral Voriconazole with follow up in ID clinic. Over the course of 2 weeks, he was readmitted twice with worsening abdominal pain. On the third admission, he had exploratory laparoscopy and found to have diffuse thrush like plaques all over the peritoneum. IV amphotericin B was added to inpatient antifungal regimen. However, he continued to deteriorate and elected to go home on hospice and passed away soon after.

Discussion: Diagnosis of fungal peritonitis in PD is challenging and oftentimes delayed. Occurrences usually follow treatment of bacterial peritonitis and mimics its clinical features. Most isolates of Trichoderma spp have shown resistance to fluconazole and 5- Fluorocytosine but show intermediate susceptibility to Amphotericin B, Itraconazole, Ketoconazole and Miconazole. Therefore, it is important to perform antifungal susceptibility tests and then adjust the final treatment. In conclusion, Physicians who treat patients on PD should be aware of the possibility of this opportunistic infection. Prompt antifungal treatment should be considered in cases of recurring peritonitis in the appropriate patients. More research is needed to guide early diagnosis and guide effective treatment of this rare fungal disease with high mortality.

PO1286

Streptococcus oralis Peritonitis in Peritoneal Dialysis

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Introduction: Peritonitis is the most common complication seen in peritoneal dialysis (PD). Although staphylococcal infections are most common, Streptococci are rare causes of ambulatory peritoneal dialysis (APD) peritonitis. We report a case of APD peritonitis due to Streptococcus oralis (also known as mitis) in a patient who habitually engages in nail-biting.

Case Description: A 57-year-old male with end-stage renal disease due to biopsy proven focal segmental glomerulosclerosis on PD since 2018 presented with 1 day of severe diffuse abdominal cramps. He has no known history of peritonitis. Vital signs were stable, and examination was notable for diffuse abdominal pain without rebound tenderness. PD catheter site was clean and dry. Abdominal CT scan did not reveal any acute intra-abdominal pathology. PD fluid was sent for cell count and culture. PD fluid was cloudy in appearance and amber in color. Due to concern for peritonitis, he was started on intraperitoneal vancomycin and tobramycin. Final fluid cell count was 20,900 WBCs/mm3 and final fluid culture was positive for Streptococcus mitis. He was successfully treated with 2 weeks of vancomycin, as he had an allergy to penicillin. He admitted that he is a habitual nail-biter. We educated him on the importance of hand hygiene and continuously adhering to a sterile dialysis technique.

Discussion: Streptococcus oralis is the most virulent of the streptococci viridians comprising normal human oral flora. It is primarily associated with dental caries but can have opportunistic pathogenicity in immunocompromised patients and can cause subacute infective endocarditis and septicemia if left untreated. Because the peritoneal cavity lacks robust innate immune response, it is a favored site for infection. Cefazolin is the antibiotic of choice for gram-positive cocci. Our patient denied breaking sterile technique but admitted that he is a nail-biter. He had no evidence of dental caries and didn't seed through hematogenous spread. The only possible route of transmission was direct contamination from biting of his nails. We recommended the use of a bitter flavored nail biting deterrent nail polish at the time of discharge that could help him break his habit.

PO1287

Effect of N-Acetylcysteine on Nontraditional Cardiovascular Risk Factors and Carotid Intimal Medial Thickness in Chronic Peritoneal Dialysis Patients

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Background: Accelerated atherosclerosis increases morbidity and mortality among PD patients. Various non-traditional risk factors (NTRFs) like oxidative stress (OS), impaired endothelial function (EF), micro-inflammation and increased homocysteine (HCS) have been implicated. N-acetyl cysteine (NAC) is an antioxidant, reduces HCS and has shown to improve EF and cardiovascular endpoints in HD patients. No study has looked at its effect on NTRFs in PD patients & its effect on structural atherosclerosis

Methods: Stable consenting patients on chronic PD (PD duration >3 months) were given oral NAC (600 mg twice daily) for 3 months. No changes were made in PD prescription. Demographic data, clinical, biochemical profile, EF, OS, HCS, highly-sensitive C-Reactive protein (Hs-CRP) and Carotid intimal medial thickness (CIMT, marker of structural atherosclerosis) were noted before and after 3 months. OS was measured by total anti-oxidant capacity (TAC) and thiobarbituric acid reactive substances (TBRAS). EF was assessed by brachial artery flow-mediated dilatation (FMD) subsequent to occlusion. CIMT of both carotids at 8 sites was assessed by high-resolution ultrasonography

Results: Of 80 patients approached by convenience sampling, 73 who completed study were analysed (2 refused consent, 5 did not follow-up at desired time). None of the patients reported any adverse events or discontinued the drug. In these patients, 28 were diabetics, 50 were males. Mean age, duration of PD and urine output: were 51.6±11.1 years, 11.6±3.2 months and 448.7±341.9 ml/day respectively. Table shows study parameters before and after NAC

Conclusions: In our open-label study NAC effectively reduced multiple NTRFs and atherosclerotic burden in PD patients. T

Parameter	Pre NAC	Post NAC	P-Value
HCS (µmol/L)	23.6±4.5	14.7±3.1	<0.001
HsCRP (mg/dl)	3.8±1.1	2.2±0.5	<0.001
FMD (%)	7.6±2.4	11.2±3.5	<0.001
TBARS (nmol/ml)	18.4±11.1	14.4±6.6	<0.01
TAC (Mmol/L)	1.01±0.2	1.14±0.3	0.03
CIMT (mm)	0.59±0.2	0.48±0.1	<0.001

NAC-N-acetyl cysteine ; HCS-homocysteine; HsCRP-highly-sensitive C-Reactive protein; FMD-brachial artery flow-mediated dilatation; TBARS-thiobarbituric acid reactive substances; TAC-total anti-oxidant capacity; CIMT-Carotid intimal medial thickness

PO1288

Outcomes of Cardiac Surgery in ESKD Patients on Hemodialysis (HD) vs. Peritoneal Dialysis (PD)

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Background: Patients with ESKD have worse outcomes following major cardiac surgery compared to those without ESKD. However, the outcomes of cardiac surgery in PD patients vs. HD patients are not well studied.

Methods: Using our EHR-based Cardio-Thoracic Surgery (CTS) registry, we compared the outcomes of 590 patients with ESKD on HD and PD undergoing Coronary Artery Bypass Graft (CABG) and/or valvular cardiac surgery. We compared baseline demographics and comorbidities between patients on PD and HD using Chi-square and t-tests for categorical and continuous variables respectively. We compared Length of Stay (LOS), days in the ICU, number of transfusions, and post surgical complications: (pericardial effusion, gastro-intestinal (GI) bleed, cardiac arrest, and in-hospital death) using Kruskal-Wallis test, Chi-square and Fisher's exact tests.

Results: Among 590 patients undergoing cardiac surgery, 62 (11%) were on PD, and 528 (89%) were on IHD. PD patients had a lower proportion of heart failure (50% vs. 72%), lower median Cardio-Pulmonary Bypass (CPB) time (106 vs. 122 minutes), and a higher proportion of dyslipidemia (92% vs. 79%) at baseline. HD and PD patients had no significant differences in post-operative length of stay, number of ICU days, and postoperative complications including GI bleed, pericardial effusion, and cardiac arrest (table 1). There was also no difference in mortality between the two groups. Out of 62 PD patients, 15 (24%) were converted to HD.

Conclusions: There were no significant differences in the measured outcomes between patients on HD vs. patients on PD post cardiac surgery and or valvular surgery.

Post-operative outcomes of HD vs. PD

Factor	N missing	Overall (N=590)	HD (N=528)	PD (N=62)	p-value
Intraoperative RBC Units	2	2.0[0.00,3.0]	2.0[0.00,3.0]	2.0[1.00,3.0]	0.84b
Post-op Length of Stay	0	11.0[8.0,18.0]	11.0[8.0,19.0]	10.0[7.0,17.0]	0.21b
ICU Total hours	2	95.7[52.2,188.8]	96.1[52.1,194.1]	93.3[57.6,164.9]	0.52b
Pericardial effusion	10	36(6.2)	32(6.2)	4(6.5)	0.99d
Gastrointestinal Event	0	48(8.1)	42(8.0)	6(9.7)	0.64c
Cardiac Arrest	0	29(4.9)	29(5.5)	0(0.0)	0.06d
In-Hospital Death	0	26(4.4)	25(4.7)	1(1.6)	0.51d

Statistics presented as Median [P25, P75], or N (column %).

p-values: b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's exact test.

PO1289

HAS2 Expression as a Novel Mechanism of TGF-β-Induced Phenotype Transition of Human Peritoneal Mesothelial Cells

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Background: Epithelial-to-mesenchymal transition (EMT) of human peritoneal mesothelial cells is one of the key mechanisms of peritoneal fibrosis in peritoneal dialysis (PD), which can be reversible at early stage of phenotype transition. Therefore,

the identification of novel molecular biomarkers of peritoneal EMT may facilitate the diagnosis of peritoneal damage allowing early initiation of treatment targeting peritoneal fibrosis. Hyaluronan (HA) is a glycosaminoglycan component of the extracellular matrix, produced by three members of HA synthase (HAS1, HAS2 and HAS3). HAS are known to be involved in EMT of cancer cells, however there is no information on the association of HAS and peritoneal EMT.

Methods: Peritoneal MCs isolated from overnight dwell dialysates from 16 PD patients (PD_MC) at 2 [baseline peritoneal equilibration test (PET)] and 6 (follow-up PET) months of the PD initiation. We divided PD patients into two groups based on the alteration of baseline and follow-up PD_MC morphology (Group 1 epithelial-epithelial and Group 2 epithelial-mesenchymal). RNA-seq analysis (Ebiogen, Korea) was performed in order to detect baseline molecular markers predicting mesenchymal phenotype in follow-up. Based on RNA-seq analysis, the expressions of HAS isoform were evaluated in MCs isolated from omentum (OM_MC) with an exploration of the role of HAS on TGFβ-induced EMT.

Results: RNA-seq analysis demonstrated the difference of gene expression related to EMT (27.6%), angiogenesis (30.2 %), cell migration (27.4%), and extracellular matrix remodeling (26.3%). Among them, HAS2 expression in baseline analysis showed the highest fold difference (28.5-folds) between group 1 and 2. In OM-MC, HAS1, HAS2 and HAS3 were constitutively expressed whereas only HAS1 and HAS2 were upregulated by TGFβ. TGFβ-induced changes in cell morphology and the expression of E-cadherin, α-SMA, and fibronectin were ameliorated by siHAS2, but not by siHAS1. HAS inhibitor (4-methylumbelliferone; 4-MU) also alleviated TGFβ-induced EMT.

Conclusions: This data suggest HAS2 plays a role in TGFβ-induced EMT of peritoneal mesothelial cells and modulation of HAS2 can protect the peritoneal fibrosis in PD patients. Both HA or HAS2 in peritoneal effluent of baseline PET also can be the markers predicting peritoneal EMT and fibrosis.

PO1290

Am80, a Synthetic Retinoic Acid Receptor α-Specific Agonist, Suppresses Peritoneal Fibrosis via Inhibition of Krüppel-Like Transcription Factor 5 in Mice

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Background: We presented previously that Am80, a synthetic retinoic acid receptor a specific agonist, inhibited the expression of Krüppel-like transcription factor 5 (KLF5) and reduced peritoneal fibrosis in mice. Now, we examined further detail about the mechanism to inhibit peritoneal fibrosis.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chlorhexidine gluconate (CG) into peritoneal cavity of ICR mice. Am80 was administered orally for every day from the start of CG injection. After 3 weeks of treatment, peritoneal tissues were examined using serial sections by immunohistochemistry to identify what kind of cells expressed KLF5. Am80 was given in mouse fibroblasts stimulated by transforming growth factor β1 (TGF-β1) and the expression of KLF5 was assessed by Western blotting.

Results: While KLF5 was expressed in the thickened submesothelial area of CG injected mice, Am80 treatment reduced KLF5 expression and remarkably attenuated peritoneal thickening. The numbers of TGFβ positive cells, a-smooth muscle actin (aSMA) or F4/80 positive cells were significantly decreased in Am80 treated group. KLF5 was expressed in aSMA, F4/80 or CD31 positive cells. Western blotting for KLF5 showed the tendency that KLF5 expression was decreased in higher concentration of Am80 in mouse fibroblasts stimulated by TGF-β1 in vitro.

Conclusions: These results indicate the KLF5 might not only associate phenotypical differentiation from fibroblasts to myofibroblasts but also regulate inflammatory responses and angiogenesis in peritoneal fibrosis model. Am80 can suppress peritoneal fibrosis through inhibiting these mechanisms.

PO1291

Peritoneal Protein Clearance and Lean Body Mass Index: Relationship in Peritoneal Dialysis Patients

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Background: An important feature of Peritoneal Dialysis (PD) is peritoneal protein loss (PPL) during dialysis. Peritoneal Protein Clearance (PPCl) is considered a better index as it reflects the individual differences of PPL and membrane function of both small and large pores. Higher PPCl has been reported to be associated with hypoalbuminemia and malnutrition, with some authors stating higher overall mortality. However, new studies failed to draw similar conclusions, arousing new insights on the peritoneal protein metabolism. Lean body mass index (LBMI) has been used as a useful marker of nutritional status in PD patients. The aim of this study was to evaluate the relationship between PPCl and LBMI.

Methods: Prevalent PD patients with peritoneal equilibration test and multi-frequency bioelectrical impedance analysis (BIA) were enrolled in the cross-sectional study in a single tertiary centre from January 2014 to December 2019. PPCl was calculated dividing 24h dialysate protein loss by serum total protein. LBM was assessed by BIA and LBMI was calculated dividing LBM by body height square. Spearman correlation test was performed to examine the association between body indexes and PPCl. Multiple regression linear model was used for exploring the associated factors of PPCl.

Results: We included 67 PD patients (54.1±17.3 years, 59.7% male, 31.3% diabetic). The mean evaluated parameters were: total Kt/V 2.52±0.8, nGFR 6.7±4.1 ml/min/1.73m2 and D/P creatinine ratio 0.63±0.01. The median PPL and PPCl were 5.2(3.8-6.7) g/day and 78.35(54.81-97.19) ml/day, respectively. PPCl was significantly positively associated with LBMI (r=0.401, P 0.001) and BSA (r=0.327, P 0.007), but not with BMI (r=0.109, P 0.381). Compared with conventional body indexes, LBMI had better performance in predicting higher PPCl. Multiple linear regression model, when adjusted for gender, nGFR, kt/V and diabetes, showed that older age (β=0.288, P 0.018), higher D/P creatinine ratio (β=0.232, P 0.050) and higher LBMI (β=0.334, P 0.014) were independent predictors of PPCl.

Conclusions: Higher LBMI is a marker of better nutritional state, which is associated with better survival in PD patients. In this study, higher LBMI was independently associated with higher PPCl, potentially explaining conflicting results on the impact of higher PPCl on mortality.

PO1292

Burden of Dialysis, Health-Related Quality of Life, and Employment Comparisons Between Peritoneal Dialysis and In-Center Hemodialysis: Findings from the DOPPS Program

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Background: The Dialysis Outcomes and Practice Patterns Study (DOPPS) and the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) collect information annually about quality of life, including employment and functional status. Differences in these domains by dialysis modality (PD vs. centre-based hemodialysis) may inform individuals in choosing a dialysis modality.

Methods: PD and HD patients with comparable characteristics were analyzed. For baseline patient questionnaire, we used logistic regression to analyze binary outcomes employment (full- or part-time versus unemployed), depression (CES-D ≥10 vs. <10), and functional status (≥11 vs. <11), and used linear mixed models to analyze continuous outcomes (PCS, MCS, and burden of kidney disease score). Change of outcomes were described descriptively.

Results: There were 3227 PD and 4544 HD patients at baseline. Burden of kidney disease scores were better for PD compared to HD (overall 9-point adjusted difference, [95%CI: 7-11]) with a higher proportion of patients on PD in the lowest burden range (10%-37%) compared to 8%-24% on HD, depending on country. PD patients also had better PCS and MCS, though these were less marked (overall adjusted difference of 0.9 [0.2-1.6] for PCS, 1.0 [0.2-1.9] for MCS). HD patients had worse functional status scores (adjusted OR HD vs. PD 0.6, [0.5, 0.8] for score ≥ 11); were less likely employed (OR=0.6, [0.5, 0.8]); and had worse CES-D scores (OR=0.8, [0.7, 1.0] for CES-D < 10). In Australia/New Zealand, HD patients had better MCS and CES-D scores and a higher proportion being employed than PD patients. 174 PD patients and 254 HD patients died within one year; 614 PD patients and 535 HD patients left the study between questionnaires. Changes over time in the continuous measures were small. Trends in employment, CES-D score, and functional status were small and not statistically significant.

Conclusions: Compared to HD patients, PD patients reported a lower burden of kidney disease score and among survivors, remains stable on either PD or HD over 12 months. This information, when shared with patients choosing a dialysis modality, could result in an increased uptake of PD.

Funding: Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUs/Support.aspx.

PO1293

H2S May Inhibit Peritoneal Dialysis-Related Fibrosis Through the Sulfhydrylation Regulation of PSMA7

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Background: Peritoneal dialysis (PD) is one of the first treatment methods for patients with end-stage renal disease, which has advantages on cardiovascular system protection, large toxin clearance and patients' life quality improvement. But statistics shows that the 5-year withdrawal rate of PD patients was around 50%, and ultrafiltration failure caused by peritoneal fibrosis is the main reason, and there is no effective clinical prevention and treatment. In our previous study, we found that the flora of PD patients was obviously maladjusted, and the production of H2S in the intestine was significantly reduced. Some evidences showed that H2S may alleviate PD-related fibrosis, suggesting that H2S may affect the fibrosis by regulating the level of sulfhydrylation, but the mechanism is not clear.

Methods: Rat peritoneal mesothelial cells were randomly assigned into different groups, 4.5% peritoneal dialysate group (PD group), PD+H2S supplement GYY4137 group and PD+H2S inhibitor PAG group. The expression of pyroptosis associated proteis, inflammatory factors and fibrosis related pathways in different groups were compared. The changes of protein sulfhydryl sulfhydrylation level were analyzed by HPLC/MS/ MS. The target protein and related pathway protein were up/down regulated by SiRNA and the downstream pathways expression were observed by PCR and Western blot.

Results: GYY4137 significantly reduced the expression of pyroptosis proteins (NLRP3, ccas-1, gsdmd-n), inflammatory factors (IL-6, IL-8, TNF - α) and fibrosis related proteins (p-smad3, Smad, TGF-β, VEGF) response to high glucose PD fluid. We found that the level of PSAM-7 sulfhydrylation in the PD group decreased significantly, but in GYY4137 group, the level of PSMA7 ulfhydrylation increased significantly. The expression of pyroptosis proteins, inflammatory factors and fibrosis related proteins were significantly increased after PSMA7 sulfhydrylation was interfered by mutant plasmids. The expression level of NLRP3 was up/down regulated by siRNA. The expression of downstream inflammatory factors and fibrosis-related proteins were significantly increased/decreased.

Conclusions: H2S has a protective effect on PD-related fibrosis through the PSMA7 sulfhydryl sulfhydrylation regulation, and further break the pathological changes of "pyroptosis- inflammation-fibrosis" axis and avoid the occurrence of inflammatory cascade reaction.

PO1294

Fatigue Predicts Higher Risk of Mortality in Peritoneal Dialysis Patients: A BRAZPD Analysis

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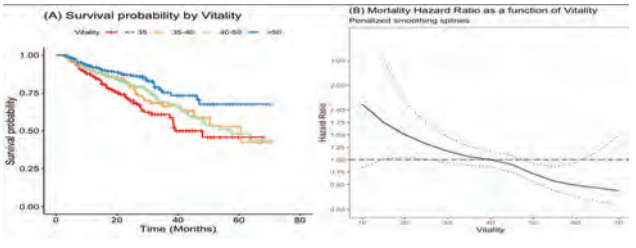
Background: End-stage kidney disease (ESKD) patients are often burdened by fatigue. Fatigue is a core outcome to peritoneal dialysis (PD) patients and providers, but its associations with clinical outcomes are unknown. We analyzed a nationally representative cohort of PD patients to test the hypothesis that higher fatigue independently associates with higher mortality risk.

Methods: We analyzed data from adult patients in BRAZPD, a nationwide Brazilian cohort across 122 PD centers. Patients incident to PD with complete KDQOL-SF survey in the first 90 days of dialysis were included. Fatigue was defined by the vitality subscale in four subgroups: >50 (high vitality), ≥40 to ≤50 (moderate vitality), >35 to <40 (moderate fatigue), ≤35 (high fatigue). We built four distinct models to estimate the association between fatigue and 12-month mortality: (i) Cox-proportional hazard model; (ii) competitive risk model accounting for technique failure events; (iii) multilevel survival analysis modeling clinic-level clusters; (iv) Cox regression with smoothing splines treating vitality as a continuous measure. Analyses were adjusted for age, comorbidities, residual kidney function (RKF), daily prescribed PD volume, and PD modality.

Results: We included data from 1,388 PD patients (mean age 58.5±15.47 years, 64% had RKF). Proportions of patients with high vitality, moderate vitality, moderate fatigue and high fatigue were 21%, 38%, 15% and 26%, respectively. Hazard-ratios (95%CI) for mortality estimated for the high vitality group (compared to high fatigue) were 0.39 (0.23-0.65), 0.41 (0.24-0.68) and 0.39 (0.22-0.68) for Cox, competitive risk and multilevel models, respectively. Results from the smoothing spline regression are shown in the Figure (B).

Conclusions: Higher fatigue in the initial months of PD was independently associated with 12-month mortality risk. Potential interventions targeting ESKD fatigue in PD patients may not only yield benefits in patient-reported outcomes but possibly also improve survival.



PO1295

Urgent-Start Peritoneal Dialysis: Experience in Mechanically Ventilated Prone Patients

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Background: Patients with respiratory failure who require prone positioning are not considered good candidates for PD due to the concerns for increased intra-abdominal pressure, impaired diaphragmatic movement, and leaking of peritoneal fluid. We addressed the COVID-related AKI (CRAKI) surge for renal replacement therapy (RRT) by initiating an acute PD program at Bellevue Hospital including prone patients.

Methods: All patients were in the ICU with COVID related hypoxic respiratory failure and acute kidney injury (AKI). 6/35 patients who received PD were treated for 16 hours per day in the prone position to improve oxygenation. The mean age was 54.6. The average BMI was 35.5. Patients were on mechanical ventilation 12-33 days. 3/6 patients were on CVVH however, switched to PD due to clotting. Patients were on PD for an average of 9.3 days. All PD catheters were placed at the bedside using an open cut down technique. PD was started the same day using manual exchanges. Dwell volume was gradually increased to 2 L. Exchanges were performed q1h while supine and q2h while prone, a total of 4-6 exchanges/day. The PD team coordinated timing with the prone team and ICU nurses to allow the continuation of the PD treatment. Patients were monitored clinically for abdominal distention and changes in respiratory mechanics.

Results: All 6 patients remained on PD for the duration of the hospitalization. There were no incidences of bowel injury, hemorrhage, exit-site infections, or peritonitis. None of the patients had any catheter malfunction. Leaking was addressed with temporarily reducing the dwell volume. Patients experienced slow draining which was due to kinking of the tubing during prone positioning. All patients were able to continue receiving PD without interruptions. Either no change or improvement in ABG and ventilator settings was noted after prone positioning and PD.

Conclusions: Due to COVID related surge, we saw a significant number of patients in the ICU with severe acute respiratory failure requiring prone positioning who also developed AKI requiring RRT. We were able to successfully provide acute PD in ventilator-dependent prone patients suffering from CRAKI. This required a team effort and some modifications in the conventional PD prescription.

PO1296

Inline Turbidity Measurement Using an Optical Sensor for Early Detection of Peritonitis

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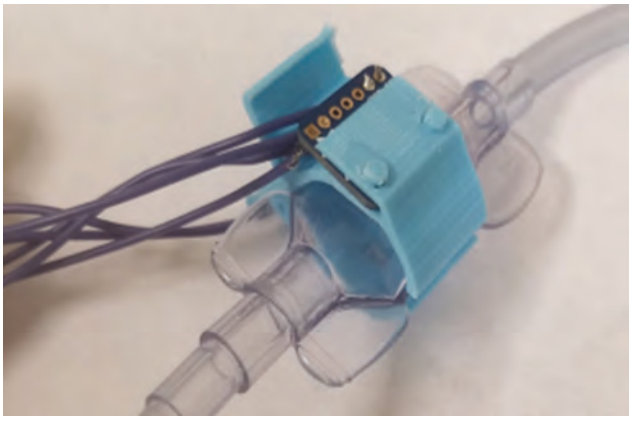
Background: Peritonitis, a serious bacterial infection, can occur in patients undergoing peritoneal dialysis (PD). Timely treatment is critical for peritonitis since delay in the initiation of antimicrobial therapy is linked with an increased risk of technical failure and death. Peritonitis was oftentimes presented with turbid PD spent dialysate induced by increased white blood cells (WBC) concentration. This can be detected by the change of light intensity transmitted through PD fluid onto an optical sensor. We have developed a low cost (<$10), reusable in-line optical sensor that can adapt to automated PD cycler tubing sets to detect turbidity in PD fluid.

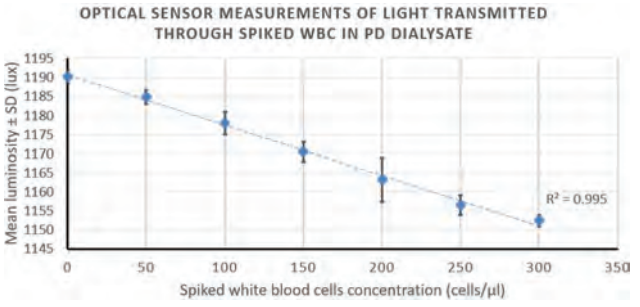
Methods: A optical sensor system with white-light LED light source was designed to clamp on the visualization chamber of Liberty cycler tubing set. Spent PD dialysate and fresh dialysate were tested through a drain line recirculation circuit by the optical sensor system at 50 and 100 ml/min flow rate. To mimic peritonitis, isolated white blood cells, ranging from 50-300 cell/ μl, were added to fresh dialysate and analyzed with the optical sensor.

Results: 12 deidentified peritonitis-negative (WBC <100 cells/μl) spent dialysate samples from stable PD patients were tested. Fresh dialysate had a similar signal magnitude compared with spent dialysate. A change of flow rate from 50 ml/min to 100ml/min did not affect the signal from the optical sensor at baseline. A linear relationship (R2=0.99) between increased concentration of WBC and decreased transmitted light intensity was captured by the optical sensor.

Conclusions: Change of WBC induced-turbidity in PD dialysate can be detected with a low cost optical sensor without alternation of an existing PD drain line.

Funding: Commercial Support - Renal Research Institute





PO1297

Peritoneal Dialysis (PD) Technique Training: What Features Influence Learning Time?

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Background: The adequate training of patients started on PD is an essential issue for technique success and basic to avoid and/or reduce complications. However, features affecting training duration have not been sufficiently studied so far. AIM: Identify features influencing PD training duration and their relation to first peritonitis episode timing and permanence on PD.

Methods: We retrospectively analysed all training sessions done with first time PD starters in our Unit (January 2001-December 2018). Demographic data on age, gender, end ESRD cause, Charlson morbidity index (CCI), number of training sessions, type of PD start, employment and education status, derivation and PD technique were recorded.

Results: 188 patients were trained, 72% male. Median age 55.49±15 yr. 25% were diabetic. Mean CCI: 4.9. Our patients required a median of 10 sessions (range 2-28) to gain sufficient skills performing the PD technique and feel confident, with a median of 19 days. Number of training sessions required increased with higher age ($p< 0.05$), higher CCI ($p< 0.05$) and diabetics ($p< 0.05$). Neither gender, cohabitation, type of PD start, education level, derivation type nor employment status were statistically significant factors affecting PD training. Assisted PD patients were older (54 vs 71 yo, p=0.00) and they required a higher number of training sessions (10 vs 15.7 sessions). Patients requiring longer training (>23 days) had more peritonitis episodes ($p< 0.05$), the first peritonitis episode happened sooner (15.7 vs 17.4 months, p=NS) and they remained less time on PD (32.57 vs 27.7 months, $p< 0.01$).

Conclusions: The PD training time needed depends on patient's age, diabetic status and comorbidities but does not relate to social, educational nor employment status. Patient's requiring less training sessions have less peritonitis episodes and it happens later, remaining longer on PD technique.

Funding: Government Support - Non-U.S.

PO1298

Clinical Outcomes of Infection-Related Hospitalization in Incident Peritoneal Dialysis Patients

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Background: Infection is the second leading cause of death in patients undergoing long-term dialysis. Peritoneal dialysis (PD) is associated with an increased risk of infection-related hospitalization (IRH) when compared with hemodialysis. However, the effects of IRH on clinical outcomes in PD patients have not been established. In this study, we investigated the influence of IRH on clinical outcomes in incident PD patients.

Methods: In total, 583 incident PD patients were selected from the Clinical Research Center Registry for End-Stage Renal Disease, a nationwide multicenter prospective observational cohort study in Korea. Incident PD patients who had been hospitalized for infection-related diseases were categorized as the IRH group. The primary outcome was all-cause mortality and the secondary outcome was technical failure. The median follow-up period was 29 months.

Results: Seventy-three PD patients (13%) were categorized as the IRH group. Multivariate logistic regression analysis showed that diabetes mellitus was a significant independent predictor for IRH (odds ratio: 2.43, 95% confidence interval [CI]: 1.12–5.29, p=0.007). The most common causes of IRH were peritonitis (64.9%) and respiratory tract infection (11.9%). Multivariate Cox proportional hazard model analysis showed that IRH was a significant independent risk factor for all-cause mortality (hazard ratio [HR]: 2.51, 95% CI: 1.12–5.62, p=0.026) and for the technical failure of PD (HR: 3.23, 95% CI: 1.90–5.51, p<0.001).

Conclusions: Our data showed that after initiation of PD, IRH was significantly associated with higher risk of all-cause mortality and technical failure. Careful consideration of infection-related disease is needed in incident PD patients.

PO1299

Fluoroscopic-Guided Peritoneal Catheter Insertion: Radiology Anthropometric Analysis for Determining Optimal Catheter Position

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Background: Placement of a functioning peritoneal catheter requires optimal catheter positioning. Traditionally the pubis symphysis has been used as a landmark for the true pelvis and referenced for catheter-tip positioning. This practice is based on physical-exam methods without the benefit of fluoroscopic imaging.

Methods: Retrospective cohort of adult, peritoneal dialysis patients in London, Ontario, who underwent percutaneous peritoneal catheter insertion using fluoroscopy spanning Feb 1, 2013 - Aug 1, 2017. Pre-specified anthropometric measures: 1) distance between deep pelvic space (outlined by caudal border of pooled radiocontrast injected intra-procedure) and cranial border of pubis symphysis; 2) distance between catheter-tip and cranial border of pubis symphysis - were measured using Citrix software of stored images. Anthropometric measures were contrasted according to sex via t-tests ($p<0.05$) and multivariable regression analyses, assessing relationships of potential predictors (age, BMI, prior abdominal surgery).

Results: 295 patients (69% male) underwent fluoroscopic catheter insertion during the study period. Average age was 60 ± 16 years (std. dev.), BMI 28 ± 5 kg/m^2. 52% of patients had no prior surgical history, 30% had 1 prior abdominal surgery, 18% had ≥2 prior surgeries. Average distance between deep pelvic space and pubis symphysis was 2.9 ± 1.5 cm, with females having a larger distance (3.4 ± 1.7 cm) compared to males (2.8 ± 1.4 cm; P=0.001); Female sex being associated with a 0.6 ± 0.2 cm, (P=0.03) increase in distance between the pubis symphysis and deep pelvic space as compared to males, adjusted for age, BMI, and number of prior abdominal surgeries. Stratified by sex: age, BMI, number of prior abdominal surgeries was not associated with distance between the pubic symphysis and deep pelvic space. Catheter-tip to pubis symphysis distance was 3.8 ± 1.7 cm and similar across sexes.

Conclusions: Fluoroscopic methods of outlining the deep pelvic space for peritoneal catheter positioning approximate traditional methods. Differences observed in the distance between the pubic symphysis and deep pelvic space according to sex may reflect the impact of anatomical differences and/or type of abdominal surgeries. However, catheter tip positioning remained unaffected.

PO1300

Blood Pressure Telemonitoring in a Large US Peritoneal Dialysis Population

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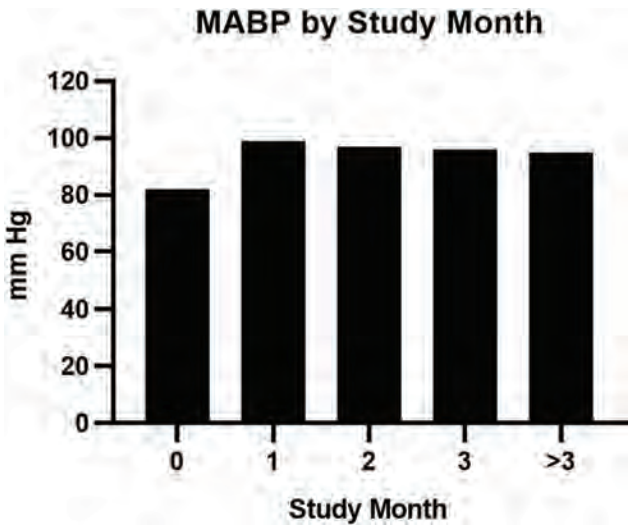
Background: Home remote monitoring (HRM) is a telehealth strategy that utilizes cellular technology to transmit patients' biometric data collected at home to the electronic health record of their dialysis provider. In April 2017, a HRM program was launched nationwide for peritoneal dialysis (PD) patients at a US large dialysis organization (LDO). Here, we report longitudinal trends in blood pressure (BP) control among PD patients participating in the HRM program.

Methods: Data for this analysis were abstracted from LDO electronic medical records. Patients included were dialyzing with PD and participating in the HRM program from Apr 2017-Jan 2020. The following outcomes were tracked monthly for all patients: mean BP, mean arterial BP (MAPB), number of transmitted BP measurements, number of BP alerts, and number of antihypertensive (anti-HTN) medications prescribed. BP alert thresholds were determined on a patient-by-patient basis by the treating physician.

Results: We identified 21,081 eligible patients (average age 59 years old; 57% male) from which >3.5 million individual BP measurements were transmitted. On average, there were 170 readings transmitted per-patient over the monitoring period of 43 months; in total, 764,658 total BP alerts occurred (36 BP alerts/patient). Only 34% of patients achieved the target BP of <130/80 mm Hg. We observed 30%, 23%, and 47%, of patients were prescribed 0, 1-3, and >3 anti-HTN medications, respectively. The most common action responding to BP alerts included changes in medications and in prescribed ultrafiltration volume. However, a significant percentage of PD patients did not see an improvement in MABP [Figure].

Conclusions: HRM identified a significant percentage of PD patients with uncontrolled BP. HRM could be a useful component of clinical programs designed to improve BP control and cardiovascular outcomes.



PO1301

Plasmatic Magnesium as a Marker of Nutrition and Inflammation in Peritoneal Dialysis?

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Background: There's an important prevalence of hypomagnesemia (hypoMg) in Peritoneal Dialysis (PD), namely due to magnesium (Mg^{2+}) losses in the dialysate. HypoMg has recently been associated with increased mortality in PD, a clearer fact in Hemodialysis. Processes involved seem to include alterations in body composition (BC) and inflammation, known as predictors of mortality in PD, beyond the risks immediately associated with hypoMg such as cardiac arrythmias. The aim of this study was to evaluate the correlations between plasmatic Mg^{2+} (pMg), BC, inflammation and nutrition in PD.

Methods: A prospective study included patients admitted at our Unit between 2010 and 2019, with simultaneous acquisition of bioelectrical impedance analysis (BIA) and pMg levels. Clinical and biochemical data were collected from clinical records. Spearman rank-correlation coefficient was used to report correlations.

Results: 54 patients were enrolled (mean age of 54.2±17.6 years, 61% men, 86.3% hypertensive and 33.3% diabetic). Mean pMg was 2.1±0.37 mg/dL and high-sensitivity C-reactive protein (hs-CRP) 10.8±20 mg/L. Inverse correlations were found between pMg and fat mass (rs=-0.356, p=0.009), body mass index (BMI) (rs=-0.414, p=0.002) and hs-CRP (rs=-0.334, p=0.014). Regarding serum markers of nutrition, a correlation with pre-albumin (rs=0.297, p= 0.036) was found. No correlations with phase angle, ratio of extracellular mass to body cell mass, lean body mass index, serum albumin, creatinine, total protein, total cholesterol or transferrin were found. Hs-CRP in turn correlates with BMI (rs=0.309, p=0.023), inversely with pre-albumin (rs=-0.353, p=0.012) and has a tendency to correlation with fat mass (rs=0.254, p=0.052) and albumin (rs=-0.267, p=0.051).

Conclusions: Lower pMg is associated with increased fat mass and higher BMI. No correlations were found with other nutrition markers. The obesity paradox is still controversial in PD and some authors defend that an elevated BMI is associated with neutral to deleterious impact on PD outcomes, fact explained by fat mass. Proinflammatory effects are also well described in relation to obesity in PD. In conclusion, hypoMg seems associated with poorer nutrition, increased fat mass and inflammation. Dietary interventions with Mg^{2+} supplementation could address this problem and should be a target of interventional studies.

PO1302

Feasibility of Using Platelet PGDprime® Rapid Assay as a Peritonitis Screen for Peritoneal Dialysis Patients

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Background: Peritoneal Dialysis (PD) patients carry the risk of bacterial infection via the catheter access site and the exit site. Peritonitis is suspected based on patient symptoms and the visual quality of effluent, but may not be confirmed until a sample of the effluent is tested at a central lab via culture. A result may take several days to generate. The Platelet PGD*prime* rapid test is a multiplexed immunoassay used to detect Gram-positive (GP) and Gram-negative (GN) bacteria in platelet units prior to transfusion. The utility of this rapid test for detection of bacteria in PD effluent was evaluated.

Methods: A sample (600 mL) of PD effluent from an asymptomatic patient was obtained and confirmed to be negative for bacteria by aerobic and anaerobic cell culture. Eight bacteria (5 GN & 3 GP) were grown in RPMI media and individually spiked at initially high levels into aliquots of the PD effluent, then serially diluted with the unspiked effluent in tenfold series. The CFU/mL of each starting spiking stock was quantified by OD at 620 nm. Each dilution was tested with PGD*prime* to determine the observed lowest detectable level of bacterial contamination by ten-fold dilution.

Results: The lowest detectable concentrations of bacteria are summarized in Table 1. The true Limit of Detection (LoD) for each species is between the lowest detectable concentration shown and the next lower logfold dilution level. Total test time was 25-35 minutes.

Conclusions: The PGD*prime* rapid test for bacteria in platelets can detect bacteria in PD effluent and may be useful for early detection of peritonitis in PD patients. Additional optimization to further adapt the test for PD effluent testing is underway.

Funding: Commercial Support - Verax Biomedical Incorporated

Table 1. Detection of Bacteria in PD Effluent by the PGDprime Rapid Test

Species	*Lowest Concentration Detected by PGDprime (CFU/mL)*
Klebsiella pneumoniae	*9.6E+04*
Serratia marcescens	*2.0E+04*
Pseudomonas aeruginosa	*2.7E+04*
Escherichia coli	*1.0E+04*
Klebsiella aerogenes	*2.5E+04*
Staphylococcus aureus	*3.5E+06*
Staphylococcus epidermidis	*2.3E+05*
Bacillus cereus	*1.0E+05*

PO1303

Omentectomy Reduces the Need for Peritoneal Dialysis Catheter Revision in Children: A Study from the Pediatric Nephrology Research Consortium

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Background: There are no recommended guidelines for performing omentectomy at the time of peritoneal dialysis (PD) catheter placement in the pediatric population. There are no multi-center studies investigating omentectomy and PD catheter revision in the pediatric dialysis population.

Methods: A multi-center, retrospective study was performed through the Pediatric Nephrology Research Consortium (PNRC). Data review included all incident tunneled PD catheters placed between 1/1/2011 – 12/31/2016 for first-time PD patients (ages 0-20). The primary outcome was the need for catheter revision and/or replacement following initial placement. Multivariable logistic regression was used to determine the independent association of omentectomy with catheter revision/replacement.

Results: Data from 184 patients (62.5 % male; 35.4 % glomerulonephritis) from 8 centers were analyzed. Median age at PD catheter insertion was 7.4 years. Omentectomy was performed in 67 children at the time of catheter placement (36.4%). Revision or replacement was required in 63 children (34.2%); median time to revision/replacement was 38.5 days (IQR 20.5, 109) after catheter insertion. Revision/replacement of the catheter occurred in 23.9% who had an omentectomy, compared to 52.2% without omentectomy (p=0.0005). Compared to younger children, those ≥ 6 years of age at the time of PD catheter placement had decreased risk of catheter revision/replacement (18.2% age ≥ 6 vs 56.5% age < 6, p <0.001). After adjusting for all clinical and surgical covariates, omentectomy reduced need for revision by almost 70%, and revision was 4x more likely in those < 6 years of age.

Conclusions: This multi-center study is the first to show that omentectomy at the time of PD catheter placement in pediatric patients is associated with decreased PD catheter revisions. Omentectomy should be strongly considered at the time of PD catheter placement, especially in children < 6 years of age who are at high risk for PD catheter malfunction.

PO1304

Quality Improvement Initiative: Suboptimal Utilization of Loop Diuretics in Peritoneal Dialysis Patients

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Background: The prescription of high dose loop diuretics is safe and beneficial for PD patients to increase urine output, control of volume status, and decrease the need for high PD fluid glucose concentrations. The aim of this study is to assess the current state and develop an algorithm for rational diuretic use in PD pts to optimize dose, frequency, and reduce pill count in patients with urine output while reducing diuretics in anuric patients.

Methods: This was a prospective cohort QI initiative in prevalent PD pts. The algorithm considered PD fluid glucose > 1.5 % used, the volume status, current and historical urine volume trend, and clinical assessment. The dosing of loop diuretics was increased in pts with residual urine output > 200 ml/24 hrs when increased ultrafiltration was needed, while diuretics were stopped in anuric pts. The outcomes were the proportion of pts on loop diuretic in those with and without urine, the dose (median total daily,

frequency) and the pill count before and 3 months after the intervention. In the algorithm, Furosemide prescriptions of 40 mg tablets were converted to 500 mg tablets divided as needed where possible.

Results: The study included 91 pts, mean age 63 yrs, 45% female, 75% Caucasian, 64% with DM, median time on PD of 1.58 yrs. Furosemide was the only loop diuretic used. At base line median total daily dose was 120 mg, BID 27 %, OD 73 %, and mean pill count was 3.6 pills/day. The proportions of patients prescribed diuretics among those with and without urine output were 54/84 (63%) and 8/17 (47%) respectively. Three months after the intervention the median total daily dose was 240 mg, BID 53 % and OD 47%, mean pill count was 2.96 pills/day, and the proportions of pts on Furosemide for those with and without urine output improved to 85% and 27% respectively (all changes $p < 0.05$).

Conclusions: This short-term study suggests that QI intervention using an algorithm aimed at optimizing loop diuretic use in PD patients based on PD fluid glucose concentration used, and urine volume can increase the prevalence of diuretic use, increase the single and total daily dose, improve dosing frequency, and reduce pill burden in patients with urine output while reducing unnecessary use in anuric pts. This study is ongoing to examine outcomes of urine volume, glucose load of PD fluid, and electrolytes with the intervention.

PO1305

Assessing Fluid Status of Peritoneal Dialysis Patients with Assistance of Lung Ultrasound (Fluid-PLUS)

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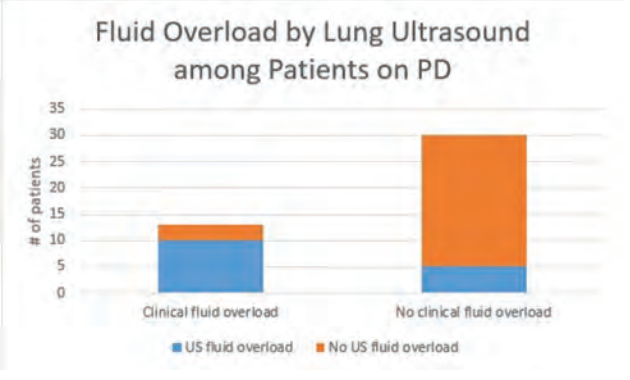
Background: Fluid overload (FO) is common in patients on dialysis, and is associated with increased cardiovascular morbidity and mortality. Clinical examination is limited in detecting FO. Lung ultrasound (US) is a portable and relatively inexpensive objective measure of FO. In this study, we aimed to evaluate the potential utility of lung US for evaluation of FO in patients on peritoneal dialysis (PD) in the ambulatory setting.

Methods: This is a cross-sectional, observational study at 4 home dialysis clinics in Northern California. Adult patients on PD attending routine outpatient visits were asked to participate. Patients on PD for less than 3 months or endorsing new or worsening shortness of breath were excluded. Participants underwent lung US examination. Based on the total number of B-lines, patients were classified as no US-fluid overload (< 16 lines), or US FO (>= 16 lines). Independently, nurses clinically evaluated patients' fluid status and determined if a patient had clinical FO or no clinical FO.

Results: 43 patients underwent full evaluation. Mean age was 55 +/- 15, 28% were female, 51% of patients had diabetes mellitus, and median PD vintage was 19 (IQR 10-37) months. Clinically, 13 (30%) of patients had FO. Lung US identified 15 patients (35%) as having FO. Clinical and US findings were congruent in 35 (81%) patients, but discordant in 8 (19%) of patients. Of the 30 patients without clinical FO, 5 (17%) were identified with US FO. On the other hand, of the 13 patients with clinical FO, 3 (23%) had no US FO. – Figure (1). Agreement between clinical examination and lung US was moderate (kappa 0.58, 95% CI 0.32 to 0.84).

Conclusions: Lung US may identify a subset of patients with FO missed by clinical examination. Further studies are required to evaluate the impact of managing patients according to lung US findings on clinical outcomes.

Funding: Commercial Support - Satellite Healthcare



PO1306

Use of Incremental Peritoneal Dialysis: Impact on Clinical Outcomes and Quality-of-Life Measures

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Background: Incremental peritoneal dialysis (PD), defined as a PD prescription that is less than the standard, full-dose prescription, has been suggested as a means of preserving residual kidney function and offering better quality of life; however, published evidence is limited.

Methods: We considered adult patients initiating PD between 31 Jul 2015 and 31 May 2019. Patients with body weight <40 kg, limb amputation, or estimated glomerular filtration rate (eGFR) >20 mL/min during first 4 weeks on PD were excluded. Exposure group was ascribed (incremental vs full PD) based on PD prescription during dialysis weeks 5 to 8. Incremental PD was defined by treatment frequency, exchanges/day, and exchange volume (for continuous ambulatory PD [CAPD] patients) or by treatment frequency and presence/absence of last fill (for automated PD [APD] patients). Analyses were performed separately for CAPD and APD patients: for each, incremental PD patients were propensity score matched to eligible full PD patients. Patients were followed for up to 12 months until censoring for loss to follow-up or study end. Outcomes were compared using Poisson models (mortality, hospitalization, PD failure), linear mixed models (eGFR), and paired t-tests (Kidney Disease Quality of Life [KDQOL] domain scores).

Results: Among CAPD patients, compared to those on full PD, incremental PD use was associated with better KDQOL scores on 3 domains: physical composite score (42.5 vs 37.7, P=0.03), burden of kidney disease (60.2 vs 45.6, P=0.003), and effects of kidney disease (79.4 vs 72.3, P=0.05). Hospitalization and mortality rates were numerically lower (0.77 vs 1.12 admits/patient-year, P=0.09 and 5.0 vs 10.2 deaths/100 patient-years, P=0.22); there was no association with residual eGFR or PD failure rate. Use of incremental PD was not differentially associated with any outcome among APD patients.

Conclusions: These results suggest that it may be beneficial to use incremental PD in the context of CAPD, particularly with respect to quality of life. No significant benefits were detected among patients initiating APD. No detrimental effects of using incremental PD were observed for either PD type.

PO1307

Combination of Hypertension and Preexisting Cardiovascular Disease and Mortality in Patients on Continuous Ambulatory Peritoneal Dialysis

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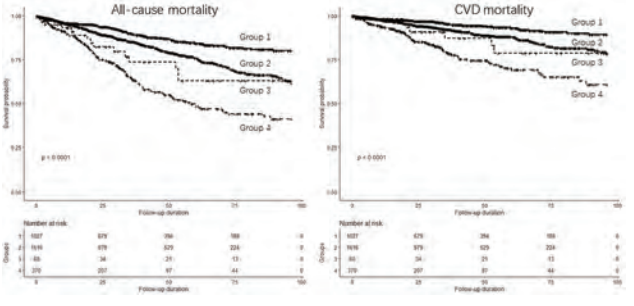
Background: Little is known about whether combination of hypertension and pre-existing cardiovascular disease (CVD) is more strongly associated with outcomes compared with either comorbidity alone in patients on continuous ambulatory peritoneal dialysis (CAPD).

Methods: We conducted a retrospective study of 3073 incident Chinese patients on CAPD from five dialysis centers between January 1, 2005 and December 31, 2018 in a real-world setting. All patients were divided four groups: group 1 (patients without either hypertension or pre-existing CVD); group 2 (patients with only hypertension); group 3 (patients with only pre-existing CVD); group 4 (patients with both hypertension and pre-existing CVD). The association between interesting comorbidities and mortality was analyzed using Cox regression models.

Results: Over a median of 33.7 months of follow-up, 581 (18.6%) patients died, with 286 (9.3%) CVD mortality. The incidence of all-cause mortality was 32.2, 56.1, 74.4, and 131.0/1000 patient-years, and the incidence of CVD mortality was 15.0, 28.2, 34.7, and 69.6/1000 patient-years in group 1, 2, 3, and 4, respectively. Cumulative survival and CVD mortality-free survival were lowest in those with both hypertension and pre-existing CVD (Figure 1). After adjusting for the demographic characteristics and laboratory parameters, group 4, 3, and 2 had 3.07 (95% CI 2.23 to 4.22), 2.05 (95% CI 1.11 to 3.80), and 1.38 (95% CI 1.08 to 1.77) of hazard ratios for all-cause mortality, and 3.20 (95% CI 2.04 to 5.03), 2.09 (95% CI 0.85 to 5.15), and 1.56 (95% CI 1.09 to 2.23) of hazard ratios for CVD mortality, respectively, compared to the group 1.

Conclusions: Combination of hypertension and pre-existing CVD was more strongly associated with mortality compared to either comorbidity alone in CAPD patients.



PO1308

Returning to Peritoneal Dialysis After Kidney Transplant Failure Is a Valuable Option

Ana Gabriela J. T. Melo, Rayra G. Ribeiro, Daniela Via Reque Cortes, Géssica S. Braga Barbosa, Carolina S. Martins, Luiza K. Araujo, Benedito J. Pereira, Hugo Abensur, Rosa M. Moyses, Rosilene M. Elias. *Universidade de Sao Paulo, Sao Paulo, Brazil.*

Background: The prognosis for patients returning to peritoneal dialysis (PD) after a failed transplant is poor and associated with peritonitis and transfer to hemodialysis. PD has an advantage over hemodialysis in preserving residual renal function, which is associated with better outcomes, including survival. Maintaining immunosuppression after starting PD can preserve transplant function but can also increase the risk for infection, and therefore is still arguable.

Methods: We have reviewed electronic charts of patients on PD in the last 8 years in a tertiary academic hospital. We compared survival, residual diuresis and reasons to discontinue PD in 2 groups: patients with graft failure that returned to PD (PD-Ktx, N=17) and other clinical conditions (PD-other, N=153). Reasons for stopping PD therapy included: dialysis inadequacy, kidney transplant, death, transfer to another center, and peritonitis.

Results: The median follow-up was 36 (12,71) months, which was similar between groups [45 (18,96) in PD-Ktx vs. 35 (12,70) months in PD-other, p=0.403]. Patients from PD-Ktx group were lighter than those from PD-other (57.2 ± 14.7 vs. 66.1 ± 16.1kg, p=0.032). Initial and final diuresis volumes were similar among groups (p=0.879 and p=0.698, respectively). Reasons for stopping PD therapy in PD-Ktx and PD-other groups were dialysis inadequacy (17.6% and 20.9%, respectively), kidney transplant (17.6% and 15.7%), death (5.9% and 12.4%), transfer to another center (17.6% and 20.9%), and peritonitis (17.6% and 14.4%). These outcomes were not significantly different between groups (p=0.921). Four out of 17 patients from PD-Ktx maintained immunosuppression and none of those had peritonitis. Kaplan Meier survival comparing PD-Ktx and PD-other showed there is no difference in stopping PD due to peritonitis (log-rank 0.543), which was confirmed in a Cox regression adjusted for weight, diabetes, residual diuresis and age (p=0.493).

Conclusions: Clinicians should leverage the risk of peritonitis versus extend PD technique by preserving residual diuresis in patients with allograft failure returning to PD. We have found similar outcomes in the current study. However, whether withdrawal immunosuppression is needed for these patients requires further investigation.

PO1309

Five-Year, Prospective, Observational, International Study on the Impact of Decision-Making Tools for Choice of Renal Replacement Therapy Modality

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Background: Decision-Making Tools (DMTs) are still not widely used but are considered the Gold Standard to ensure patients are well informed to choose renal replacement therapy (RRT) modality. OBJECTIVE: To analyze the impact of a structured modality information program (via DMTs) on RRT modality choice and start.

Methods: All 2014-2017 predialysis patients (pts) with CKD G4-G5 and those starting unplanned dialysis without a prior information process underwent a DMTs process for RRT choice and were followed up to Dec.31st, 2018. DMTs included values evaluation, RRT information with different tools, staff deliberation support and patient modality choice. Results shown as percentage of pts who reached a certain stage over the total number of pts under evaluation.

Results: 2012 pts (mean age 61 y.) from 48 clinics (cl.) in Poland (PL, 19 cl., 980 pts), Romania (RO, 12 cl., 351 pts), Hungary (HU, 10 cl., 341 pts), Germany (DE, 6 cl., 292 pts) and Argentina (AR, 1 cl., 48 pts) underwent DMTs. Staff considered PD contraindicated in 29% of pts, hence optimal candidates for HD/PD were 1408 pts. (mean age 60y. and 46% prone for a home therapy). Early referral (≥3 m. in clinic before DMT started): 51%. Aids used included written information (97% of pts), DVD in 27% and HD/PD utility visits in 49%. Relatives' participation in the process was 82%. Most pts (91%) considered the program useful whilst 64% of staff felt that this program was better than the prior one. PD choice (35%) varied among countries: 15% (RO), 30% (PL), 36% (HU), 62% (DE) and 98% (AR). For pts who had started dialysis by study closure (n=948), PD as chronic RRT was 31% (9% after an unplanned HD start); 13% (RO), 27% (PL), 34% (HU), 54% (GE) and 83% (AR).

Conclusions: Use of DMTs at the time of RRT modality choice complies with patient empowerment and decision sharing (patients-relatives-staff). PD choice and take-on varied among countries. Most patients who chose PD were chronically ascribed to PD representing at least one third of the suitable patients for both dialysis modalities.

PO1310

Peritoneal Dialysis or Haemodialysis for Polycystic Kidney Disease? Ten Years' Experience in a Single Centre

Zi Chan, Ka Lok Chan, Chi Kwan Lam, Wai ping Law, Wai lun will Pak, Patrick Y. Wong, Sunny S. Wong. *United Christian Hospital, Hong Kong, Hong Kong.*

Background: When polycystic kidney disease (PKD) progresses into end-stage renal disease (ESRD), the choice of dialysis modality is not straight forward. PKD may increase risk of complication and technique failure (TF) in peritoneal dialysis (PD). We looked at the long-term outcomes of PKD patients put on either PD or haemodialysis (HD).

Methods: New cases of ESRD due to PKD entered into dialysis program of a regional hospital in Hong Kong from December 2009 to November 2019 were identified. Their baseline demographics, mean kidney size and clinical outcomes were recorded. Hong Kong has a 'PD first' policy. But for PKD patients, the decision to start PD or HD is by the nephrologists' clinical judgment. For statistical analysis, chi-square test and t-test were used for categorical and continuous variables respectively. Kaplan-Meier curve was used to analyse survival.

Results: A total of 45 patients were identified, 31 were put on PD, 14 were put on HD. Their baseline characteristics were shown in Table 1. HD patients had higher mean kidney size to body weight ratio compared to PD patients. The median survival of those on PD (7.1 years) and HD (7.2 years) were not significantly different. For patients on PD, the 5 year TF rate was 0.22, which was similar to overall PD patients in our centre. Four patients had early TF (mean time 1.6 years). Two of them had significant pressure symptoms, the other two had inadequate dialysis. Further analysis showed that for those with TF, both mean kidney size and mean kidney size to body weight ratio were significantly higher than those without TF (Table 2).

Conclusions: This study showed that for PKD patients with moderate enlarged kidneys, PD could be a reasonable choice. However, for patients with very large kidneys, early TF rate with PD was high, HD would be a better choice for these patients.

Table 1

	PD	HD	p-value
Patient number	31	14	
Age	54.9 ± 8.5	53.0 ± 10.0	0.513
Gender (male)	45.2%	35.7%	0.553
Diabetes Mellitus	22.6%	0.0%	0.053
Hypertension	54.8%	57.1%	0.885
Previous abdominal surgery	12.9%	14.3%	0.899
Mean kidney size (cm)	15.7 ± 4.5	17.7 ± 7.3	0.266
Mean kidney size to body weight ratio (cm/kg)	0.25 ± 0.08	0.32 ± 0.12	0.029
Liver involvement	61.3%	50.0%	0.674

Table 2

	Early TF	No early TF	p-value
Patient number	4	27	
age	53.0 ± 7.7	55.2 ± 8.7	0.638
Gender (male)	50.0%	44.0%	0.835
Diabetes Mellitus	0%	25.9%	0.247
Hypertension	50.0%	55.6%	0.835
Previous abdominal surgery	0.0%	14.8%	0.409
Mean kidney size (cm)	20.0 ± 5.3	15.0 ± 4.1	0.036
Mean kidney size to body weight ratio (cm/kg)	0.32 ± 0.08	0.24 ± 0.07	0.048
Liver involvement	75.0%	59.3%	0.546

PO1311

Peritoneal Dialysis in the Setting of Acute Brain Injury, an Underappreciated Modality

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Introduction: Dialysis is complicated in the setting of acute brain injury due to a number of factors including acute shifts of solute, acute acid base shifts, need for anticoagulation, and changes in intracranial pressure. For these reasons, CRRT is the modality of choice when renal replacement therapy is needed. PD is less discussed but shares many of the benefits often attributed to CRRT. We describe a case successfully managed with PD.

Case Description: A 25-year-old male with history of ESRD secondary to FSGS on CCPD for 5 years presented to the hospital with headache and altered mental status. He was in his usual state of health until the day prior to admission. Initial imaging revealed a large intraventricular hemorrhage extending to the 4th ventricle. He underwent an emergent right depressive hemicraniectomy and clot evacuation. Patient was admitted to NCCU. Post-operative imaging revealed worsening cerebral edema, intraventricular hemorrhage, and hydrocephalus. As the patient had a functioning tenkhoff catheter, the decision was made to continue peritoneal dialysis, which he tolerated well until the need for a percutaneous gastrostomy tube arose. He was transitioned to hemodialysis transiently but returned to peritoneal dialysis once he was able to tolerate oral food. He has now continued on PD for 1 year.

Discussion: In the dialytic management of patients with acute brain injury, a number of considerations must be undertaken including the avoidance of hypotension to minimize ischemia reperfusion injury and maintain cerebral perfusion pressure, avoidance of anticoagulants that can precipitate or worsen bleeding, the potential for the precipitation of cerebral edema by rapid solute clearance and osmotic dissipation of therapeutic hypernatremia, and the mitigation of intracellular acidosis from bicarbonate delivery. Peritoneal dialysis is an ideal but underreported modality as evidenced by the case presented.

PO1312

Peritoneal Ultrafiltration Is Associated with Improvement of Functional Class in Patients with Congestive Heart Failure

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Background: Congestion is considered an integral component of heart failure syndrome and is a key driver of adverse outcomes. Peritoneal ultrafiltration (PUF) has emerged as an efficient therapeutic modality for management of fluid overload in patients with congestive heart failure (CHF) without end-stage kidney disease (ESKD). The efficacy of therapies of CHF are conventionally assessed through their effect on New York Heart Association (NYHA) classification. We sought to explore the reported impact of PUF on functional class of these patients.

Methods: Articles cited in PubMed database using keywords "heart failure", "peritoneal ultrafiltration", and "peritoneal dialysis" were searched. Available data from contemporary clinical trials of PUF in patients with CHF (without ESKD) that were performed between January 2010 and August 2019, and included more than 20 patients were selected and reviewed. Those trials evaluating the impact of PUF on NYHA functional class were included. Pertinent data were extracted and recorded.

Results: Out of 10 clinical studies meeting the criteria, 4 did not have the needed data on NYHA class; 6 studies (3 retrospective and 3 prospective) with a total of 408 participants and a mean age of 71.9 were included. The pre-PUF mean left ventricular ejection fraction and weight were 34.4% and 78.6 Kg respectively. The median follow up was 13.7 months. There was substantial variation in the reporting of time point for various endpoints. These studies unanimously reported improvement in NYHA functional class, which was close to -1 class for those that assessed the entire study population.

Conclusions: Available data based on contemporary clinical trials suggests that PUF, when used for management of patients with CHF, is associated with improvement of functional class. This finding is in keeping with our previous report on the salutary impact of PUF on volume status of these patients. Future controlled studies are needed to explore whether these benefits would translate into improved survival.

PO1313

Blood Urea Nitrogen/Creatinine Ratio and Mortality in Patients on Continuous Ambulatory Peritoneal Dialysis

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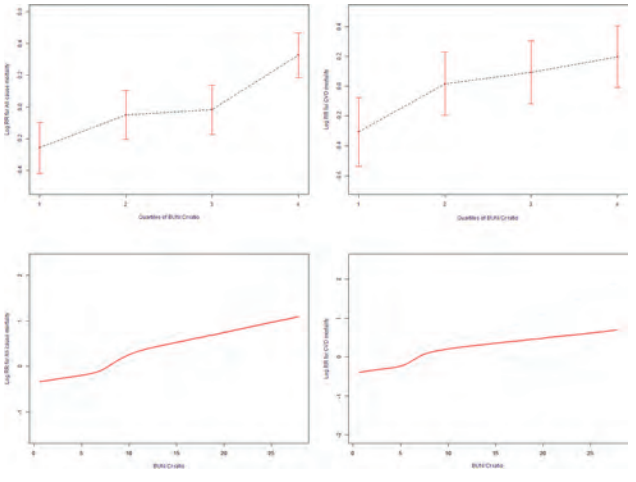
Background: Little is known about the association between the Nitrogen/Creatinine (BUN/Cr) ratio and mortality in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods: We conducted a retrospective study of eligible 2837 patients on CAPD from five dialysis centers in Chinese between January 1, 2005 and December 31, 2018. We calculated baseline BUN/Cr ratio, and then estimated the hazard ratio (HR) of BUN/Cr ratio for all-cause mortality using Cox hazard regression models, and used the restricted cubic spline curve to evaluate the association between the BUN/Cr ratio and mortality, with adjusting for confoundering factors.

Results: The median age of at baseline was 50.0 years (39.0-61.0) and the baseline median BUN/Cr ratio was 7.02 (5.43-9.13). The median observational period was 35.3 (18.3-61.9) months. During this period, 509 (17.9%, 95% CI 16.5 to 19.4%) of 2837 patients died, with 253 (8.9%, 95% CI 7.9% to 9.9%) CVD mortality. The incidence of all-cause mortality was 39.8, 48.9, 50.2 and 70.7/patient-years, and CVD mortality incidence was 19.0, 26.0, 28.1, 30.9/1000 patient-years among quartile 1, quartile 2, quartile 3, and quartile 4, respectively. When using BUN/Cr ratio of ≤5.43 as a reference, those with BUN/Cr ratio ≥9.14 had 1.72 (95% confidence interval, 1.34 to 2.22) of HR for all-cause mortality and 1.66 (95% confidence interval, 1.15 to 2.40) of HR for CVD mortality, after adjusting for baseline characteristics and laboratory variables. Cubic spline showed there was a linear association between the baseline BUN/Cr ratio and the risk of all-cause and CVD mortality, with a higher risk of mortality at a higher BUN/Cr ratio (Figure 1).

Conclusions: In conclusion, the BUN/Cr ration at the start of dialysis therapy was independently associated with all-cause and CVD mortality among CAPD patients, with a higher risk of mortality at a higher BUN/Cr ratio.



PO1314

Abstract Withdrawn

PO1315

Between Gradients and Ratios

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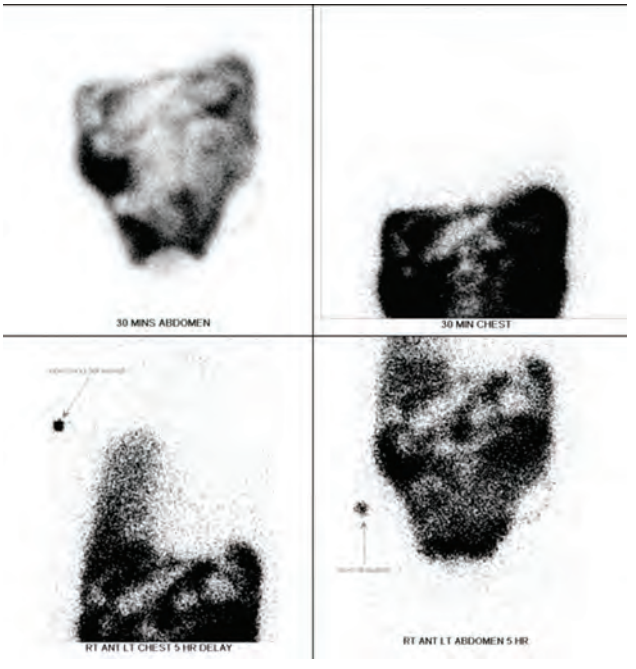
Introduction: Hydrothorax due to peritoneal dialysis is a rare but known outcome from dialysis mainly in continous ambulatory peritoneal dialysis [CAPD]. Around 80% cases are due to a pleuroperitoneal fistula (PPF), an abnormal communication between the pleural and peritoneal space allowing leak of dialysate. A pleural fluid glucose to serum glucose gradient of >50 mg/dl is 100 % specific for detecting the leak of glucose rich dialysate via the fistula.

Case Description: A 63-year-old man with history of heart failure with reduced ejection fraction and end stage renal disease [ESRD] on continuous cyclic peritoneal dialysis [CCPD] for 3 months, presented with recurrent hydrothorax. CXR showed worsening right sided hydrothorax despite a recent paracentesis. He continued CCPD as his initial pleural to serum [PF-S] glucose gradient was normal at 21 mg/dl. However, PF-S glucose ratio was >1 raising the clinical suspicion. For confirmation, a peritoneal scintigraphy with nuclear technetium 99 scan was performed that revealed a pleuroperitoneal fistula as the source of the recurrent hydrothorax.

Discussion: Peritoneal dialysis can be complicated by development of a hydrothorax in both CAPD and CPPD. Hydrothorax development is often attributed to a pleuroperitoneal leak which can be congenital or acquired. Initial diagnosis can be supported by increased PF-S glucose gradient >50mg/dl, but in our case, this did not prove to be a reliable indicator. Literature suggests that the pleural effusion is unlikely to be due to a pleuroperitoneal communication with a low PF-S glucose gradient of <50 mg/dL. However, there is also evidence that supports that peritoneal leak as the only cause for pleural glucose to be higher than the serum, i.e. a PF-S glucose ratio >1.0. The PF-S glucose > 1.0 in our case also supports the higher sensitivity of this approach.



PO1316

Impact of Obesity on Success of Peritoneal Dialysis in ESRD Patients

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Background: Obesity rate is rising in the US and 1 in 4 adults are projected to have severe obesity by 2030. Prevalence of obesity in ESRD patients is also rising. Higher BMI has been shown to be associated with better survival in HD patients. However, data is inconsistent for PD patients. We examine the impact of different BMI classes on PD outcomes

Methods: This is a single center retrospective cohort study. Inclusion criteria includes patients >18 yrs, > 3 month PD vintage and patients who received PD from 2014-2018. Exclusion criteria includes patients with BMI <20, patients with no Kt/V data or missing BMI. SAS statistical software was used for data analysis

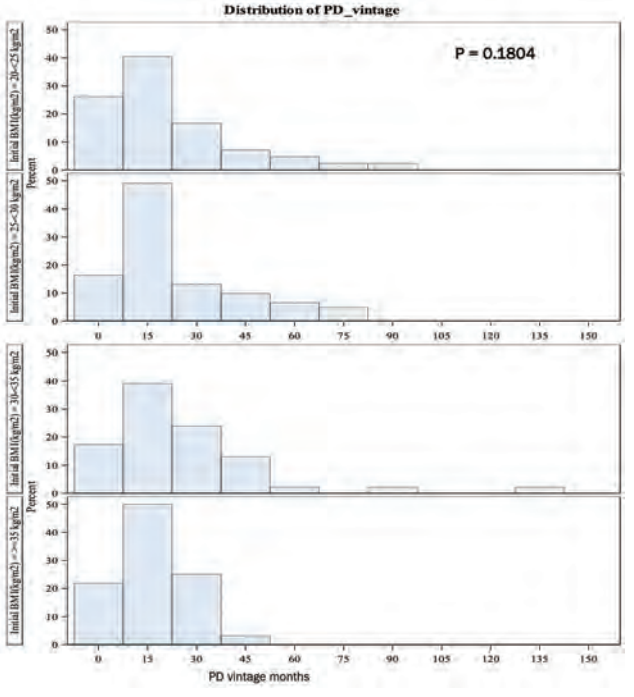
Results: 181 total patients are divided into 4 groups. Baseline characteristics were similar in all groups (fig 1). Outcomes include transition from PD to HD, transplantation rate, mortality rate, number of hospitalizations, PD vintage and catheter related infections. Our data showed that there is no difference in outcomes among different BMI groups (tab1, fig 2)

Conclusions: Our single study shows that obesity is not associated with poor peritoneal dialysis outcomes. People with high BMI should still be offered PD as a modality

Outcomes	BMI 20-24.9 kg/m2	BMI 25-29.9 kg/m2	BMI 30-34.9 kg/m2	BMI >35 kg/m2	P value
Transition from PD to HD	26.2%	26.2%	30.4%	50%	0.092
Transplantation	33.3%	34.4%	30.4%	21.9%	0.638
Deceased	16.7%	23%	21.7%	21.9%	0.886
Number of hospitalization	1.74 (1.95)	2.4 (2.95)	2.5 (3.06)	2.3 (2.56)	0.534

Figure 1: Baseline characteristics across 4 BMI groups

	BMI 20-24.9 (kg/m2)	BMI 25-29.9 (kg/m2)	BMI 30-34.9 (kg/m2)	BMI >35 (kg/m2)	P value
N (181)	N= 42	N= 61	N= 46	N= 32	
Average BMI	22.8 (±1.55)	27.3(±1.35)	32.1(±1.52)	39 (±3.88)	
Age	59 (±17)	62(±15)	58(±12)	58(±14)	0.514
PD vintage	22.3(±20.9)	23.5(±19.3)	25.5(±24.5)	16.8(11.8)	0.297
Gender					
Male	52.4%	57.4%	50%	43.8%	0.647
Female	47.6%	42.6%	50%	56.2%	
Ethinicity					
African America	33.3%	47.5%	50%	53.1%	0.377
White	57.1%	44%	45.7%	46.9%	
Other	9.5%	8.2%	4.3%	0%	
Education					
High school	19%	31.1%	47.8%	25%	0.223
College	61.9%	47.5%	37%	50%	
Above College	16.7%	14.8%	8.7%	18.8%	
Unkown	2.4%	6.6%	6.5%	6.2%	
Mode					
CAPD	9.4%	9.8%	17.4%	15.6%	0.3
CCPD	57%	44.3%	56.5%	59.4%	
CAPD/CCPD	33.3%	45.9%	26.1%	25%	
Prior HD	21.4%	19.7%	15.2%	28.1%	0.576
Urgent Start	11.9%	18%	13%	6.3%	0.45



PO1317

Late Onset of Sweet Hydrothorax: A Rare Complication of Peritoneal Dialysis

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Introduction: Peritoneal dialysis (PD) has a variety of complications, with diaphragmatic leak causing pleural effusions occurring in 1.6% of cases within 30 days of initiation of PD. We present a case of late-onset right sided pleural effusion, 14 months after initiation of PD, due to spontaneous pleuro-peritoneal leak and the course leading to this rare diagnosis.

Case Description: A 34-year-old female with polycystic kidney disease, bilateral native nephrectomies, and failed kidney transplant receiving PD presented with three days of right sided chest tightness and shortness of breath associated with ultrafiltration failure on PD. Chest x-ray on admission showed a large right-sided pleural effusion (Figure1A). The patient received PD using 2.5% dextrose dianeal; 2 hours after thoracentesis was performed with placement of a chest tube. Fluid analysis revealed a transudative effusion, with glucose of 322 mg/dL with corresponding plasma glucose of 147 mg/dL, consistent with dianeal solution in pleural space. Figure 1B demonstrates passage of the radiotracer from the peritoneal cavity (B) to the pleural space (A), suggestive of right-sided pleuro-peritoneal fistula (C). PD was discontinued and the patient was transitioned to hemodialysis (HD).

Discussion: This case demonstrates a rare complication of PD. Hydrothorax can occur due to increased intra-abdominal pressure causing migration of dialysis fluid from the peritoneal cavity into the pleural space by opening of defects in the diaphragm communicating the two cavities; negative intrathoracic pressure and transiently increased hydrostatic pressure of the dialysate may cause dialysate leak. This phenomenon typically occurs more frequently in women with polycystic kidney disease due to reduced abdominal capacity. Increased glucose in pleural fluid, CT peritoneography and NM scintigraphy are methods of confirming diagnosis. Transition to HD with monitoring for spontaneous closure of the pleuro-peritoneal leak is first line conservative treatment. If the leak persists, surgical repair of the diaphragmatic defect is definitive treatment to resume PD.

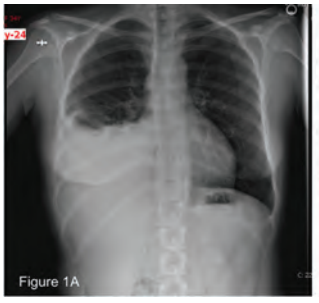
Figure 1A

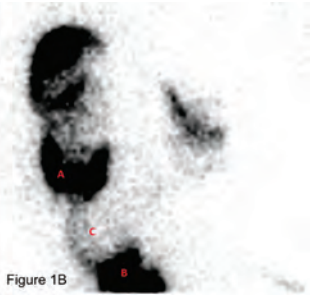

Figure 1B

PO1318

Ochrobactrum Peritonitis in Peritoneal Dialysis: A Rare Case and Literature Review

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Introduction: Ochrobactrum are glucose-non-fermentative, non-fastidious, motile gram-negative bacilli typically isolated in aqueous environments. Reported infections by this pathogen primarily occur in immunocompromised hosts from environmental exposure, nosocomial contamination of sterile fluids and/or indwelling catheter use. Due to impaired immunity and exposure to exogenous microbes, peritonitis is a common and feared complication of peritoneal dialysis. We present a case of *Ochrobactrum Anthropi* peritonitis and review the literature of similar case.

Case Description: A 67-year-old male with history of ESRD secondary to IgA nephropathy on CCPD for 4 years presented to the hospital with fevers, nausea, abdominal pain and generalized weakness. He experienced an episode of acute bacterial peritonitis 1-month prior to this hospitalization secondary to Pseudomonas aeruginosa treated with ciprofloxacin and no other previous PD complications. A peritoneal effluent sample showed 347 nucleated white blood cells. He was empirically initiated on intraperitoneal cefepime and vancomycin, as well as oral fluconazole for fungal prophylaxis. Peritoneal effluent culture grew Orchrobactrum anthropi, sensitive to fluoroquinolones and carbapenems but resistant to cefepime. Antimicrobials were subsequently transitioned to ciprofloxacin and fluconazole, and he completed the antibiotic course with resolution of symptoms and peritoneal leukocytosis.

Discussion: We present the 8th case of *Ochrobactrum Anthropi* peritonitis in a peritoneal dialysis patient. Zero of the published cases were associated with bacteremia. Attempted treatments have typically included carbapenems, aminoglycosides, and fluoroquinolones. Three of eight cases required removal of the tenkhoff catheter. Peritonitis related mortality was zero percent. This case and review of the literature can serve to inform future occurrences.

PO1319

The Utility of Point-of-Care Reagent Strips for Rapid Rule out of Peritonitis in Patients on Peritoneal Dialysis

Madhuri Ramakrishnan, Andy Chuu, Frank J. O Brien. *Washington University in Saint Louis, Saint Louis, MO.*

Background: 10% of all end stage renal disease (ESRD) patients in the United States use peritoneal dialysis (PD). An important complication in this population is PD-related peritonitis, which is a risk factor for hospitalizations, mortality and is the most common cause of transition to hemodialysis. The diagnosis of PD-related peritonitis requires the presence of white blood cell count of > 100/μL or positive culture from the effluent dialysate in the setting of abdominal pain and cloudy effluent dialysate. This method requires time and access to a diagnostic facility, which may not be easily available to all patients on PD. Point-of-care strips that utilize colorimetric changes in leukocyte esterase reagent can be used to provide a quick, presumptive diagnosis of peritonitis. We evaluate the specificity or true negative rate of two reagent strips – PeriScreen and Multistix 10 SG.

Methods: We are conducting a diagnostic test study in a prospective cohort at the home dialysis clinic at Washington University in Saint Louis. We plan to include 100 patients to achieve a power of 80% to be able to obtain a 95% specificity. We are including

patients who are asymptomatic i.e. without abdominal pain or cloudy dialysate effluent. We will be obtaining four 20 mL aliquots of their effluent dialysate, taken at the time when their dialysis kinetics are being measured. Two samples will be sent to the laboratory to obtain white blood cell count, and bacterial culture. PeriScreen and Multistix 10 SG reagent strips will then be dipped in the remaining two samples. The results from all four tests are reported as positive or negative, and the results of the reagent strips will be compared to the gold standard of white blood cell count and culture. Specificity will then be calculated.

Results: Data from 10 patients has been obtained to-date. The average age of these patients was 60.1 (± 14.7) years, with 50% of them being females, and 50% of them were Caucasians. In these patients, the Periscreen was found to have specificity of 100% and the Multistix 10 SG was found to have specificity of 100%.

Conclusions: Based on preliminary results, both PeriScreen and Multistix 10 SG reagent strips appear to have specificity >95%. Using this data, we aim to create a protocol for patients to use these strips at home to help rule out PD-related peritonitis in a more efficient manner.

PO1320

Acyclovir for Herpes Zoster Encephalitis: Panacea or Problem?

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Introduction: Herpes zoster, which is the reactivation of varicella-zoster virus (VZV), is more common in immunocompromised patients, with a higher incidence of encephalitis. The treatment of choice is intravenous acyclovir, with one of its adverse effects being neurotoxicity. We present a case where the disease effects and the medication side effects were difficult to distinguish.

Case Description: A 59-year-old man with ESKD and a history of failed allograft on peritoneal dialysis (PD) presented with one day of acute onset headache, confusion and ataxia. Two days prior, he was diagnosed with dermatomal zoster and was treated with valacyclovir 1000 mg thrice daily. Lumbar puncture showed no pleocytosis, but protein elevation at 90 mg/dL. EEG showed no epileptiform activity and MRI and MRA brain were normal. Because his symptoms started after the initiation of overdosed valacyclovir, medication toxicity was considered more likely than VZV encephalitis. PD was continued, but he deteriorated with worsening mental and pulmonary status after aspiration, requiring intubation. Subsequently, he underwent 3 daily hemodialysis (HD) treatments without improvement. On the 3rd day post-intubation, the CSF VZV PCR returned positive prompting intravenous acyclovir at 5mg/kg/day. Over the next day, he showed marked mental status improvement and got extubated. The serum VZV PCR also resulted positive which was diagnostic of disseminated herpes zoster with encephalitis. After 6 days of intravenous acyclovir therapy, he was discharged on valacyclovir 500mg twice daily to complete 21 days of therapy.

Discussion: Herpes zoster encephalitis and valacyclovir neurotoxicity can lead to similar presentations and pose a diagnostic challenge. Due to low volume of distribution and low protein binding, valacyclovir is highly dialyzable. Hemodialysis can be helpful diagnostically. Our patient's neurologic symptoms started after an inappropriately high dose of valacyclovir was prescribed. He did not improve with hemodialysis, pointing away from valacyclovir overdose and more toward VZV encephalitis. This case underscores the need for dosing adjustments in patients with renal insufficiency and the need for clinical awareness to keep both diagnoses in mind.

PO1321

Pittsburgh Sleep Quality Index Score Predicts All-Cause Mortality Independently in Chinese Dialysis Patients

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Background: Poor sleep quality (SQ) is common in dialysis patients. The Pittsburgh Sleep Quality Index (PSQI) is a standard tool for evaluating SQ with high validity and reliability. The relationship of PSQI score to survival in dialysis patients has not been well studied. Less was reported in China. The aim of this study was to explore the association between PSQI score and all-cause mortality in Chinese dialysis patients.

Methods: Dialysis patients who were treated for more than 3 months in Sun Yat-sen Memorial Hospital of Sun Yat-sen University between April 1, 2006 and Aug 1, 2017 and completed questionnaires on SQ were enrolled in this retrospective study. The PSQI was used to evaluate SQ. PSQI score >5 or ≤5 were considered to indicate "poor sleepers" or "good sleepers" respectively. The primary outcomes was all-cause mortality. Restrictive cubic spline (RCS) regression models were used to examine the dose-response relationship between PSQI score and all-cause mortality. Cox proportional hazards regression analysis was performed.

Results: 109 patients were included, composed of 51 hemodialysis and 58 peritoneal dialysis patients. Mean follow-up time was 69.1 ± 29.9 months, during which 21 deaths occurred. 67 (61.5%) patients had poor SQ. Compared with poor sleepers, good sleepers had significantly higher levels of hemoglobin [78.0 (68.0, 97.0) vs. 74.0 (61.0, 85.0), $P = 0.030$] and carbondioxide combining power (20.0 ± 3.7 vs. 18.0 ± 4.5, $P = 0.022$). RCS analysis showed that 7 was the cutoff value at which the effect of PSQI score on mortality changed. More than 7 of PSQI score increased the risk on all-cause mortality. When PSQI score was analyzed as a continuous variable in the multivariate Cox proportional hazards model, it was associated significantly with all-cause mortality (hazard ratio [HR] = 1.20, 95% confidence interval [95% CI] 1.05, 1.36, $P = 0.007$). While a threshold of 7 on the PSQI score was used in an additional adjusted model, a PSQI score > 7 was associated with a 2.96 times increase in the hazard for all-cause mortality (HR = 2.96, 95% CI 1.15, 7.61, $P = 0.025$).

Conclusions: PSQI score > 7 predicted all-cause mortality independently in Chinese dialysis patients. Further studies are needed to confirm decreasing PSQI score less than 7 in Chinese dialysis patients will improve survival.

PO1322

Patient Characteristics and Frequency of Prescription (Rx) Alterations in Automated Peritoneal Dialysis (APD)

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Background: APD provides the flexibility to adapt PD Rx to the needs, lifestyle, and health status of a patient (e.g. residual renal function [Kru], volume and transport status). The alterations may include changes in dwell volumes, dwell times, or number of exchanges. The current analysis aims to describe frequency of APD Rx alterations and patient (pt) characteristics associated with these alterations

Methods: All de-identified demographic, lab, and Rx data were extracted from Fresenius Kidney Care clinical data warehouse. Adults who were incident to APD from 01/01/2015 to 12/31/2019, completed APD training and ≥1 treatments, and had no change in PD modality or data quality issues with their records were included. Any change in dwell volumes, dwell times, or number of exchanges was considered an alteration. Characteristics of the pts in the month leading up to their most recent alteration were described and stratified by the number of Rx alterations they received at followup.

Results: 15,237 pts were eligible for inclusion. The majority (72.7%) of pts had ≥1 PD Rx alterations during a mean follow-up time of 418 days (compared to 201-day follow-up for pts with 0 alterations). Most pts (53%) had dwell volumes adjusted, with 52%, 4%, and 44% having increases, decreases, or both increases and decreases in dwell volume, respectively. The table details pt characteristics prior to alteration by frequency of Rx alterations.

Conclusions: Compared to pts with no Rx alterations, pts with more Rx alterations were heavier, had higher serum phosphorus, lower PD Kt/V, and lower Kru. The number of alterations along with the timing and direction of these changes need to be further studied to help determine if a pattern of changes is associated with risk of PD technique failure and switch to HD.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Number of Rx alterations	n (%) Patients	Systolic Blood Pressure, mmHg	Diastolic Blood Pressure, mmHg	Weight, kg	PD Kt/V	Residual Kidney function ml/min/1.73 m^2	Serum phosphorus, mg/dL	Serum albumin, g/dL
0	4,160 (27.3%)	142 ± 25	81 ± 14	86.2 ± 24.4	2.4 ± 0.7	4.6 ± 3.5	5.4 ± 1.6	3.5 ± 0.5
1	3,603 (23.6%)	139 ± 24	81 ± 15	85.8 ± 23.9	2.3 ± 0.7**	4.1 ± 3.5**,#	5.5 ± 1.6	3.5 ± 0.5*
2	2,625 (17.2%)	139 ± 26**	80 ± 15	86.4 ± 23.5	2.2 ± 0.7**	3.6 ± 3.2**,#	5.6 ± 1.7**,#	3.5 ± 0.5*
3	1,743 (11.4%)	139 ± 25**	81 ± 15	87.3 ± 24.2	2.2 ± 0.6**	3.3 ± 3.2**,#	5.6 ± 1.7**,#	3.5 ± 0.5*
4	1,193 (7.8%)	137 ± 25**,#	80 ± 15	87.8 ± 23.0*	2.2 ± 0.6**	3.0 ± 3.2**,#	5.8 ± 1.8**,#	3.5 ± 0.5
5	742 (4.9%)	136 ± 26**,#	80 ± 14	88.6 ± 25.1*	2.1 ± 0.6**,#	2.9 ± 4.9**,#	5.8 ± 1.8**,#	3.5 ± 0.5
6 - 10	1,098 (7.2%)	136 ± 26**,#	80 ± 15	88.4 ± 23.5*	2.1 ± 0.6**,#	2.3 ± 2.8**,#	5.9 ± 1.8**,#	3.5 ± 0.5*

** P<0.001; * P<0.05

PO1323

Mitochonic Acid 5 Alleviates Chlorhexidine Gluconate-Induced Peritoneal Fibrosis in Mice

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Background: Peritoneal fibrosis is one of important complications induced by long-term peritoneal dialysis. Mitochondrial dysfunction causes an increase of oxidative stress and depletion of ATP. Thus, it may be associated with fibrosis and other diseases in several organs. Recently, mitochonic acid 5 (MA-5), which is a derivative of the plant hormone indole-3-acetic acid, was synthesized and its therapeutic potential for mitochondrial dysfunction in kidney disease models has been reported. In this study, we investigated the effect of MA-5 for peritoneal fibrosis in mice.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chlorhexidine gluconate (CG) every other day for 3 weeks in C57BL/6 mice. MA-5 was administered at 2 mg/kg by gavage every day. Control mice received only a vehicle

(distilled water). After 3 weeks of treatment, the animals were sacrificed and the peritoneal tissues were collected. The peritoneal sections were stained with Masson's trichrome for light microscopic examination and the fibrotic thickening of parietal peritoneum was measured on the randomly selected different regions on each section. The expressions of F4/80, which is a marker of macrophages, monocyte chemotactic protein-1 (MCP-1), transforming growth factor-β (TGF-β) and α-smooth muscle actin (α-SMA) were examined by immunohistochemistry.

Results: Compared with control mice, the fibrotic thickening of parietal peritoneum was significantly attenuated in MA-5 treated mice (the thickness of submesothelial area: 100.24 ± 13.67 vs 54.78 ± 7.43 μm ($p<0.05$)) with the lower number of TGF-β positive cells and α-SMA positive myofibroblasts. The infiltration of macrophages was markedly reduced with the decreased expression of MCP-1 in MA-5 treated mice than those in control mice.

Conclusions: Our results suggest that MA-5 alleviates peritoneal fibrosis with the reduction of macrophages infiltration. Thus, MA-5 may have a therapeutic potential in the progression of peritoneal fibrosis as well as kidney disease models.

PO1324

Longitudinal Changes in the Use of Peritoneal Dialysis Assistance for Patients Maintained on Peritoneal Dialysis

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Background: Home dialysis therapies such as peritoneal dialysis (PD) offer flexibility and improved wellbeing for older individuals. However, a substantial proportion require assistance with personal care and health self-management. The study objective was to assess whether the nature of, and need for, assistance with PD management tasks changes over time. We hypothesized that patients and families would require less assistance as they became more familiar with PD management.

Methods: Using a multicentred, prospective observational study design, we recruited patients aged ≥50 years initiating PD. Patients underwent formal evaluation at baseline using validated components of a Comprehensive Geriatric Assessment. They then completed a monthly questionnaire for 6 months about their need for assistance with PD management tasks.

Results: 111 patients (age 69 ± 10 years, 68% male, 56% diabetic) were followed for a total of 609 patient-months. Assistance for PD management tasks remained generally stable throughout follow-up, and did not vary according to age, frailty, functional dependence or cognitive impairment. The proportion of patients needing assistance varied widely across the 13 different PD management tasks, but the proportion of patients needing help for each task remained relatively stable across time (Figure 1). Of those who needed assistance, 40% had help from a family member and 33% were helped by nurses. The family/nurse caregiver ratio for the different tasks did not change over time.

Conclusions: Older patients initiating PD, in the outpatient setting, have a high need for assistance with PD-related tasks which appears to persist over the initial 6-month period. It emphasizes the importance of starting discussions early, and addressing advance care plans, goals and most importantly expectations, as patients approach dialysis initiation.

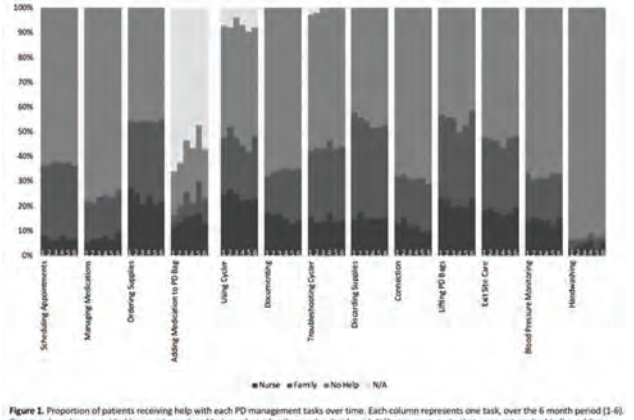

Figure 1. Proportion of patients receiving help with each PD management tasks over time. Each column represents one task, over the 6 month period (1-6). Care may have been provided by a paid caregiver (dark grey) or a family member (mid grey). N/A represents tasks that were not applicable (i.e. adding medication to PD bags or using a cycler). Sample sizes for months one through six were 109, 104, 101, 93, and 91 subjects, respectively.

PO1325

Vascular Access Type and Risk of Mortality and Hospitalization Among Elderly Hemodialysis Patients: A Target Trial Emulation Approach

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Background: Evidence is mixed regarding optimal choices of incident vascular access type for elderly patients on hemodialysis (HD). Prior studies have primarily compared functioning arteriovenous fistula (AVF) to arteriovenous graft (AVG) and been limited to survival outcome. We used a target trial emulation approach and intention to treat (ITT) analyses to compare AVF versus AVG placement among elderly patients on HD.

Methods: Patients eligible for the target trial were those ≥67 years old at HD initiation, with no AVF/AVG placed before HD initiation, referred for AVF/AVG placement, and had AVF/AVG within 1 year after HD initiation. Patients would be randomly assigned to AVF or AVG and be followed right after AVF/AVG placement for 5 years. Outcomes including mortality, all-cause hospitalization, and cause-specific hospitalization (infection, cardiovascular disease (CVD), and vascular access (VA) related) within 6 months, 1 year, 3 years, and 5 years would be assessed. ITT analysis based on patients' first AVF or AVG placed would be applied. We used USRDS data from 2010-2016 to emulate the target trial and propensity score (PS) matching to balance the groups' characteristics.

Results: A total of 37,890 (out of 47,912) patients who had AVF/AVG placed within 1 year after HD initiation were included after PS matching. Among them, 28,847 (76.1%) had AVF placed and 9,043 (23.9%) had AVG placed. AVF was associated with lower risk of mortality over follow-up. Within 6 months after AVF/AVG placement, incidence of all-cause and VA-related hospitalization was significantly lower in the AVF group (RR 0.85 (95% CI: 0.78-0.93) for all-cause hospitalization; RR 0.68 (0.62-.74) for VA hospitalization), but not infection- or CVD-related hospitalization. AVF was associated with significantly lower incidence of all-cause and VA-, infection-, and CVD-related hospitalizations in longer follow-up time (RR 0.84 (0.82-0.87) for all-cause hospitalization within 3 years; RR 0.63 (0.59-0.67) for VA-related hospitalization within 3 years).

Conclusions: Our primary analyses found elderly patients on HD may benefit from getting an AVF compared to an AVG. We will further test whether these results hold true in patients within strata of age group, comorbidities, probabilities of AVF maturation, and life expectancy.

PO1326

Implementing Multidisciplinary Pre-ESRD Program to Improve Vascular Access in New-Start Dialysis Patients

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Background: Tunneled dialysis catheters (TDC's) are associated with morbidity and mortality in dialysis patients. In the U.S., more than 80% of patients start dialysis with a TDC and even higher rates for ethnic minorities. As part of the Santa Clara County healthcare system, we care for an underserved population, predominately of ethnic minorities. To reduce our TDC rates, we implemented a Pre-ESRD program that encompasses a multidisciplinary team, EMR tracking, access referral guidelines, and culturally relevant patient education. We assessed whether this program reduced the proportion of patients starting dialysis with a TDC and no other vascular access (TDC-Only).

Methods: We performed a retrospective chart review of new start dialysis patients in 2014 (before program implementation) and in 2017 (after program implementation). Patients must have been seen in renal clinic for at least 3 months before starting dialysis. We compared the proportion of TDC-Only between the two groups using the Chi-Square Test. We also compared the type of vascular access placed between the two groups.

Results: 87 patients started dialysis in 2014 and in 2017. There was no difference in age (58 vs 56 years) or diabetes (61% vs 70%) between the two groups. The two groups consisted mostly of minorities (Hispanic: 52% vs 55%, Asian: 31% vs 26%, Black: 7% vs 3%, and White: 10% vs 14%) and non-English speakers (44% vs 46%). The type of access at dialysis start is summarized in the table. The proportion of TDC-Only reduced by 21% after program implementation but did not reach statistical significance: 62% of patients started with TDC-Only in 2014 compared to 49% in 2017 ($p=0.09$). In addition, AVF placement more than doubled after program implementation (19% vs 42%, $p=0.001$).

Conclusions: Implementation of a multidisciplinary Pre-ESRD program reduced the number of TDC-Only and increased the number of AVF's in new dialysis start patients. Our study is unique due to our patient population of predominantly minorities and non-English speakers.

Initial Vascular Access

	2014 (n=87)		2017 (n=87)	
TDC-Only	54	62%	43	49%
TDC w/Other Access	3	3%	11	13%
AVF	15	17%	25	29%
AVG	5	6%	2	2%
PD	10	11%	6	7%

PO1327

Conversion to Arteriovenous Fistula but Not Arteriovenous Graft Is Associated with Improved Hemodialysis Efficacy Markers in Children: Pediatric Nephrology Research Consortium Study

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Background: Arteriovenous fistulae (AVF) and arteriovenous grafts (AVG) are preferred vascular access for chronic hemodialysis (HD) patients. Our objective was to investigate the impact of switching from tunneled cuffed catheters (TCC) to AVF or AVG on HD efficacy markers in pediatric HD patients.

Methods: Retrospective chart reviews were completed on individual patients from 20 pediatric HD centers. All the patients used TCC prior to AVF/ AVG and each patient acted as his/her own control. Data on dialysis efficacy markers were collected at creation of AVF/AVG and for two years follow-up, along with patient demographics and clinical information. Statistical methods used included hypothesis testing and statistical modeling after adjusting for relevant demographic variables.

Results: First PVA was created in 98 individual children: 87 (89%) were AVF and 11 (11%) were AVG. The mean TCC vintage prior to AVF/AVG was 10.4± 17.3 months. At one-year follow-up, AVF patients improved the Kt/V by 0.23 (p=0.008) and URR by 5.4% (P<0.001). At second year follow-up, both Kt/V and URR remained higher than values at creation (p=0.02, p<0.0001, respectively), being similar to first year's values (p=0.57, p=0.36, respectively). Furthermore, AVF patients improved serum albumin by 0.33 gram/dl (p<0.0001) and serum hematocrit by 2.94% (p<0.0001) at one-year and maintained similar improved values at second year follow-up (p=0.001, p=0.003, respectively). These observations were further supported by the adjusted models. Children with AVG did not demonstrate any statistically significant change in Kt/V, URR, serum albumin or hematocrit at either one-year or second year follow-ups.

Conclusions: Switching to AVF was associated with improved HD efficacy markers (Kt/V, URR, serum albumin and hematocrit). Surprisingly, conversion to AVG was not associated with a similar positive impact for the above markers.

PO1328

Study of Impact of Preoperative Venogram as an Adjunct to Doppler Imaging in Difficult Vascular Access

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Background: As the number and complexity of patients on dialysis increases, this presents an increasing challenge for vascular access. Successful renal access surgery requires both careful planning and technical skill. Venography offers direct imaging of both peripheral and central veins in the upper limb.

Methods: Venography was done at our institute prospectively for difficult vascular access cases between Oct 2019 & Mar 2020. All patients who had prior 2 failed AVF surgeries were included in study and were evaluated with physical examination, Doppler imaging and Venography. We prospectively analysed venograms and also compared the outcomes before and after venography based on historic control before venogram with same inclusion criteria. Both groups were compared with respect to vascular access type, patency, complications.

Results: During the study period, venography prior to surgery was performed in **30 patients**. Venography of one upper limb (right/left: 6/30) was performed in **6 patients(20%)**. The **remaining 80%** patients underwent bilateral venography, resulting in a total of 54 upper limb venograms. **9 patients**(30%) were considered unsuitable for native AVF creation based on the venograms. **3** underwent a haemodialysis AV-graft (AVG) creation (2 autologous saphenous vein AVG grafts, 1 synthetic graft), two opted for CAPD, **remaining 4** surgery was not done.

Conclusions: Venography is a useful imaging modality in preoperative venous mapping prior to difficult vascular access surgery along with preoperative Doppler imaging, resulting in increased patency rates. In our study, preoperative venous imaging in adjunct with color Doppler imaging helped in choice of AVF site planning and avoiding complications and ruling out central venous obstruction and a better patency rates although limited by shorter follow up and small size.

DEMOGRAHIC PARAMETERS –

S .NO	PARAMETER	VENOGRAM (PE +DI+V)	CONTROL (PE + DI)
1	MALE	23	18
2	FEMALE	7	12
3	MEAN AGE	52.06	52.86
4	MEAN PRIOR AVF SURGERY	2.86	2.16

COMPARATIVE ANALYSIS SHOWING RESULTS OF AVF AND PATENCY AT 3 MONTHS –

S.NO	Avf created	Venogram group	Patency at 3 months	% Patency	Control	Patency at 3 months	% Patency
1	FOREARM						
	RC	4	3	75%	2	1	50%
	HIGH RC	4	4	100%	1	1	100%
2	ARM						
	CEPHALIC	8	7	87.5%	13	7	53.84%
	BASILIC	5	4	80%	11	6	54.4%
3	AVG						
	SAPHNOUS AVG	2	1	50%	0	0	0
	BRACHIO AXILLARY	1	1	100%	3	2	66.6%
	TOTAL	24	20	83.3	30	17	56.6%

OUTCOMES OF PATENCY OF AVF AT 3 MONTHS –

	PATENCY AT 3 MONTHS	FAILURE	TOTAL
VENOGRAM GROUP	20	4	24
CONTROL	17	13	30
TOTAL	37	17	54

Chi square = 4.40, P value 0.036.

LYMPHOEDEMA IN AVF –

LYMPHOEDEMA	YES	NO	TOTAL
VENOGRAM	0	24	24
CONTROL	5	25	30
TOTAL	5	49	54

Chi square 4.41, P value = 0.0358

FOREARM AVF –

RC AVF	YES	NO	TOTAL
VENOGRAM	8	16	24
CONTROL	2	28	30
TOTAL	10	44	54

Chi square – 6.28, P value = 0.012

PO1329

Analysis of Vascular Distensibility Measured by Ultrasound Speckle Tracking

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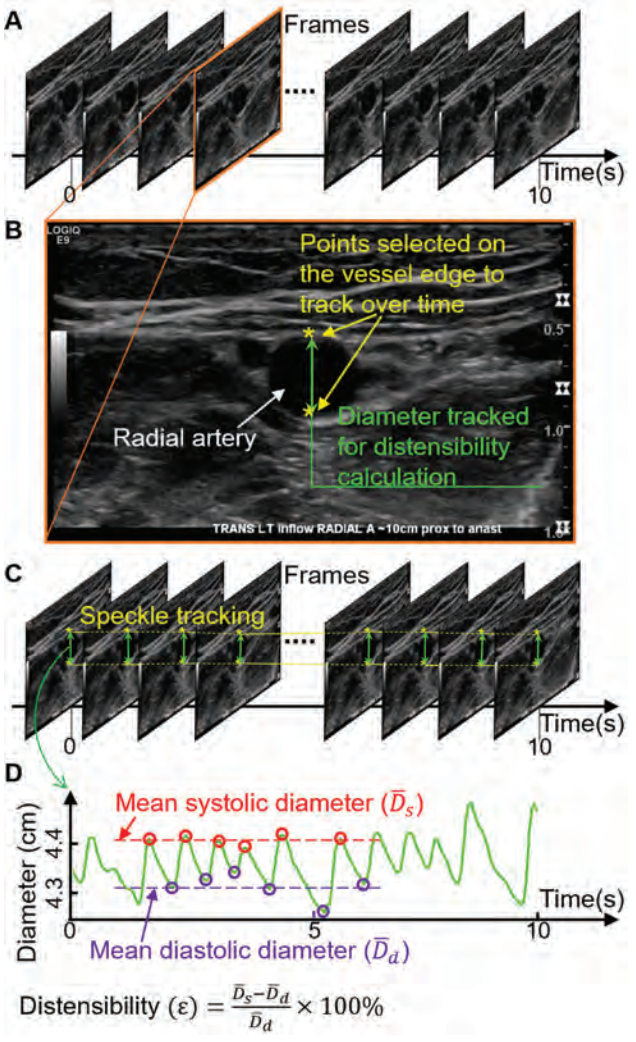
Background: We have developed a novel open source ultrasound software program that measures vascular strain and distensibility using conventional ultrasound Digital Imaging and Communications in Medicine (DICOM) data for use in the dialysis vascular access setting. In this study, we evaluated the variation in measurement from operator point selection and physiologic beat to beat variation of the arterial wall.

Methods: Ten subjects scheduled for arteriovenous fistula (AVF) creation were enrolled in the study. Ultrasound scanning of the brachial/radial arteries was performed. Ten users were prompted to select two points of interest at the top and bottom of the arterial vessel wall in each of the ten subjects. These points were tracked using the Kanade-Lucas-Tomasi (KLT) tracking algorithm.

Results: Sub-millimeter resolution (less than 100 micron) measurements were obtained. We found variation point selection by the users for the ten cine loops to be up to 120 pixels for the top and up to 140 pixels for the bottom of the vessel wall. The range in measured variation attributable to user point selection was 5.79 to 47.29% and inter-cardiac (physiologic) variation was 6.41 to 17.68%.

Conclusions: Despite the low resolution of conventional DICOM images, we are able to measure sub-millimeter distensibility. In order to better understand the physiologic variation in vascular wall compliance, a formalized approach to point selection is needed. We are evaluating algorithms and statistical ensemble methods for use in studies to predict AVF maturation.

Funding: Veterans Affairs Support



From image cine loop (A), a single frame (B) is used to select vessel wall edge points, for image tracking (C), to determine sub-millimeter resolution wall strain and distensiblity (D) showing beat to beat variation.

PO1330

Relationship of Vascular Access Flow and Stenosis Detected by Frequency Domain Analysis of Videos Taken with a Smartphone

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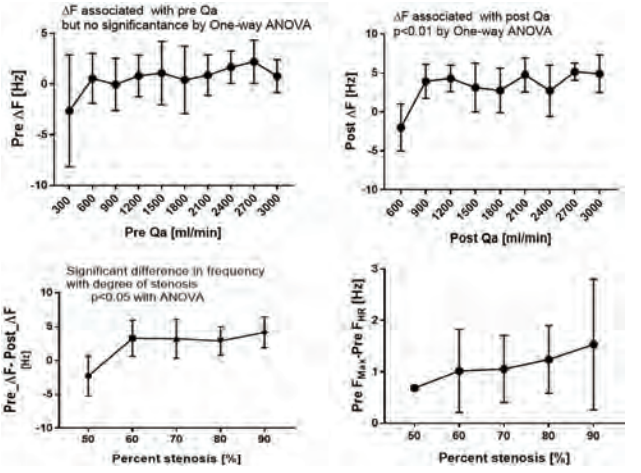
Background: We developed a video image processing (VIP) technique with frequency domain analysis to assess arteriovenous fistula (AVF) blood flow. This study aimed to investigate the relationship of heart rate and access blood flow rate (Qa) represented by the frequency signals at maximum (F_{Max}, Hz) and minimum (F_{Min}, Hz) of magnitude in frequency domain analysis.

Methods: We employed VIP pre- and post-endovascular interventions in 90 hemodialysis patients (age 63.3 ± 14.3, 41 females, weight 78.6 ± 21.5 kg). F_{Max} and F_{Min} pre- and post-intervention were recorded. ΔF was defined as F_{Min} - F_{Max} for each video. Qa was measured pre- and post-intervention by HVT100 endovascular flowmeter (Transonic Systems Inc., Ithaca, NY, USA). The degree of stenosis (%) was quantitated by angiography. Heart rate (HR, beats/min) was expressed as a frequency (F_{HR}, Hz).

Results: The pre- and post-intervention differences between F_{Max} and F_{HR} were 1.14±0.74 Hz and 1.38±1.44 Hz, respectively. ΔF was associated with Qa pre- (Fig 1(a)) and post-intervention (Fig1(b)). ΔF increased most when Qa increased from pre-intervention range of 300 to 600 ml/min to post-intervention 600 to 900 ml/min. Fig 1(c) shows the relationship between % stenosis and the change in ΔF between pre- and post-intervention. The difference between F_{Max} and F_{HR} was associated with % stenosis pre-intervention (Fig. 1(d)).

Conclusions: The relationship between F_{Max} and F_{HR} suggests that the signal of F_{Max} represents an important hemodynamic component of Qa. ΔF may be used as an index to predict low levels of stenosis. The use of frequency domain analysis from video image data provides a contact-free method to ascertain Qa and to indirectly indicate the degree of stenosis. Further study is needed to standardize the quality of video and streamline the methodology.



PO1331

Impact of Ultrasound Guidance in Assessment of the Maturity and Cannulation of New Arteriovenous Fistula (AVF): A Quality Improvement Initiative

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Background: A common complication during cannulation, particularly in new AVF, is needle infiltration. AVF infiltration is associated with major morbidity, including additional interventions, prolongation of catheter dependence and access failure. Judicious use of ultrasound guidance has been successfully used in difficult peripheral as well as central venous access to reduce iatrogenic injury. We hypothesized that the use of portable ultrasound for cannulation of hemodialysis (HD) access would minimize infiltration during cannulation of new AVF in HD patients at Emory Dialysis over a 6-month period as compared to a control period without the use of ultrasound guidance for cannulation.

Methods: We implemented an educational protocol to train 18 members of our dialysis staff in the use of portable ultrasound for evaluation of dialysis access. 2 dedicated vascular access coordinators were trained as "access champions" and led the initiative. Each of the 4 HD units were equipped with a portable ultrasound machine. All new AVF were evaluated by ultrasound 4-6 weeks post-operatively. Immature AVF were sent for further evaluation/interventions. Mature AVF were cannulated under real-time ultrasound guidance. All data, including AVF infiltrations, were recorded prospectively.

Results: Infiltration data of new AVF for the control period was obtained from a retrospective database. The infiltration rate was 14% in our dialysis (calculated by dividing the number of new AVF infiltrations by the total number of new AVF cannulated). During the study period (8/15/2019 to 2/14/2020), 39 new AVF were evaluated for cannulation using a combination of physical examination and ultrasound guidance. There were only 4 infiltrations of new AVF. The rate of infiltration was thus 10.2% in our patients, a decrease of 3.8% from baseline.

Conclusions: The use of portable US devices for assessment of maturity and cannulation guidance is feasible even in busy HD units. We were able to reduce the infiltration rate with the use of US guidance for cannulation in combination with physical examination. We plan to expand ultrasound education to include all members of the dialysis staff involved with cannulation within our dialysis units. Regular competency checks are essential to identify and supplement gaps in knowledge.

PO1332

The Effect of Nitrate as a Vasodilator to Vascular Access Patency in Patients Undergoing Hemodialysis

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Background: Maintaining the patency of vascular access (VA) is very important to achieve adequate hemodialysis (HD) dose in HD patients. Failure of vascular access is associated with morbidity and mortality. Thus, maintaining the patency of VA is challenging. In this study, we investigated the effects of nitrate as a vasodilator on VA patency in HD patients.

Methods: We investigated study on the Korean insurance claims data of the HD patients between January 2012 and December 2017. All patients divided into nitrate therapy group and no therapy group depending on whether nitrate was administered. The nitrate therapy group included only patients who received the drug for 30 days or more. The primary outcome was the primary patency of VA. Effect of nitrate treatment was examined using Kaplan Meier analysis and Cox proportional hazard, after adjusting for covariates.

Results: A total 7,428 participants were included in this study, and nitrate therapy was noted in 7.7% of total patients. 1,178 patients underwent the angioplasty. In Kaplan-Meier analysis, nitrate therapy was lower probability of angioplasty than non-user (log-rank, P<0.001). The risk of angioplasty was low in patients receiving mononitrate and nicorandil (hazard ratio (HR) 0.18, [95% confidence interval 0.07-0.45]; HR 0.15, [0.06-0.41]). But, dinitrate and molsidomine were not associated with the risk of angioplasty. Multivariate Cox proportional analysis revealed that nitrate therapy with mononitrate and nicorandil had a decreased risk of angioplasty after adjustment for age, sex, hypertension, and diabetes (HR 0.17, [0.05-0.53]; HR 0.14, [0.04-0.45]).

Conclusions: In this large national database, we showed that nitrates such as mononitrate and nocorandil were associated with improved primary patency in HD patients. Nitrate treatment may have a beneficial effect for maintaining vascular access patency in patients undergoing HD, and further research is needed to relate nitrate therapy to VA patency.

PO1333

Influence of CKD on In Situ Tissue Formation in Biodegradable Vascular Grafts

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Background: Vascular access is considered the Achilles' heel of hemodialysis, requiring frequent interventions to maintain patency. One proposed solution is a self-healing *in situ* tissue engineered vascular access graft. This requires the presence of a functional wound healing response capable of initiating tissue formation. However, it is unknown whether tissue formation is negatively affected by chronic kidney disease(CKD). In this study, we aim to investigate the effect of CKD on *in situ* tissue formation in vascular grafts in a rat model.

Methods: To mimic the effect of CKD in humans, a rat 5/6th nephrectomy model was created. Control animals underwent a sham operation. When CKD animals reached a threshold of 50mg/24h proteinuria an electrospun biodegradable vascular graft, made from supramolecular polymers, was implanted in the abdominal aorta. Explantation was performed at 2, 4, 8 and 12 weeks, to follow the different phases of wound healing and early tissue formation. Explants were examined for cell infiltration and proliferation, presence of immune, endothelial, smooth muscle cells, and extracellular matrix components.

Results: Cytometry of circulating immune cells shows an increase in monocytes($CD11b^+$) and macrophages($CD68^+$) in CKD animals. Histological analysis indicates that all implanted grafts contain infiltrated cells throughout the material with a non-significant increase over time in both groups. Both groups show a peak in proliferating cells at week 8, with virtually no proliferating cells at 12 weeks. Infiltrated macrophages ($CD68^+$ & $CD163^+$) show no significant difference between sham and CKD and peak at week 8 followed by a decline. Masson trichrome and Sirius red stains show an increase in ECM formation over time with no significant difference between groups. Mature vascular cells such as smooth muscle cells and endothelial cells are found from week 8 onward, indicating a shift from a proliferative phase to a remodeling stage.

Conclusions: The found difference in circulating immune cells this did not translate in a significant difference in tissue build up, cell type, ECM production, scaffold breakdown and patency between sham and CKD animals. Our data suggests that uremic conditions have a limited effect on tissue formation in creating *in situ* tissue engineered vascular grafts.

Funding: Government Support - Non-U.S.

PO1334

Use of Ticagrelor to Preserve Hemodialysis Vascular Access

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Background: Hemodialysis (HD) is the main renal replacement therapy for end stage renal disease (ESRD) patients in the USA. Arteriovenous fistulas (AVF) remain the access of choice due to their superior patency and infection risk when compared to other access forms. The main complications of AVF are stenosis and thrombosis which lead to increased morbidity and hospitalizations in HD patients. There is currently no consensus as to whether thrombo-prophylaxis is warranted. Multiple studies have looked at various antiplatelet agents; however, none have looked at Ticagrelor, a newer antiplatelet that has been shown to inhibit platelet aggregation more effectively than Clopidogrel and is hepatically eliminated.

Methods: We underwent a randomized placebo-controlled single blind pilot study to evaluate the efficacy and safety of Ticagrelor in HD patients with AVF. 33 HD patients aged 18 to 35 years old with AVF were randomized to receive either Ticagrelor 90 mg orally twice a day (n=17) or placebo (n=16) for 6 months. Patients were seen twice a month while on therapy and monthly for 6 months post therapy. The number of vascular interventions and bleeding complications pre-treatment, during treatment, and for 6 months after treatment were recorded to determine efficacy and safety of Ticagrelor, respectively.

Results: No statistically significant difference was noted between Ticagrelor and placebo in terms of number of vascular interventions pre-study, while on therapy, or 6 months post therapy. When adjusting for access vintage, age, and race there was no statistically significant difference between both groups. There was also no statistically significant difference in bleeding complications between both groups.

Conclusions: We conclude that while using Ticagrelor in patients with ESRD on HD is safe, we could not demonstrate a therapeutic superiority in preserving the patency of AVF using this drug compared to placebo. This study is limited by the number of patients and more studies may be warranted in the future.

Funding: Commercial Support - AstraZeneca

Outcomes

Endpoint		Placebo	Ticagrelor	p-value (Fisher's exact test)
Intervention month 0-6	None	14 (87.5%)	13 (76.5%)	0.66
	1+	2 (12.5%)	4 (23.5%)	
Intervention month 7-12	None	13 (81.3%)	15 (88.2%)	0.66
	1+	3 (18.8%)	2 (11.8%)	
Bleeding complication	None	13 (81.3%)	16 (94.1%)	0.34
	1+	3 (18.8%)	1 (5.9%)	

PO1335

The Integrated Program of Needle Dislodgement Bleeding Alarm System Is Associated with a Decreased Incident of Venous Needle Dislodgement or Bleeding

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Background: A puncture of vascular access is commonly used in clinical treatment, such as hemodialysis or central venous catheters. There are some devices for detecting the presence of needle dislodgement in the market. Still, there are no large-scale reports for the integrated program for nursing training and device implantation. This study aims to conduct a program for an integrated training course and the VND device. We hope to reduce the incidence of needle removal and blood leakage.

Methods: This study was divided into two phases, the control period, and the study period. In the control period, the abnormal events of venous needle dislodgement and blood leakage was recorded in the hemodialysis unit room during the first three months. Before the study period, we introduced an integrated program, including the standard process of fistula puncture, care during hemodialysis, an inspection of the venous puncture site and an alarm system. In the study period, we also conducted the standard program and collected the data of the events of venous dislodgement or bleeding.

Results: The control period was conducted from July 2019 to September 2019, and the study period was performed in November 2019. A total of 62 patients completed the study. During the control period, there were a total of 2087 dialysis treatments, of which 30 patients had venous needle dislodgement or bleeding. There were a total of 71 events of venous needle dislodgement or bleeding, and the incidence rate was 3.3 events per 100 sessions. There were a total of 682 dialysis sessions and 15 events of venous needle dislodgement or bleeding during the study period. The incidence rate was 2.1 events per 100 sessions. The incidence rate of moderate and severe cases were 1.1 events per 100 sessions in the control period and 0.3 events per 100 sessions in the study period.

Conclusions: This study introduced venous needle dislodgement or bleeding alarm system and training program in the hemodialysis unit. The incidence of venous needle dislodgement or bleeding was lower after the program The incidence rate in the moderate and severe groups was also decreased. This program can improve the quality of patient care.

Funding: Commercial Support - Acusense

PO1336

Evaluation of Stable Permanent Hemodialysis Access Bleeding Time After Dialysis Needle Removal

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Background: Prolonged bleeding time (BT) after dialysis needle removal may signify permanent hemodialysis access (PHA) dysfunction but "normal" BT is not well defined.

Methods: This was an observational study examining 35 patients receiving chronic hemodialysis with PHA using 15-g needles for ≥3m at Stratton VAMC, Albany NY. BT was determined as no bleeding at dialysis needle removal site after manual pressure applied for at least 10min with additional 1-5 minutes increments, if needed. The mean BT for arterial and venous sites were calculated for each patient over 1-month period. Associations between BT and baseline characteristics were evaluated using adjusted regression analysis.

Results: The mean age of patients was 73 yrs, 97% were males, 63 and 31% were Whites and Blacks, respectively. The mean (SD) hemoglobin concentration and platelet count were 10.4 (1.0)g/dL and 184 (77)x10^9/L, respectively. Sixty and 74% of patients were on oral antiplatelet agents and intradialytic heparin. The mean (SD) BT after arterial and venous needle removal were 12.7 (2.1) and 12.9 (2.2) minutes. In the adjusted analyses, there was strong correlation between arterial and venous BT (r^2=0.98, p<0.016), however, no correlations were seen between arterial and venous BT and any baseline variables (Table).

Conclusions: In this study, BT after dialysis needle removal was between 10 and 15 min in patients with stable PHA. Future studies are needed to understand what changes in BT may predict PHA dysfunction.

Variable	Arterial Needle Site		Venous Needle Site	
	Correlation Coefficient	P-value	Correlation Coefficient	P-value
Age	0.17	0.4	0.18	0.4
Gender	-0.07	0.7	-0.06	0.8
Ethnicity	-0.09	0.7	-0.03	0.9
BMI	0.11	0.6	0.13	0.6
Permanent Dialysis Access	-0.04	0.8	-0.05	0.8
Previous Access Complications	0.24	0.3	0.26	0.2
Diabetes	-0.01	0.9	-0.02	0.9
Hypertension	-0.05	0.8	-0.04	0.9
Heparin Use	-0.13	0.6	-0.14	0.5
Heparin Dose	-0.22	0.3	-0.28	0.2
Antiplatelet Use	-0.24	0.3	-0.23	0.3
Hemoglobin Concentration	0.27	0.3	0.21	0.3
Platelet Count	-0.33	0.1	-0.29	0.2

PO1337

Natural Vascular Scaffolding Therapy for Arteriovenous Fistula Development in Rats

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Background: Arteriovenous fistula (AVF) maturation failure results from insufficient lumen dilation and progressive inward neointimal hyperplasia (NH). Vascular wall distention is likely affected by the integrity of vascular extracellular matrix (ECM). We hypothesized that preserving ECM integrity at the time of AVF creation surgery could improve AVF maturation. Natural Vascular Scaffolding (NVS) Therapy is known to interlink collagen and elastin, the most abundant vascular ECM components, by covalently linking these proteins via photoactivation. We investigated the effect of NVS treatment on AVF development in a rat model.

Methods: Femoral AVFs were created in young Wistar male rats as an end-to-side anastomosis. Immediately after the blood flow was restored to dilate the femoral vein by arterial pressure, a 10 µl-drop of the NVS compound (2 mg/ml in phosphate buffered saline (PBS)) was placed at the anastomosis perivascularly and incubated for 5 minutes to allow full vessel wall penetration, followed with 1-min illumination of the anastomosis area by 450-nm light. The control group received a 10 µl-drop of PBS and the same light activation. The skin was closed immediately after light activation. Each group had 10 rats. Rats were euthanized 4 weeks post-AVF creation for histology, morphometry, immunohistochemistry of interleukin-6 (IL-6, an inflammation marker), and second-harmonic-generation evaluation by multiphoton microscopy of collagen fibers.

Results: Rats tolerated the NVS treatment well. The NH area was similar in both groups. The AVF vein's open lumen area and % open lumen area in treated rats were significantly larger than in control rats (4.18-fold p=0.014 and 1.98-fold p=0.009, respectively). IL-6 intensity was significantly smaller in the NVS group than the PBS group (p=0.027). Collagen fibers in the NVS-treated AVFs trended towards perpendicular alignment with respect to the lumen circumference, with greater roundness, roughness, and eccentricity than in the PBS-treated AVF vessels.

Conclusions: Our studies showed that the NVS treatment significantly increased the AVF open lumen area, without significantly affecting the NH area. This suggests that NVS treatment may have therapeutic potential by facilitating lumen expansion while allowing a concomitant outward remodeling of the veins potentially leading to enhanced AVF maturation in patients.

Funding: Commercial Support - Alucent Biomedical Inc., Salt Lake City, UT, United States

PO1338

Geometry and Interuser Variability of Arteriovenous Fistulas in Mice and Rats

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Background: Arteriovenous fistula (AVF) maturation failure is a significant and unresolved clinical issue. Although rodent models have been used extensively to investigate the pathobiology and treatment of AVF maturation failure, the literature has largely relied on histology to analyze rodent AVF remodeling. Information regarding three-dimensional (3D) AVF lumen geometry in live animals is lacking. Our group has developed a magnetic resonance imaging (MRI)-based protocol to quantitively characterize 3D AVF lumen geometry in mouse and rat AVFs. Inter-user variabilities were also determined.

Methods: Carotid-jugular AVFs were created in C57BL/6 mice (n=21). Femoral AVFs were created in Sprague Dawley rats (n=7). Both had the arterial-side-to-venous-end configuration. Black blood MRIs were taken at 7 or 21 days post-AVF creation. Two users reconstructed the AVF lumens and computed the cross-sectional lumen area, anastomosis angle, nonplanarity angle magnitude, and tortuosity, using a centerline-based approach.

Results: Mice had a greater anastomosis angle (94.29° vs. 38.75°) and tortuosity (0.42 vs. 0.035) than rats (p<0.05). The nonplanarity angle magnitude was similar for mice and rats (~8.5°). Geometries of mouse and rat AVFs from the two users are overlaid in Figure 1. Inter-user variabilities were predominately small, indicating the reliability and reproducibility of our protocol.

Conclusions: Our work is the first detailed study of luminal changes in rodent AVFs using MRI. The anastomosis angles of mouse and rat AVFs are similar to human brachiocephalic AVFs (~70-90°) and radiocephalic AVFs (~30-60°) in the literature, respectively. These data suggest the clinical relevance of our rodent AVF models and set the stage for future studies on how these geometrical parameters affect AVF maturation and the mechanisms leading to geometrical changes.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

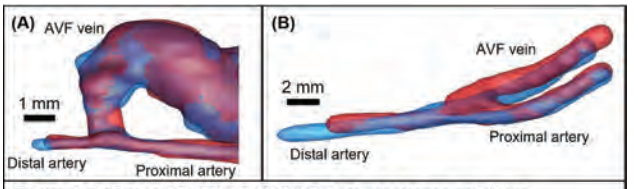

Figure 1. AVF reconstructions by two users. (A) Mouse and (B) rat reconstructions from two users (red and blue).

PO1339

Longitudinal Geometry of Pig Arteriovenous Fistulas (AVFs)

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Background: Hemodynamics has been postulated to be an important factor contributing to successful versus failed AVF maturation. Pigs, in general, have hemodynamic features that are similar to those in humans, and thus are an attractive animal model for investigating the mechanisms underlying and the interventions for promoting AVF maturation. A few earlier small clinical studies found associations between AVF geometry and maturation. Since geometry is a critical determinant of hemodynamics, we investigated the geometry of pig AVFs using magnetic resonance imaging (MRI) technology.

Methods: Carotid (side)-jugular (end) AVFs were created in female Yorkshire cross domestic pigs. Non-contrast black-blood MRIs were obtained at 1, 2, and 6-10 weeks (wks) post-AVF creation (n=3 per time point) and used to reconstruct AVF lumen geometries. Lumen area, anastomosis angle, venous tortuosity, and nonplanarity angle magnitude were quantified.

Results: The non-surgery lumen area of the external jugular vein was ~7 mm^2. The AVF vein lumen area (mean ± standard deviation) significantly (p=0.0370) increased from 25.3 +/- 11.1 mm^2 in wk 1, to 32.3 +/- 4.3 mm^2 in wk 2, then to 62.7 +/- 21.3 mm^2 in wks 6-10 suggesting that our pig AVF is a model for successful AVF maturation. Importantly, we also observed an increasing trend in the lumen areas from wk 1 to wks 6-10 of the proximal artery (24.0 +/- 17.3 mm^2 vs. 28.0 +/- 8.60 mm^2) and the distal artery (24.5 +/- 16.1 mm^2 vs. 34.8 +/- 13.9 mm^2). The anastomosis angles were similar in wk 1 and 2 (51.6 +/- 23.2° vs 50.2 +/- 21.0°) then decreased to 25.8 +/- 17.3° in wks 6-10. Venous tortuosity slightly increased from 0.13 +/- 0.05 in wk 1 to 0.15 +/- 0.05 in wk 2 then to 0.17 +/- 0.06 in wks 6-10. Non-planarity angle magnitude was 14.9 +/- 8.9° in wk 1 then decreased to 10.7 +/- 8.5 in wk 2 then increased to 24.6 +/- 9.4° in wks 6-10.

Conclusions: This is the first serial and detailed study of pig AVF geometric parameters. The anastomosis angles of our pig AVFs were in line with human radiocephalic AVFs in the literature (~30-60°). Our study sets the stage for examining the role of geometry in alterations in hemodynamic forces and in AVF maturation processes.

Funding: NIDDK Support, Other NIH Support - NHLBI

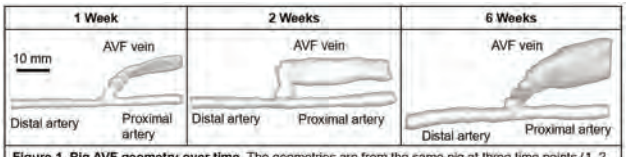

Figure 1. Pig AVF geometry over time. The geometries are from the same pig at three time points (1, 2, and 6 weeks). The scale bar applies to all geometries.

PO1340

To Study Real-World Effectiveness of Paclitaxel Drug-Coated Balloon Angioplasty in Hemodialysis Patients

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Background: A large, multicenter randomized study has shown that use of drug coated balloon (DCB) in angioplasty improves vascular access patency trend over control at 9-month during 2-year study period. We have conducted a retrospective study to see if there is a real-world effectiveness of DCB angioplasty in maintaining vascular access patency in hemodialysis patients.

Methods: We retrospectively reviewed 83 drug coated balloon angioplasties performed in our hospital from April 2018 to April 2020 and compared them with a control group of 83 angioplasties done by non-drug coated balloon matched by the date

of procedure. Target lesions were categorized as central, peripheral, anastomotic and in-stent for both arteriovenous fistulae (AVF) and arteriovenous grafts (AVG). Patient demographics (Age, Sex) and risk factors (Hypertension, Hyperlipidemia, Vascular Disease, Diabetes Mellitus) were also compared. The duration of target lesion patency (in days) before and after the DCB interventions were compared with date matched non-DCB interventions (control group).

Results: There are 83 angioplasties in each group (DCB versus control group). The average duration of target lesion patency (in days) before intervention in DCB and control group were 152 versus 137 (P value = 0.57) for AVF and 163.3 versus 191.3 (P value = 0.70) for AVG respectively. The average duration of target lesion patency (in days) after intervention in DCB group and control group were 114.8 versus 161.7 (P value = 0.03) for AVF and 177.9 versus 221.5 (P value = 0.5) for AVG respectively.

Conclusions: As opposed to the randomized controlled trial, our study shows that the average duration of target lesion patency of AVF after drug coated balloon angioplasty was significantly shorter than non-drug coated balloon. Greater severity of lesions in the DCB group could be the reason for this observation.

Target Lesion Patency Outcomes

Type of Access	Duration of Patency (Days)	Drug Coated Balloon N=83	Non Drug Coated Balloon N=83	P-Value
AVF	Pre-intervention	152.5	137.9	0.57
	Post-intervention	114.8	161.7	0.03
AVG	Pre-intervention	163.3	191.3	0.70
	Post-intervention	177.9	221.5	0.50

PO1341

Estimated Upper-Body Blood Flow and Central-Venous Oxygen Saturation Before and After Percutaneous Transluminal Angioplasty in Newly Created Vascular Access

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Background: Arterio-venous fistula (AVF) is the most effective vascular access in hemodialysis (HD) patients and, assessing AVF maturation is critical to initiate its timely use. Previously we have demonstrated that central-venous oxygen saturation (ScvO2) and estimated upper-body blood flow (eUBBF) increase during AVF maturation. We assessed ScvO2 and eUBBF before and after percutaneous transluminal angioplasty (PTA).

Methods: We studied HD patients from an ongoing AVF quality improvement project. ScvO2 and hematocrit were measured with Crit-Line (FMC, Waltham, MA) between minutes 5 and 20 into HD. eUBBF was computed and described previously (Rosales, Blood Purif, 2019). Five out of 19 patients underwent PTA during AVF maturation and subsequent successful cannulation.

Results: Three of five patients (mean age 71±11) were males two were incident patients. Four interventions were due to venous stenosis and one was due to arterial anastomosis stenosis. Two patients underwent PTA 2.2 ± 0.3 weeks after AVF creation and the remaining 3 patients within 11.2 ± 4 weeks. Following PTA ScvO2 increased in all, except in patient #1, eUBBF increased in every patient (Table 1).

Conclusions: Our preliminary results indicate that ScvO2 and eUBBF provide functional information that can be obtained non-invasively. These point-of-care bio-signals reflect hemodynamic cardiovascular adaptation following successful PTA. Future studies are warranted if knowledge of ScvO2 and of eUBBF shorten catheter residence time.

Table 1. $ScvO_2$ and eUBBF before and after percutaneous transluminal angioplasty

N=5		Before Intervention		After Intervention	
	Time to Intervention [Weeks]	$ScvO^2$ [%]	eUBBF [L/min]	$ScvO^2$ [%]	eUBB F [L/min]
Patient 1	2.0	68.4 ± 1.5 [67.3; 69.5]	1.2 ± 0.0 [1.2; 1.3]	64.4 ± 1.7 [63.3; 65.6]	1.3 ± 0.0 [1.3; 1.3]
Patient 2*	2.4	63.5	1.3	68.3 ± 3.1 [66.2; 70.7]	1.7 ± 0.2 [1.5; 1.8]
Patient 3	7.0	71.8 ± 0.4 [71.5; 72.1]	1.8 ± 0.1 [1.8; 1.9]	73.1 ± 2 [71.7; 74.6]	2.1 ± 0.5 [1.7; 2.5]
Patient 4	13.0	66.8 ± 0.8 [66.3; 67.3]	1.4 ± 0.0 [1.4; 1.4]	71.2 ± 0.8 [70.7; 71.7]	1.8 ± 0.1 [1.7; 1.9]
Patient 5	13.7	64.6 ± 4.6 [61.4; 67.9]	1.0 ± 0.2 [0.9; 1.2]	67.4 ± 0.2 [67.4; 67.5]	1.3 ± 0.0 [1.3; 1.3]

*Patient # 2 had only the average of 1-week measurements prior intervention. Data are expressed as mean, standard deviation, minimum and maximum values.

PO1342

Association Between FGF-23 Serum Levels with the Maturation Process of a Native Arteriovenous Fistula in Patients with End-Stage CKD

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Background: The process of maturation of an arteriovenous fistula (AVF) is complex and difficult to predict. It is known that high levels of fibroblast growth factor 23 (FGF-23) could be related to endothelial dysfunction, which could also influence the maturation of an AVF. Our goal is to know the association between serum levels of FGF-23 and the maturation of an AVF

Methods: This is a prospective cohort study with patients who underwent an AVF. The primary outcome was ultrasonic maturation at 6 weeks defined by the Birmingham criteria (diameter >0.4 cm and blood flow more than 500 ml/min).

Results: Forty-nine patients with a mean age of 48 ±14 years were included and 24% were women. The most common cause of CKD was diabetic nephropathy (55%). 49%, 25%, 10% and 16% were brachycephalic, brachyimedian, brachybasylic and other AVF respectively. thirty nine percentage of AVFs did not mature at 6 weeks. No significant differences were identified when comparing the agreement with maturation or not of the AVF in age, comorbidities, BMI, previous number of hemodialysis catheters, history of thrombosed catheter or catheter infection, hemodialysis vintage, residual diuresis, surgical time, hemoglobin, creatinine and serum calcium or phosphorus. However, the length of the arteriotomy was greater in the fistulas that do not mature with respect to the mature fistulas (7 mm vs. 6 mm p = 0.03). Likewise, the use of loop diuretics was more prevalent in AVF that did not mature (without maturation: 74% vs. maturation: 43%, p = 0.03). None of the distal radiocephalic AVF reached maturity. There were no association between serum levels of cFGF-23 and maturation of AVF, nor was the correlation between serum levels of cFGF-23 and the diameter or flow of the fistulas at six weeks.

Conclusions: The prevalence of maturation failure in AVFs was 39% according to Birminghams criteria. There is no correlation between serum levels of cFGF-23 and the flow or diameter of the AVF at six weeks. A larger population is required to corroborate these results.

PO1343

Effect of Hemodialysis Vascular Access Type on Serum Interleukin-6 (IL-6) Levels in ESRD

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Background: Chronic inflammation is prevalent and associated with poor outcomes in end stage renal disease(ESRD), and may be related to underlying comorbid conditions like diabetes mellitus. It is unclear if dialysis vascular access type may affect inflammation. We evaluated the effect of hemodialysis vascular access type on serum IL-6 level.

Methods: 15 patients with ESRD on chronic maintenance hemodialysis at McGuire Hunter Holmes VAMC were enrolled. Blood samples were drawn at 0, 30, 60, 90, 120, 180, and 240 minutes after starting dialysis. Serum IL-6 was measured using ELISA. Data were analyzed using t-test and is presented as Mean±SD.

Results: 6 patients had catheter (mean age 71.3±3.3 years), and 9 (mean age 64.5±4 years) had AV access. All were male. 5 patients in each group were African-American. 2 patients with catheter and 7 patients with AV access had diabetes. IL-6 level was higher at all time points(statistically significant) in patients with catheter compared to patients with AV access (Fig 1. and Table 1.)

Conclusions: ESRD patients with catheters had higher serum IL-6 levels compared to AV access inspite of lower proportion of diabetics. Catheters may contribute to inflammation, which may partly explain worse outcomes seen with catheters.

Funding: Veterans Affairs Support

Table 1.IL-6 Level at different time points (Mean+/-SD)

Time Point (Minutes)	AV access	Catheter	P value
0	2.87+/-1.53	11.96+/-9.47	0.009
30	2.1+/-1.14	11.29+/-10.29	0.011
60	2.73+/-1.53	11.6+/-8.92	0.004
90	3.15+/-1.51	12.32+/-9.42	0.006
120	3.14+/-1.65	13.11+/-9.53	0.003
180	3.32+/-1.57	13.76+/-9.75	0.003
240	3.27+/-1.26	14.8+/-11.08	0.003

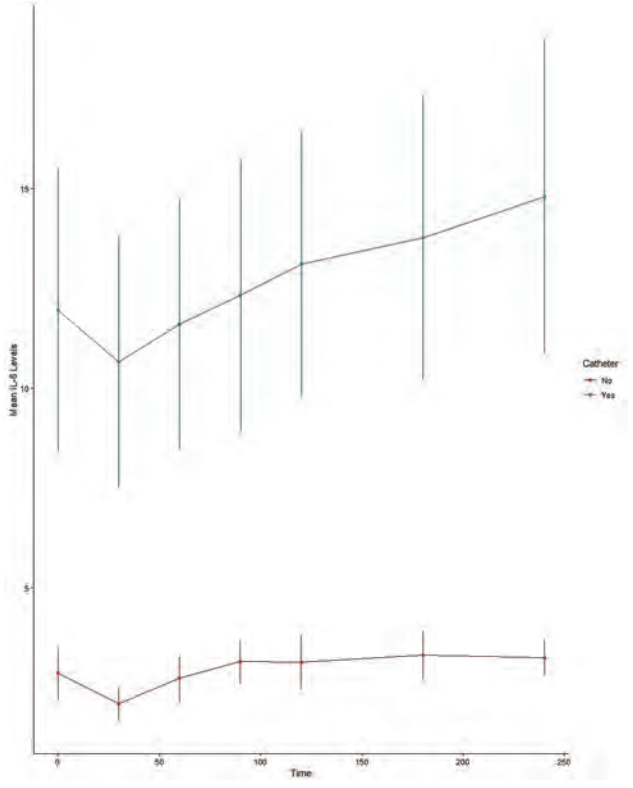

Fig1. IL-6 levels by Type of Vascular Access.

PO1344

Assessment of Arteriovenous Fistula Dysfunction with Access Stenosis in Hemodialysis Patients Using Smartphone Videos

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Background: Hemodynamically relevant stenoses in arteriovenous fistulas (AVF) lead to a reduction in access flow rate (Q_a). We hypothesized that these changes in blood flow patterns may be detectable in video recordings done with commercially available smartphones.

Methods: We studied HD patients with AVF dysfunction requiring balloon angioplasty. One-minute video recordings of the skin above the AVF and Q_a measurements were conducted before and after the intervention by an iPhone 6S. Q_a was measured by HVT100 Transonic flowmeter. Degree of stenosis was assessed by angiography. Frame-to-frame pixel changes in video images were amplified; time-domain data were transformed into the frequency-domain signals. Fifty random 10-second segments were sampled per one-minute video, and the frequency with the lowest magnitude (F_{min}) was determined in each sample (Fig. 1). The average F_{min} was assessed for its association with the degree of stenosis.

Results: Ninety subjects were studied (63±14 years, HD vintage 4.1±3.5 years). Post-intervention Q_a (1638±714 ml/min) was on average 1.23-fold higher than pre-intervention Q_a (1373±684 ml/min; P<0.01, paired t-test). Subjects were grouped by degree of stenosis, and the number of subjects in each category is shown in Fig. 1B. Higher degrees of stenosis were associated with greater increases in Q_a from before to after the intervention (Fig. 1C). Interestingly, the degree of AVF stenosis was also positively related with the change in F_{min} from before to after the intervention (Fig. 1D).

Conclusions: Smartphone video recordings of AVF appear to contain frequency-domain information that correlates with hemodynamic changes caused by AVF stenoses. While the F_{min} metric employed in our analysis is not ideal, these results should encourage the quest for other parameters that exhibit higher correlations with vascular access dysfunction, allowing timely referrals and avoidance of emergency interventions.

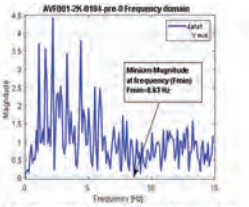

Fig 1A. An example of sample frequency domain analysis

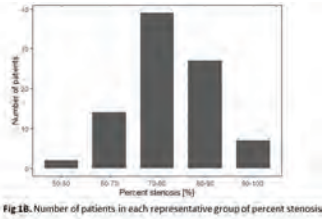

Fig 1B. Number of patients in each representative group of percent stenosis

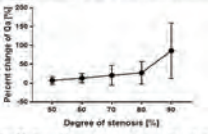

Fig 1C. Percent change of Qa versus degree of stenosis. P < 0.01 by one-way ANOVA. Percent changes are expressed relative to pre-intervention values.

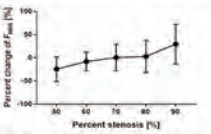

Fig 1D. Percent change of F_{min} versus percent stenosis. P = 0.08 by one-way ANOVA

PO1345

Surgical or Endovascular Intervention for Dialysis Access Thrombosis?

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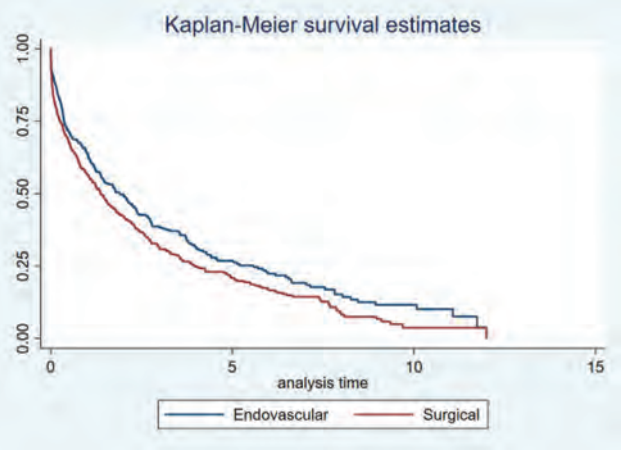
Background: Thrombosis is the most common cause of arterio-venous (AV) access failure in patients on hemodialysis. It is unknown if this complication is best treated by surgical or endovascular intervention. We compared the influence of surgical or endovascular intervention for AV access thrombosis on access survival using real-life data from a national AV access registry.

Methods: Patients from the Swedish Renal Access Registry (SRR-Access) with a prevalent and functional AV access who underwent surgical or endovascular intervention for their first thrombosis between Jan 1, 2008 and April 20, 2020 were included. The primary outcome was access survival. Secondary outcomes were time to next intervention and 30-day mortality. Access characteristics (date for access creation, upper or forearm access, graft or fistulae, first cannulation, date of thrombosis and time to next intervention) were obtained from SRR-Access. Patient characteristics were collected from SRR (age, sex, primary renal disease, comorbidities and start date of dialysis). The outcomes were assessed with Cox proportional hazard regression models adjusted for demographics, clinical, and access variables (previous interventions and time to first thrombosis). Analyses were stratified by age, sex, type of access and comorbidities.

Results: In total, 904 patients with access thrombosis were included. The mean age was 62 years, 60% were women. A large proportion (75%) had hypertension, 33% had diabetes, 54% were fistulas and 35% upper arm accesses. The median follow-up time was 1.1 year (0.2-2.9). The adjusted total risk of access abandonment was increased if the thrombosis was treated with surgical thrombectomy, HR 1.22 (1.04-1.44). There was no significant difference in time to next intervention or mortality. The results were consistent within subgroups.

Conclusions: Endovascular intervention was associated with better long-term access survival in hemodialysis patients with AV access thrombosis.



PO1346

Efficacy and Long-Term Patency of Kissing Stent Technique for Endovascular Reconstruction of the Axillary Vein: A Case Report with Long-Term Follow-Up

Sami M. Akram, Khurram Saleem, Mohamed A. Rahman. *Nephrology Associates of Northern Illinois and Indiana, Oak Brook, IL.*

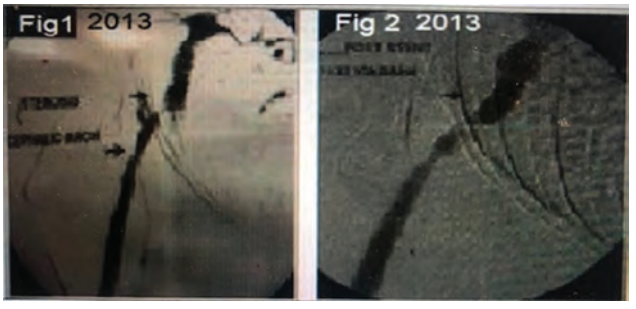
Background: Purpose: to report the endovascular reconstruction (EVR) of axillary vein (AXV) with kissing stent technique (KST) following AXV obstruction due to proximal stent migration (PSM) from the cephalic arch (CA). We suggest a strategy to minimize this problem. PSM in venous system is rare but dreadful complication of EVR. Increasing venous sizes towards the heart predisposes to PSM. We report a case of AXV obstruction due to stent migration into subclavian vein (SCV). We describe the successful use of kissing stent technique (KST) to reconstruct the AXV.

Methods: Case report and review of literature.

Results: Case report: MS is an 81-yr-old female with right brachiocephalic arteriovenous fistula (R BCAVF) for chronic hemodialysis. She has recurrent cephalic arch stenosis (RCAS) (Fig1). A Viabhan 11 x 5 stent was placed which, partially migrated into the SCV, blocking the AXV (Fig2 & Fig3). The Basilic vein (BV) was cannulated and a straight glide wire introduced. A Luminex 10 x 6 stent was delivered next to Viabhan stent in the AXV. Both stents were expanded with 10 x 4 angioplasty balloon restoring the forward flow in the AXV (Fig4). At 5-year follow up both stents were patent (Fig5) except for pre and post stent stenosis, successfully treated with angioplasty. **Discussion:** EVR is employed to treat RCAS[1,2]. However, there is risk of PSM. A strategy we implement to reduce PSM is to avoid complete dilatation of lesion prior to stenting which, in this case prevented full migration of the stent. KST for EVR of superior vena cava[3] and common iliac veins[4] has been reported but not for EVR of AXV. We report the first case of utilizing KST for EVR of the AXV with 5-year follow up.

Conclusions: KST for EVR of the Axillary vein is technically feasible and has long term efficacy.

Funding: Private Foundation Support



Partially migrated stent

KST

PO1347

Understanding the Transition to Standardized Fistula Rate (SFR) and Long-Term Catheter Rate (LTCR) Measures in the Medicare ESRD Quality Incentive Program (QIP)

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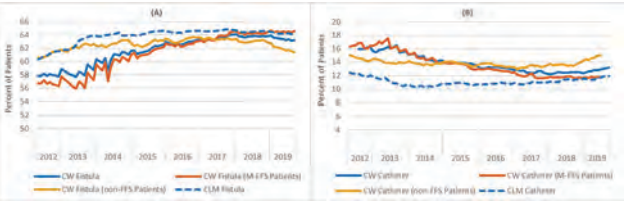
Background: In ESRD QIP Payment Year (PY) 2021, vascular access measures change to the SFR and LTCR measures. The changes involve transition of the data source from Medicare claims (CLM) to CROWNWeb (CW), expansion from Medicare fee-for-service (M-FFS) to all ESRD patients, revised numerator criteria (e.g. multiple access types), expanded patient exclusions (e.g. limited life expectancy), and case-mix adjustment for SFR.

Methods: The degree of concordance in reporting vascular access type reported in CLM and CW was assessed and trends in arteriovenous fistula use (AVF) and long-term catheter use (LTC) with the CLM-based and CW-based methods were evaluated from calendar year (CY) 2012-2019. Facilities' performance rates for the CW-based measures were calculated using PY20 data and compared to their PY20 performance for the CLM-based measures.

Results: The degree of reporting concordance between CLM and CW was high for fistula use (κ=0.95; p<0.01) and slightly lower for catheter use (κ=0.76; p<0.01). The agreement of all access types increased from 90% in CY12 to 97% in CY18. National trends in vascular access were consistently worse for CW-based measures, although this gap narrowed over time (Figure). PY20 data indicate facilities achieved a lower median SFR by 0.8% (vs. CLM-based AVF rate) and higher median LTCR by 1.4% (vs. CLM-based LTCR); however, accompanying changes to performance standards (using baseline data) result in simulated ESRD QIP measure scores increasing by approximately 0.5 points.

Conclusions: Vascular access reporting concordance in CLM and CW improved considerably in CY 2018, which corresponds to the first year of use in the ESRD QIP. The CW-based vascular access performance rates were worse than CLM-based rates; these differences are primarily attributed to the poorer performance of non-FFS patients included in the CW-based measures. While the new vascular access measures have worse performance rates, average ESRD QIP measure scores increase slightly.

Funding: Other U.S. Government Support



AVF (Left) and LTC (Right) National Trends based on CW and CLM Reporting

PO1348

Hemodialysis Access Surveillance Evaluation (HASE) Study

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Background: Arteriovenous (AV) access thrombosis remains one of the most troubling AV access related complication affecting hemodialysis patients. It necessitates an urgent and occasionally complicated thrombectomy procedure and increases the risk AV access loss. The routine use of AV access surveillance for early detection and management of stenosis to reduce thrombosis remains controversial.

Methods: We conducted a multicenter, prospective, randomized clinical trial comparing standard of care with monthly Ultrasound Dilution Technique (UDT) flow surveillance using a Transonic flow measurement device (Transonic Systems Inc., 34 Dutch Mill Road, Ithaca, NY 14850, USA) to standard of care alone.

Results: We prospectively randomized 436 patients with end stage renal disease (ESRD) on hemodialysis with arteriovenous fistula (AVF) or graft (AVG) using cluster (i.e. dialysis shift) randomization to either standard of care with monthly blood flow surveillance or standard of care alone. There were no statistically significant differences in the baseline demographic data between the two groups except for ethnicity (p=0.017). Patients were followed on average for 15.2 months. There were significantly less per patient thrombotic events (Poisson rate) in the surveillance group (0.12/patient) as compared to the control group (0.23/patient) (p=0.012). There was no significant difference in total number of procedures between the two groups, irrespective of whether thrombectomy procedures were included or excluded. There was no statistically significant difference between the two groups in the rate of or the time to a first thrombotic event or number of catheters placed due to thrombosis.

Conclusions: The use of monthly AV access surveillance with UDT flow measurement in this multicenter randomized control trial reduced the per patient thrombotic events without significantly increasing the total number of angiographic procedures. Even though there is a trend, surveillance did not reduce the first thrombotic event rate. **Funding** Transonic Systems Inc., 34 Dutch Mill Road, Ithaca, NY 14850, USA

PO1349

Right Heart Dysfunction in Hemodialysis Patients

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Background: Despite emerging evidence that right ventricular dysfunction (RVD) is a major determinant of outcome, previous studies have largely neglected the RV in ESRD patients.

Methods: We conducted a cross-sectional study on patients who received maintenance hemodialysis (HD) between Jan 1 - Dec 31, 2010 and were cared for by URMC nephrology faculty. For this cohort, all ambulatory trans-thoracic echocardiograms (TTEs) between Jan 1 2010 and Dec 31, 2018 were identified. Only TTEs with images of sufficient quality to assess the RV were included. Those with pre-existing congenital heart disease, atrial fibrillation, or prior valve surgery were excluded. Subjects might have more than one included TTE. Data from subject's charts were extracted.

Results: We identified 425 individuals on HD. Of these, there were 141 ambulatory TTEs, of which 64 TTEs met all inclusion criteria. RVD is defined as abnormality in any of the following echocardiographic parameters: S' (< 9.5 cm/sec), TAPSE (< 17 mm), Free Wall Right Heart Strain (> - 20%), or RV Fractional Area Change (< 35%). Of the 64 TTEs, 19 had one or more parameters indicating RVD. Select findings with bivariate analysis are summarized in the Table 1. Continuous variables are expressed as means (S.D.) and analyzed by ANOVA. By multivariate logistic regression, dialysis vintage < 10 years, history of vascular disease, and absence of AVS were associated with RVD. There was a trend with OSA. Limitations include retrospective analysis, small numbers, and heterogeneity in patients with respect to history of dialysis access type prior to undergoing TTE.

Conclusions: RVD is common finding on TTEs in HD patients, but is under recognized. A larger prospective study is needed to identify factors that are associated with development of RVD that could potentially be modifiable.

Table 1

	Whole Group N=64	Normal N=45	RVD N=19	P Value
Male Sex	35.9%	37.8%	31.6%	0.637
Age in years	50.2 (11.8)	48.6 (11.9)	53.8 (10.8)	0.109
African American	53.1%	53.3%	52.6%	0.959
Vintage in years	9.88 (5.8)	10.9 (6.3)	7.5 (3.8)	0.032
OSA	26.6%	20.0%	42.1%	0.067
Vascular Disease	25.0%	17.8%	42.1%	0.040
AVS present	84.4%	91.1%	68.4%	0.023

PO1350

Catheter Care in a Hemodialysis Unit: "Do It Daily," a Multimodal Patient Education Approach

Miten Dhruve. *Michael Garron Hospital Foundation, Toronto, ON, Canada.*

Background: Central venous catheters or CVLs are the leading cause of mortality and morbidity in the dialysis population. The HDU personnel wanted to empower the patients to manage and care for their catheters. We developed a standardized educational framework in collaboration with **healthcare professionals** and the **Patient Experience Panel. Objectives:** Our ultimate goal was to reduce the rates of catheter infections in our hemodialysis unit by improving patient's knowledge, confidence, and skills related to catheter self-care. Our immediate goal was to improve patients' catheter care knowledge and skills and to standardize and optimize nursing skills and knowledge

Methods: The patients were given a pre-education survey to establish baseline knowledge, attitudes and skill levels. Educational materials were developed based on the patients' feedback, knowledge and needs, and also on practice guidelines and best practice recommendations from **CDC, KDIGO, and ORN**. Nursing education involved updating nursing policies, and a nursing catheter care certification program. Educational materials included a video, posters, pamphlets and fridge magnets using the catchphrase **"Do it Daily".** The acronym **"DAILY"** represents the following: **D** for "dressing, soiled wet or damaged", **A** for "any rash, itching or broken skin, **I** for "increased pain at catheter site, **L** for "length of catheter changed" and **Y** for "you have redness, pus, fever". Post education surveys were conducted to assess the patients' knowledge and skill levels.

Results: Thirty-three patients completed baseline surveys, education programs and post education surveys. No significant difference in proportion of patients answering yes to Knowledge or Skill assessment pre- and post-education survey. Although, there was a trend of patients stating they had received enough teaching about catheter care, knew how to keep catheter clean and dry, recognize complications and not adjust catheter by themselves. Eighty-nine percent of patients found the education/training easy to understand.

Conclusions: Use of Multi-Modal patient education material is an easy to understand and feasible tool to help patients understand proper care of their dialysis catheters.

PO1351

A Retrospective Study of Tunneled Dialysis Catheters with Exposed Cuff and Risk of Subsequent Catheter-Related Bloodstream Infection

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Background: Tunneled dialysis catheters (TDC) are prevalent in patients with end stage renal disease (ESRD) on hemodialysis (HD). Exposure of catheter cuff leads to replacement of TDC over guidewire (TDCEx). It is unclear if exposed catheter cuff increases the risk of infection if exchanged over guidewire.

Methods: This single center retrospective study reviewed TDCEx procedures in patients with ESRD on HD using a TDC for at least 14 days. The primary endpoint was catheter related bloodstream infections within 30 days or within 90 days of catheter exchange. Infection rate (IR) were reported as total infections per 1000 catheter days.

Results: 1030 procedures were reviewed; 537 were included. TDCEx for mechanical dysfunction (n=305) and exposed cuff (n=130) were compared to TDC with infection (n=102). Catheters with infection were mainly treated with removal and delayed insertion. IR based on indications were, 0.78 (95% confidence interval (CI), 0.38-1.38) for infections, 0.64 (95% CI, 0.24-1.14) for exposed cuffs, 0.46 (95% CI, 0.25-0.76) for mechanical dysfunction. When comparing all TDCEx due to non-infectious reason to the catheters with infection, no significant difference was found for IR within 30 days [hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.21-2.82; p-value 0.700] or within 90 days (HR, 0.51; 95% CI, 0.24-1.07; P=0.075). Comparing TDCEx due to exposed cuff with TDCEx for a mechanical dysfunction, insignificant difference in IR was noted at 30 days [HR, 1.59; 95% CI, 0.45-5.63; P=0.474] and at 90 days (HR, 1.65; 95% CI, 0.71-3.87; P=0.246). No significant difference was seen in IR between catheters with infection and TDCEx for exposed cuffs at 30 days [HR, 0.95; 95% CI, 0.21-4.25; P=0.948] or at 90 days (HR, 1.42; 95% CI, 0.58-3.51; P=0.442). Catheters with infection compared to TDCEx for mechanical dysfunction had a significantly increased IR at 90 (HR, 2.36; 95% CI, 1.03-5.37; P=0.042) with no significant difference at 30 days [HR, 1.52; 95% CI, 0.38-6.06; P=0.556].

Conclusions: TDCEx for catheters with exposed cuff do not increase the risk for catheter related bloodstream infections at 30 or 90 days. Infected catheters continue to have a higher risk for CRBSI at 90 days even with removal and delayed insertion.

PO1352

Meta-Analysis of Antibiotic and Non-Antibiotic Lock Solutions for Prevention of Hemodialysis Catheter-Related Infections

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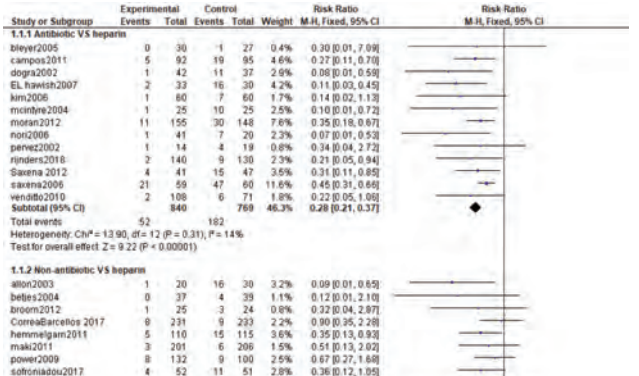
Background: Catheter-related bloodstream infection (CRBSI) associated with hemodialysis catheters are associated with increased mortality and morbidity whilst posing a significant financial burden on health care. The effects of antibiotic and antimicrobial locking solutions on the risk of CRBSI are unclear.

Methods: From inception to April 2020, we looked for relevant clinical controlled trials in the following databases: EBSCO, PubMed, Cochrane CENTRAL, MEDLINE, EMBASE, clinicaltrial.gov, Google Scholar and performed a meta-analysis of the identified studies.

Results: 26 studies with 4,967 patients reported on the incidence of catheter-related bacteremia (CRBSI). The overall pooled Risk Ratio (RR) was lower in the intervention group signaling a 70% lower incidence of CRBSI compared with the heparin group (RR= 0.30, 95% CI [0.25, 0.36], p<0.001). Subgroup analysis showed that the administration of antibiotic regimens led to a 72% decrease in the risk of CRBSI episodes (RR=0.28, 95% CI [0.21, 0.37], p<0.0001), whereas non-antibiotic antimicrobial solutions reduced the risk of CRBSI by 68% (RR= 0.32, 95% CI [0.25, 0.41], p<0.0001). A test for subgroup differences revealed no significant difference favoring either of the two interventions.

Conclusions: Both antibiotic and antimicrobial solutions are effective in reducing CRBSI.



PO1353

The Catheter Tip Position as the Main Non-Infectious Cause of Catheter Replacement Survival

Joana G. Navarro gallardo, Pablo Maggiani, Noe Martinez murillo, Jorge J. Font, Jonathan Chavez, Jose A. Torres, Christian P. Flores. *Universidad de Guadalajara, Guadalajara, Mexico.*

Background: Identify the risk factors associated with catheter (Cath) replacement **(CR)**. Novel anatomic variables analyzed

Methods: Our objectives: Identify risk factors associated with **CR**. The Cath were placed guided by ultrasound (US). We analyze age, gender, height, previous number of Cath and placement, lab tests, blood pressure, anatomic position, extrasystoles, # punctures, Jugular Vein (JV) collapsibility, Cath TUG, TIP and TOP, tunneled or not, Heparin, complications, Skin-JV Distance, Neck circumference, cath insertion to clavicula distance (CICD), JV and Carotid diameter and distance between JV and Carotid.

Kaplan Meier survival analysis. Multivariable logistic regression model was performed. $P < 0.05$ which is significant

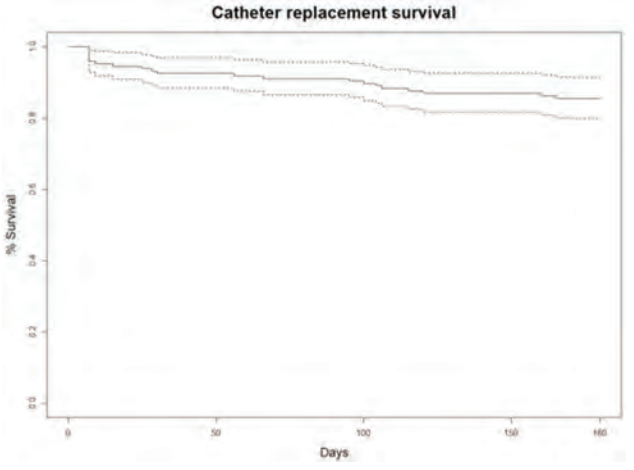
Results: From Feb-Dec 2019 with a 180 days follow-up, 147 vascular Cath placements were analyzed. The **CR** was presented in 21 patients (14.2%) with a survival of 85.5% (95% CI 0.80 to 0.91) (figure 1). The correct position of the Cath TIP decreases risk of **CR** (OR 0.81, 95% CI 0.73-0.90, p <0.001). Cath-related bloodstream infection (CRBI) increases the risk of **CR** (OR 2.52, 95% CI 2.13-2.98, $P < 0.001$). **CICD** >3.4 cm decrease risk of **CR** due to CRBI. (OR 0.89, 95% CI 0.81-0.97, $P < 0.01$)

Conclusions: Only the correct position of the Cath TIP protects vs **CR** while CRBI increases the risk. The shorter the CICD the less **CR** due to CRBI.

Funding: Other NIH Support - Universidad De Guadalajara Jalisco, Hospital Civil Fray Antonio Alcalde De Guadalajara

Multivariable logistic regression model to determine the variables associated with catheter replacement during the 180 days follow-up

VARIABLE	OR		95% IC	P Value
CATHETER INSERTION TO CLAVICULA DISTANCE (CM)	0.99	0.98	1.01	0.57
BREASTBONE-CHIN DISTANCE (CM)	1.01	0.99	1.03	0.10
TUNNELED CATHETER	0.98	0.90	1.06	0.67
CATHETER-RELATED BLOODSTREAM INFECTION	2.52	2.13	2.98	<0.001
NECK CIRCUMFERENCE (CM)	0.99	0.99	1.00	0.86
NORMAL TIP*	0.81	0.73	0.90	<0.001
ANATOMIC POSITION RIV	0.97	0.87	1.07	0.57



PO1354

NitriCap Hemodialysis Catheter Insert to Prevent Catheter-Related Bloodstream Infection

Alexander S. Yevzlin,[1] Karthik Ramani,[1] Maria Kim,[2] Joshua Doverspike,[1,2] Faroug Suliman,[1] Marie Cornell,[1] Alvaro Rojas-Pena.[1] *[1]University of Michigan, Ann Arbor, MI; [2]NOTA Labs, Ann Arbor, MI.*

Background: Tunneled dialysis catheters (TDCs) are associated with blood stream infections. We developed a novel nitric oxide (NO) eluting catheter insert and tested its effects *in vitro* and in sheep for two weeksto assess itsbacteriocidal activity.

Methods: Two cm long inserts using S-nitrosoglutathione (GSNO) as the NO donor and various other components were prepared and tested for their real-time NO release. *In vitro* studies were done to test the insert's bactericidal effects in a real catheter hub antimicrobial model with *S. aureus* and *P. aeuruginosa*. NO releasing inserts (NitriCap) were compared to a control (without NO releasing). After 72 h of incubation at 24°C, the amount of viable bacteria in the fluid was quantified for each sample. Subsequently, the antimicrobial/anti-biofilm efficacy of NitriCap was tested in a 14-day ovine model of microbe rich natural environment and compared to controls (without NO).

Results: A formulation was devised with an initial burst of NO (>100 flux), followed by sustained NO flux for 72 h duration (>20 flux). This formulation lead to a 6.6 log reduction of *S. aureus* and 6.7 for *P. aeruginosa* using NitriCap compared to a control of no insert. The *in vivo* 14-day sheep studies showed a log reduction of 3.9 by Day 4 and 5.4 by the end of the study (Day 14) in the NitriCap group when compared to controls, **(Fig. 1)**. After the 14 day sheep study was completed, the amount of bacteria/biofilm adhered to the inner lumen walls in four different regions of each catheter showed a 1.9 log reduction of bacteria even at the proximal tip for NitriCap vs. controls. Fluorescent microscopic images of bacteria/biofilm were taken of the inner lumen wall of each sample to qualitatively show the difference in bacterial/biofilm growth at four different regions of the catheter for NitriCap vs. control **(Fig. 2)**.

Conclusions: This data strongly suggests that the NitriCap displays significant antimicrobial/anti-biofilm effects during *in vitro* and large animal *in vivo* studies, demonstrating that its implementation could minimize catheter related blood stream infections.

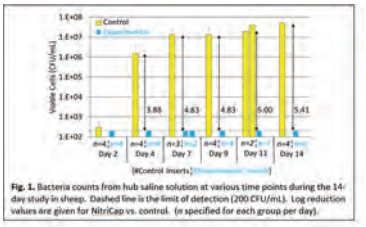


Fig. 1. Bacteria counts from hub saline solution at various time points during the 14-day study in sheep. Dashed line is the limit of detection (200 CFU/mL). Log reduction values are given for NitriCap vs. control. (n specified for each group per day).

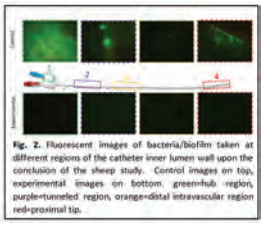


Fig. 2. Fluorescent images of bacteria/biofilm taken at different regions of the catheter inner lumen wall upon the conclusion of the sheep study. Control images on top, experimental images on bottom. green=hub region, purple=tunneled region, orange=distal intravascular region red=proximal tip.

PO1355

Catheter Dependency After Vascular Access Placement Among Elderly Patients on Hemodialysis: An Intention-to-Treat Analysis

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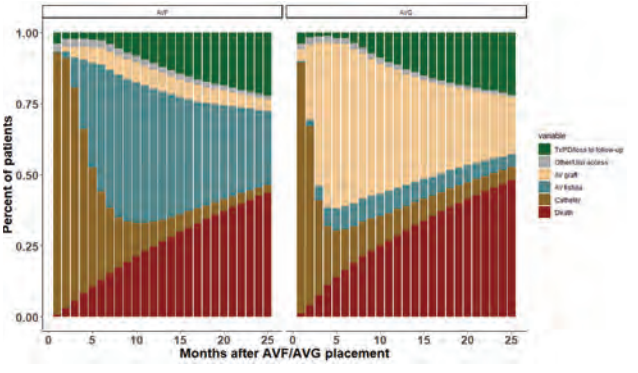
Background: Evidence is mixed regarding optimal choices of incident vascular access type for elderly patients on hemodialysis (HD). Arteriovenous fistula (AVF) may be desirable given its better long-term outcomes. However, many elderly patients have a lower probability of AVF maturation and limited life expectancy that may limit the potential long-term benefit of AVF. We aimed to use an intention-to-treat (ITT) analysis to assess catheter dependency after incident AVF/arteriovenous graft (AVG) placement among elderly patients on HD

Methods: Patients who were ≥67 years old at HD initiation, with no AVF/AVG placed before HD initiation, and had a first AVF/AVG placed within 1 year after HD initiation between May 2012 and May 2017 in the USRDS were included. Patients were followed from the first AVF/AVG placement using ITT analysis principles. Vascular access in use for HD was assessed using CrownWeb data. Catheter dependency was defined as using catheter only or using AVF/AVG combined with a catheter for HD.

Results: A total of 39,036 patients were included. Among them, 31,190 (79.9%) had AVF and 7846 (21.1%) had AVG placed. A substantially lower proportion of patients in the AVG group relied on catheter for HD early after VA placement (88.2% vs 91.9% in AVG and AVF, respectively, at 1m after placement; 23.3% vs 64.3% at 3m; 16.4% vs 28.9% at 6m, Fig1). In longer follow-up, proportion of catheter dependency was similar among patients remaining on HD in both groups, with slightly higher proportion in the AVG group observed at 1 year and beyond (14.8% vs 12.3% at 12m; 14.6% vs 9.6% at 24 m). Risk of mortality was high in both group (24.8% in AVF vs 28.7% in AVG by 12m; 42.4% in AVF vs 46.7% in AVG by 24m after VA placement).

Conclusions: AVG is associated with substantially less catheter dependency than AVF in the short-term and only slightly higher catheter dependency at one year and beyond. AVG placement may be beneficial in selected elderly patients to minimize catheter use.



PO1356

Detecting the Prevalence of Bacterial Colonization on Tunneled Hemodialysis Catheters Using 16S rRNA Gene Sequencing and Scanning Electron Microscopy: Lack of Evidence for Universal Colonization

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Background: Tunneled cuffed hemodialysis catheters (TCC) are claimed to be colonized by microorganisms early after placement, increasing risk for catheter related bacteremia (CRB). Our objective was to detect the prevalence of bacterial colonization of TCC by using 16S rRNA gene sequencing (qPCR) and investigate its association with intraluminal biofilm coverage.

Methods: 45 TCC were investigated; 10 were removed due to CRB and 35 were removed for non-infectious reasons. 16S rRNA qPCR technique was used to detect intraluminal bacterial colonization after scraping the intraluminal biologic material. Proximal, middle and distal TCC were evaluated by scanning electron microscopy to

determine the percentage (%) of intraluminal biofilm surface area coverage (BSA). All catheters were cultured for bacterial growth following sonication.

Results: Twenty-seven catheters were 16S rRNA qPCR (+) (60%). Eight of these catheters were removed due to CRB. 16S rRNA qPCR (-) results were associated with the absence of bacteremia (negative predictive value of 89% and Odds Ratio = 8.0). 16S rRNA qPCR (-) results were not predicted by catheter vintage or dialysis vintage. All catheter segments were covered by biofilm with a mean % BSA of 68.4 ± 26.1%. There was statistically significant difference between the % BSA of the three catheter segments (p=0.0344). The proximal catheter segments had larger % BSA compared to distal segments. The intraluminal % BSA was inversely correlated with dialysis vintage (p<0.01). There was no statistical difference for % BSA when catheters were compared according to their 16S rRNA qPCR, catheter culture, or blood culture results.

Conclusions: For this cohort, biofilm accumulation on TCCs was universal but bacterial colonization was not, as measured by three different methods, suggesting that biofilm may precede colonization of TCC by microorganisms. This piece of evidence may help to improve prophylactic strategies against CRB.

PO1357

Are Rescue Maneuvers More Efficient for Tunneled Catheter Late Dysfunction Than Wire Guide Catheter Replacement?

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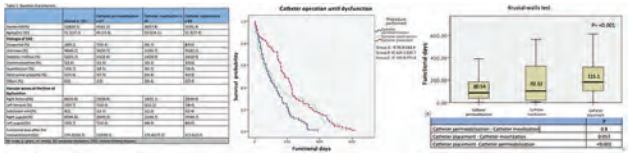
Background: Late catheter dysfunction is a common complication in HD patients. Complications associated with vascular accesses account for approximately 30% of hospital admissions for chronic HD patients. It also increases mortality. It is diagnosed when a catheter has been used successfully and later becomes dysfunctional. Thrombotic occlusion is the main cause. It is traditionally managed by placing a new catheter, wich may later lead to vascular access exhaustion. The purpose of this study was to assess the efficacy and safety of rescue maneuvers to treat late dysfuntional tunneled catheters versus catheter replacement.

Methods: Prospective, observational study. 195 procedures were performed between 2018 and 2019 in patients with late tunneled catheter dysfunction. Patients were ramdomly assigned to one group: group A, high pressure saline solution infusion into both lumens until obtaining good patency (permeabilization); B, catheter tip mobilization to reposition catheter tip until obtaining good patency; C, wire guide catheter replacement. Variables analyzed: age, gender, CKD etiology, vascular access site at the time of dysfunction, patency after rescue maneuvers (days). Percentages, means, Kruskal Wallis and Kaplan Meir and chi-square test were used.

Results: 118 were male (60.5%), with mean age of 51.2 years (17.3). CKD etiology was of unknown origin in 90 patients (46.2 %) and 52(26.7%) had diabetes mellitus. The right jugular vein was the most common anatomical site at the time of dysfunction (n=87, 44.8%). Catheter patency: group A, 119 days (99.3); group B, 175.4 days (175.5) and group C 217.6 days(157). Kruskal-Wallis test in the comparison between groups: group A vs B, p=0.8; C vs A, P=0.001; C vs B, p=0.057. The Kaplan Meir curve showed that group B and C had a longer catheter survival than A group (p=<0.001). Complications: six patients (3.1%) had bleeding from the catheter exit site in group C (p=0.015).

Conclusions: In late vascular catheter dysfunction, catheter tip mobilization is a rescue maneuver as effective as wire guide replacement tunneled catheter and with fewer complications.



Baseline characteristic-kruskal wallis test- kaplan meir curve

PO1358

Use of Diphenhydramine as Adjuvant to Conscious Sedation in Patients Undergoing Interventional Nephrology Procedures

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Background: Benzodiazepine and opioids are commonly used for conscious sedation during interventional nephrology procedures but are associated with adverse events such as bradycardia and respiratory depression. We are proposing to use Diphenhydramine as adjuvant medication to decrease the required dose of benzodiazepine and opioid.

Methods: We compared patients who received conscious sedation with IV midazolam and IV fentanyl as per standard practices to patients who received IV diphenhydramine prior to receiving IV midazolam and IV fentanyl. Level of sedation was managed as per guidelines of moderate sedations. Data collected included baseline patient characteristics, dose of midazolam and fentanyl used, duration of the procedure, type of the procedure and incidence of bradycardia and hypoxia during procedure. We also looked at if sedation was administered by physician vs nurse.

Results: Out of total 407 patients included in the study, 225 patient received Diphenhydramine as adjuvant to conscious sedation. Diphenhydramine use significantly reduced midazolam (2.2 mg vs 2.88 mg, p valuve <0.001) and fentanyl (88.2 mcg vs 102.07 mcg p value 0.005) dose requirements during procedures. It was not associated with increased rates of bradycardia and hypoxia. When comparing who administered sedation, physician administered sedation was associated with lower midazolam (2.18 mg vs 3.37 mg, p value < 0.001) and fentanyl (99.29 mcg vs 105.97 mcg, p value 0.04) dose without any difference in the rate of side effects, as compare to nurse administered sedation.

Conclusions: Our study indicates that the use of IV diphenhydramine is safe and effective as conscious sedation for patient undergoing Interventional Nephrology procedures and associated with reduction in benzodiazepine and opioid dose requirements.

PO1359

Perforation of Superior Vena Cava: A Rare Complication of Tunneled Hemodialysis Catheter Placement

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Introduction: Placement of tunneled hemodialysis catheter (TDC) is a fairly common procedure performed in hospitals and outpatient vascular centers. It is considered a fairly simple and risk free procedure for most part. Perforation of SVC while passing guide wires or dilating the tract is very rare and has been reported only in a very few case reports in the literature. We report a case that highlights this rare but frightful complication. This case also highlights the risk of deep central vein thrombosis associated with dialysis catheters.

Case Description: A 40-year-old female had a left subclavian vein temporary HD catheter placed in ER for emergent HD for ethylene glycol poisoning related complications. After one week, the temporary HD catheter was exchanged for a TDC under fluoroscopy. Shortly after the procedure the patient became dyspneic, tachycardic, and hypotensive. Imaging revealed perforation of SVC by the catheter tip resulting in a large Rt hemothorax. Immediate chest tube was placed followed by Thoracotomy and repair of SVC perforation and removal of TDC. One week later she developed left arm swelling and was diagnosed with deep vein thrombosis of the left subclavian vein, left internal jugular vein and the left axillary vein. The patient continued HD through a femoral HD catheter. She was started on heparin drip and systemically anticoagulated. The renal functions eventually recovered and arm swelling resolved and she was able to be discharged from hospital.

Discussion: Teaching Points: This case highlights rare but frightful complications of placement of a tunneled hemodialysis catheter, especially involving the left side neck veins. SVC perforation is a potentially fatal complication that can occur during placement of HD catheters. Immediate recognition, chest tube insertion for drainage, and/or pericardiocentesis along with emergent SVC repair are the key factors to management. Given the high frequency of HD catheter placements, providers should be aware and know how to treat and manage these complications in a timely manner.

PO1360

Unusual Dialysis Catheter Location in a Transplant Patient

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Introduction: Persistent left superior vena cava (PLSVC) is the most common thoracic venous malformation, despite its low incidence. PLSVC is generally discovered fortuitously without clinical signs. Serious hemodynamic complications may occur during the implantation and the permanency of a hemodialysis vascular access on this vessel.

Case Description: A 56-year-old woman, kidney transplant recipient 8 years ago, was admitted to the Intensive Care Unit with septic shock secondary to disseminated shingles after immunosuppressive therapy for acute cellular rejection. The patient developed acute kidney injury requiring renal replacement therapy. Due to history of right internal jugular vein thrombosis, the left internal jugular vein was catheterized with a non-tunneled double lumen hemodialysis catheter (12 French, 20 cm) without any complications. Routine post-procedure chest radiograph showed that the catheter was descending straight into the left border of the mediastinum (Image 1A). CT angiography (CTA) of the neck and thorax revealed the catheter localized on the PLSVC (Image 1B). The patient was placed on hemodialysis through this access uneventfully throughout the hospitalization period.

Discussion: PLSVC is a congenital malformation reported in 0.4-0.5% of the general population. Patients are mostly asymptomatic and the anomaly is frequently underdiagnosed or only noticed incidentally during imaging studies. Some patients can present with arrhythmias and sudden death. Screening diagnostic studies include chest radiograph and echocardiography, confirmed by CTA, magnetic resonance and cardiac catheterization. The possibility of catheterization of PLSVC is uncertain. Some authors argue that this vessel is too thin to keep a long-term catheter, but others suggest that if an accurate assessment of inner diameter of the vein can be performed before catheterization, it could be used as a site for conventional vascular access. However, there are reports of serious complications during catheterization such as pneumothorax, hemothorax, arrhythmias and cardiac arrest.

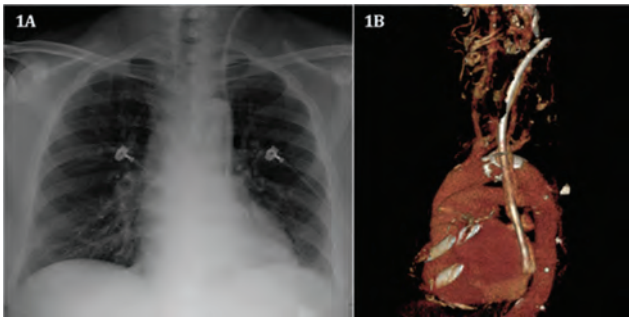

Image 1A/1B.

PO1361

Percutaneous Thrombectomy of an Ipsilateral Arteriovenous Dialysis Graft in a Patient with Dextrocardia

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Introduction: Dextrocardia with situs solitus (DSS) and associated duplicated left superior vena cava (DLSVC) is a rare condition. In affected patients with end-stage kidney disease (ESKD) the preferred dialysis access type and site are unclear, however anatomical variations may impact feasibility and success of dialysis access related procedures. In the setting of the altered anatomy, drainage of an access to the right atrium takes an altered pathway with differing technical concerns for stent deployment and avoidance of thrombus propagation in a clotted AVG.

Case Description: We report a rare case of covered stent placement during thrombectomy of a clotted ipsilateral right forearm loop AVG in the setting of DSS in an ESRD female. Given a severe venous anastomotic lesion and severe draining brachial vein stenosis, a covered stent was placed across the length of the stenosis. However, a guidewire could not be parked in the IVC to safeguard against potential stent migration to the heart, given the presence of dextrocardia, and the procedure was associated with a high risk of thrombus migration. An associated DLSVC draining into the CS (Coronary Sinus) was present, thus creating a direct path from the AVG through the central veins and the CS down to the heart. A right brachiocephalic vein was not present, and the right subclavian vein drained directly into the persistent right SVC (right part of duplicated left). After repeating the angiogram, measuring the length and marking it on the imager, a 6.10 cm Viabahn stent graft was passed to the level of the stenosis bridging the lesion with 2 cm maintained in the Acuseal 6 mm AVG and deployed. Thrombus was cleared with a 4 French Fogarthy catheter and after installation of TPA and excellent flow return achieved.

Discussion: DSS is a rare malformation which may impact the preference of dialysis access site and type in ERSD patients. Possible complications due to the altered anatomy need to be further evaluated. Appropriate precautions to prevent thrombus migration from a clotted ipsilateral graft in the setting of dextrocardia need to be further discussed. This case shows the feasibility of stent placement in a clotted AVG despite the inability of placing a guidewire down the IVC due to dextrocardia.

PO1362

Missed Central Venous Stenosis Causing Unilateral Arm Swelling

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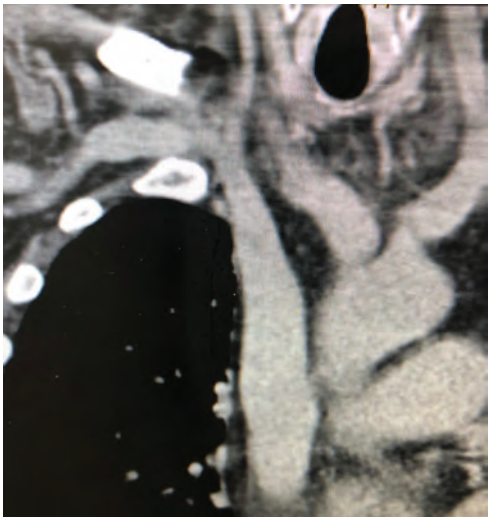
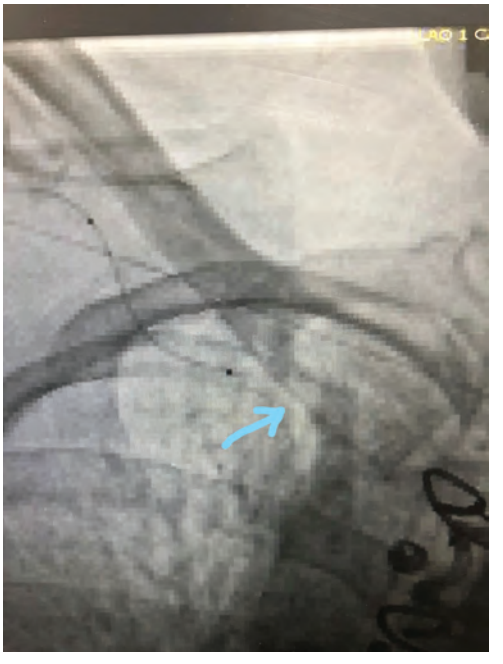
Introduction: The patient is a 67YOM with a history of ESRD, right mandible SCC treated with resection, chemotherapy, and radiation with a right sided PowerPort placed for chemo, removed after roughly 1 year. Prior to initiation of dialysis the patient had a right upper extremity brachiocephalic fistula created leading to unilateral right arm swelling shortly afterwards.

Case Description: Fistulogram was performed showing no significant stenosis. Persistent arm swelling continued. CT venogram showed no areas of central stenosis nor any external mass compression (figure 1). Repeat fistulogram showed similar findings; however, pressure wire measurement was obtained showing a gradient of 20 mmHg at the right innominate/SVC junction. Catheter directed injection revealed a near complete stenosis (figure 2). Angioplasty was performed with an 8 mm balloon. Repeat pressure measurements showed a decrease to 10 mmHg with angiogram demonstrating significant improvement in the lesion.

Discussion: Over two weeks he had swelling resolution. This case highlights physical exam findings of central vein stenosis. Despite being absent on multiple imaging modalities persistent physical exam findings necessitated continued evaluation. The validity of pressure wire measurements to help guide further imaging and treatment options is also highlighted.





PO1363

Arterial Emboli in the Setting of Prolonged Dialysis Access Thrombosis

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Introduction: Thrombosis of the dialysis access is a frequent complication that is encountered in dialysis patients and is associated with poor access outcomes. Delaying dialysis access thrombectomy decreases the chances of re-establishing the flow within the access circuit. However, it is unclear whether this delay would be associated with emboli of the arterial tree. Here we report on two patients in which the access declotting was delayed resulting in arterial emboli.

Case Description: Patient 1: A 32-year-old male with a history of end stage renal disease (ESRD) on hemodialysis via right upper arm HeRO graft who presented with clotted access and volume overload. Due to the severe respiratory distress, he underwent a temporary catheter insertion and urgent dialysis. He came back after 4 days for access declotting. Initial arteriogram revealed right axillary and brachial artery emboli that was removed successfully using tissue plasminogen activator (tPA) catheter infusion followed by and Fogarty balloon. Patient 2: A 65 yr. old male with ESRD on hemodialysis via right upper extremity AV graft who presented with clotted access for one week. The angiogram revealed total occlusion of the venous anastomosis that was treated with angioplasty. The arteriogram demonstrated an embolus within the brachial artery distal to the anastomosis and another embolus in the distal radial artery. Both emboli were treated successfully with selective tPA infusion using Kumpe catheter.

Discussion: These two cases showed that prolonged dialysis access thrombosis can be complicated with arterial embolic events that require high suspicion and immediate treatment.

PO1364

Associations Between Length of Dialysis Facility Ownership and Vascular Access

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Background: Length of dialysis facility ownership may be associated with facility performance in achieving guideline-recommended clinical indicators and outcomes measures. Using publicly available dialysis facility-level data, we sought to assess dialysis facility performance on 2 clinical indicators prior to and after facilities were acquired by a large dialysis organization (LDO).

Methods: Using data from Dialysis Facility Compare, we compared units that the LDO acquired during 2013 through 2016 to existing units by looking at 3 time frames: change from the year prior to acquisition, the year of acquisition, and the year following acquisition. These were compared to facilities under LDO ownership for at least 3 years and facilities not owned by the LDO. The measures assessed were percentage of patients with a catheter in use for more than 90 days and percentage of patients with an arteriovenous (AV) fistula in use.

Results: Sixty-seven units were acquired by the LDO during 2013 through 2016. Units acquired by the LDO had a higher percentage of patients with catheter use ≥90 days in the year prior to acquisition than units owned by the LDO for at least 3 years and units not owned by the LDO and improved during the year acquired and the year following acquisition (14.1%, 12.8%, 11.4%, respectively). Similar improvements were observed for AV fistula use (see Table).

Conclusions: Prior research has posited both positive and negative effects of acquisition on quality of patient care. The current results do not find negative effects and suggest possible improvements in care over the course of 1 to 2 years following acquisition, which suggests that implementation of LDO patient care protocols in newly acquired facilities may take time to unfold.

Funding: Commercial Support - DaVita

% of Patients With a Catheter ≥90 Days	Year Prior	Year Acquired	Year After
Acquired by LDO	14.1%	12.8%	11.4%
Owned by LDO for at least 3 years	8.5%	8.5%	9.0%
Not owned by LDO	12.0%	11.8%	12.0%
% of Patients With AV Fistula in Use			
Acquired by LDO	63.4%	63.1%	64.7%
Owned by LDO for at least 3 years	65.8%	67.3%	67.3%
Not owned by LDO	63.0%	64.5%	64.8%

PO1365

Data-Backed Multidisciplinary Care Substantially Improves Renal Replacement Therapy Outcomes

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Background: The Rogosin Institute created the Program for Education in Advanced Kidney Disease (PEAK), a multidisciplinary care team that assists patients in making a smooth transition to renal replacement therapy (RRT) in 2015. In October 2018 the PEAK team transitioned to using a machine learning (ML) algorithm and care platform devised by pulseData to identify their highest risk patients and increase the rate of optimal RRT starts and increase support for patients in choosing a home dialysis modality.

Methods: The ML model continually surveys the Electronic Health Record (EHR) to identify patients at risk of progression to an eGFR <10 or RRT start in the next six months for referral into the PEAK program. The patient review platform presents a longitudinal view of the patient's data, allows for the documentation of the RRT care plan and is used to review the high risk patients at a weekly care planning session. The care team updates patient progress and the platform highlights patients who have had no recent care actions.

Results: Home dialysis rates increased 50% after the ML/platform deployment (30% vs 20%). Home dialysis rates among graduates of the PEAK program are now 10x the NYC average (27% since January 1, 2019 vs 2.5%). Patients who spend more time in the PEAK program are more likely to receive an optimal dialysis start (as an outpatient and with venous access) ($p<0.00002$, unequal variances t-test); the mean PEAK duration for an optimal start is 316 days vs. 196 for non-optimal starts. Optimal starts are also associated with a greater number of PEAK appointments, (4.9 appointments vs 3.7; $p<0.0004$, unequal variances t-test). Further, of patients starting dialysis using a central venous catheter (CVC), PEAK program graduates remove them significantly sooner (mean 88.57 days for non-PEAK vs. 54.71 mean days for PEAK ($p<0.02$, unequal variances t-test).

Conclusions: The PEAK MDC-pulseData partnership has dramatically improved care coordination resulting in a substantial increase in home dialysis modality and optimal dialysis starts and reduced the amount of time dialysis patients spend using a CVC.

Funding: Commercial Support - pulseData

PO1366

Education and Experience Gained Through Nephrology Business Leadership University (NBLU) Provide Valuable Benefits to Graduating Nephrology Fellows: A Survey-Based Study

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Background: Nephrology fellowship programs provide excellent clinical training but education regarding the economic, business, and leadership aspects of practicing as a nephrologist are lacking. Nephrology Business Leadership University (NBLU) addresses these needs in order to provide graduating fellows with practical tools for navigating their early private practice or academic careers.

Methods: We surveyed attendees of NBLU from each of the four years since the conference was created. An anonymous survey was sent to alumni electronically and focused on how the experiences and knowledge gained at NBLU have impacted their early careers.

Results: Seventy-one percent of fellows who were contacted responded to the survey. Respondents represented all four years of NBLU and all geographic areas of the U.S. All fellows indicated that they would recommend NBLU to other fellows, with 91% indicating that they would highly recommend it. Respondents reported that NBLU increased their knowledge about the nephrology job market, the economics of nephrology practice, and the various ways to engage in leadership opportunities in nephrology, including by using social media platforms for education and networking. Fellows reported enhanced knowledge regarding both private and academic nephrology careers and most established lasting relationships with colleagues from across the country which they intend to maintain throughout their careers.

Conclusions: Nephrology fellows report a significant need for business and leadership education which is currently lacking from fellowship programs. NBLU provides a week-long curriculum which has a lasting positive impact on graduating nephrology fellows. Empowering nephrology trainees on the verge of entering the workforce has the power to strengthen the field as these early career nephrologists inspire other trainees to join this challenging yet fulfilling field.

PO1367

Medicine Residents' Perception of the Nephrology Specialty

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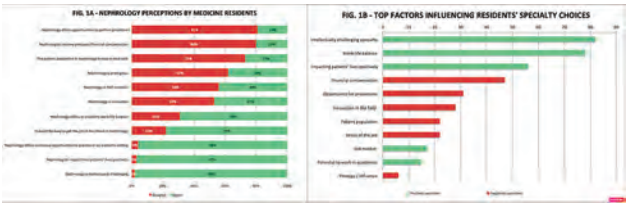
Background: Interest in nephrology as a specialty has been declining among residents. As a result, more than half of the programs remain unfilled. The residents' perceptions of the nephrology field that might account for this loss of interest are unknown. We aimed to identify factors influencing residents' views on pursuing a career in nephrology.

Methods: We used the results of our previously published qualitative analysis on residents' perception of nephrology to inform and design a survey of 60 questions. The survey was delivered using the secure we application "REDCap to 680 residents across eight medicine residency programs in different regions nationally.

Results: 184 residents (27%) responded to the survey. 56% (103) were male, 77% (142) were American graduates and 21% (42) were international graduates. Major positive perceptions of nephrology were: intellectually challenging, positively impacts patients' lives, opportunity to obtain the job of choice with possibility to practice in an academic setting, and a good work-life balance (Fig. 1A). Those aligned well with the top factors influencing residents' choice of specialty (Fig. 1B). The major negative perceptions included: inability to perform procedures, financial compensation, and patient population (Fig. 1A). Those aligned poorly with many of the key factors influencing residents' choice of specialty (Fig. 1B).

Conclusions: Nephrology is well perceived in the top three categories of factors that influence residents' specialty choices. This suggests that negative factors such as inadequate financial compensation, inability to perform procedures, lack of innovation, and a difficult patient population largely outweigh the positives. In order to attract more candidates, the nephrology community should highlight the innovations and policy initiatives such as the Kidney Precision Medicine Project, the Kidney Innovation Accelerator, and the Advancing American Kidney Health initiative. Nephrologists should also consider creating/expanding interventional nephrology programs and increasing resident exposure to outpatient nephrology.

Funding: Private Foundation Support



PO1368

Clinical Practice Guideline Adoption and Nephrologist Demand

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Background: It is unknown how clinical practice guidelines (CPGs) can affect subspecialty consult (and subspecialist) demand. This study sought to quantify how nationwide adoption of a CKD evaluation and management CPG could influence consult volume, nephrologist demand, and existing geographic maldistribution of nephrologists.

Methods: We projected the volume of nephrology consults based on KDIGO's *2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* recommendations for nephrology consultation. KDIGO's CPG recommends a nephrology consult for patients with either a) eGFR <30 ml/min/1.73 m^2; b) urine ACR ≥300 mg/g; or c) eGFR <60 ml/min/1.73 m^2 and/or ACR >30 mg/g and refractory hypertension (BP ≥140/90 mmHg despite ≥4 antihypertensives). We used data from the National Health and Nutrition Examination Survey (NHANES) from 2011–2016 weighted equally across three survey periods, and disaggregated data at the Census Division level to capture geographic variation in potential demand. We calculated eGFR using the CKD-EPI formula and projected KDIGO-recommended nephrology consults as number of weighted individuals per Census Division meeting KDIGO criteria. We quantified nephrologist demand as a ratio of consult volume per nephrologist at the Census Division level using data from the 2014 American Medical Association Masterfile.

Results: Projected nephrologist demand varied geographically, from 1.67% in the Middle Atlantic to 2.33% in the South Atlantic (Table 1), translating to 330–1553 consults/nephrologist if KDIGO's CPG were implemented nationwide. Maldistribution in the Mountain (2.19 nephrologists/100K population) and West North Central (2.44) exacerbated consult demand.

Conclusions: Implementing a CKD CPG could lead to increased demand for nephrologists, which may exacerbate the suboptimal geographic distribution of kidney health specialists.

Results

Census Division	NHANES 2011–2016 Weighted Population	Meet KDIGO Criteria (Weighted Total)	Meet KDIGO Criteria (%)	Nephrologists (2014 AMA)	Nephrologist/100K Population (2014 Census Estimate)	Additional Consults Per Nephrologist
New England	29,970,615	564,870.2	1.88%	509	3.46	1,109.76
Middle Atlantic	14,304,792	239,159.2	1.67%	1,596	3.86	149.85
South Atlantic	39,132,703	913,497.4	2.33%	1,854	2.97	492.72
East South Central	20,078,680	387,114.7	1.93%	537	2.86	720.68
West South Central	18,225,756	411,108.8	2.26%	1,032	2.68	398.36
East North Central	25,156,334	453,289.0	1.80%	1,252	2.68	362.05
West North Central	34,689,394	699,921.9	2.02%	512	2.44	1,367.03
Mountain	39,604,381	699,921.9	1.99%	507	2.19	1,553.26
Pacific	23,670,640	787,804.4	1.87%	1,337	2.58	330.77

PO1369

Association Between Different Payment Models, Workload, and Job Satisfaction of Nephrologists in Lebanon and Jordan

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Background: The main challenges that nephrologists are facing worldwide are lower income, dissatisfactory payment models, long work hours and burnout. This study aimed to identify factors associated with nephrologists' satisfaction in Lebanon and Jordan.

Methods: An online survey was sent to all 250 Lebanese and Jordanian nephrologists, including data on demographics, education, academic activities, job satisfaction, burnout, workload and reimbursement.

Results: A total of 59 nephrologists responded. Mean age was 46.9 ±12.5 years, 39% women. Respondents reported low rates of satisfaction in job opportunities (20%), income (25%) and administrative support (32%). On the other hand, 68% reported that nephrology is stressful. High satisfaction rates were found in relationship with patients (78%) and colleagues (73%). Income was significantly higher among males than females ($p < 0.001$). Satisfaction towards income was significantly lower in females, mean score difference 0.71 ± 0.30 (95%CI: 0.10,1.32; p=0.024). A greater proportion of male over female practitioners wanted to follow above the 40-dialysis-patient regulation ($p<0.001$) and preferred pay-for-performance over fee for service. Satisfaction with income and work-life balance was positively correlated with age and young nephrologists had significantly lower satisfaction with job opportunities (11%). Driving over 1 hour daily to work was significantly associated with dissatisfaction in work-life balance (p=0.029), stress and burnout (p=0.016). Using regression analysis, longer delay in payment predicted worse work-life balance among Lebanese nephrologists (p=0.04). Compared to male practitioners, female practitioners spent more time on teaching ($p < 0.001$), and more female had academic rank and publications ($p < 0.001$). Gender discrimination was perceived significantly among women.

Conclusions: Unfair and delayed reimbursement is associated with dissatisfaction among the surveyed nephrologists. Gender differences are very significant with lower income and satisfaction rates among women. Similarly, it seems that the younger generation perceives low job potentials. Decision makers need urgently to empower women, address payment delays conduct market analysis and accordingly regulate nephrologists' entry to avoid oversupply or unemployment.

PO1370

Assessing Nephrology Competency in General Pediatrics

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Background: General pediatricians may be the first-line providers to care for children with kidney disease, however studies suggest they find nephrology to be a difficult subject. This study aimed to identify areas of lowest perceived competency and importance within nephrology for general pediatricians.

Methods: A web-based survey was distributed to general pediatricians through the Paediatricians of Ontario network, to all Pediatrics Residency Program Directors in Canada and to Pediatric Nephrologists in the Canadian Association of Paediatric Nephrologists. Pediatricians were asked to rate nephrology objectives of training on a 5-point Likert scale for perceived competence and importance. Program Directors and Nephrologists were asked for perceived importance of each objective for general pediatricians. Scores were analyzed using Student's t-test and mean scores were calculated. Knowledge Gap scores were calculated as the difference between perceived importance and competence scores.

Results: ***General Paediatricians.*** 60/350 (17%) responded to the survey. Domains scoring significantly below the mean in terms of competency (2.9/5) and importance (3.2/5), respectively, were kidney stones (2.5 and 2.6), AKI (2.5 and 2.4), CKD (1.9 and 2.1), Tubular disorders (1.8 and 2.0), and kidney transplant (1.6 and 1.7). Hypertension had the most significant knowledge gap score (0.8/5, 16%, $p<0.05$). ***Program Directors.***

9/17 (53%) responded to the survey. ***Nephrologists.*** 20/80 (25%) responded to the survey Program Directors and Nephrologists agreed that Stones, CKD, Tubular disorders, and Transplant were of lower importance. AKI was the domain with the largest discrepancy in perceived importance rated between nephrologists (4.2) and Program Directors (4.2) compared to general pediatricians (2.4) (1.8/5, 36%, p<0.05).

Conclusions: General pediatricians do not feel comfortable with AKI and do not find this topic important to their practice, contrary to Program Directors' and Nephrologists' opinions, and despite growing evidence in recent years of the under-recognition, poor follow-up, and significant long-term implications of AKI. Hypertension is the area with the largest knowledge gap, which also raises concerns due to its rising prevalence in pediatrics. Educational interventions are needed to address deficits in these crucial domains of renal health in general pediatrics.

PO1371

Assessment of Faculty Developed e-Curriculum in Hemodialysis

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Background: E-learning is gaining popularity in medical education and offers several advatages. We have developed a comprehensive, hands-on online E-curriculum in hemodialysis based on ACGME competency requirements. The curriculum includes two online modules on Hemodialysis kinetics/adequacy; and Hemodialysis access. In this study we describe the experience among nephrology trainees, of using this E-curriculum, and assess its effectiveness as a teaching tool.

Methods: This pilot study sample included 11 nephrology fellows (8 from Yale and 3 from other US nephrology programs). **Design**: A mixed methods approach using a triangulation model. **Data collection**: A Qualtrics survey was distributed to the participants after curriculum completion. This was followed by a 15 minute zoom interview of each individual participant. This study was approved by our local IRB.

Results: The study sample had an even distribution of participants across all levels of training. 6/11 identified themselves as visual learners. Irrespective of the learner type, animated videos were the most desired feature of the E-modules and helped visualization of abstract concepts. Concepts of flux vs. efficiency; convection vs. diffusion, Kt/V, physical examination of an AV fistula, and access recirculation were topics reviewed repetitively. Based on survey data, there was 100 % agreement among the learners that the websites were easy to navigate; the content represented common clinical scenarios and the interactive knowledge testing helped in concept retention and improving student engagement. Statistical analysis (paired t-tests) showed that there was significant improvement in perceived knowledge by the learner in 6 core competencies after module completion (p<0.01). The advantages of an E-curriculum were reported to be simplified visualization of key concepts; excellent clinical application, time flexibility;repetitive review, standardization of content, learner centric approach; and a flipped classroom model. The disadvantages were the lack of community learning and the inability to ask questions immediately.

Conclusions: In conclusion, the hemodialysis E-curriculum was an effective educational platform for nephrology fellows. Although an E-curriculum allows standardized learning with a learner-centric approach, it can cause social isolation and requires a self-motivated learner. A blended learnng approach, combining E-learning and traditonal methods may be ideal.

PO1372

Implementation and Assessment of Virtual Standardized Patient Sessions to Teach Communication Skills to Nephrology Fellows During COVID-19

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Background: Standardized patients (SP) are routinely used in medical education teaching learners how to communicate in traditionally challenging environments like end-of-life discussions or delivery of a difficult diagnosis. Adherence to the need for social distancing during COVID-19 has eliminated in-person SP encounters and necessitated virtual sessions using a video conferencing software. We assessed the impact of virtual, SP-based communication skills workshops on a cohort of nephrology fellows.

Methods: Over two weeks, nephrology fellows were invited to participate in two 90-minute communications workshops with a SP conducted over Zoom. Workshops included a didactic portion and SP interviews simulating difficult conversations. Fellows observed each other and provided feedback during the interviews. A 10-question survey was then distributed to the participants to evaluate the training sessions and compare them to analogous in-person communication workshops.

Results: All invited fellows participated in at least one session and completed the survey (100%, 12/12). Five first-year fellows (42%, 5/12), 5 second-year fellows (42%, 5/12), and 2 third-year fellows (17%, 2/12) participated. 67% (8/12) of participants reported that they found the sessions useful. Of the fellows who had attended a prior in person simulation-based workshop (67%, 8/12) with standardized patients, 88% (7/8) rated the virtual session as good as or better than in-person role-playing. 83% (10/12) of respondents reported that skills learned during the virtual session would be used in their clinical practice. 83% (10/12) felt observing their co-fellows was useful. Write-in comments indicated a barrier to using virtual role playing was a challenge in recognizing emotion and empathy.

Conclusions: Virtual training sessions with SP actors were rated highly by the fellows and provided an opportunity for them to practice communication skills to incorporate into current practice. The virtual workshops were easily implemented, well-received, and should be considered as an alternative training format, especially when in-person workshops cannot be conducted. Future trainings can incorporate communication challenges that arise during telemedicine video or telephone encounters.

PO1373

Dose Adjustment of Rheumatologic and Allergic Medications in CKD: Awareness and Knowledge Among Internal Medicine House Staff

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Background: Patients with chronic kidney disease (CKD) are at increased risk for adverse drug events due to medication dosing errors. We study the awareness and knowledge among Internal Medicine house-staff (IMHS) of proper dose adjustment of commonly used rheumatology and allergy/immunology medications for patients with CKD.

Methods: We surveyed 353 IMHS to evaluate their awareness of medication dose needs adjustment for patients with CKD and knowledge for medication adjustment by level of glomerular filtration rate for common rheumatology and allergy/immunology medications.

Results: There was lack of awareness and knowledge for both rheumatology and allergy/immunology medications. Not correct awareness and knowledge were: allopurinol (21.2%, 73.4%), colchicine (19.0%, 75.9%), diphenhydramine (34.0%, 34.0%), loratadine (82.2%, 93.2%), and montelukast (34.0%, 34.0%). Exploratory logistic regression analyses showed PGY1 residents had higher odds for lack of awareness for allopurinol (OR:24.57, 95% CI:4.69, 99.13, p<0.001), colchicine (OR:3.98, 95% CI:1.50, 10.51, p<0.01), diphenhydramine (OR:2.24, 95% CI:1.10, 4.54, p<0.04), and montelukast (OR:2.45, 95%CI:1.20, 5.00, p<0.05) than PGY3 residents. Nephrology rotation in medical school was associated with lower odds for incorrect knowledge for allopurinol (OR:0.46, 95%CI:0.25, 0.87, p<0.05) and montelukast (OR:0.50, 95%CI:0.27, 0.92, p<0.05).

Conclusions: Overall, awareness and knowledge was poor among IMHS for dose adjustments of rheumatology and allergy/immunology medications in patients with CKD. Proper education and exposure to nephrology during training may improve quality and safety of care for patients with CKD.

PO1374

Emerging Therapies for Managing Patients with Alport Syndrome: Online Medical Education Improves Knowledge and Confidence of Nephrologists

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Background: As new therapies for Alport syndrome continue to progress through development, nephrologists need an increased understanding of these drugs. We sought to determine if online education for nephrologists could improve clinical knowledge and confidence in managing patients with Alport syndrome with current and emerging treatment strategies.

Methods: The continuing medical education (CME) activity was an online video panel discussion among 3 faculty on current and emerging strategies for the management of Alport syndrome. Three multiple-choice knowledge questions and 1 self-reported confidence question were presented both before and immediately after the CME activity. A repeated pairs pre-/post-assessment study design was used and a chi-square test (P <.05 is considered significant) assessed educational effect for each activity. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activity launched online on March 1, 2019, and data were collected through April 2, 2019.

Results: Overall, knowledge and confidence improved among nephrologists (n = 71, V=.348, P<.001) from pre- to post-assessment: 24% demonstrated improved understanding of important factors when prescribing renin-angiotensin-aldosterone system (RAAS) inhibitors in patients with Alport syndrome (V=.216 (considerable educational impact), P<.05) 32% demonstrated improved recognition of efficacy data for bardoxolone methyl in Alport syndrome increase in the number of nephrologists (V=.297 (extensive educational impact), P<.001) 63% demonstrated improved identification of adverse effects for emerging treatments for Alport syndrome (V=.581 (extensive educational impact), P<.001) 38% reported increased confidence in understanding of role that chronic renal inflammation plays in AS Continued educational gaps: 41% failed to recognize impact of bardoxolone methyl on Alport syndrome 20% did not recognize important factors when prescribing RAAS inhibitors in patients with Alport syndrome

Conclusions: The online video panel discussion CME activity demonstrated success in improving knowledge and confidence of nephrologists related to current and emerging therapies for the management of Alport syndrome. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Reata

PO1375

Online CME Effectively Improves Nephrologists' Knowledge, Competence, and Confidence Related to Hyperkalemia Management

Amy Larkin, David R. Anderson, George Boutsalis. *Medscape LLC, New York, NY.*

Background: To improve outcomes for patients, clinicians must be able to implement evolving standards of care and apply relevant data on hyperkalemia management. We sought to determine if a series of online continuing medical education (CME) activities could improve the clinical knowledge, competence, and confidence of nephrologists related to hyperkalemia management.

Methods: The curriculum consisted of 2 online, 30-minute activities related to new data and case-based application of data in common patient cases. The educational effects were assessed using a repeated pairs preassessment/postassessment study design. For all questions combined, the McNemar's chi-squared test assessed differences pre to post. P values <.05 are statistically significant. Cramer's V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activities launched in March and June 2019, and data were collected for 4 weeks for each activity.

Results: Improved knowledge and competence was demonstrated among nephrologists (N= 371): 17% increase in selecting a treatment strategy when a patient becomes euvolemic but still shows slightly elevated potassium levels (N=188; V=.191; $P < .001$) 24% increase in recognition of long-term data for newer potassium binders (N=183; V=.193; $P < .001$) 26% (N=183) had a measurable increase in confidence in using a potassium binder to treat a patient hyperkalemia 34% (N=188) had a measurable increase in confidence in applying team-based strategies to better manage patients with HF who present with hyperkalemia Persistent knowledge/competence gaps remain: 56% of nephrologists (N=183) incorrectly identified incidence of hyperkalemia in patients with heart failure treated with renin-angiotensin-aldosterone system (RAAS) inhibitors 49% of nephrologists (N=183) could not recognize long-term efficacy data for newer potassium binders 74% of nephrologists (N=188) made an incorrect clinical-decision in a patient who was euvolemic but had elevated potassium levels

Conclusions: This study demonstrates the success of an online curriculum with multiple educational components at improving knowledge, competence, and confidence of nephrologists related to hyperkalemia management. Persistent gaps were identified for future educational targets.

Funding: Commercial Support - independent educational grant from Astrazeneca

PO1376

Case-Based, Interactive Medical Education Significantly Improves Management of Chronic Hyperkalemia in Complex Patients

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape LLC, New York, NY.*

Background: We sought to determine if interactive, case-based online continuing medical education (CME) for nephrologists could improve clinical knowledge, competence, and performance in the area of chronic hyperkalemia management in complex patients.

Methods: The instructional method consisted of an online, case-based, interactive text activity. Clinicians were presented with 2 patient cases that included multiple-choice knowledge or competence questions allowing them to make clinical decisions about treatment. Educational effect was assessed using a 4-question repeated pairs pre-/post-assessment and McNemar's chi-squared test. *P* values are shown as a measure of significance; *P* values <.05 are statistically significant. Cramer's V determined the effect size (<0.05 no effect; 0.06-0.15 small effect; 0.16-0.30 medium effect; >0.30 large effect). The activity launched May 15, 2019; data were collected through June 24, 2019.

Results: Significant overall improvements were seen (n = 59; *P* =.003; V= 0.156) as a result of participation in the CME activity. Specific areas of improvements include: 8% of nephrologists (*P*=.05; V=.179) improved at using a loop diuretic when a low-potassium diet was unsuccessful at lowering potassium levels 25% of nephrologists (*P*=.008; V=.241) demonstrated improvement at prescribing a newer potassium binder in a patient with consistently elevated potassium despite a low potassium diet and loop diuretic 10% of nephrologists (*P*=.4; V=.076) improved at using a newer potassium binder in a patient on dialysis with hyperkalemia 36% of nephrologists reported increased confidence using potassium binders in patients on RAAS inhibitors Continued educational gaps: 29% of nephrologists did not initiate a newer potassium binder in an appropriate patient

Conclusions: This study demonstrates the success of an online, highly interactive, case-based educational intervention on improving knowledge, competence, and performance of nephrologists regarding complex management of chronic hyperkalemia.

Funding: Commercial Support - Relypsa, a Vifor Company

PO1377

Curriculum-Based Online Education Effectively Improves Nephrologists' Ability to Manage Hyperkalemia in Practice

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape LLC, New York, NY.*

Background: The goal of continuing medical education (CME) is professional growth and improved patient care. We sought to determine if a series of online continuing medical education (CME) activities could improve the clinical knowledge, competence, and confidence of nephrologists related to hyperkalemia management.

Methods: The online CME curriculum consisted of 6 activities. Of these, 5 were video-based and used repeated pairs pre-/post-assessment study design and McNemar's test (P <.05 is considered significant) to assess educational effect. The last activity was a medical patient simulation that utilized tailored clinical guidance (CG), based on current evidence and expert recommendation, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions. The activities launched in 2019 and data were collected for up to 12 weeks.

Results: The education reached over 14,000 physicians, including over 3,200 nephrologists. Overall, knowledge improved by 29%, competence by 14% and performance by 150% (all relative improvements, P<.001) by nephrologists. Specific improvements: 22% relative increase in knowledge related to rationale for optimizing RAAS inhibitors in patients with chronic hyperkalemia (P<.001) 15% relative increase in competence related to effective use of pharmacotherapy for hyperkalemia (P<.001) 441% and 231% relative increases in performance (2 patient simulation cases) related to effective use of pharmacotherapy for hyperkalemia (P<.001) Of the nephrologists who were included, 36% reported increased confidence in managing hyperkalemia, with the largest confidence gains being related to effective use of potassium binders.

Conclusions: This curriculum demonstrates that by increasing knowledge and competence related to hyperkalemia management in a curriculum approach, large improvements in performance can be achieved (over 90% were effectively using pharmacotherapy post-CG). Learners, on average, knew 70% of the information assessed and still require more education in optimizing RAAS inhibitors in patients with chronic hyperkalemia and use of diet to manage hyperkalemia. Among the learners, 36% gained confidence regarding hyperkalemia management in practice, but are still not fully confident. As such, further education is needed in these areas.

Funding: Commercial Support - Relypsa, a Vifor Company

PO1378

An Analysis of Scientometrics and Social Media in Nephrology

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Background: In the past decade, the use of social media to disseminate scientific literature, particularly in the Nephrology community, has exponentially increased to educate, network, mentor. The hallmark of scientometrics has traditionally been based on Journal Impact Factor (JIF), calculated from the citations of each article. It has been previously demonstrated that twitter mentions of published works, correlate with citations, and therefore JIF, in the fields of Urology, Biomedical Science, and Ecology. However, this relationship has yet to be established in the field of Nephrology.

Methods: The top 5 journals in Nephrology, based on impact factor (Kidney International, Nature Reviews Nephrology, AJKD, JASN and CJASN), published 76 articles in January of 2018 in print. Altmetrics bookmarklet was used to collect twitter demographics on each article (number of tweets, by whom, and number of followers). Citation data was sourced from Web of Science's InCites Journal Citation Reports. Articles were categorized as 'highly cited or tweeted' when they were ≥ 75th percentile of citations or tweets, and 'less cited or tweeted' at ≤ 25th percentile.

Results: Of the article cohort, the most common article types were clinical investigations (42%), followed by basic research (20%), and reviews (10%). The citation mean was 18.29 ± 15.87 citations per article, while the twitter mentions mean was 28.38 ± 68.97 tweets. The Spearman correlation coefficient for Twitter mentions and citations was 0.25 (p = 0.026). The odds ratio of an article being both highly cited and highly tweeted was 3.6 (CI: 0.71 to 18.25). The relative risk showed that highly tweeted articles were 1.87 (CI: 0.83 to 4.19) times more likely to be highly cited than less cited. Finally, the peak tweets (279) occurred in October of 2017 while the peak in citations occurred in 2019.

Conclusions: The preliminary analysis showed a significant but weak correlation of twitter mentions and citations. This suggests that twitter increases an article's reach, its likelihood of becoming cited, and therefore the JIF. Future directions will include exploring a larger sample size and confounding factors such as word count, number of authors, and number of citations.

PO1379

Qualitative Interview Study on Advanced Care Planning for Patients with Advanced CKD and Their Families: The Impact of the MY WAY Advance Care Planning Intervention

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Background: Despite recommendations for shared decision-making approaches to advance care planning (ACP) for people with chronic kidney disease (CKD), doctor-patient conversations about ACP are infrequent. The MY WAY educational and patient-coaching intervention aims to elicit patient values to increase rates of ACP. This qualitative sub-study sought to: (1) gain understanding of participant responses to MY WAY ACP materials, and (2) learn about participant wishes for kidney care within ACP.

Methods: We conducted semi-structured interviews with participants from the intervention arm of the MY WAY study. Fifteen people with CKD were queried about their experiences of the MY WAY print materials and coaching session. Interviews were recorded and transcribed for simultaneous coding by two researchers. Data were analyzed using thematic analysis.

Results: Fifteen intervention participants ages 59-87 were interviewed (10 women, 5 men). Five major themes emerged: participant advice for interventionists; experience with ACP before and after the intervention; participant experience of printed materials; participant response to coaching session; and chronic kidney disease thoughts and communication. Differences between participant experiences of general and CKD-specific ACP emerged, including willingness to discuss care wishes with family members and clinicians.

Conclusions: Participants perceived the coaching session to have high utility in facilitating ACP, but expressed less engagement with CKD-specific care plans. Findings suggest that characteristics of the coach, including empathy and problem-solving, play a key role in participant comfort with ACP conversations, and that engagement with ACP may not correlate with engagement with CKD-specific care wishes. Notably, even participants who engaged actively with general ACP expressed that kidney-specific care would be addressed with their nephrologists if or when the need arose. Future studies should further explore the interrelation of general ACP and CKD-specific care planning.

Funding: Private Foundation Support

PO1380

Enhancing Patient Care by Partnering with Patients in Kidney Health Research

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Background: Canada's Strategy for Patient-Oriented Research (SPOR) has raised awareness of the need to generate knowledge that is more relevant to patients and to accelerate the translation of evidence into clinical care. Members of the Canadian nephrology community have come together to develop a national patient-oriented research network, Can-SOLVE CKD, that is partnering with patients to close existing gaps in kidney disease knowledge in order to deliver better health outcomes. The Can-SOLVE CKD Network brings together patients and nephrology researchers to transform treatment and care for Canadians living with or at risk for chronic kidney disease.

Methods: The network's 18 research projects are informed by two national priority-setting exercises conducted with patients, their families and care providers. As the network executes the projects, patients have been integrated into research teams, bringing an enhanced "patient lens" to bear on all aspects of the research life cycle: design, development, recruitment, implementation, and dissemination. Patients are also at the centre of the network's governance model, which incorporates a Patient Governance Circle and an Indigenous Peoples' Engagement and Research Council.

Results: Can-SOLVE CKD researchers have reported the positive impact of partnering with patients. "My research is better" is often cited as an outcome of patient engagement within the network. Patient partner involvement on the network's Research Operations Committee has enriched the annual review of projects, resulting in valuable, real-world feedback to project teams. Respondents to the network's patient engagement survey report feeling better informed about and having greater trust in kidney research as a result of their participation.

Conclusions: We have witnessed a shift in the culture of nephrology research in Canada paralleling the broader movement toward patient-oriented research. The traditional role of patients as research subjects has evolved to include patients as valuable and equal members of Can-SOLVE CKD's research projects.

Funding: Government Support - Non-U.S.

PO1381

Online Patient/Caregiver Education on Hyperkalemia Can Improve Knowledge and Confidence as Well as Prompt Real-Life Changes

Amy Larkin, Donald Blatherwick. *Medscape LLC, New York, NY.*

Background: Managing hyperkalemia with a strict diet is limiting and difficult for patients. We sought to measure the impact of online education for patients/caregivers on knowledge and confidence as well as prompting change in daily life.

Methods: The patient/caregiver education was designed as 2 online, interactive activities. Both were comprised of text and integrated visuals, the second also included a patient commentary video. Demographic questions were asked prior to starting the education. A knowledge question was asked both before and after the activity to assess learning gains, as well as intent to change and confidence questions at the end. The activities launched in March and May of 2019, and data collected through September 2019.

Results: To date, 72,440 learners have participated in the patient/caregiver activity. Activity 1: Do You Have High Potassium? Here are Some Tips for Managing Potassium in Your Diet Participants: 35, 889 Completers of all questions (included in outcomes analysis): 4,305 Demographics: 65% female; 63% white, non-Hispanic; 67% over the age of 54; 45% have hyperkalemia, 42% were interested in learning more about the condition Knowledge changes: 24% improvement in recognizing foods high in potassium (50% pre to 74% post) Intent-to-act: 81% plan to identify and avoid foods high in potassium Confidence changes: 79% reported increased confidence talking to their doctor about ways to lower their potassium levels Activity 2: Are Medicines That Lower Potassium Right for You? Participants: 36, 551 Completers of all questions (included in outcomes analysis): 2, 917 Demographics: 59% female; 70% white, non-Hispanic; 82% over the age of 54; 58% were interested in learning more about the condition and 29% have this condition Knowledge changes: 23% improvement in recognizing how potassium binders work to treat hyperkalemia (42% pre to 65% post) Intent-to-act: 69% plan to talk to their healthcare provider about medicines that can treat hyperkalemia Confidence changes: 73% reported increased confidence talking to their doctor about medicines that can treat hyperkalemia

Conclusions: The metrics and outcomes gathered in this assessment are a strong indicator that these patient/caregiver-focused online educational activities improved knowledge and confidence, and prompted intent to act by patients/caregivers related to hyperkalemia.

Funding: Commercial Support - Relypsa, a Vifor Company

PO1382

Rethinking Renal Caregiving in Anthropological Terms: An Interdisciplinary Methodological Approach

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Background: Rethinking caregiving in nephrology through an anthropological lens may bring a new perspective to a holistic understanding of renal care by encouraging health professionals to reflect critically on the complex webs of care, culture, and ethics in which renal medicine is enmeshed.

Methods: This study draws on anthropological methodology and ethnographic research to develop a framework for reconceptualizing renal care. An extensive review of the anthropological literature on renal care is used to illustrate some of the multifaceted challenges of caregiving in nephrology and to develop a framework for use in the clinical encounter to better understand patients' illness-related beliefs and their relevance for clinical practice.

Results: The key domains in renal care are framed by diverse cultural, societal, and individual beliefs regarding the organ's function and the causes of kidney disease. Ethnographic data from dialysis and renal transplant patients in the United States, Europe, Mexico, and China show that diverse and controversial disease and treatment beliefs pose a different kind of challenge to the communication between health professionals and their patients. Based on these findings, a framework has been developed that can be integrated in medical education programs and provides a guide for health professionals to think through the complex psychological, ideological, and ethical underpinnings of nephrology's central therapeutic modalities such as transplantation and dialysis.

Conclusions: Bringing an anthropological sensibility to the clinical gaze may help to understand the cultural and moral world in which the caregiver-patient relationship needs to be formed. The integration of the medical humanities into the educational programs of renal caregivers can be used to develop a better understanding of patients' diverse disease and treatment beliefs which will ultimately improve the caregiver-patient relationship.

Funding: Private Foundation Support

PO1383

WeChat Platform and Specialty Nursing Outpatient Clinics to Improve the Compliance of a High-Quality Low-Protein Diet in Patients with CKD Stage 3-5

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Background: Low protein diet (LPD) has become one of the important means to treat chronic kidney disease (CKD) patients. At present, the low protein diet compliance of CKD patients in China is not ideal, the compliance rate is only 48.3% - 54.5%. The dietary compliance of CKD patients is based on the knowledge of diet, and the survey shows that CKD patients and their families have a low level of knowledge of diet of kidney disease. Therefore, in order to improve the low protein diet compliance of ckd3-5 patients and reduce the incidence of malnutrition, we set up a wechat group through the network platform to guide the low protein diet of ckd3-5 patients. The nutrition team regularly issues the low protein diet knowledge, and makes an appointment for the follow-up of patients to the specialized nursing clinic every 1-3 months to provide one-to-one guidance services. To explore the effect of continuous care based on We-Chat platform and Specialist Nursing Outpatient Clinics on the compliance of high-quality low-protein diet in patients with Chronic Kidney Disease (CKD) stage 3-5.

Methods: 46 cases of diagnosed CKD 3-5 patients were randomly divided into a control group (22 cases) and an observation group (24 cases). The control group conducted routine nursing and high-quality low-protein diet nursing guidance, and the observation group implemented a high-quality low-protein diet nursing strategy based on We-Chat platform and Specialist Nursing Outpatient Clinics on a routine basis. Compare the performance and effect of high-quality low-protein diet between the two groups.

Results: In the observation group, there were 10 men and 12 women with an average age of 42.6 ± 2.3 years; in the control group, there were 12 men and 12 women with an average age of 40.2 ± 2.1 years. There was no significant difference between the two groups in height, weight, education level, and basic diseases ($P > 0.05$). The observation group's preparation of CKD high-quality low-protein diet,three-day diet diary,and daily protein intake were better than the control group ($P < 0.05$).

Conclusions: The continuous nursing strategy based on We-Chat platform and Specialist Nursing Outpatient Clinics can effectively improve the compliance of CKD3-5 patients with high-quality low-protein diet.

PO1384

A Kidney Education Program Integrated into Middle School Science Classes Increases Student Kidney Knowledge, Improves Health Behaviors, and Increases Kidney Health Literacy

Julie A. Wright Nunes, Panduranga S. Rao, Ben Ransier, Jean DuRussel-Weston, Brad Newman, Julie Ma, Kenneth A. Resnicow, Kim Eagle. *University of Michigan, Ann Arbor, MI.*

Background: Chronic kidney disease (CKD) is a serious and growing public health problem. Literature shows primary disease prevention is successful when incorporated early in life. There are few reports about CKD prevention efforts in youth.

Methods: A 3-lesson kidney program was designed by health and wellness staff, school teachers and researchers, and aligned with U.S. school science standards. It was integrated into two middle school science classes, located in high-risk areas of renal failure. The 3-lesson program covered kidney physiology, epidemiology and environmental and genetic risk factors. Students were tested before and after the kidney program. We used linear regression to examine bivariate and multivariate associations between demographics and test responses comparing pre- and post-tests.

Results: Two-hundred and nine 6th and 7th grade students received the 3-lesson kidney program. One-hundred and eighteen (57%) were male, 44 (23%) non-Hispanic Caucasian, 26 (12%) non-Hispanic African American, 26 (12%) other races, and 98 (48%) were Hispanic. Post-tests increased significantly for health literacy (from mean SD 3.1 (0.05) to 3.4 (0.05) p=0.02), kidney general knowledge (2.3 (1.1) to 3.9 (1.6) p<0.01), kidney physiology (3.9 (1.1) to 4.6 (1.0) p<0.01) and student ratings of kidney importance (4.0 (0.9) to 4.3 (0.7) p<0.01). Students also reported increases in daily activity and reduced consumption of fruit juices. In analyses adjusted for school, race, gender, ethnicity and age, health literacy, kidney general knowledge, kidney physiology, kidney importance and behaviors remained significantly improved.

Conclusions: A 3-lesson kidney program seamlessly delivered by teachers during science classes at two middle schools in high-risk areas for renal failure improved student health literacy, knowledge and behaviors. Next steps will be to examine impact in larger cohorts and clinical indices over time.

Funding: Other NIH Support - UL - NIH - NCATS grant

PO1385

Nephrology Exposure and Quality of Education in Residency and Medical School

Georges Nakhoul,[1,2] Ali Mehdi,[1,2] Jonathan J. Taliercio,[1,2] Patricia F. Kao,[3] Grace Mcnutt,[1] Jessica Greenfield,[1] Abby L. Spencer,[1,2] John F. O'Toole,[1,2] Joseph V. Nally,[1,2] John R. Sedor,[1,2] S. beth Bierer.[1,2] *[1]Cleveland Clinic, Cleveland, OH; [2]Case Western Reserve University, Cleveland, OH; [3]Washington University in Saint Louis, Saint Louis, MO.*

Background: Interest in nephrology as a specialty has been declining among residents. Lack of exposure to nephrology has been identified as one of the factors possibly accounting for this loss of interest.

Methods: We used the results of our previously published qualitative analysis on residents' perception of nephrology to inform and design a survey of 60 questions. The survey was delivered using the secure we application "REDCap to 680 residents across eight medicine residency programs in different regions nationally.

Results: 184 residents (27%) responded to the survey. 56% (103) were male and 77% (142) were American graduates. During medical school, 82% of respondents were taught nephrology as a unique discipline, while 33.5% rotated on a nephrology service. During residency, 75% of respondents rotated in nephrology and the rotation took place during PGY1 for 68% of the respondents. On a scale of 1 (poorest) to 100 (best), the quality of nephrology education was rated favorably during residency and during the pre-clinical years of medical school, and less favorably during the clinical year of years of medical school (Fig. 1). Out of 134 residents (73%) who expressed interest in pursuing fellowship training, only 5.8% selected nephrology. Only 6.3% of residents identified a mentor in nephrology vs. 29.7% in general medicine and 26.6% in cardiology (Table 1).

Conclusions: We observed a "dip" in the quantity and quality of nephrology exposure during the clinical years of medical school. More work is needed to characterize the significance of this dip and to understand whether or not this may represent an opportunity to improve the visibility and impact of nephrology on trainees.

Funding: Private Foundation Support

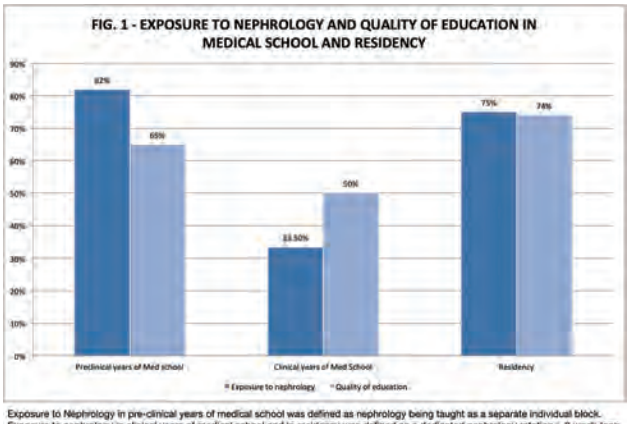

Figure 1

	Fellowship I intend to pursue	Specialty of mentor in Residency	Rotations I rotated in during Med School	Mandatory rotations in Med School
CARDIOLOGY	34 (24.8%)	34 (26.6%)	107 (58.2%)	46 (25%)
GASTRO-INTESTINAL	29 (21.2%)	25 (19.5%)	74 (40.2%)	19 (10.3%)
ONCOLOGY	20 (14.6%)	17 (13.3%)	65 (35.3%)	16 (8.7%)
PULM/CRIT	14 (10.2%)	16 (12.5%)	104 (56.5%)	60 (32.6%)
RHEUMATOLOGY	12 (8.8%)	7 (5.5%)	32 (17.4%)	11 (0%)
NEPHROLOGY	8 (5.8%)	8 (6.3%)	62 (33.7%)	10 (5.4%)
ENDOCRINOLOGY	7 (5.1%)	6 (4.7%)	32 (17.4%)	12 (6.5%)
INFECTIOUS DISEASE	3 (2.2%)	8 (6.3%)	69 (37.5%)	10 (5.4%)
GENERAL MEDICINE	2 (1.4%)	38 (29.7%)	155 (84.2%)	176 (95.7%)
OTHER	8 (5.8%)	5 (3.9%)	0	6 (3.3%)
TOTAL RESPONDERS	137	128	184	184

Table 1

PO1386

Internal Medicine Residents' Perceptions of Nephrology as a Career: A Focus Group Study

Natalie Beck, Seth B. Furgeson, Michel Chonchol, Jessica B. Kendrick. *University of Colorado Denver School of Medicine, Aurora, CO.*

Background: The interest in nephrology as a career has declined dramatically over the past several years. Only 62% of nephrology fellowship positions are filled for the upcoming 2020 appointment year. The purpose of this study was to identify perceptions, attitudes, motivators and barriers to a career in nephrology among internal medicine residents.

Methods: Focus groups of internal medicine residents (N=25) from the University of Colorado were performed. Questions were aimed at exploring perceptions, attitudes, and barriers to a career in nephrology and ways to increase interest in nephrology. All focus groups were conducted on the University of Colorado Denver Anschutz Medical Campus. Focus groups were recorded and transcribed. Thematic analysis was used to identify key concepts and themes.

Results: Residents' described many barriers to a career in nephrology including lack of exposure, lack of advances in the field, low monetary compensation, too complex, lack of role models/mentors and low prestige/non-competitive. Most residents had no exposure to outpatient nephrology. Lack of new therapeutics was a significant deterrent to nephrology. Nephrology teaching in medical school was described as not clinically relevant and too complicated. Several residents felt they were not smart enough for nephrology. Only 3 residents had a role model within nephrology. Residents used the word "stigmatized" to describe nephrology and discussed how low prestige decreases their interest in a field. Participants expressed suggestions to increase interest in nephrology through earlier and more outpatient nephrology exposure, enhanced interactions with nephrologists and research and advancements in the field.

Conclusions: Residents' identified several modifiable barriers to a career in nephrology. Changing how nephrology is taught in medical school, enhancing interactions with nephrologists through increased exposure and highlighting research and advancements in nephrology may change the perception of nephrology and increase the number of residents entering the field.

Funding: Other NIH Support - NHLBI R01 HL132868

PO1387

Changes in the Demographics and Research Focus of Renal Physician-Scientists in the United States

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Background: The enormous strides in biomedical research made over the past 50 years are in large part due to the contributions of physician-scientists. However, while the renal physician-scientist workforce has been thought to be falling, these changes have not been quantified. The purpose of this study was to compare changes in the demographics and the research focus of established physician and non-physician principal investigators

(PIs) with active kidney-focused RO1s in 2005 and in 2020. We also compared changes in the demographics and research focus of more junior physician PIs by examining the K series grants over the same period that have focused on the kidney.

Methods: We mined NIH RePORTER for NIDDK-funded, kidney-focused RO1s and K series grants to determine the PI demographics, the terminal degree(s) of the PIs (physician versus non-physician) and to determine the relative number of clinical and basic science proposals. As an age-surrogate, we compared the year at which the respective RO1 PIs received either their M.D. (physicians) or their Ph.D. (non-physicians) degrees. Taking these values, along with published data as to the median age at which students received their M.D. or Ph.D. in the U.S. in both 2005 and 2020, we estimated the ages of the NIDDK RO1-funded physician and non-physician workforce doing kidney research in the U.S.

Results: Amongst grants focused on kidney, the apparent median age of non-physician, RO1-funded PIs was similar in 2005 and in 2020. However, the apparent median age of physician, RO1-funded PIs is approximately 6 years older in now in 2020 than that in 2005. While the number of basic science grants was similar for physician PIs in 2005 and 2020, the number of clinically-focused RO1s increased. The number of NIDDK K series-funded physicians peaked in 2010 and then declined. However, the percent of physician-scientist RO1s held by women has risen from 15% in 2005 to 25% in 2020, while physician-scientist K series awards held by women has risen from 35% to 48% over that time period.

Conclusions: The representation of women in the physician-scientist workforce doing kidney research has increased. However, this physician-scientist workforce is older and relatively fewer are engaged in basic science research.

Funding: NIDDK Support

PO1388

"I Hear and I Forget. I See and I Remember. I Do and I Understand." Incorporating Emergency Room-Based, High-Fidelity Medical Simulation into the Undergraduate Nephrology Course

Ewa Pawlowicz, Michelle Kulesza, Aleksandra Szymanska, Anna Masajtis-Zagajewska, Maria K. Bartczak, Michal P. Nowicki. *Medical University of Lodz, Uniwersytet Medyczny w Lodzi, Lodz, Poland.*

Background: Medical simulation develops clinical skills by implementing scenario in a true-to-life environment, but without exposing patient to any risk. There has been no information on use of high-fidelity simulation in undergraduate nephrology teaching. Scenarios are provided in Fig. 1. Aim of this study was to analyze students' opinions and reactions to the simulation module in nephrology.

Methods: The survey consisting of the Satisfaction with Simulation Experience scale (SSES) and open-ended question concerning the overall impression of classes was conducted among 103 5-year medical students, who took part in the simulation training in nephrology. SSES consisted of three parts (debriefing, reasoning, education). Statements from the open-ended question were interpreted by means of the *Atlas.ti* software for qualitative data analysis.

Results: The overall score for simulation classes was 4.39±0.69 points. Students rated debriefing, reasoning and education at 4.43±0.78, 4.32±0.7 and 4.39±0.73 points, respectively. 87.4% and 84.5% of participants agreed that simulation developed their clinical reasoning and decision-making skills in nephrology, respectively. Thematic analysis revealed that students evaluated the module as 'interesting', 'useful' and 'informative', but they found number of classes significantly insufficient. Students pointed out that due to the small emphasis placed on practical aspects in the existing curriculum e.g. routes of drug administration and conversion of doses, they could not fully benefit from simulation.

Conclusions: Medical simulation is a valuable constituent of the nephrology course. Putting greater emphasis on practical aspects from the beginning of training may enable students to benefit more from simulation modules.

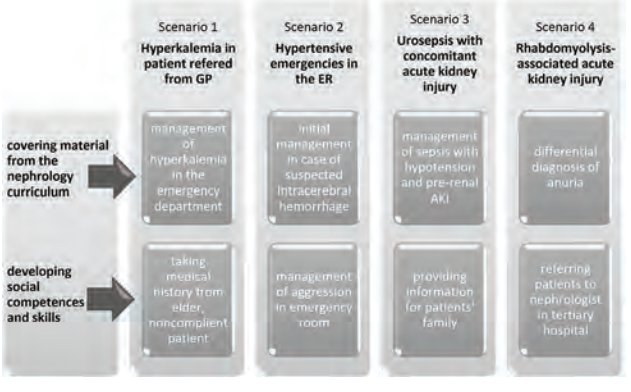


Figure 1. Medical simulation scenarios conducted as a part of undergraduate nephrology course.

PO1389

The Skeleton Key Group: The Impact of Fellow-Led Education

Amy Yau,[1] Joel M. Topf,[2] Sayna Norouzi.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Oakland University William Beaumont School of Medicine, Rochester, MI; [3]Baylor College of Medicine, Houston, TX.*

Background: The Skeleton Key Group (SKG) is an online collective of trainees working to generate free, open-access medical education focusing on the pathophysiology, presentation, and management electrolyte disorders. The final product is a monthly case report published at Renal Fellow Network. Trainee created and edited visual abstracts, tweetorials, and Twitter polls supplement the report. All content is reviewed by senior fellows and an experienced attending nephrologist.

Methods: The SKG formed in September 2019, and group members were continually added. An anonymous survey was sent to the 32 members from May 3-20, 2020. Data here was censored May 2020.

Results: Response rate was 62.5% (n=20). 65% were nephrology fellows with 3 independently practicing nephrologists and 4 residents. The impact of involvement in the SKG on members' medical education was positive (Fig 1). 85% of respondents felt the experience improved their medical knowledge, and 70-80% noted improved manuscript construction (Fig 1). Secondarily, 50-55% noted improved ability to edit, review, and write a peer reviewed publication. Over 75% of respondents stated an improved ability to educate and mentor trainees and increased desire to continue/pursue nephrology training. Surveyees' primary goal was to learn (90%, Fig 2). 60% met all and 30% met some of their goals. Among low-engagement members (n=10), defined as < 25% involvement, a busy work/life schedule was the largest barrier, yet still 50% met some and 30% met all of their goals.

Conclusions: Members felt participation in the SKG added to their medical education regarding knowledge and manuscript construction. Involvement provides the skills needed to continue scholarly activities, and it may help familiarize and motivate trainees to pursue nephrology and subspecialty nephrology training. Even low level involvement in our educational fellow led forum enhanced the education of future nephrologists.

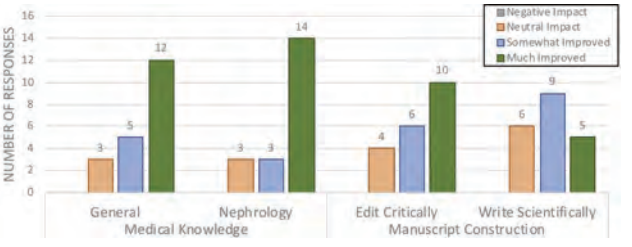


Fig 1. Impact of Involvement in the SKG on Medical Education

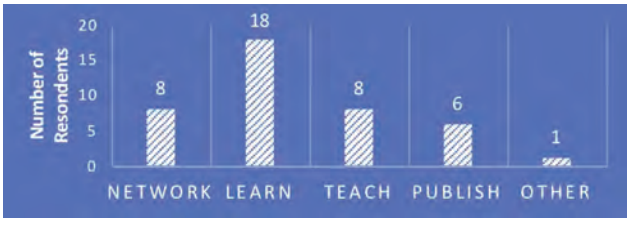


Fig 2. Goals of Members

PO1390

The Skeleton Key Group: Teaching Electrolyte Disorders Using Social Media Tools and Spaced Learning

Sayna Norouzi,[1] Joel M. Topf,[2] Amy Yau.[3] *[1]Baylor College of Medicine, Houston, TX; [2]Oakland University William Beaumont School of Medicine, Rochester, MI; [3]Mount Sinai Hospital, New York, NY.*

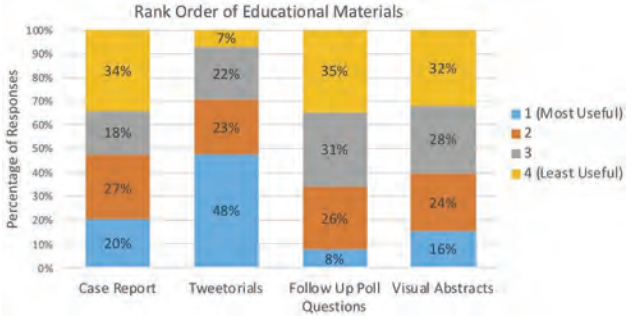
Background: Social media is being adopted by healthcare professionals as a platform for education. It's ability to close geographic gaps and flex to busy schedules is increasing the demand for online educational platforms. The Skeleton Key Group (SKG) is a free open access medical education (FOAMed) platform focusing on electrolyte physiology and management. Group members collaborate to publish a monthly case report with learning objectives on the Renal Fellow Network (RFN) website. Content is supplemented by a visual abstract, tweetorials and follow up quizzes to ensure effective long-term learning and reach multiple learning styles.

Methods: An anonymous survey was conducted and disseminated on Twitter to gather information from users to evaluate if SKG teaching methods added to their education. Questions were designed as multiple-choice answers or qualitative responses on a 0-100 scale.

Results: There were a total of 130 responses from 32 different countries. The majority were nephrology fellows (33%), followed by internal medicine residents/interns (29%), attending physicians (23%), other specialty trainees (10%) and medical students (5%). On a scale of 1-100 (100 is considered highest quality), the mean score was 91±15.5 for the quality of our case reports. Overall, 95% of surveyors found our educational materials useful with tweetorials ranked highest (Fig 1). As training level progresses, a

larger percentage of readers found the tweetorial more useful compared to the case report. Around 80% confirmed their educational experience was affected during the pandemic, and 90.4% found the SKG an effective educational experience during this time period.

Conclusions: Innovative teaching methods provided by the SKG was found to be beneficial in teaching complicated electrolyte concepts. Our data reinforces the ability of FOAMed to cater to different learning styles and to complement traditional medical education specifically during periods of social distancing such as COVID19 pandemic.



PO1391

Glomerular Disease Education Experience Across Nephrology Fellowship Programs

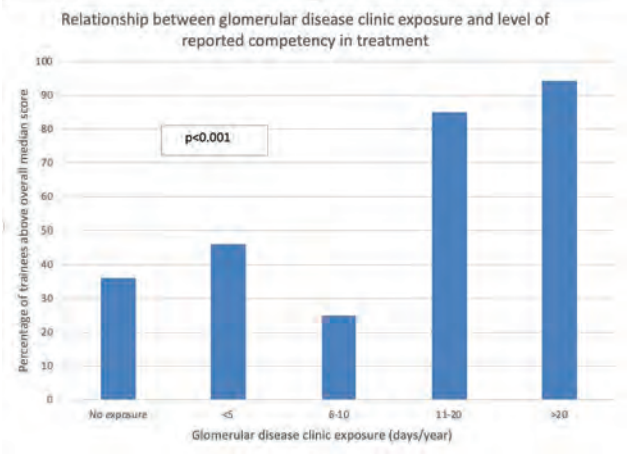
Sayna Norouzi,[1] Harish Shanthanu Seethapathy,[3] Ali Poyan-Mehr.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Kaiser Permanente, San Franciso, CA; [3]Massachusetts General Hospital, Boston, MA.*

Background: Glomerular disease (GN) education is an important, albeit a challenging component of nephrology fellowship training. We hypothesized that trainee experience varies widely across programs, leading to differences in self-reported competency levels in the diagnosis and managing of GN.

Methods: The Glomerular Disease Study & Trial Consortium (GlomCon) conducted an anonymous online survey to evaluate the educational experience of nephrology trainees. We used multiple-choice questions to obtain data about a) curriculum-based education, b) dedicated specialty clinic, and c) exposure to pathology. We leveraged a visual analogue scale of 1-100 (higher number indicating a higher comfort level) to assess self-reported levels of clinical competency. The survey was disseminated via email, the GlomCon website, and Twitter.

Results: There were 107 responses across all years of fellowship training – first-year (25%), second-year (34%), third-year (22%), and fourth-year (19%). A total of 44% reported no GN clinic at their institutions. The presence of an onsite nephropathologist was reported by 63% of responders and 37% reported no onsite nephropathologist or limited exposure. In a visual analogue, the mean competency for GN diagnosis and treatment were 59±26 and 52±25, respectively. Trainees with no onsite nephropathologist and those with limited exposure scored significantly lower in diagnosing GN as compared to those with an onsite nephropathologist (51±25 vs. 64±26, $p<0.05$). Trainees with more exposure to GN specialty clinic had a higher comfort level in treating GN (Fig). Figure demonstrates frequency of trainees in each group with a comfort level above the overall median score (51).

Conclusions: Trainees report a wide variation in GN education across fellowship programs. A lack of exposure to onsite nephropathologist and a dedicated GN curriculum were associated with lower scores in self-reported clinical competency in caring for patients with glomerular disease.



PO1392

Frequency and Severity of Moral Distress in Nephrology Fellows: A National Survey

Fahad Saeed,[1] Paul Duberstein,[2] Ronald M. Epstein,[1] Valerie J. Lang,[1] Scott E. Liebman.[1] *[1]University of Rochester Medical Center, Rochester, NY; [2]Rutgers School of Public Health, Piscataway, NJ.*

Background: Moral distress is a negative affective response to a situation that conflicts with an individual's values. Health care practitioners who care for chronically ill patients frequently experience moral distress. Little is known about the frequency and severity of moral distress in nephrology fellows.

Methods: We used the modified Moral Distress Scale-Revised to assess the frequency and severity of moral distress in nephrology fellows. Using a 5-point (0-4) scale, fellows rated both the frequency (never to very frequently) and severity (not at all disturbing to very disturbing) of scenarios commonly encountered in training. Responses of ≥ 3 were used to define "frequent" and "moderate-to-severe" moral distress. We identified scenarios most commonly associated with moderate-to-severe moral distress. The survey was sent to 148 program directors with a request to forward to their fellows.

Results: The survey was forwarded by 64 fellowship directors to 386 fellows, 142 of whom (40%) responded. Their mean age was 33 ± 3.6 years; 43% were female; and 55% were international medical graduates. The most common scenarios causing moderate to severe moral distress include: Other providers giving overly optimistic descriptions of the benefits of acute (54% seeing frequently, 64% rating the distress as moderate to severe) or chronic dialysis (43%; 64%), initiating dialysis in patients when they deemed it futile (50%; 77%), continuing dialysis in a hopelessly ill patient (45%; 81%) and carrying a high patient census (43%, 75%). Approximately 27% considered quitting fellowship during training, including 9% at the time of survey completion.

Conclusions: Moral distress is frequently encountered by nephrology trainees and is often moderate to severe in intensity. To address this issue, organizational changes (e.g., reduced workload, ethics guidelines), curricular changes (emphasizing primary palliative care, communication, and ethical decision-making skills) as well as opportunities for reflection and self-care (e.g., Balint groups, Schwartz rounds) may be helpful.

Funding: NIDDK Support, Private Foundation Support

PO1393

The Sustainable Pediatric Nephrology Workforce Project (SUPER-POWER): A Pilot Study of Burnout and Resilience

Susan M. Halbach,[1] Kartik Pillutla,[3] Alan Schwartz,[4] Patricia Seo-Mayer,[5] Darcy K. Weidemann,[6] John D. Mahan.[2] *[1]Seattle Children's Hospital, Seattle, WA; [2]Nationwide Children's Hospital, Columbus, OH; [3]Dell Children's Medical Center of Central Texas, Austin, TX; [4]University of Illinois at Chicago, Chicago, IL; [5]Inova Fairfax Hospital, Falls Church, VA; [6]Children's Mercy Hospitals and Clinics, Kansas City, MO.*

Background: Physician well-being is an important contributor to both job satisfaction and patient outcomes. Rates of burnout among physicians vary by specialty, ranging from 35-70%. Among pediatric residents, longitudinal data demonstrates consistent rates of burnout around 50-60%, although little is known about burnout among pediatric subspecialty fellows. The degree of burnout among pediatric nephrologists specifically remains unknown. We sought to evaluate prevalence and predictors of burnout among U.S. pediatric nephrology fellows and faculty, and their interactions.

Methods: A multi-center pilot survey of United States pediatric nephrology training programs from February – April 2020. Burnout was assessed through abbreviated Maslach Burnout Inventory and predictors included demographic, job-related and career satisfaction questions. Other validated assessments included: quality of life, perceived stress, resilience and sleep.

Results: A total of 30/34 available fellows and 86/102 faculty from 11 institutions (of 42 programs nationally) completed the survey. The prevalence of burnout was 13% among fellows and 16% among faculty. Demographic (age, gender, year of training, faculty rank, marital status) and program factors (fellowship size, faculty size, current block/rotation, vacation or weekend off timing) were not significantly associated with burnout. Faculty and fellows with burnout reported significantly lower quality of life (5.3 vs 7.9), higher perceived stress (2.4 vs. 1.4) and lower satisfaction with career choice (66% vs. 22%) and work life balance (28% vs. 0%), compared to those without burnout ($p<0.05$ for all). Other important factors associated with burnout included lower institutional support for wellness programs and lower satisfaction with both colleague and faculty support.

Conclusions: Larger studies are needed to explore if burnout is truly less prevalent among pediatric nephrology fellows and faculty than pediatric residents and graduate physicians. Future studies should explore how to promote well-being through addressing key factors such as overall learning/working environment, stress reduction, and building resilience.

PO1394

Protein Kinase A Catalytic-α and Catalytic-β Proteins Have Non-Redundant Functions

Viswanathan Raghuram, Chin-Rang Yang, Euijung Park, Mark A. Knepper. *National Institutes of Health, Bethesda, MD.*

Background: Vasopressin regulates osmotic water transport in the renal collecting duct by PKA-mediated control of the water channel aquaporin-2 (AQP2). Collecting duct principal cells express two seemingly redundant PKA catalytic subunits, PKA catalytic α

(PKA-Cα, Gene symbol: *Prkaca*) and PKA catalytic β (PKA-Cβ, Gene symbol: *Prkacb*). At an amino-acid level, the two are 91 percent identical and the catalytic domains are virtually identical. However, whether the two PKA catalytic subunits have redundant functions, as is implicitly assumed in many studies involving PKA-mediated regulation, has not been tested.

Methods: To identify the roles of these two protein kinases in in kidney collecting duct cells, either PKA-Cα or PKA-Cβ was deleted using CRISPR-Cas9-based genome editing. Controls were cells carried through the genome editing procedure, but without deletion of either PKA catalytic subunit. Protein mass spectrometry-based quantitative proteomics and phosphoproteomics was carried out in both PKA catalytic-α and PKA catalytic-β single knockouts cells. TMT mass tagging was used for protein mass spectrometric quantification.

Results: Of the 4635 phosphopeptides that were quantified 67 were significantly altered in abundance with PKA-Cα deletion, while 21 were significantly altered in abundance with PKA-Cβ deletion. However, only four sites were changed in both. The target proteins identified in PKA-Cα-null cells were largely associated with cell membranes and membrane vesicles, while target proteins in the PKA-Cβ-null cells were largely associated with the actin cytoskeleton and cell junctions. In contrast, in vitro incubation of mpkCCD proteins with recombinant PKA-Cα and PKA-Cβ resulted in virtually identical phosphorylation changes. In addition, analysis of total protein abundances in the in vivo samples showed that PKA-Cα deletion resulted in a near disappearance of AQP2 protein, while PKA-Cβ deletion did not decrease AQP2 abundance.

Conclusions: We conclude that PKA-Cα and PKA-Cβ serve substantially different functions in renal collecting duct cells and that differences in phosphorylation targets may be due to differences in protein interactions, e.g. mediated by AKAP, C-KAP or PDZ binding.

Funding: Other NIH Support - Intramural Grant

PO1395

Single-Cell RNA Sequencing Reveals Transcriptomes of DCT1, DCT2, Macula Densa, and Two Subtypes of Cortical Thick Ascending Limb Cells

Lihe Chen, Chung-Lin Chou, Mark A. Knepper. *National Heart Lung and Blood Institute, Bethesda, MD.*

Background: Several distinct epithelial cell types have been proposed to form the transition region from the cortical thick ascending limb of Henle (CTAL) to the distal convoluted tubule (DCT) to the connecting tubule (CNT). However, a complete understanding of the cellular composition and transcriptional profiles of the cells in this region is lacking.

Methods: We developed a FACS protocol to enrich cells from the mouse CTAL-DCT-CNT region and carried out single-cell RNA-seq analysis (scRNA-seq) of 9099 such cells. We also used small-sample RNA-Seq to determine transcriptomes of microdissected tubules corresponding to 14 distinct mouse renal tubule segments.

Results: Unbiased clustering and UMAP visualization revealed a single cluster of cells showing *Slc12a3* expression without *Pvalb*, which we identified as DCT2 cells. These cells express ENaC subunits but little or no *Hsd11b2* or *Aqp2* mRNA. These DCT2 cells also express *Calb1, Slc8a1, S100g, Ptges,* and *Trpv5*. In contrast, there were 6 tightly arranged clusters of cells expressing both *Slc12a3* and *Pvalb,* which we identify as DCT1 cells. DCT1 heterogeneity appears to be associated with variable expression of *Slc8a1, Calb1,* and *Ckb* among other mRNAs. An additional DCT1 (*Slc12a3*$^{+}$*Pvalb*$^{+}$) cluster showed marked enrichment of cell cycle and cell proliferation associated mRNAs (e.g. *Pcna, Mki67, Cdk1,* and *Top2a*), which fits with the known plasticity of DCT cells. In addition, scRNA-seq identified three distinct CTAL (*Slc12a1*$^{+}$) cell subtypes. One of these expressed *Nos1, Avpr1a,* and *Pappa2,* consistent with macula densa cells. The other two CTAL clusters were distinguished by *Cldn10* and *Ptger3* in one and *Cldn16* and *Foxq1* in the other. These two CTAL types were also distinguished by alternative expression of Iroquois homeobox transcription factors, with *Irx1* and *Irx2* in the *Cldn10*$^{+}$ CTAL cells and *Irx3* in the *Cldn16*$^{+}$ CTAL cells.

Conclusions: This work identifies unexpected diversity among cell types populating the CTAL and DCT. The new data have allowed the creation of a publicly accessible web resource for the support of future studies.

Funding: Other NIH Support - ZIA-HL-001285 and ZIA-HL-006129

PO1396

Dietary Potassium Restriction Induces Nephrogenic Diabetes Insipidus

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Background: Dietary potassium deficiency is well-appreciated to induce diabetes insipidus (DI) but the underlying mechanisms have not been established.

Methods: C57BL6J mice were randomized to control or diets with graded reductions in dietary K^+ for 8 days. Kindey function tests were performed in metabolic cages, and tissues were harvested for western blotting and immunocytochemistry at the end of the experiment.

Results: We found that C57BL6J mice rapidly develop DI when potassium is eliminated from the diet, coincidence with the development of hypokalemia. Loss of free-water reabsorption, polyuria and polydipsia was observed within four days, despite increased plasma copeptin, a vasopressin surrogate. In contrast to control mice, desmopressin treatment failed to increase urine osmolality and urine volume after potassium deprivation. Altogether, these observations indicate dietary potassium restriction induces nephrogenic DI (NDI). Characterization of responses to graded reductions in dietary K^+ diet revealed NDI was dependent on the development of hypokalemia. Females were more prone to develop hypokalemia, even in response to modest changes in dietary potassium, and displayed more severe DI than males. Females also exhibited a much greater decrease in AQP2 and phosphorylated s256AQP2 in response to dietary potassium deprivation.

Conclusions: This data together indicate that i) hypokalemia-induced DI is nephrogenic, ii) a tight relationship links hypokalemia to renal concentrating ability, ii) females are more prone to develop hypokalemia and as a consequence, more prone to NDI.

Funding: NIDDK Support

PO1397

Tfap2a Integrates Cellular Patterning and Barrier Formation in the Renal Collecting Duct

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Background: The renal collecting duct plays important roles in fine-tuning urinary composition, electrolyte and water balance, blood pressure, as well as acid-base regulation. The patterning and molecular signatures of principal cells (PCs) and intercalated cells (ICs) of the collecting duct are tightly controlled by transcriptional processes and determine collecting duct physiological function and related clinical abnormalities. The transcription factor Tfap2a has previously been implicated in epithelial differentiation, in pronephros development in zebrafish, and in human congenital kidney defects. Using an integrated bioinformatics approach, we predicted that Tfap2a may critically control collecting duct functions. We tested our hypothesis using experimental model systems.

Methods: A collecting duct-specific knockout of Tfap2a was generated in mice. Additionally, mouse inner medullary collecting duct (IMCD3) cells were engineered to harbor CRISPR/Cas9-induced knockouts (KO) of Tfap2a. Deregulated genes were identified by mRNA sequencing. Patterns of principal and intercalated cells in mouse kidneys were analyzed by microscopy. Additionally, the in vivo model was used in metabolic studies to analyze urinary concentration ability.

Results: Mice lacking Tfap2a in the collecting duct were viable and fertile but showed a defect of urinary concentrating ability. mRNA sequencing of Tfap2a-deficient kidneys and cells and subsequent gene ontology analysis indicated an impact of Tfap2a on molecular processes including Notch signaling, focal adhesion formation and tight junction formation. Further experiments indicated abnormalities of PC/IC patterning in Tfap2a-deficient collecting ducts.

Conclusions: Our data suggest that Tfap2a controls transcriptional processes that integrate patterning and barrier formation in the collecting duct.

PO1398

The Phosphorylated States of Human Aquaporin 2 Revealed by Liquid Chromatography Coupled to Tandem Mass Spectrometry Phosphoproteomic Analysis of Urinary Exosomes

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Background: Aquaporin-2 (AQP2) is a key water channel to enhance water permeability of collecting ducts. Multiple phosphorylation sites at the C-terminal of AQP2 have been identified including S256 (serine at the 256 residue), S261, S264 and S/T269. Moreover, the phosphorylation profile induced by vasopressin (VP) seems to affect AQP2 trafficking to and from the plasma membrane in rodent AQP2, with limited studies in human AQP2 whose residue at 269 is T instead of S. As AQP2 is abundantly excreted in urinary exosomes, they will be useful to examine the phosphoprotein profile of human AQP2 modulated by VP.

Methods: We examined the phosphorylation profile of urinary exosomal human AQP2 to obtain the insight into the mechanism of AQP2 trafficking by VP. Human urinary exosomes were digested with trypsin or glutamyl endopeptidase (Glu-C) to apply for the liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) phosphoproteomic analysis, in parallel with immunoblots by commercially available phosphoryation-site specific anti-human AQP2 antibodies.

Results: The most dominant phosphorylated AQP2 peptide was phosphorylated at S256 (pS256), followed by pS261, less pS264 and much less pT269. The results were confirmed by the western blot analysis using antibodies specific to each phosphorylated AQP2. To document the time-course of urinary exosomal AQP2 phosphorylation by VP, a VP analogue was administered to a patient with central diabetes insipidus. It induced total exosomal AQP2 urinary excretion plateauing at 60 min with a transient increase (peaking at 30~60 min) of pS261 and a progressive increase of pS256. All four corresponding phosphorylation sites of human AQP2 including T269 were phosphorylated and the phosphorylation sites at S256 and S261 were tightly linked to toal exosomal AQP2 urinary excretion.

Conclusions: We conclude that human AQP2 is predominantly phosphorylated at S256 and moderately at S261 in urinary exosomes. T269-phosphorylation may not be needed for exosomal AQP2 excretion in human urine.

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PO1399

Bayesian Identification of Transcription Factors That Regulate Aqp2 Transcription

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Background: Renal collecting duct and connecting tubule cells selectively express the water channel aquaporin-2 (AQP2) and *Aqp2* gene transcription is strongly regulated by vasopressin. However, the transcription factors (TFs) responsible for regulation of expression of AQP2 remain largely unknown. Here, we used Bayesian data integration techniques to identify these TFs.

Methods: The general strategy is to use Bayes' Rule to integrate several -omic datasets to stratify a curated list of 1344 TFs present in the mouse genome with regard to probability of regulating *Aqp2* gene transcription. First, existing proteomic and transcriptomic data were used to select the TFs most strongly expressed in mpkCCD cells. Then, we used our existing ATAC-Seq, histone H3K27-acetylation ChIP-Seq, and RNA-polymerase II ChIP-Seq data to identify enhancer regions in the CTCF loop surrounding the *Aqp2* gene. The sequences within these enhancers were analyzed to identify recognized TF binding motifs within them; and these motifs were matched to TFs on the Bayesian list to identify the TFs most likely to bind *Aqp2* regulatory regions.

Results: The analysis showed that the TFs most likely involved in regulation of *Aqp2* gene expression are associated with six enhancer regions in the CTCF loop surrounding the *Aqp2* gene. Of the six enhancers, of particular interest is a 517 bp region identified 5.0 kb upstream from the *Aqp2* transcription start site (TSS) that is predicted to bind Tcf7l2 (Wnt signaling), Tead2 (Hippo signaling) and Gli3 (Hedgehog signaling). Also within this enhancer region are high probability binding sites for TFs previously identified to regulate *Aqp2* gene transcription, viz. Nfat5/NfatC3, Nfkb1/Rela, and Grhl2. Another enhancer is 5.8 kb downstream from the *Aqp2* TSS and contains binding sites for three TFs already implicated in *Aqp2* transcriptional regulation, namely Cebpb, AP-1 (Jun/Fosl2) and Elf1/Elf3, as well as sites for several TFs that are so far unstudied with respect to *Aqp2* regulation.

Conclusions: The Bayesian analysis has defined the enhancer regions within the CTCF loop surrounding the *Aqp2* gene and identified the TFs most likely to bind to these regions, providing a roadmap for future studies to understand regulation of *Aqp2* gene expression.

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PO1400

Kidney Osmoregulation Is Regulated by RNA Polymerase Pausing

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Background: Osmoregulation is a complex but critical component of renal physiology that relies on the regulation of gene expression. While many genes and some transcription factors that are involved in osmoregulation have been identified, the initiating regulatory step that triggers the gene expression response to changes in osmolarity remains unknown. To address this knowledge gap, we identified the pausing of RNA polymerase II as a key regulatory step.

Methods: We used the Precision nuclear Run-On and Sequencing assay (PRO-seq), to identify locations of nascent RNA bound to actively transcribing RNA polymerases in inner medulla collecting duct cells (IMCD).

Results: We began by studying *Akr1b3*, the gene that encodes aldose reductase which is the enzyme that reduces glucose to sorbitol and is essential for osmoregulation in the kidney. We exposed IMCD cells to increasing concentrations of sodium chloride and confirmed that the transcript expression of *Akr1b3* increased in a dose-dependent manner. Then we asked how *Akr1b3* is regulated transcriptionally. The PRO-seq assay was used to trace the first steps in the synthesis of RNA transcripts for aldose reductase. In IMCD cells at baseline, there is an accumulation of RNA Pol II in the promoter of *Akr1b3* consistent with RNA polymerase pausing. Under hypertonic conditions, the paused polymerase is released resulting in the synthesis of aldose reductase transcripts, and subsequent increase in *Akr1b3* gene expression level. We confirmed this result by treating IMCD cells with flavopiridol, a drug that increases the stability of proteins in the pausing complex, and *Akr1b3* was no longer induced in hypertonic conditions. Next by RNA-sequencing, we found that in addition to *Akr1b3*, there are over 500 osmotically-induced genes that are regulated by RNA polymerase pausing. These include membrane transporter proteins such as the sodium/myo-inositol cotransporter (*Slc5a3*) as well as protein chaperones like heat shock protein H1 (*Hsph1*).

Conclusions: These results indicate RNA Pol II pausing plays a key role in the regulation of gene expression during osmoregulation. In this presentation, I will present data from this study and discuss the tight coupling of gene regulation with renal physiology.

Funding: Private Foundation Support

PO1401

Flow Regulation of WNK1 in the Cortical Collecting Duct (CCD)

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Background: A high K diet (HKD) x 10 d increases (i) luminal flow rate in the distal nephron and (ii) expression of apical immunodetectable L-WNK1 in CCD intercalated cells (IC), which we propose enhances apical BK channel activity measured as flow-induced K+ secretion (FIKS) (Webb et al, 2015). We previously demonstrated that fluid shear stress (FSS) x 30 min induces expression of ERK and p-38, both BK channel modulators, in a CCD principal cell (PC) model (Carrisoza-Gaytan et al, 2014). The objective of this study was to test the hypothesis that an increase in tubular fluid flow rate rapidly induces apical localization of L-WNK1 in the CCD.

Methods: CCDs isolated from NZW rabbits fed a HKD x 10 d were microperfused at slow (n=4) or fast (n=4) luminal flow rates x 1 hr, fixed on the rig, immunoperfused with antibodies (Abs) directed against L-WNK1 (+ A488-fluorescent 2o Abs) and rhodamine-conjugated peanut lectin (PNA) or Dolichus biflorus lectin (DBA), which bind to apical surfaces of IC and PC, respectively, and examined by confocal microscopy. MDCK cells were subject to no (static), low or high FSS x 1 hr (n=3 each condition) and fixed for immunodetection of L-WNK1 and BKα in situ or harvested for semi quantitative immunoblotting of isolated plasma membranes.

Results: Expression of IC apical L-WNK1 relative to that in the total cell was 40.0±1.1 % greater in CCDs perfused at fast flow compared to those perfused at slow flow rates ($p<0.001$). In plasma membrane preparations of MDCK cells subject to low and high FSS, L-WNK1 abundance was 5.4±0.3 and 10.6±1.7 fold greater, respectively, to that measured in the absence of flow ($p<0.001$). In static MDCK cells, BKα did not colocalize with L-WNK1 at the apical membrane; however, colocalization of the two proteins was detected in cells subject to low or high FSS.

Conclusions: In conclusion, (i) apical expression of L-WNK1 in ICs in microperfused CCDs is rapidly stimulated by increases in luminal flow rate, and (ii) FSS favors apical colocalization of L-WNK1 with BKα, responses that may facilitate BK channel-mediated FIKS in the CCD.

Funding: NIDDK Support

PO1402

Inhibition of Actin-Related Protein 2/3 Complex Blocks Vasopressin-Induced AQP2 Membrane Accumulation

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Background: Aquaporin 2 (AQP2) is a water channel protein located primarily on principal cells of the kidney collecting ducts and is crucial for regulating body water homeostasis. Regulation of AQP2 trafficking is subject to hormonal control, mainly via the canonical vasopressin (VP) signaling pathway which stimulates AQP2 membrane accumulation. Active actin cytoskeleton remodeling has been known to also play an important role in AQP2 trafficking, however, the mechanism is incompletely understood.

Methods: We applied CK-666, a pharmacological inhibitor of actin nucleator actin-related protein (Arp) 2/3 complex on our AQP2-transfected cells and animal (rat) models. Results were observed by using immunohistochemistry and confocal microscopy. VP signaling pathway and phosphorylation of AQP2 on various serine residues were studied with Western blotting.

Results: Using CK-666, an Arp2/3 complex inhibitor, we found that VP induced AQP2 membrane accumulation was inhibited both in rat kidneys and LLC-AQP2 cells in vitro. Instead of distributing throughout the cytoplasm, AQP2 in cells treated with CK-666 was concentrated in vesicles forming a perinuclear patch, which was also positive for Rab-11 (a recycling endosome marker) and clathrin (a trans-Golgi Network (TGN) marker). Similar perinuclear AQP2 patches appear in cells incubated at 20°C (cold block), which allows endocytosis to continue, but prevents protein exit from the TGN. By rewarming the cells to 37°C, these perinuclear patches dissipate, and AQP2 quickly redistributes throughout the cytoplasm (cold block release). However, we found that in cells exposed to a 20°C cold block and treated with CK-666, AQP2 patches failed to dissipate upon rewarming, suggesting that CK-666 blocked the release of AQP2 from the TGN in the exocytotic pathway. This effect of CK-666 was independent of VP signaling and did not alter the VP-induced phosphorylation state of AQP2 at residues serine-256, S269, and S261.

Conclusions: Inhibition of the Arp2/3 complex blocks VP-induced AQP2 plasma membrane accumulation by blocking AQP2 exocytosis at the level of the TGN and the recycling endosome but did not affect VP signaling pathway. This result suggests that actin filament nucleation and growth via Arp2/3 activity is essential for AQP2 recycling and trafficking.

PO1403

STCH Regulates NKCC2 Biogenesis by Both the Endoplasmic Reticulum-Associated Degradation and the Endoplasmic Reticulum-to-Lysosome-Associated Degradation Pathways

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Background: Mutations in the apically located Na-K-2Cl co-transporter NKCC2 lead to type I Bartter syndrome, a life-threatening kidney disease. We previously showed that export from the ER constitutes the limiting step in the maturation and cell surface expression of NKCC2. Yet very little is known about the molecular components of NKCC2 ER quality control. Using the yeast two hybrid system and co-immunoprecipitation assays, we identified chaperone stress 70 protein (STCH), as a binding partner of the immature form of NKCC2. STCH is supposed to function as an ER chaperone but the precise molecular role of STCH remains obscure.

Methods: Protein expression was monitored in transiently transfected HEK cells, using immunoblot and confocal imaging. Protein maturation and stability were assessed by Endo-H digestion and cycloheximide chase (CHX) assay.

Results: Co-immunolocalization experiments revealed that NKCC2 interacts with STCH mainly at the ER. However, CHX assay together with Endo-H digestion revealed that STCH is initially synthesized in the ER as a core-glycosylated protein before being gradually converted to a hybrid N-glycosylated form. These data are in an agreement with a previous study showing that STCH contains a mannose-6-phosphorylation site, suggesting therefore that STCH expression is not restricted to the ER. STCH knock-down increased NKCC2 protein abundance in a dose-depend manner, whereas STCH over-expression had the opposite effect. CHX assay showed that in cells over-expressing STCH, NKCC2 stability and maturation are heavily impaired. STCH induced reduction in NKCC2 expression were offset partially by the proteasome inhibitor MG132. Interestingly, leupeptin and chloroquine, two potent inhibitors of the lysosome, mimicked MG132 effect on NKCC2 regulation. Accordingly, the simultaneous presence of proteasome and lysosome inhibitors, completely abolished STCH-induced down-regulation of NKCC2.

Conclusions: Our data demonstrate the presence of an STCH mediated ER quality control of NKCC2 in renal cells. They suggest a model whereby, in addition to the proteasome-dependent ERAD, the ER quality control of NKCC2 mediated by STCH, involves also the ER-to-lysosome-associated degradation pathway, revealing therefore a new regulatory mechanism governing the co-transporter biogenesis.

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PO1404

$P2Y_2$ Receptor Directly Mediates Collecting Duct Remodeling Induced by Acid Loading in Mice

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Background: Previously we reported that genetic deletion of $P2Y_2$-R suppresses lithium(Li)-induced collecting duct (CD) remodeling. Since genetic deletion of $P2Y_2$-R has a generalized ameliorating effect on Li-induced diabetes insipidus, here we evaluated the direct effect of $P2Y_2$-R in CD remodeling using a model of acid loading.

Methods: Groups of WT or $P2Y_2$-R knockout (KO) mice (B6D2; N = 3 or 4/group) were fed standard rodent chow and given tap water with/without addition of 0.28 M NH_4Cl for 9 days and humanely euthanized. AQP2 and $[H^+]$-ATPase double immunolabeling was used to identity the principal (PC) and intercalated (IC) cells of the medullary CD, respectively.

Results: As reported previously, KO mice developed more severe metabolic acidosis than WT after NH_4Cl loading (not shown here). Furthermore, as shown in the pie charts, statistical analysis of the numbers of cells found a marked increase in the number of medullary ICs in NH_4Cl-treated vs. untreated control (CT) mice in WT (28 ± 2 vs. 6 ± 1), but only a blunted response in $P2Y_2$ KO mice (10 ± 1 vs. 4 ± 1, $P < 0.001$ *WT vs. KO*). These increases in ICs were associated with significant decreases in the proportion of PC cells in NH_4Cl-treated vs. untreated CT mice in WT (72 ± 2 vs. 94 ± 1), and again a blunted response in $P2Y_2$ KO mice (90 ± 1 vs. 96 ± 1, $P < 0.001$ *WT vs. KO*).

Conclusions: The data clearly show that $P2Y_2$ receptor has a "direct effect" on CD remodeling in the kidney following acid-loading.

Funding: NIDDK Support, Veterans Affairs Support

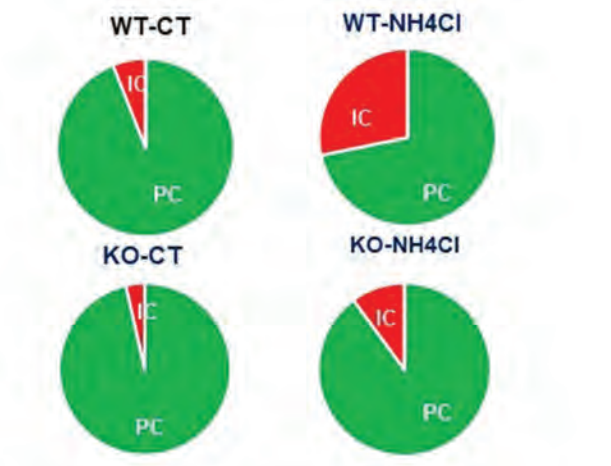

Figure 1. Pie charts of data from immunofluorescence analysis of NH_4Cl-induced changes in medullary CD cell composition in wild type WT or KO mice. AQP2 (green) and $[H^+]$ATPase (red) double-immunolabeling was used to identify the principal (PC) and intercalated (IC) cells of the collecting duct, respectively. CT – control group.

PO1405

Resolving the Kidney's Reaction to Acute Dehydration on the Single-Cell Level

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Background: Dehydration is a common clinical finding and frequent among the elderly or patients with chronic diarrhea. Acute kidney injury frequently develops as a result of a fluid deficit. There is growing evidence that recurrent dehydration can cause chronic kidney disease. The kidney's response to fluid deprivation is incompletely understood. Having a gene expression atlas of the kidney's reaction to fluid deprivation at single cell resolution might help to understand biological mechanisms but also to identify biomarkers and therapeutic targets.

Methods: We performed single-cell RNA sequencing of dissociated mouse kidneys after 24 hours of water restriction (n=2) and control kidney (n=2). We assigned cell type information based on known marker genes, and systematically analyzed gene expression differences between baseline and water-restricted animals within different cell types. We furthermore applied a computational approach to spatially sort cells based on gene expression similarities to investigate corticomedullary gene expression profiles.

Results: Our data show cell type-specific differential gene expression in all kidney tubule cells with the most prominent response in collecting duct principal cells (CD-PC). Pathways dysregulated in CD-PC included sodium and water reabsorption, immune system modulation and endoplasmatic reticulum (ER) stress. Pathway activation displayed regional cortico-medullary differences.

Conclusions: Fluid deprivation induces regional and cell type-specific responses in kidney cells. Genes and pathways identified by single cell transcriptomics comprise biomarkers and therapeutic targets for dehydration-associated pathologies.

PO1406

Angiotensin II Receptor Blockade Alleviates Calcineurin Inhibitor Nephrotoxicity by Restoring p38 MAPK/NF-kB/COX-2 Signaling in Kidney Cortex

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Background: Immunosuppression based on calcineurin inhibitors (CNI) such as cyclosporine A (CsA) is the current standard for patients undergoing organ transplantation. Nephrotoxic side effects of CNI include reduction of renal cortical cyclooxygenase 2 (COX-2) expression along with pathophysiological alterations of glomerular filtration rate and sodium balance. The underlying molecular mechanisms are poorly understood. Since CNI stimulate the renin-angiotensin system (RAS), we hypothesized that the suppression of COX-2 is related to enhanced RAS activity.

Methods: To test this hypothesis, short- (3 days) and long-term effects (3 weeks) of CsA (25mg/kg*d), candesartan (5mg/kg*d), celecoxib (50 mg/kg*d) or their combinations

were evaluated in Wistar rats to monitor COX-2 and RAS, as well as kidney physiology, morphology and biochemistry. Cultured macula densa (MD) cells were treated with CsA, angiotensin II (Ang II), p38 MAPK inhibitor or NF-kB inhibitor in various combinations to reveal molecular pathways mediating effects of RAS on COX-2.

Results: Inhibition of calcineurin in cultured MD cells using CsA or siRNA increased COX-2 activity via stimulation of p38 MAPK and NF-kB. Concomitant application of Ang II abolished these effects suggesting a dominant role for RAS. In rats, 3 days and 3 weeks CsA treatments led to increased renin biosynthesis, decreased cortical COX-2 expression, reduced creatinine clearance, and sodium retention due to activation of major distal salt transporters, NKCC2 and NCC. These deteriorations were partially or completely normalized by simultaneous administration of a RAS inhibitor candesartan for 3 days or 3 weeks, respectively. In contrast, administration of a selective COX-2 inhibitor, celecoxib, largely recapitulated effects of CsA and significantly reduced the beneficial effects of candesartan by concomitant drug application. Therefore, COX-2 suppression is a major factor contributing to CNI nephrotoxicity.

Conclusions: In summary, the present study established calcineurin as an endogenous COX-2 inhibitor, acting via suppression of p38 MAPK and NF-kB activity in MD cells. CNI-induced RAS activation critically reduces cortical COX-2 activity, thus overriding local stimulatory effects of calcineurin inhibition. Our data support the use of RAS inhibitors for alleviation of CNI nephrotoxicity.

Funding: Government Support - Non-U.S.

PO1407

A Novel Mouse Model for Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC) Bearing the Most Frequent Human CLDN16 Mutation

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Background: Mutations of claudin (CLDN) 16 and CLDN19 cause FHHNC, characterized by a urinary loss of calcium (Ca) and magnesium (Mg), hypomagnesemia, nephrocalcinosis and renal failure. Cldn16 and Cldn 19 are co-expressed at the tight junction (TJ) of the thick ascending limb (TAL) of Henle's loop and play a key role in paracellular reabsorption of Ca and Mg. Here, 25% of filtered Ca and 70% of filtered Mg are reabsorbed. Cldn16 knock-out mouse model failed to faithfully recapitulate the human disease, as it was complicated by neither nephrocalcinosis nor renal failure. Cldn 16 knock-down mice have a renal loss of NaCl and hyperaldosteronism. We hypothesized that a knock-in model bearing the most frequent human CLDN 16 mutation (p.L151F) would be helpful to delineate the abnormalities caused by mutated Cldn16.

Methods: Cldn $16^{L151F/\ L151F}$ mice were generated by CRISPR Cas9-based mutagenesis. Cldn $16^{+/+}$ and Cldn $16^{L151F/\ L151F}$ female mice were housed in metabolic cages at 3 months of age. Daily food and water intake, body weight were recorded. Blood and urine composition were analyzed. Nephrocalcinosis and Cldn expression in TAL were studied on kidney sections by alizarin red coloration and immunofluorescence.

Results: At 3 months, weight, food and water intake, blood parameters (Na, Cl, Ca, Mg, Pi, creatinine) did not differ between Cldn $16^{+/+}$ and Cldn $16^{L151F/\ L151F}$ mice. Cldn $16^{L151F/\ L151F}$ mice had significantly higher urinary excretions of Ca, Mg and Pi and a lower urinary pH; urine volume, osmolality, Na, K and aldosterone were unaltered. At 6 months calcitriol was significantly increased in Cldn $16^{L151F/\ L151F}$ mice. No nephrocalcinosis was seen at 12 months. Cldn 16 was almost never seen at TJ and Cldn 19 seems to be less expressed at TJ in Cldn $16^{L151F/\ L151F}$ mice suggesting that Cldn 16^{L151F} has a negative effect on Cldn19 expression.

Conclusions: Cldn $16^{L151F/\ L151F}$ mice have a urinary loss of Ca and Mg, as typically observed in patients with FHHNC. No evidence of NaCl wasting was found. Further studies are ongoing on male mice, renal function and PTH, bone and dental phenotypes. This model will help to better understand the link between an altered CLDN 16 and defective Ca and Mg handling.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1408

Sex Differences in Expression of Renal Urate Transporters

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Background: Elevated urate (UA) levels in the serum (hyperuricemia, HUA) can contribute to the development of diseases, including kidney stones, chronic kidney disease, cardiovascular disease, metabolic syndrome, and gout. Men are 5x more likely to have HUA than women, yet this risk increases in women 4x after menopause. This suggests premenopausal women are protected against developing HUA, but the mechanisms have yet to be elucidated. These differences are echoed in our HUA mouse model, where insertion of an orthologous human pathological UA transporter ABCG2 variant Q141K (Q140K in mice) causes significant HUA in the male but not female mice. Paradoxically, we found female mice had lower fractional UA excretion than males, suggesting complex differences in the renal UA handling between the sexes. We hypothesized that these differences were likely due to either UA transporter expression or regulation.

Methods: RNA-Seq was performed on male and female wild type (WT) and Q140K mice, followed by DESeq2 analysis to determine differentially expressed genes between both sexes of each genotype.

Results: Targets of interest included 12 transporter and 3 transcription factor (TF) genes that associated with serum UA levels in humans in recent genome wide association studies. We found small (0.49–2.1-fold) but statistically significant changes in many of these transporter genes. Specifically, female mice had lower expression of UA transporters *SLC22A12, SLC22A6, SLC17A1,SLC17A3,* and *ABCA1*. These genes have variants that associated with lower UA levels in human populations, consistent with female mice potentially more efficiently excreting surplus UA. Females also had significantly lower levels of the 3 key UA associated TFs, *HNF1A, HNF4A,* and *HNF4G,* providing a possible mechanism of differentiation. The Q140K mice DESeq2 analysis reveals 273 alterations in male Q140K kidney gene expression as compared to WT, including 5 potentially compensatory SLC transporters. None of these changes were observed in female Q140K mice, indicating that changes are the result of the elevation in SUA and not due to mutant ABCG2 protein.

Conclusions: Female sex may confer protection from developing HUA and related conditions. Further understanding this mechanism should lead to improved understanding of UA homeostasis and new insights into HUA treatment.

Funding: NIDDK Support

PO1409

SPAK Signaling Stimulates the Activity and Protein Expression of Large Conductance Ca^{2+} Activated Potassium (BK) Channels

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Background: Ste20-like proline alanine rich kinase (SPAK) plays important roles in regulating the function of numerous ion channels and transporters. With-no-lysine (WNK) kinase phosphorylates SPAK kinase to active the SPAK signaling pathway. Our previous studies indicated that WNK kinases regulate the activity of the large-conductance Ca^{2+}-activated K^+ (BK) channel and its protein expression via the ERK1/2 signaling pathway. It remains largely unknown whether SPAK kinase directly modulates the BK activity and protein expression in kidney.

Methods: Electrophysiology, cell culture, western blot, siRNA knockdown, and SPAK knockout (KO) mice were used in the study.

Results: We first determined the effects of SPAK gene depletion using SPAK KO mice on BK channel activity in the isolated, split-opened renal collecting ducts (CD) from WT and SPAK KO mice. We found that there is no BK channel activity in principal cells (PCs) of cortical CD (CCD) in SPAK KO mice, whereas there is BK channel activity in PCs from WT mice. We further investigated the effects of overexpression and siRNA knockdown of SPAK expression on BK in HEK293 cells. Overexpression of SPAK significantly increased BK protein expression with decreasing ERK 1/2 phosphorylation, whereas knockdown of SPAK expression using siRNA significantly reduced BK protein expression associated with increased ERK1/2 phosphorylation, both in a dose-dependent manner. Knockdown of ERK1/2 prevented SPAK siRNA-mediated inhibition of BK protein expression. Similarly, pretreatment of HEK293 cells with either the lysosomal inhibitor bafilomycin A1 or proteasomal inhibitor MG132, reversed the inhibitory effects of SPAK knockdown on BK protein expressions. In addition, we found that BK protein abundance in the renal cortex of SPAK KO mice was significantly decreased and ERK1/2 phosphorylation was significantly enhanced. A high potassium diet significantly increased BK protein abundance and SPAK phosphorylation levels in WT mice, while reducing ERK1/2 phosphorylation levels.

Conclusions: These findings suggest that SPAK stimulates BK channel activity and protein expression by reducing ERK1/2 signaling-mediated lysosomal and proteasomal degradations of the BK channel.

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PO1410

High Dietary K^+ Attenuates Salt-Induced NCC and mTORC1 Activity in Dahl Salt-Sensitive Rats

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Background: Na^+ reabsorption by renal Na^+-Cl^- cotransporter (NCC) plays a key role in blood pressure (BP) regulation. Dahl Salt-Sensitive (DSS) rats exhibit aberrant NCC activity and salt-sensitive hypertension (HTN) when fed a high-salt diet. The renal mammalian target of rapamycin complex 1 (mTORC1) is also implicated in the pathogenesis of DSS HTN. Studies in normotensive mice suggested an inverse relationship between blood [K^+] and NCC activity; however, the effect of dietary K^+ on NCC activity in DSS rats is still controversial. Moreover, the impact of dietary K^+ on mTORC1 activity is unknown. **Hypothesis:** Dietary K^+ supplement downregulates salt-induced NCC and mTORC1 activity in DSS rats.

Methods: 3 month old male DSS rats were randomly placed on high salt (4% NaCl, HS, n=3) or HS + high K^+ (5% K^+, HS+HK, n=4) diet for 28 days. Another group of DSS rats, maintained on HS diet for 14 days, were placed on HS+HK for another 14 days (HS→HS+HK, n=4). NCC activity was assessed by Hydrochlorothiazide (HCTZ, NCC antagonist) injection (20 mg/kg, intraperitoneal) induced natriuretic response. Protein abundance was determined by western blotting. The ratio of phosphorylated ribosomal protein - $S6^{Ser235/236}$ to total S6, was used as mTORC1 activity marker.

Results: In response to HCTZ, urinary Na^+ excretion was trending lower in HS+HK and HS→HS+HK than HS group, while the baseline excretion was unaltered. Total NCC (tNCC) and phosphorylated NCC (pNCC) abundance, a surrogate for NCC activity,

were trending lower in HS→HS+HK compared with HS group. Interestingly, mTORC1 activity was significantly reduced in HS→HS+HK.

Conclusions: Trending lower response in HS+HK and HS→HS+HK to HCTZ suggests that dietary K^+ may counteract and reduce salt-induced NCC activation. Downregulation of mTORC1 reveals that dietary K^+ can reverse salt-induced mTORC1 activation. Critically, our data suggest that compared with the initial phase, K^+ is more effective in reducing salt-induced NCC and mTORC1 activity when added later to the diet, which may attenuate established HTN in DSS rats.

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	HS (n=3)	HS+HK (n=4)	HS→HS+HK (n=4)
Urinary Na+ excretion (baseline) (µmole / 7 hrs.)	158.2 ± 92.10	245.8 ± 136.2	140.6 ± 42.38
Urinary Na+ excretion (HCTZ test) (µmole / 7 hrs.)	1055 ± 10.26	559.2 ± 119.5	589.8 ± 190.9
tNCC abundance (%)	100 ± 11.42	93.86 ± 18.53	61.53 ± 0.98
pNCC abundance (%)	100 ± 38.22	64.12 ± 36.38	41.24 ± 18.42
mTORC1 activity (%)	100 ± 19.64	63.35 ± 15.39	44.63 ± 6.80*

Table 1: Data analyzed by one-way ANOVA, Dunnett's multiple comparison test; *p<0.05 vs. HS; data presented as mean ± SEM.

PO1411

Four Weeks of Dietary Potassium Restriction Causes Distal Convoluted Tubule Remodeling

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Background: Previous studies have described a 'renal potassium switch' within the distal nephron that turns on the thiazide-sensitive Na-Cl cotransporter (NCC) in the distal convoluted tubule (DCT) in response to low potassium intake and off in response to high potassium intake. Studies using genetically modified mice indicate that decreased NCC activity is associated with decreased DCT length and mass; increased NCC activity is associated with increased, DCT length and mass. The aim of our study was to test whether dietary potassium intake causes the DCT remodeling physiologically.

Methods: Male C57Bl/6 mice were provided either control potassium diet or low potassium diet for four weeks and blood and kidneys were harvested. To determine the length of the DCT in three dimensions, we used Ethyl-cinnamate-based optical clearing, combined with whole-mount immunolabeling, confocal microscopy and three-dimensional morphometric analysis.

Results: Mice on low potassium diet for four weeks were severely hypokalemic (plasma potassium <2 mM) compared with mice on control diet (4.2 mM). Western-blot analysis of the whole kidney confirmed that total and phosphorylated NCC were higher in mice on low potassium diet, compared to mice on control diet. By immunolabeling with pThr53-NCC antibody, we visualized the DCTs in optically cleared kidney slices. Three-dimensional morphometric analysis suggested that four-weeks of low potassium diet (465±14 µm, n=6) increased DCT length by 13% compared to NK diet (412±9 µm, n=5).

Conclusions: Our results indicate that the DCT remodels physiologically to maintain potassium homeostasis. Additional animals are currently being studied.

Funding: NIDDK Support

PO1412

Pendrin Null Mice Develop Hypokalemia During Dietary Na^+ Restriction Through an Epithelial Sodium Channel-Dependent Mechanism

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Background: Pendrin is an electroneutral Cl^-/HCO_3^- exchanger expressed in the apical regions of intercalated cells. It is thought to modulate NaCl absorption, while mitigating urinary K^+ loss. However, the effect of pendrin gene ablation on K^+ homeostasis has not been examined directly. The purpose of this study was to determine if pendrin gene ablation reduces serum K^+ concentration, the conditions under which this occurs and the mechanism(s) responsible.

Methods: Pendrin null and wild type mice were given a diet deficient in Na^+, K^+ and Cl^- or diet supplemented with Na^+, K^+, Cl^- and/or water. We measured urine and serum electrolytes as well as K^+ channel and Cl^- transporter abundance by immunoblot and immunohistochemistry.

Results: Serum K^+ was ~1 mEq lower in pendrin null than in wild type mice after 7 days of the Na^+, K^+, Cl^--deficient diet. This difference was attenuated, but not eliminated, with moderate dietary K^+ supplementation. Differences were eliminated with either dietary Na^+ supplementation or with ENaC blockade, while differences were enhanced when ENaC was constitutively upregulated. Further studies determined whether the lower serum K^+ observed in the pendrin null mice occurs from greater urinary K^+ excretion. Over the first 3 days of the Na^+, K^+, Cl^--deficient diet, pendrin null mice develop a lower serum K^+ and a higher arterial pH and HCO_3^- concentration, likely from greater intravascular volume contraction from their enhanced urinary Na^+ excretion, although urinary K^+ excretion was similar in both groups over this time period. However, starting at day 4 of the diet, the pendrin null mice excrete more K^+ than the wild type mice. At day 8 of the ion-deficient diet, pendrin null mice have marked hypokalemia, likely due to both the metabolic alkalosis as well as greater urinary K^+ excretion, in part, from inappropriately high Maxi-K^+ channel abundance.

Conclusions: Pendrin null mice develop marked hypokalemia during dietary Na^+ restriction in part due to a contraction alkalosis as well as increased urinary K^+ excretion that occurs in part from relatively high Maxi K channel abundance.

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PO1413

Architecture of the Distal Nephron Mineralocorticoid Receptor-Dependent Transcriptome Defined

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Background: The mineralocorticoid receptor (MR, *Nr3c2*) is responsible for aldosterone-regulation of Na^+ and K^+ balance and blood pressure. Although a handful of aldosterone/MR-dependent genes have been identified, their regulation cannot fully explain how aldosterone activates electrogenic Na^+- K^+ exchange in the aldosterone sensitive distal nephron (ASDN). Here, we apply RNA-Seq and bioinformatic approaches in isolated tubule segments of MR KO vs. Control mice to define a more complete inventory of MR-dependent genes.

Methods: $MR^{fl/fl}$/Pax8-rtTA/LC1 mice were used as a doxycycline (DOX)-inducible *Nr3c2* gene KO model. After DOX treatment, four groups were prepared to distinguish between K^+ and MR effects: 1) control mice on normal K^+ diet (CT-NK) or 2) high K^+ diet (CT-HK) and 3) MR knockout mice on normal K^+ diet (KO-NK) or 4) low K^+ diet (KO-LK). RNA-Seq analysis was carried out in the micro-dissected connecting tubule and cortical collecting duct tubule segments (5-6 mice per group and ~10 fresh ASDN tubules per mouse). Differential expression (DE) genes were identified (FDR < 0.05) and used for further bioinformatic analyses.

Results: 927 and 2010 DE genes were identified from comparisons of MR KO-NK vs. CT-NK and MR KO-LK vs. CT-HK, respectively. Diet effects were not detected. Absence of transcripts on the third exon of *Nr3c2* gene confirmed complete disruption of *Nr3c2* gene in the MR KO. All known aldosterone-response genes, including *Sgk1*, *Scnn1a*, *Ndrg2*, *Per3*, *Tsc22d3*, *Zbtb16*, *Mlph* and *Atp1a1* were significantly decreased in MR KO-LK compared to CT-HK. In addition, 5 DE genes (*Sgk1*, *Scnn1a*, *Nedd4l*, *Fxyd4* and *Atp1a1*) were mapped on small known "Aldosterone-regulated sodium reabsorption" profile. However, genome-wide identification of GR and MR binding sites revealed that 526 of the significantly down-regulated genes in MR KO mice are potential MR-regulated genes. Pathway enrichment analysis of 2010 DE genes showed that DE genes were highly enriched in mitochondria-associated metabolic processes.

Conclusions: The inventory of MR-regulated genes in the ASDN is much larger than previously imagined. In addition to pathways that directly up-regulate epithelial sodium channel (ENaC) and the Na^+-K^+ ATPase, the data suggest that aldosterone-MR may directly influence metabolism to make energy-consuming transport highly efficient.

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PO1414

Effect of Patiromer and Sodium Zirconium Cyclosilicate on Blood Pressure in a Rat CKD Model Induced by 5/6th Nephrectomy

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Background: Patiromer (PAT) is a sodium-free, non-absorbed polymer drug approved for treatment of hyperkalemia (HK) in adults. In clinical studies of patients with CKD and HK, decreases in BP were observed during PAT treatment. The objective of this study was to evaluate effect of PAT and another K^+ binder, sodium zirconium cyclosilicate (SZC), on BP in a CKD rat model.

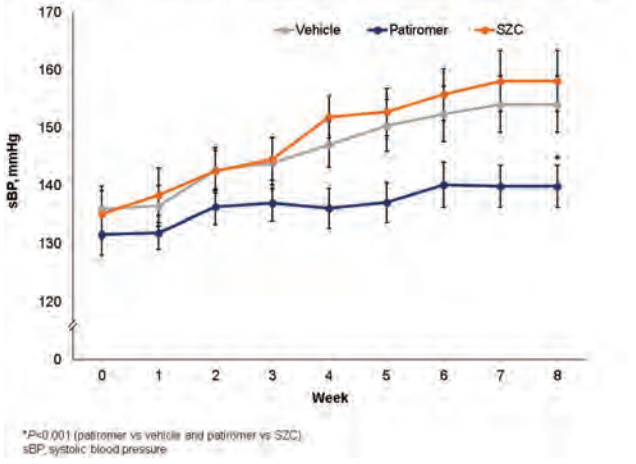
Methods: 36 Sprague Dawley (SD) rats underwent 5/6 nephrectomy (Nx) and each had a telemetry device implanted. Animals were randomized into 3 groups of 12. PAT (4 g/kg), SZC (4 g/kg), or vehicle was administered daily via oral gavage for 8 wks. Telemetry data was collected for at least 24 hrs once weekly from baseline (BL). Blood and urine samples were collected weekly. All values are mean ± SD.

Results: Systolic BP from BL to Wk 8 increased in vehicle-treated rats (136 ± 4.0 mmHg to 154 ± 4.8 mmHg), PAT-treated rats (132 ± 3.7 mmHg to 140 ± 3.6 mmHg), and SZC-treated rats (135 ± 4.1 mmHg to 158 ± 5.3 mmHg). PAT-treated rats had significantly lower systolic BP at Wk 8 compared to rats in vehicle and SZC-treated groups (P<0.001) (**Figure**). Mean BP change from BL in PAT-treated rats (8 ± 3.2 mmHg) was significantly lower vs vehicle group (18 ± 2.9 mmHg, P<0.001) and vs SZC-treated group (23 ± 4.2 mmHg, P<0.001), while mean BP change from BL in SZC-treated rats was significantly higher vs vehicle group (P<0.005). Serum K^+ levels were in range of normokalemia (4.0-6.2 mEq/L in normal SD rats) from BL to Wk 8 in all groups (5.6 ± 0.26 mEq/L to 5.5 ± 0.22 mEq/L in vehicle-treated rats, 5.6 ± 0.43 mEq/L to 5.5 ± 0.25 mEq/L in PAT-treated rats, and 5.3 ± 0.36 mEq/L to 4.9 ± 0.35 mEq/L [P=0.02] in SZC-treated rats). There was no difference in serum creatinine levels among the 3 groups during the study.

Conclusions: With 8 wks of PAT treatment, SD rats with 5/6 Nx exhibited significantly lower BP compared to vehicle-treated and SZC-treated rats. Additional analyses are warranted to determine mechanism of PAT's effect on BP in this model of CKD.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Group Company

Figure. Mean BP in Vehicle-, Patiromer-, and SZC-treated Groups (n=12/group)



*P<0.001 (patiromer vs vehicle and patiromer vs SZC).
sBP, systolic blood pressure

PO1415

PF-06869206 Is a Selective Inhibitor of Phosphate Transport: Evidence from In Vitro and In Vivo Studies

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Background: The kidneys are key players in maintaining the body's phosphate (P_i) homeostasis, and patients with chronic kidney disease (CKD) develop hyperphosphatemia. Two renal transporters mediate the majority of P_i reabsorption, the Na^+-phosphate cotransporters Npt2a and Npt2c, with Npt2a accounting for ~80% of P_i reabsorption. The aim of the current study was to determine the *in vitro* effects of a Npt2a-I (PF-06869206) in opossum kidney (OK) cells as well as its *in vivo* effects in Npt2a knockout ($Npt2a^{-/-}$) mice.

Methods: To study the *in vitro* effects of Npt2a-I (0.1-100 μmol/L) on P_i uptake, ^{32}P radiotracer was used in OK cells. *In vivo*, Npt2a-I dose-response (3-300 mg/kg, 1% bw by oral gavage) effects on urinary P_i excretion were assessed in metabolic cages for 3 hours in wild-type (WT) and $Npt2a^{-/-}$ mice. Effects on plasma P_i were studied before (baseline) and 2 hours after application of Npt2a-I (30 mg/kg, 1% bw by oral gavage).

Results: *In vitro* Npt2a inhibition caused a dose-dependent decrease in P_i uptake, showing a half-maximal inhibitory concentration of ~1.4 μmol/L. Kinetics of Npt2a uptake inhibition showed an increased Michaelis-Menten constant in response to Npt2a-I compared to vehicle (~2.4 fold); in contrast, V_{max} was unaffected, indicating competitive inhibition. No differences were observed in live or dead cell populations after 24-hours treatment between vehicle or Npt2a-I. Parathyroid hormone (PTH) caused a dose-dependent decrease in P_i uptake, with 10 nmol/L being equivalent to the maximal inhibitory effect of Npt2a-I. No additional inhibitory effect was observed by co-incubation of PTH and Npt2a-I. *In vivo*, Npt2a inhibition caused a dose-dependent increase in urinary P_i excretion in WT mice with an EC_{50} of ~23 $mg*kg^{-1}$. No effect on urinary P_i excretion was observed in $Npt2a^{-/-}$ mice. In WT mice, Npt2a-I caused a ~31% ($P<0.05$) decrease in plasma P_i levels; in contrast, plasma P_i levels were unchanged in $Npt2a^{-/-}$ mice.

Conclusions: Our studies show that PF-06869206 is a competitive inhibitor of P_i transport in OK cells and the effect on urinary P_i excretion and plasma P_i levels are mediated by Npt2a. Human studies are needed to identify if Npt2a inhibition is a useful treatment for hyperphosphatemia.

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PO1416

Critical Role of Threonine Residue in PDZ-1 Binding Motif of Type 2a Sodium-Phosphate Cotransporter (Npt2a)

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Background: Npt2a brush border membrane (BBM) expression is the major determinant of proximal tubule phosphate reabsorption. Binding of the Npt2a carboxy terminus Class I PDZ binding motif (S/T-x-Φ-COOH) to NHERF1 (sodium-hydrogen exchange regulatory factor 1), a PDZ protein, is critical for Npt2a BBM expression. We have shown that NHERF1 deficiency results in increased binding of Npt2a to 14-3-3 epsilon, a chaperone protein with a Class III PDZ-binding domain. Phosphorylation of the Class I PDZ binding motif Thr residue converts it into a Class III binding motif (pT-x-x-COOH). We hypothesize that phosphorylation of the Thr residue prevents NHERF1 interaction, promotes 14-3-3 epsilon interaction, and inhibits BBM expression of Npt2a.

Methods: We generated cDNA constructs modifying the Thr residue at position -2 (T635) in the Npt2a PDZ binding motif to phosphomimic (T635E) or phosphonull (T635A) status. We sub-cloned WT and mutant Npt2a cDNAs alone, with NHERF1, or with 14-3-3 epsilon in an IRES-containing bicistronic mammalian expression vector. We transiently transfected these cDNA constructs in NHERF1-deficient opossum kidney cells, assessed membrane expression by confocal microscopy, and Npt2a function by (^{32}P) phosphate uptake.

Results: Npt2a (T635), Npt2a (E635), or Npt2a (A635) alone showed dense cytosolic expression and negligible ^{32}P uptake. Npt2a (T635) with NHERF1 colocalized at the plasma membrane and increased ^{32}P uptake seven-fold. Npt2a (E635) and Npt2a (A635) appeared at the plasma membrane, but neither co-localized with NHERF1 nor showed ^{32}P uptake. Each Npt2a plus14-3-3 cDNA construct exhibited apparent membrane localization, but none co-localized with 14-3-3 epsilon or exhibited significant ^{32}P uptake.

Conclusions: We conclude that the -2 Thr of the Class I PDZ binding motif of Npt2a is essential for interaction with NHERF1 and functional activity of the cotransporter. 14-3-3 promotes Npt2a membrane localization but not function in NHERF1 deficient states and may not be dependent on the phosphorylation status of the -2 Thr.

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PO1417

Metabolic Acidosis Exacerbates Pyelonephritis in Mice Prone to Vesicoureteral Reflux

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Background: Acute pyelonephritis is a serious bacterial infection in children. The prevalence of acute pyelonephritis is due at least in part to vesicoureteral reflux (VUR). Although an association between pyelonephritis and abnormalities in acid-base balance is common in young children, the impact of metabolic acidosis (MA) on progression of acute pyelonephritis is not fully understood. In the current study the effect of metabolic acidosis on pyelonephritis was studied in C3H mouse strains prone to VUR.

Methods: MA was induced in female C3H mice via NH_4Cl (2% w/w) supplementation of food. Acid-base state was assessed by blood /gas analysis using an iSTAT® G3+ and urine pH. UPEC-UTI: Urinary Tract Infection of mice (6-8 wks) with Uropathogenic E. Coli (UPEC strain CFT073) 0.5-$1X10^7$ cfu/50 μl was performed via the transurethral inoculation. Bacteria burden (cfu/g) in bladder and kidney was determined by culture of tissue homogenates. Collecting duct (CD) fragments and neutrophils were enriched from collagenase-digested kidney by magnetic-sorting utilizing DBA-lectin and monoclonal anti-Ly6G (1A8). Cytokine (IL-1β, TNFα, IL-6) and chemokine (CXCL1, CXCL2, CXCL5) RNA in CD cells was quantitated by qRT-PCR. Ly6G$^+$ cells were enumerated by imaging utilizing a Cellometer K2 Image Cytometer. Statistics: T-test or two-tailed Mann-Whitney U-Test $p<0.05$ or $P \leq 0.02$ for Bonferroni correction.

Results: NH_4Cl fed-mice were acidotic (s[HCO_3^-]: 17±0.6*, Ur pH: 5.8±0.02*) compared to normal (s[HCO3-]: 22.2±0.68; Ur pH: 6.8±0.01, N≥4; *p<0.05). MA concurrent with UPEC-UTI markedly increased kidney UPEC burden in innate immune competent HeN mice (HeN = 4E2±2E2 versus MA HeN= 1E6±1E6; $p<0.02$ MW U-TEST), but not Tlr4-deficient HeJ mice (HeJ = 2E6 ±1E6 versus MA HeJ = 5E5±1E5). MA markedly increased CD inflammation in infected HeN mice characterized by an 18-124 fold increase in chemokine/cytokine mRNA abundance and a 4.5±0.6 fold increase in Ly6G+ neutrophil infiltrates over normal-infected mice, N=3; $p<0.01$ versus normal, TTEST.

Conclusions: Concurrent metabolic acidosis exacerbates pyelonephritis in innate immune competent mice that is characterized by an elevated cytokine and chemokine expression and kidney neutrophil infiltrates.

PO1418

Oxidized Alkyl Phospholipids Stimulate Proximal Tubule Sodium Transport via PPARγ/ERK Pathway

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Background: We previously reported thiazolidinediones stimulated proximal tubule (PT) sodium transport via non-genomic PPARγ/ERK pathway. However, the contribution of endogenous PPARγ ligands to PT transport has been unknown. In this study, we investigated effects of 1-O-hexadecyl-2-azelaoyl-*sn*-glycero-3-phosphocholine (azPC), an endogenous lipid oxidation product (LOP) acting as a potent PPARγ agonist, on PT sodium transport.

Methods: We measured basolateral Na^+/HCO_3^- cotransporter 1 (NBCe1) activity in lumen-collapsed PTs and luminal Na^+/H^+ exchanger (NHE) activity in freshly-isolated rat and human PTs obtained during surgery for renal cell carcinoma by using a pH-sensitive dye BCECF. NBCe1 activity in lumen-collapsed PTs was measured by the rate of pH_i decrease in response to HCO_3^- reduction. Luminal NHE activity in lumen-opened PTs was measured by the rate of pH_i decrease caused by Na^+ removal in the presence of VATPase inhibitor, Bafilomycin A_1. To examine the signaling pathway of azPC, we used a PPARγ antagonist (GW9662) and a MEK inhibitor (PD98059) and siRNA against PPARγ. The expression of PPARγ mRNA was determined by quantitative PCR. ERK phosphorylation was analyzed by western blotting.

Results: In freshly-isolated human and rat PTs, 0.3 μM azPC stimulated NBCe1 and NHE activity. The stimulatory effects were completely suppressed by GW9662 or PD98059 without affecting the basal activities. siRNA against PPARγ completely suppressed the stimulation of both NBCe1 and NHE activities by azPC in rat PTs. We

found that azPC enhanced ERK phosphorylation in human and rat renal cortex tissue. This phosphorylation was also completely suppressed by GW9662 or PD98059.

Conclusions: These results indicated azPC stimulated both NBCe1 and NHE activities through PPARγ/ERK pathway in PTs. The stimulatory effect of azPC, one of the LOPs on PT sodium reabsorption, could be a novel mechanism of volume expansion and hypertension induced by atherosclerosis.

PO1419

A Novel Distal Convoluted Tubule-Specific Tamoxifen-Inducible Cre-Recombinase Driven by the NaCl Cotransporter Gene

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Background: The use of knockout and transgenic mouse models coupled with Cre-lox technologies has revolutionized research in kidney transport physiology by allowing site-specific genetic recombination in individual nephron segments. Although several groups have tried to generate a distal convoluted tubule (DCT)-specific mouse Cre-recombinase driven by the thiazide-sensitive NaCl cotransporter (NCC) promoter, this goal has remained elusive. The only previously recognized mouse model available allowing targeted gene modification in the DCT is the DCT1-specific mouse with Cre-recombinase under control of the *Pvalb* gene encoding parvalbumin. The model, however, has limitations including activity in neurons that prevent comprehensive characterization of transport pathways in the DCT.

Methods: CRISPR/Cas9 was used to introduce Cre-ERT2 into the 3′ UTR near the stop codon of the *Slc12a3* gene encoding NCC (*Slc12a3*-Cre-ERT2 mice). Here, we crossed *Slc12a3*-Cre-ERT2 mice with YFP floxed mice to test whether the Cre expression would mimic that of NCC, and to determine whether the construct is 'leaky'.

Results: Without tamoxifen, approximately 6% of NCC positive cells expressed YFP, indicating minimal leakiness. After five days of tamoxifen injection, mice showed YFP expression in almost all NCC positive cells and there was complete overlap of YFP expression in NCC positive cells. Crossing to TdTomato mice revealed higher leakiness (64.5%), suggesting differential sensitivity of the floxed site. Western blotting revealed no differences in abundances of total or the active-phosphorylated form of NCC in *Slc12a3*-Cre-ERT2 mice of either sex compared to controls. Furthermore, functional analysis of NCC showed no effects on NCC activity in *Slc12a3*-Cre-ERT2 mice. Plasma K^+ and Mg^{2+} concentrations, and thiazide-sensitive Na^+ and K^+ excretion did not differ in *Slc12a3*-Cre-ERT2 mice compared to controls.

Conclusions: Thus, the *Slc12a3*-Cre-ERT2 mice have high recombination efficiency and complete fidelity in cell-specificity. Our data show that Cre expression is entirely localized to the DCT and the genetic modification has no effect on NCC expression and renal function. The *Slc12a3*-Cre-ERT2 mice are the first mice generated with Cre recombinase activity along the entire DCT, and will be a powerful tool to study DCT function.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

PO1428

A Case of Central Diabetes Insipidus due to Pituitary Adenoma Complicated by Amphotericin-Induced Nephrogenic Diabetes Insipidus

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Introduction: Amphotericin B (Amph B) is an anti-fungal agent that exhibits its action by binding to ergosterol, the main component of the fungal cell wall and shares a similar structure to the human cell membrane. Its main site of action is the principal cell where it causes an increase in membrane permeability by insertion of pores into the membrane, causing leaking of potassium into tubular lumen leading to hypokalemia. It also causes nephrogenic diabetes insipidus (NDI) by preventing insertion of vasopressin-induced aquaporin 2 (AQP-2). Reports in the literature have suggested that liposomal formulations might be less nephrotoxic than conventional ones.

Case Description: A 37-year-old male with history of pituitary adenoma s/p trans-sphenoidal resection of pituitary tumor with subsequent central diabetes insipidus (CDI) on maintenance desmopressin DDAVP 1mcg BID presented to hospital for suspected meningitis. He was started on liposomal Amph B 5mg/kg (550mg) for empiric fungal coverage. Lumbar drain cultures returned positive for Candida albicans on Hospital Day (HD) 1 and Amph B was continued. Renal was consulted for evaluation of worsening polyuria. Increased dose of DDAVP was recommended. He continued to be polyuric despite this dose adjustment. Amph B induced NDI was suspected secondary to refractory polyuria and hypokalemia. Amph B was discontinued on HD 7, after which his polyuria improved gradually. He was switched to fluconazole to complete the remainder of the treatment duration.

Discussion: Our patient with h/o CDI developed worsening polyuria on Amph B treatment, unresponsive to escalating DDAVP. Improvement with cessation of Amph B supports causality of concurrent drug-induced NDI. Amph B renal toxicity frequently presents with AKI with potassium wasting. NDI induced by Amph B is rare. A high index of suspicion is required for diagnosis of NDI occuring on top of CDI. Early discontinuation of Amph B usually leads to resolution of symptoms.

Hospital Day(HD)	Urine Osm (mOsm/kg)	Urine Output(L/day)	Ampho-B
1	118	3.8	started
5	191	14.7	continued
7	471	8.6	discontinued
14	590	3.8	

PO1429

Water Load Test in the Diagnosis of Syndrome of Inappropriate Antidiuresis (SIAD): Results from the Waterline Study

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Background: SIAD is caused by an inadequate kidney reabsorption of water, mainly under the action of antidiuretic hormone. The latest international recommendations stated the diagnosis of SIAD relies on hypotonic hyponatremia with inadequate urine osmolality. Blood volume has to be normal, with adrenal, thyroid, and renal insufficiency excluded. These guidelines ruled out the usefulness of abnormal response to water load test (WLT) due to the lack of published evidence.

Methods: In the Waterline study (NCT04256499), we retrospectively analyzed data from patients who underwent a WLT (oral administration of 20 mL/kg of water) in our department.

Results: From 02/2001 to 10/2019, 173 adults were included. Out of them, 80(46%) had a SIAD and 21(12%) were considered 'normal', 72(42%) had hyponatremia of other origin. Among the SIAD patients, 33(41%) had a fasting plasma sodium (PNa) ≥135mM ('normonatremic SIAD'), 47(59%) had 'hyponatremic SIAD': We found no differences in demographic data or medical history between these two groups. During WLT, 'normonatremic SIAD' patients behaved specifically by exerting hyponatremia (while normal individuals did not), resembling 'hyponatremic SIAD' patients (**Figure 1**). While their fasting urine osmolality (U-Osm) was initially higher, 'normonatremic SIAD' and 'hyponatremic SIAD' patients reached the same minimum U-Osm (389±257 *vs.* 350±202mOsm/kgH_2O, p=0.76). Additionally, they reached a higher minimum value of PNa than 'hyponatremic SIAD' patients (132±2 *vs.* 127±3mM, p<0.0001). These results were confirmed in an independent cohort of 38 WLT where 24 (63%) were 'normonatremic SIAD'.

Conclusions: We conclude that, without WLT, a diagnosis of SIAD could be missed in 40 to 63% of SIAD patients.

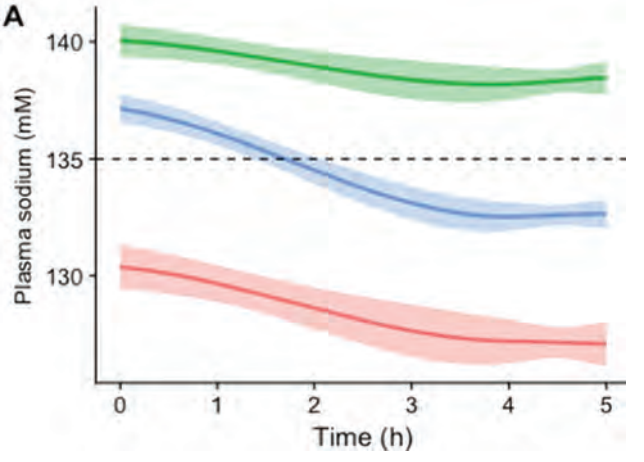

Figure 1. Evolution of PNa during WLT in normal (green), 'hyponatremic SIAD' (red), and 'normonatremic SIAD' (blue) patients.

PO1430

Reconsidering the Edelman Equation: Impact of Individual Total Body Cation Content and Body Weight

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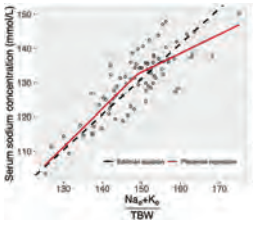
Background: Treatment of hypo- and hypernatremia is guided by formulas that are based on the Edelman equation, including Adrogue-Madias' and others. This equation is the result of a unique study in which serum sodium concentration ($[Na^+]$), total body exchangeable Na^+ and potassium (K^+) and total body water (TBW) were measured in a highly heterogeneous population. However, the Edelman equation does not account for the recently uncovered body compartment where Na^+ can be temporarily stored and released without affecting TBW.

Methods: We performed a post-hoc analysis of original data from the Edelman study. In a linear regression model, the effects of important clinical characteristics on the relation between (Na_e+K_e)/TBW and serum [Na^+] were examined: sex, age, body weight and presence of edema. Using piecewise regression, we analyzed differences in slope and y-intercept for increasing values of (Na_e+K_e)/TBW. Serum [Na^+] was calculated by multiplying serum water [Na^+] by 0.93.

Results: Data was available for 85 measurements in 82 patients; 57 males, 25 females, with a mean age of 57±15 years. Serum [Na^+] ranged from 103 to 150 mmol/L. The association between serum [Na^+] and (Na_e+K_e)/TBW was different for high and low weight categories (table). Sex, age or presence of edema did not alter the association. In piecewise regression, a significant change in slope was found at 149 mmol/L (Na_e+K_e)/TBW (figure; 1.12 vs 0.56, p = 0.01).

Conclusions: The coefficients of the Edelman equation are significantly affected by weight and total body cation content. The less steep slope for the higher (Na_e+K_e)/TBW and high weight groups may reflect an increase in osmotically inactive Na^+ storage. This may explain the inaccuracy of Edelman based formulas in daily clinical practice.



Subgroup		Slope ± SE	Intercept ± SE	p
Sex	*Male*	0.83 ± 0.08	6.4 ± 11.2	Slope: 0.47
	Female	0.93 ± 0.11	-6.1 ± 17.1	Intercept: 0.55
Age	*≤ 58 years*	0.93 ± 0.11	-7.7 ± 16.0	Slope: 0.45
	> 58 years	0.83 ± 0.08	7.2 ± 11.7	Intercept: 0.46
Weight	*≤ 59.6 kg*	1.05 ± 0.08	-26 ± 12.0	**Slope: 0.004**
	> 59.6 kg	0.69 ± 0.09	28 ± 13.6	**Intercept: 0.003**
Edema	*Yes*	0.96 ± 0.08	-13.1 ± 12.4	Slope: 0.06
	No	0.71 ± 0.10	26.1 ± 15.6	Intercept: 0.06

PO1431

Hyponatremia: It's in the Eye of the Beholder

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Introduction: An 85 year old Asian American female presented with 2 days history of worsening right eye pain, headache, scalp tenderness, and hypertensive urgency. Medical history was notable for keratoconjunctivitis sicca, osteoarthritis, and central retinal occlusion of the left eye. Initial labs showed erythrocyte sedimentation rate of 75 mm/hr. and C reactive protein of 3 mg/dL. A presumptive diagnosis of Giant Cell Arteritis (GCA) was made. She was started on high dose oral prednisone. Hypertension was treated with labetalol, amlodipine, and pain with opioids. Over the course of the next 36 hours she began to have somnolence. Initial sodium (Na) on admission was 131 mmol/L, with prior normonatremia. She was given a normal saline bolus followed by infusion due to concern for hypovolemia and reduced oral intake. This resulted in a consistent drop in her serum sodium acutely to 116 mmol/L and a nephrology consultation was sought.

Case Description: Our evaluation showed euvolemia with confusion and obtundation. Labs showed serum osmolality of 252 mosm/kg, urine osmolality of 626 osm/kg and Urine Na consistently around 90-129 mEq/L. A diagnosis of SIADH with desalination was made. She was treated with free water restriction, 3% saline, salt tablets, and furosemide. Na improved to 120 mmol/L however it dropped again next day to 117mmol/L requiring repeated doses of 3% Saline. Daily urine osmolality continued to decrease to 500s osm/kg and later to 360 mosm/kg as did urinary sodium 48 hours after these interventions. Peri-ocular swelling and a herpes zoster rash appeared on her eye 48 hours later. PCR for herpes was positive.

Discussion: Acyclovir was started and corticosteroids stopped. Over 8 days the hyponatremia resolved with Herpes Zoster Opthalmicus (HZO) treatment. HZO is a rare cause of SIADH thought to be due to dysregulation of stimulating signals from nucleus tractus solitarious to the supraoptic and paraventricular nuclei in the brainstem. In our case pain and opioids may have also been factors. Desalination needs to be considered in the correction of hyponatremia in SIADH, hyponatremia correction in HZO takes an average of 7 days although up to 4 months has been reported in 1 case series[1]. HZO should be considered in the differential diagnosis of SIADH.

PO1432

Acute Hemodialysis Prescription in Severe Hyponatremia Patient

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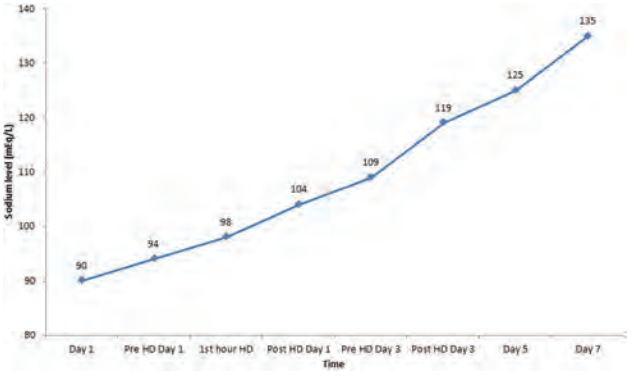
Introduction: Severe hyponatremia in end-stage renal disease with fluid overload give rise to clinical dilemma. Dialysis and ultrafiltration are needed to reduce uremic toxins and fluid overload, yet there is a danger of osmotic demyelination syndrome if blood sodium level rapidly increase above the permissible range.

Case Description: 60 years old male patient was admitted with acute pulmonary oedema due to chronic kidney disease. He came with ureum 140 mg/dl, creatinin 20.3 mg/dl and had severe hyponatremia 94 mEq/L. He underwent hemodialysis with low blood flow rate (50 ml/min) and low dialysate sodium (130 mEq/L). Second hemodialysis was done with blood flow rate 100 ml/min and dialysate sodium 130 mEq/L. With this approach, we succeeded in increasing sodium gradually, not exceeding the limit of 10 mEq/day.

Discussion: In order to avoid rapid increment of serum sodium level, the sodium in dialysate can be set as low as possible to 130 mEq/L. We aim to limit the increment of serum Na to 10 mEq/day. Since the patient's total body water is approximately 36 L, an increase of 3 mEq/L/hour during 3-hour dialysis session would require a transfer of 108 mEq of Na per hour or total 324 mEq. We set a very slow blood flow rate, set dialysate rate to 800 ml/min and we assume that there is a 100% equilibration of Na between the patient's blood and the dialysate, resulting in net transfer of 36 mEq Na ($Na_{dialysate}$ - Na_{serum}) to each liter of blood that flow through the dialyzer. As the desired total Na transfer was 324 mEq, and 36 mEq would be added for every litre of blood dialyzed, we estimated that 9000 ml of blood needed to be dialyzed. The amount of blood divided by 3 hour hemodialysis treatment time leads to a blood flow rate 50 ml/min. With this approach, post dialysis sodium level increase 10 mEq/L. Similar approach gave similar finding in second hemodialysis. In conclusion, hemodialysis in severe hyponatremia patient needs several modifications in order to limit the increment of sodium within safe and permissible range.



Serum sodium level increment

PO1433

Urea as a Newer Therapy for Hyponatremia

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Introduction: Hyponatremia is the most common electrolyte disorder observed in hospitalized patients and is associated with increased mortality, length of stay and readmission rates. Treatment includes fluid restriction, salt tablets, intravenous (IV) hypertonic saline and Antidiuretic Hormone (ADH) antagonists. Urea is a known therapy option for SIADH, but has been an infrequent choice.

Case Description: We present five cases of hyponatremia. The ages of the first four patients who had good response to urea were all older than 50 years. They included three SIADH patients and one hypervolemic hyponatremia. The hypervolemic patient had a reduced ejection fraction and had no improvement with diuresis and salt tablets and responded to urea. Of the other three, one required hypertonic saline and transition to urea, the other had been treated with tolvaptan and switched to urea due to cost concerns and the third patient had a component of low solute intake which responded well to urea. The fourth patient had SIADH secondary to malignancy and needed a combination of salt tablets and urea to achieve goal sodium. Addition of urea to salt tablets lowered the dose of salt tablets needed to maintain goal sodium. The last and youngest patient did not respond well to urea and needed tolvaptan to maintain sodium levels at goal.

Discussion: The treatment of hyponatremia is challenging as the correction has to be controlled to avoid osmotic demyelination syndrome from rapid fluid shifts. While hypertonic saline is a reliable treatment in hospitalized patients, it can prolong hospital stays. Tolvaptan helps with sodium correction, but is limited by its cost and liver toxicity. Urea increased serum sodium levels reliably in our older patients and reduced dose of salt tablets needed. In comparison to Tolvaptan, urea is a cost-effective alternative. Salt tablets are more affordable but cause volume overload. Hence, we think urea is a newer, well-tolerated and safer option in the treatment of hyponatremia either alone or in combination with other therapies.

Case Description

Patient	Age/Sex	Admission Na+ (meq/L)	Discharge Na+ (mEq/L) and treatment	Duration of admission (days)	Urine Osmolality (mOsm/kg)	urine Na+ (mEq/L)
1	61 yo Female	118	135 Salt tablets/diuresis/tolvaptan Lastly urea with good response	26	211	34
2	77 yo Male	117	131 Hypertonic saline and tolvaptan Switched to urea due to cost	13	427	27
3	70 yo Male	123	128 0.9% NS and then urea	5	561	49
4	59 yo Male	127	129 0.9% NS and urea with salt tablets	16	629	181
5	39 yo Male	115	135 Hypertonic saline, urea with variable response Tolvaptan worked well	14	735	53

PO1434

Should Sodium Monitoring Be Included in Routine Prenatal Care?

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Introduction: The American College of Obstetricians and Gynecologists does not recommend serum chemistries as part of routine prenatal care. Our case demonstrates the clinical utility in diagnosing hyponatremia prior to symptom development in mother or newborn.

Case Description: A 39-year-old pregnant female with no known prenatal issues underwent a spontaneous vaginal delivery; the infant was initially apneic and had a witnessed seizure. His initial serum sodium was 120mEq/L, and he was treated with phenobarbital and hypertonic saline. Serum sodium corrected by 4mEq/L during the first 7 hours, and increased from 120 to 133mEq/L over the first 24 hours. Brain MRI performed on day 4 demonstrated no abnormal findings. The mother's baseline sodium level was unavailable. She received 1L of D5LR and 1L of LR during labor. She had urinary retention following delivery and a foley catheter immediately drained 2L of urine. Her initial postpartum sodium level was 123mEq/L without associated symptoms. Urine osmolality was 64 mOsm/kg on admission. History revealed typical daily fluid consumption of 6L. Two days prior to admission, she had abruptly increased fluid intake to 13L per day in response to contractions. Twelve hours into admission, serum sodium corrected from 123 to 134 mEq/L in the setting of a relative reduction in fluid intake to 5L. Due to concern for a chronic component of hyponatremia, free water and DDAVP were given to slow the rate of correction. With the effect of DDAVP, urine concentrated to 695 mOsm/kg, illustrating the regeneration of an osmotic gradient within 30 hours.

Discussion: Primary polydipsia served as the leading driver of acute hyponatremia in this mother and infant, appropriately associated with ADH suppression. Although well-known drivers of increased ADH secretion were present, such as urinary retention and labor pain, their effects were less significant, as evidenced by very dilute urine on presentation. She was not exposed to the antidiuretic effects of oxytocin, which is an additional consideration in the peripartum period. Higher plasma volume during pregnancy and chronic polydipsia increased the mother's propensity to develop clinically significant hyponatremia in this case. This may have been detected earlier had serum sodium testing been included in routine prenatal care.

PO1435

Hyponatremia: A Real Headache

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Introduction: Pituitary apoplexy is a condition characterized by pituitary gland injury via either infarction or hemorrhage. This can result in endocrinological dyscrasias. We describe a case of SIADH secondary to pituitary apoplexy.

Case Description: A 70 year old female with a past medical history of atrial fibrillation on rivaroxaban presented to the hospital with nausea, vomiting, and new onset headache for 1 week. She received 1 L of saline in the emergency room and her nausea resolved. Basic chemistry was significant for a serum sodium of 124 mEq/L. A physical exam including neurological assessment was unremarkable as was a CT scan of the head. The patient was admitted and placed on a 1.5 L fluid restriction. By the next morning, she had a serum sodium of 112mEq/L, serum osmolality at 238 mOsm/kg, urine osmolality at 434 mOsmol/kg, urine sodium at 143 mmol/L, and urine potassium at 45 mmol/L. The patient was immediately transferred to the ICU and nephrology was consulted for severe hyponatremia due to SIADH. Given the acute drop from 124 mEq/L to 112 mEq/L over a 20-hour period, the patient was aggressively treated with hypertonic saline boluses as well as continuous infusion. Fluid restriction was tightened to 500 ml daily. SIADH was initially thought to be due to hypovolemia and vomiting, however, the differential was revisited when the severe hyponatremia persisted despite resolution of her nausea and hypovolemia. Given the new onset headache in an older adult, a MRI of the brain was obtained which revealed a convexity in the sella that was identified as a 1 cm pituitary hemorrhage. Rivaroxaban was discontinued. Further evaluation of pituitary hormones were all within normal limits. The hyponatremia corrected over 3 days and the patient was discharged home with a sodium of 132 mEq/L.

Discussion: SIADH is a rare finding in pituitary apoplexy that can be seen transiently 3-11 days after a pituitary surgery or injury. The mechanism is not known but is suspected to be due to the release of intracellular ADH stores from injured posterior pituitary cells. Pituitary apoplexy should be considered in the differential diagnoses for SIADH in the setting of recent brain surgery or new red flag neurological symptoms.

PO1436

Dysnatremias and Mortality in CKD: Analysis of the Chronic Renal Insufficiency Cohort (CRIC) Study

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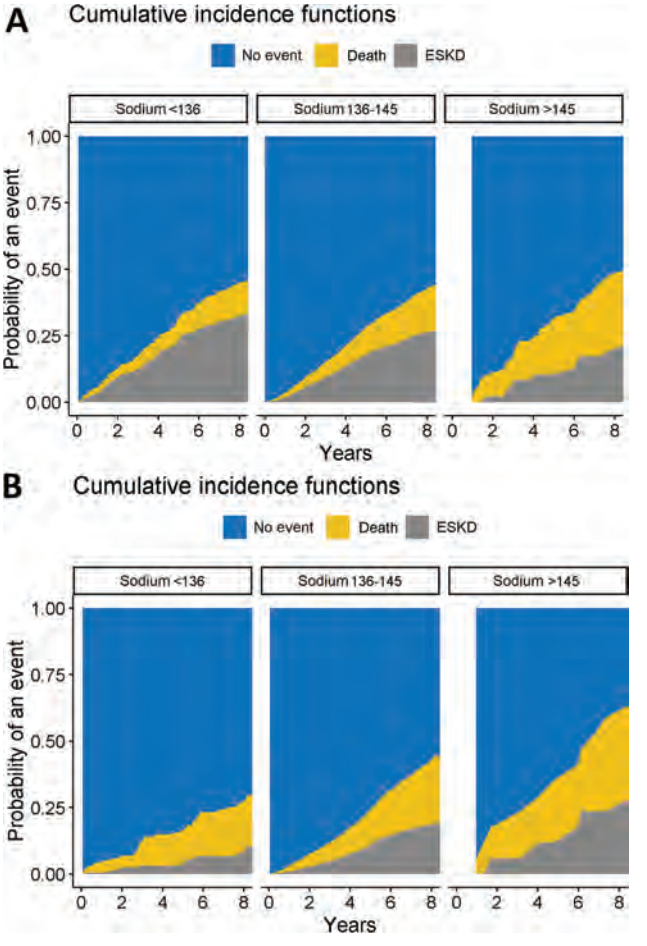
Background: Dysnatremias have been associated with increased mortality in patients with chronic kidney disease (CKD). We studied the association of dysnatremias with mortality and end-stage kidney disease (ESKD) in patients with CKD.

Methods: We included 5,444 patients from the Chronic Renal Insufficiency Cohort (CRIC) over a median time of 8.8 years. We analyzed baseline and time-dependent hyponatremia (<136 mmol/L) and hypernatremia (>145 mmol/L) with all-cause mortality and risk of ESKD using Cox proportional hazard models and competing risks models.

Results: Hyponatremia and hypernatremia were found in 9% and 1% of patients, respectively. In adjusted Cox models, time-dependent hyponatremia and hypernatremia were significantly associated with mortality (hyponatremia HR 1.37, 95% CI: 1.15, 1.63, and hypernatremia HR 1.60, 95% CI: 1.08, 2.39). Among age <65, baseline and time-dependent hyponatremia were associated with increased risk of ESKD (baseline hyponatremia HR 1.27, 95% CI: 1.008, 1.61, time-dependent hyponatremia HR 1.38, 95% CI: 1.10, 1.72). Time-dependent hypernatremia was associated with increased risk of ESKD regardless of age (HR 1.58, 95% CI: 1.02, 2.45).

Conclusions: In the CRIC, time-dependent hyponatremia and hypernatremia were significantly associated with mortality suggesting frequent measurements is predictive of prognosis. Time-dependent hypernatremia was associated with increased risk of ESKD at all ages. Baseline and time-dependent hyponatremia were associated with increased risk of ESKD in patients <65. Subjects ≥ 65 may have competing risk factors or progression of underlying comorbidities that supersede the detrimental effects of hyponatremia.



Cumulative incidence of death and ESKD across sodium groups – Graph A: Age <65, B: Age ≥ 65

PO1437

The Prognostic Importance of Serum Sodium Levels at Hospital Discharge and 1-Year Mortality Among Hospitalized Patients

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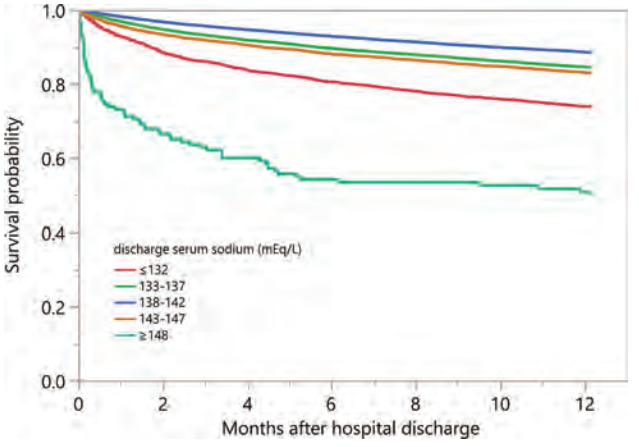
Background: The optimal range of serum sodium at hospital discharge is unclear. Our objective was to assess the one-year mortality based on discharge serum sodium in hospitalized patients.

Methods: We analyzed a cohort of hospitalized adult patients between 2011 and 2013 who survived hospital admission at a tertiary referral hospital. We categorized discharge serum sodium into five groups; ≤132, 133-137, 138-142, 143-147, and ≥148 mEq/L. We assessed one-year mortality risk after hospital discharge based on discharge serum sodium, using discharge sodium of 138-142 mEq/L as the reference group.

Results: Of 55,901 eligible patients, 4.9%, 29.8%, 56.1%, 8.9%, 0.3% had serum sodium of ≤132, 133-137, 138-142, 143-147, and ≥148 mEq/L, respectively. We observed a U-shaped association between discharge serum sodium and one-year mortality, with nadir mortality in discharge serum sodium of 138-142 mEq/L. When adjusting for potential confounders, including admission serum sodium, one-year mortality was significantly higher in both discharge serum sodium ≤137 and ≥143 mEq/L, compared

with discharge serum sodium of 138-142 mEq/L. The mortality risk was the most prominent in elevated discharge serum sodium of ≥148 mEq/L (HR 3.86; 95% CI 3.05-4.88), exceeding the risk associated with low discharge serum sodium of ≤132 mEq/L (HR 1.43; 95% CI 1.30-1.57).

Conclusions: The optimal range of serum sodium at discharge was 138-142 mEq/L. Both hypernatremia and hyponatremia at discharge were associated with higher one-year mortality. The impact on higher one-year mortality was more prominent in hypernatremia than hyponatremia.



PO1438

Peripheral Administration of 3% Sodium Chloride Is Not Associated with Local Infusion Reactions

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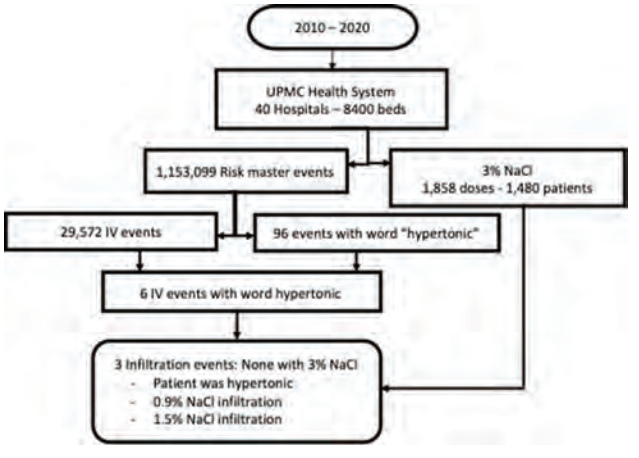
Background: Three-percent sodium chloride (3% NaCl) is a hyperosmolar agent indicated for the treatment of hyponatremic encephalopathy or to raise the serum osmolality in other cases of increased intracranial pressure. A barrier to the use of 3% NaCl is the perceived risk of a local infusion reactions when administered through a peripheral vein (Front Med. 2019 Mar 15;6:47), even though it has not been reported in large case series of 3% NaCl (AJKD. 2015 Mar;65(3):435-42). We sought to evaluate reports of local infusion reactions associated with 3% NaCl over a 10-year-period throughout a large healthcare system.

Methods: A query was conducted through Risk Master database to determine if there were any local infusion reactions associated with peripheral 3% NaCl administration throughout the entire UPMC health system over a 10-year time period from May 14, 2010 to May 14, 2020. Search terms included infiltrations, extravasations, phlebitis, IV site issues and IV solutions.

Results: In over 1.1 million events (figure), there were 23,714 intravenous events which were non-chemotherapeutic or non-contrast of which 4,648 (19.7%) were in children. 617 (2.59%) of these events were deemed serious by a patient safety officer. There were no reported local infusion reactions with 3% NaCl.

Conclusions: There were no reported local infusion reactions events associated with 3% NaCl in a large healthcare system despite widespread use of 3% NaCl and numerous intravenous events reported. This suggests that 3% NaCl can be safely administered through a peripheral IV.



Local Intravenous Infusion Reactions

PO1439

Hyponatremia: Mind the (Osmolar) Gap

Joy Ayyoub, Shahrzad Zonoozi, Pooneh Alborzi. *Penn Medicine, Philadelphia, PA.*

Introduction: Hyponatremia, one of the most commonly encountered electrolyte abnormalities, is associated with considerable mortality and morbidity. It is important to rule out pseudohyponatremia by determining serum tonicity.

Case Description: 65-year-old female with history of hypertension presented with worsening painless jaundice. Initial investigation was notable for an obstructive liver injury; total bilirubin of 28.4 mg/dL (direct 19.5 mg/dL and indirect 8.9 mg/dL), ALP 1225 U/L, AST 237 U/L, ALT 384 U/L and GGT 2274 U/L. She was also found to have a sodium of 126 mmol/L and potassium of 2.5 mmol/L. With fluids and potassium repletion, her sodium plateaued at 131 mmol/L. Further investigation revealed a measured serum osmolality of 301 mOsm/kg with an osmolar gap of 33 mOsm/kg, and a urine osmolality of 589 mOsm/kg. Sodium analysis using ion-selective electrode (ISE) showed a correction in the sodium from 131 mmol/dL to 139 mmol/L on the same specimen, confirming the diagnosis of pseudohyponatremia. Lipid panel showed severe hypercholesterolemia (total cholesterol 1016 mg/dL, LDL 868 mg/dL, HDL 31 mg/dL and triglycerides at 604 mg/dL). Patient underwent endoscopic retrograde cholangiopancreatography and biliary sphincterotomy with biopsy consistent with adenocarcinoma of the pancreas. Following sphincterotomy, lipid panel and serum sodium normalized without further intervention.

Discussion: Serum cholesterol is elevated in cholestasis because its metabolic degredation and excretion are impaired. Much of the cholesterol is in the form of lipoprotein-X, an abnormal lipoprotein observed only in patients with cholestasis. Standard methods of sodium analysis, indirect ISE, calculates electrolyte concentration on the assumption that the non-aqueous portion of serum, predominantly proteins and lipids, comprises approximately 7% of a patient's plasma volume. In our patient with significant hyperlipidemia, this led to falsely low indirect ISE values. Direct potentiometric measurements use undiluted samples and are not subjected to this artifact, a method also used in blood gas analysis. This case demonstrates a rare presentation of pseudohyponatremia and highlights the importance of its consideration in cases where the serum osmolarity is normal or when an osmolar gap is present suggesting reduced plasma water content or the presence of ineffective osmoles.

PO1440

Development of Hyponatremia and Overcorrection in a Patient with COVID-19 and Vasopressin Exposure

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Introduction: Hyponatremia in the setting of elevated antidiuretic hormone (ADH) is a common phenomenon. However, exogenous ADH from vasopressin administration for hemodynamic support does not cause clinically relevant hyponatremia, despite its widespread use. Further, discontinuing vasopressin may lead to rapid rises in sodium that may be missed. Here, we present a case of a critically ill patient who developed hyponatremia in the setting of vasopressin use, with subsequent rapid overcorrection that required re-lowering of serum sodium after discontinuing vasopressin.

Case Description: A 40-year-old male with no known history was admitted to the ICU for respiratory failure due to COVID-19 pneumonia. Initial labs showed normal renal function and electrolytes. He received azithromycin, hydroxychloroquine, and glucocorticoids and required extracorporeal membrane oxygenation. During the first 45 days of hospitalization, he had persistent hypernatremia(sodium as high as 154 mEq/L) despite free water flushes(FWF) and intermittent IV 5% dextrose in water(D5W). On day 45, vasopressin and norepinephrine were initiated for hypotension. Over the next 72 hours, serum sodium decreased from 148 to 128 mEq/L (Figure 1). Urine osmolality(UOsm) and sodium were 684 mOsm/Kg and 145 mEq/L, respectively. During this 72-hour period, the patient received about 1L/day FWF. On day 55, vasopressin was discontinued for 11 hours, during which time the sodium rose from 126 to 138 mEq/L and UOsm decreased from 705 to 82 mOsm/kg. He received D5W to re-lower the sodium. Vasopressin was also restarted, and the sodium stabilized near 132mEq/L.

Discussion: Although pneumonia may have contributed to high ADH release in this patient, the timing of vasopressin administration prior to the development of hyponatremia and the acute rise in sodium after vasopressin discontinuation suggests an important role for exogenous ADH. Clinicians should pay close attention to fluctuations in sodium levels in patients receiving IV vasopressin, particularly when therapy is discontinued, given the risk of rapid overcorrection and development of osmotic demyelination syndrome.

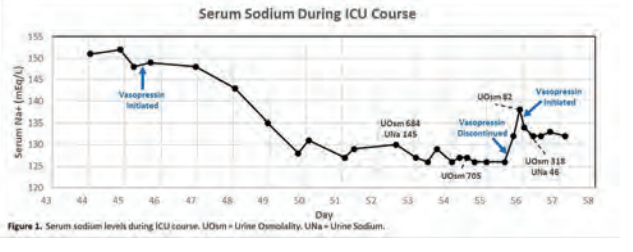

Figure 1. Serum sodium levels during ICU course. UOsm = Urine Osmolality. UNa = Urine Sodium.

PO1441

Continuous Renal Replacement Therapy (CRRT) for Overcorrection of Hyponatremia After Left Ventricular Assistance Device (LVAD) Placement

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Introduction: Rapid correction of severe hyponatremia can result in osmotic demyelination syndrome, central pontine myelinolysis and locked-in syndrome. Rapid correction is defined as an increase in serum sodium (Na) by 10-12 mEq/L in the first 24 hours and 18 mEq/L in the first 48 hours. Rapid lowering serum Na in a short period after rapid correction of hyponatremia could prevent these complications. Conventional strategies use hypotonic intravenous fluids and desmopressin to lower overcorrected hyponatremia. However, CRRT can correct serum sodium in a very predictable and controlled manner.

Case Description: A 35-years old woman with a history of non-ischemic cardiomyopathy with an ejection fraction of 5-10% was admitted with an acute CHF exacerbation. Her hospitalization was complicated by AKI and hyponatremia. She underwent LVAD placement and her sodium increased from 111 to 137 mEq/L within 18 hours of surgery. She was started on CRRT using continuous venovenous hemodiafiltration (CVVHDF) with post-filter 5% dextrose in water to lower her sodium level to close to 120 meq/L. The patient tolerated the treatment very well with no immediate central nervous system complications or even delayed neurological complications at the two month follow up.

Discussion: To our knowledge, this is the first case report describing the use of CRRT for overcorrection of hyponatremia after LVAD placement. The overcorrection of hyponatremia after LVAD placement was likely due to the kidney's restored ability to excrete diluted urine from improved renal perfusion. Given the total fluid volume of hypotonic intravenous fluids and unpredictability of desmopressin we recommend considering early initiation of CRRT to treat overcorrection of hyponatremia after LVAD placement. Another consideration should be made for Initiation of CRRT prior to LVAD placement in patients with severe hyponatremia to prevent the rapid correction from occurring in the intraoperative setting.

PO1442

Neuroprotective Hypernatremia in Acute Liver Failure Using CRRT: A Challenging Scenario

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Introduction: Acute liver failure is associated with severe complications, including encephalopathy. Cerebral edema may occur, leading to increased intracranial pressure. Urgent medical management sometimes includes neuroprotective hyperosmolality and ammonia control using convective techniques. We describe a patient where high-volume CVVHDF was used to increase ammonia clearance while maintaining therapeutic hypernatremia.

Case Description: A 64-year-old female with severe bipolar disorder presented into the ED ~24hours after voluntary ingestion of ~150 tablets (75g) of acetaminophen. She was initially confused with normal blood pressure. Laboratory work showed severe metabolic acidosis with the following values: lactate 9.1 mmol/L, pH 6.99, ammonia 409 mmol/L, ALT 6398 U/L, creatinine 44 μmol/L, INR 9.1 and acetaminophen 250.2 mg/L. NAC and IV bicarbonate were quickly initiated, and a short plasmapheresis treatment was started 12hours later, inducing moderate hypercalcemia, hypernatremia (153 mmol/L) and normalising INR temporarily. Encephalopathy, oliguria and hemodynamic instability progressed. High-volume CVVHDF (90 mL/kg/h) was started at day 3 to optimise ammonia clearance and electrolytes. Hypertonic NaCl 23.4% (50 mmol) was added to a low-calcium 5L dialysate preparation (PrismOcal22) to obtain [Na] of 150 mmol/L. Over the next 3 days, additional hypertonic NaCl was required (until 80 mmol) (dialysate [Na] 156 mmol/L) to reach the ~150 mmol/L serum sodium targeted. However, after numerous medical complications, the patient was declared ineligible to liver transplantation and palliative care was initiated. She died 3 weeks after initial admission.

Discussion: Usage of high-volume CRRT in severe hepatic encephalopathy increases despite the paucity of evidence. Commercial standard solutions of dialysate used for CRRT usually have fixed sodium concentration (140 mmol/L). Adding sterile hypertonic NaCl into the dialysate bag allows us to modify its tonicity to obtain neuroprotective hypernatremia. However, as shown in our case, complete sodium equilibration between dialysate and patient, even when using high-volume CVVHDF, is unlikely because of residual kidney function and concomitant hypo- and isotonic IV medications. To obtain and maintain therapeutic hypernatremia in these conditions, the CRRT dialysate tonicity should be slightly higher than the targeted serum sodium.

PO1443

Unraveling the Role of Serum Chloride Level as a Strong Predictor of Outcomes in Patients with Heart Failure: A Systematic Review and Meta-Analysis

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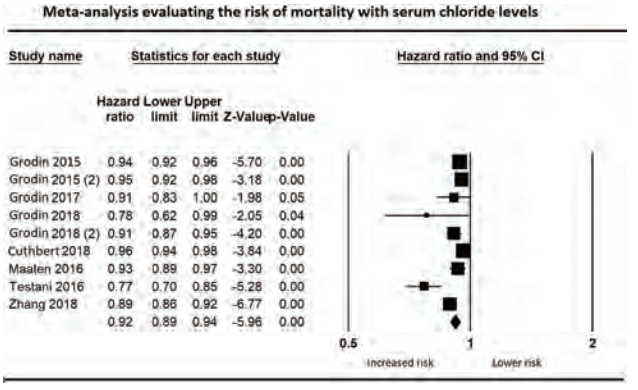
Background: The field of heart failure (HF) is conventionally sodium-centric. Low serum sodium concentration has long been recognized as an established marker of adverse outcomes and is commonly included in HF risk prediction models. Not only could the mechanisms leading to hyponatremia result in concurrent hypochloremia, but chloride also has distinct biological roles (e.g. modulating renin secretion) that are relevant in HF. We sought to explore the impact of hypochloremia on the outcomes of patients with a HF.

Methods: This is a PRISMA-guided systematic literature review and meta-analysis (registered in PROSPERO). We searched PubMed, Cochrane, and Embase databases from January 2010 to March 2020 for clinical trials exploring relationship between serum chloride and the outcomes of HF patients. A cumulative analysis of Hazard Ratios (HR) with 95% confidence intervals (CIs) was done using comprehensive meta-analysis software.

Results: A total of 9 studies with 15,979 patients were eligible for analysis; 5 had patients with systolic HF, 3 with both systolic and diastolic HF, and 1 with diastolic HF only. These studies reported HR for risk of mortality with change in serum chloride levels stratified by unit, standard deviation, or predefined groups, and adjusted for serum sodium and a variety of potential confounders. On cumulative analysis we found that serum chloride levels are inversely associated with risk of long-term mortality HR 0.92 (95% CI 0.77 - 0.96; p<0.01).

Conclusions: Based on the data from currently available studies, we identified low serum chloride level as a strong independent predictor of mortality in various phenotypes of HF. While it remains to be elucidated whether it represents a marker of disease severity or reflects an actual pathogenetic mechanism, our results suggest that inclusion of serum chloride in HF risk models is likely to improve their predictive value.



PO1444

Patiromer vs. Kayexalate: Comparison of Potassium Binding Efficacy and Impact on Other Electrolytes in Infant Milk Formula Similac PM 60:40

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Background: Hyperkalemia is one of the common metabolic abnormalities seen in patients with renal failure. Management includes combination of low-potassium diet with additional potassium-binding medications if necessary. However, these measures are impractical in infants whose dietary intake is predominantly milk based and both breast as well as the renal milk formula, Similac PM 60:40, have high potassium content. Low-potassium milk formulas such as Renastart® and Renalcal® are not readily available. Pretreatement of milk with Kayexalate has been utilized as an effective means of reducing the milk potassium content. As Kayexalate exchanges sodium for potassium, it results in extra sodium load that is undesirable in patients with hypertension; moreover, Kayexalate also binds calcium thus decreasing calcium intake. Patiromer (Veltassa®), a recently introduced sodium-free potassium-binder exchanges calcium for potassium thus avoiding both hypernatremia and hypocalcemia.

Methods: Potassium binding effectiveness of Patiromer was comapred with Kayexalate by pretreating Similac® PM 60:40 milk formula. Three different concentrations of Kayexalate (3.4, 6.8, and 13.6 g/L) and Patiromer (8.4, 16.8, and 33.6 g/L) were used. Supernatant samples were collected at 30, 60, and 120 minutes respectively. Samples were analyzed for sodium, potassium, calcium, and magnesium. The experiment was conducted in duplicate.

Results: Results are shown in Table.

Conclusions: Both Kayexalate and Patiromer were effective in lowering the potassium concentration. While Kayexalate increased the sodium content of the formula by almost 100 to 300%, and reduced the calcium concentration by 40%, Patiromer did not affect the sodium concentration and increased the calcium concentration by 40%. Both Kayexalate and Patiromer decreased the magnesium concentration with the decrease being more pronounced with Kayexalate. Knowledge of these electrolyte changes is crucially important in the care of infants with renal disease as they are vulnerable to negative consequences of electrolyte imbalance.

Funding: Commercial Support - Relypsa, Inc

Table: Percentage changes in electrolyte concentrations at the end of 30 minutes with three different doses of Kayexalate and Patiromer

Medication	Kayexalate			Patiromer		
Electrolytes	3.4 g/L	6.8 g/L	13.6 g/L	8.4 g/L	16.8 g/L	33.6 g/L
Potassium	↓15%	↓33%	↓61%	↓7%	↓15%	↓22%
Sodium	↑87%	↑239%	↑300%	↓3%	↓6%	↓9%
Calcium	↓13%	↓19%	↓41%	↑19%	↑37%	↑43%
Magnesium	↓31%	↓46%	↓69%	↓15%	↓30%	↓38%

PO1445

Post-Discharge Outcomes Among Hyperkalemic Patients Treated with and Without Sodium Polystyrene Sulfonate in the Inpatient Setting

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Background: Sodium polystyrene sulfonate (SPS) is a common treatment option for hyperkalemia (HK) in the inpatient (IP) setting. However, the post-discharge outcomes of patients with HK treated with and without SPS in the IP setting are not well characterized.

Methods: Adult patients with ≥1 IP stay with HK (≥1 potassium [K] lab >5.0 mEq/L) were identified using electronic medical record data from the Research Action for Health Network (2012-2018). Patients treated with SPS during the IP stay were matched 1:1 to patients not treated with SPS on discharge status (dead/alive) and HK severity (most severe K lab during IP stay). Patient characteristics, K levels, HK treatments, length of stay (LOS) and death during IP stay were described. All-cause and HK-related IP readmission, and HK recurrence (in any setting) within 30, 60 and 90 days post-discharge were described and compared using conditional logistic regressions.

Results: A total of 4,847 SPS users were matched to non-SPS users (23.2% K>5.0-5.5, 36.8% >5.5-6.0, 40.0% >6.0 mEq/L). During the stay, 11.7% of patients died in both cohorts. Mean age was 65.7 and 62.1 years for the SPS and non-SPS users. SPS users had a higher burden of comorbidities than non-SPS users, including CKD (79.1% v 57.2%) and heart failure (49.8% v 37.7%; both p<0.001). The average LOS was similar for SPS and non-SPS users (9.0 v 9.1 days) and most patients had their last K level normalized (≤5.0 mEq/L) during the stay (83.0% v 86.2%, p<0.001). Use of temporizing agents was common for SPS and non-SPS users (58.2% v 43.5%, p<0.001); however, very few SPS users received SPS at discharge (0.4%). The 30-day all-cause and HK-related IP readmission rates were 27.0% and 13.6% for SPS users and 19.3% and 5.4% for non-SPS users, respectively. HK recurred within 30 days in 23.0% of SPS users and 7.1% of non-SPS users. The differences remained after adjusting for baseline and IP stay characteristics (odds ratio [95% CI]: all-cause readmission=1.4 [1.2, 1.6]; HK readmission=2.4 [2.0, 2.9]; HK recurrence=3.1 [2.7, 3.6]). The adjusted results were similar for 60 and 90 days post-discharge.

Conclusions: Despite treatment with SPS in the IP setting there was a high burden of readmission and HK recurrence among patients with HK.

Funding: Commercial Support - AstraZenca

PO1446

Serum Potassium Levels at Hospital Discharge and 1-Year Mortality Among Hospitalized Patients

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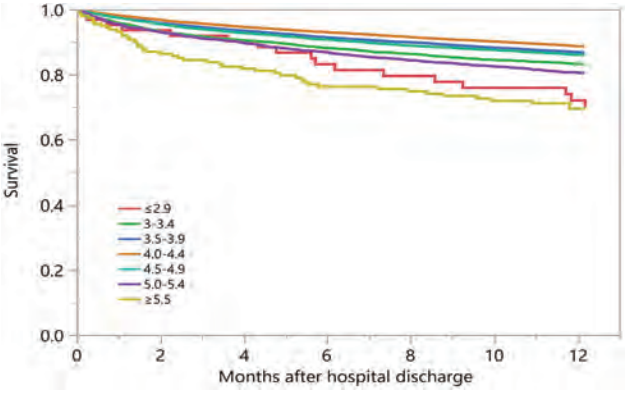
Background: The aim was to assess the relationship between discharge serum potassium levels and one-year mortality in hospitalized patients.

Methods: All adult hospital survivors between years 2011 and 2013 at a tertiary referral hospital who had available admission and discharge serum potassium levels were enrolled. End-stage kidney disease patients were excluded. Discharge potassium was defined as the last potassium measured within 48 hours prior to hospital discharge and categorized into ≤2.9, 3.0-3.4, 3.5-3.9, 4.0-4.4, 4.5-4.9, 5.0-5.4 and ≥5.5 mEq/L. Cox proportional hazard analysis was performed to assess the independent association between discharge potassium and one-year mortality after hospital discharge, using discharge potassium of 4.0-4.4 mEq/L as the reference group.

Results: Of 57,874 eligible patients, with a mean discharge serum potassium of 4.1±0.4 mEq/L, the estimated one-year mortality rate after discharge was 13.2%. A U-shaped association was observed between discharge potassium and one-year mortality, with nadir mortality in the discharge potassium of 4.0-4.4 mEq/L. After adjustment for clinical characteristics, including admission potassium, both discharge potassium of ≤3.9 mEq/L and ≥4.5 mEq/L were significantly associated with increased one-year mortality, compared with the discharge potassium of 4.0-4.4 mEq/L. Stratified analysis based on admission serum potassium showed similar results except that there was no increased risk of one-year mortality if discharge potassium group was ≤3.9 mEq/L in patients with an admission potassium of ≥5.0 mEq/L.

Conclusions: The association between discharge serum potassium and one-year mortality after hospital discharge had a U-shaped distribution and was independent of admission potassium. Favorable survival outcomes occurred when discharge potassium was within the range of 4.0-4.4 mEq/L.



The Kaplan-Meier plot of one-year mortality based on discharge serum potassium levels

PO1447

Mitragyna speciosa (Kratom)-Induced Hyperkalemia

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Introduction: Kratom is a non-controlled herbal supplement that has been used for its opioid-like effects. Case reports of different organ toxicities from Kratom have been reported in the literature. However, little is known regarding its effects on potassium (K) homeostasis. We present here the first case-report of kratom-induced hyperkalemia.

Case Description: A 61 yo male with a history of degenerative disc disease and hyperlipidemia, referred to nephrology clinic for unexplained hyperkalemia for the past 2 months. He was asymptomatic. His only home medication was rosuvastatin. Serum (K) was elevated in four different occasions with 5.8 mmol/L being the highest (non-hemolyzed samples). He denied NSAID or antibiotic use, smoking, alcohol intake, illicit drug abuse, sickness, or high (K) diet intake. No family history of renal diseases. Physical exam was unremarkable with a blood pressure of 124/76 mm Hg without orthostatic changes. Serum creatinine (Cr) was 0.8 mg/dL, eGFR >60 mL/min, plasma aldosterone was 3.6 ng/dL, rennin activity was 0.88, urine (K) was 14 mmol/L and urine Cr was 16 mg/dL, (K) fractional excretion was 15%, sodium of 141 mmol/L, CO2 33 mmol/L and the rest of the electrolytes were normal. TSH, CPK, AM cortisol, and WBC were within normal limits and he had no hematuria or proteinuria. Kidney ultrasound was normal. Upon re-interrogation, patient admitted taking daily Kratom for recreational purposes for the past 4 months as herbal supplement. A repeat blood chemistry 4 weeks after patient confirmed abstinence from Kratom, revealed normalization of (K) down to 4.6 mmol/L.

Discussion: *Mitragyna speciose (Kratom)* is a herbal supplement with potential abuse due to its opioid-like properties. Our patient had hyperkalemia unexplained by low renal clearance, adrenal insufficiency, medication use, or other etiologies. A study in cultured heart cells revealed a blocking effect of the cardiac (K) inward rectifier channels (Kir 2.1) by Mitragynine causing prolonged QT interval arrhythmia. Kir family does exist along the nephron with little known about Kir 2.1. Whether Kratom has effect on renal Kir 2.1, or other Kir channels is yet to be further studied. This case-report serves to highlight the importance of the identification of lesser-known supplements with potential abuse that can cause life-threatening side-effects.

PO1448

The Relationship Between Comorbidities and Hyperkalaemia in Patients with CKD

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Background: Hyperkalaemia (HK) is common in patients with chronic kidney disease (CKD) due to the role the kidneys play in maintaining normal potassium (K^+) homeostasis. The presence of comorbidities in patients with CKD may further increase HK risk. Therefore, this study explored the incidence of HK in CKD patients with different comorbidities.

Methods: A retrospective cohort study was conducted using primary and secondary care data from the UK Clinical Practice Research Datalink and linked Hospital Episode Statistics, respectively. Eligible patients had non-dialysis dependent CKD, with or without resistant hypertension (RHTN); heart failure (HF) or diabetes (type 1 or type 2) recorded between January 2003 – June 2018. Patients were grouped according to CKD severity (stage 3a, 3b, 4 and 5) and follow-up time was partitioned based on their current status. Crude rates of HK per 1,000 patient-years were analysed for each group and the data was further categorised according to HK-defining serum K^+ thresholds: ≥5.0, ≥5.5 and ≥6 mmol/L.

Results: In total, 229,350 patients with CKD stage 3+ contributed to follow-up, including 514, 250, 114 and 39 thousand patient years in the CKD only, RHTN, diabetes and HF cohorts, respectively. Declining renal function was consistently associated with increasing incidence of HK at all K^+ thresholds. Additionally, within the same CKD stage, comorbidities were also consistently associated with an increase in HK incidence. Patients in the diabetes cohort were consistently at the greatest risk of HK, with a significant ($\alpha = 0.05$) increase in risk of HK (defined at ≥5.0 mmol/L) compared with other comorbid groups. Conversely, patients without any comorbidities were at the lowest risk of HK, regardless of CKD stage and HK threshold.

Conclusions: In patients with CKD, comorbidities – specifically HF, diabetes, and RHTN – increase the risk of HK. This risk increases as renal function declines. As such, CKD patients, particularly those with comorbidities, may benefit from additional monitoring for HK.

Funding: Commercial Support - AstraZeneca

PO1449

Hyperkalemia Secondary to Carbapenem Use

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Introduction: Hyperkalemia can be a life-threatening complication and can often occur in the hospital setting as the result of the use of certain medications. In particular, hyperkalemia has already been described as a rare complication of ertapenem use.

Case Description: A 24 year-old gentleman with no past medical or surgical history presented with a one week history of abdominal pain and nausea. He underwent a CT scan that showed a perforated appendix with small abscesses. Upon admission, his creatinine level was 1.28 mg/dL and his potassium level was 4.24 mEq/L. He was initiated on intravenous fluids and ertapenem 1g IV once daily. His renal function improved and his creatinine level decreased to 0.83 mg/dL however he developped hyperkalemia with a potassium level that peaked at 5.9 mEq/L. He was switched to meropenem, however the hyperkalemia persisted and resolved only when he was switched to ciprofloxacin.

Discussion: Carbapenem use is associated with severe hyperkalemia and this complication seems to stem from a class-effect rather than the effect of a specific drug.

PO1450

Relationships Between CKD Duration, Serum Potassium Level, and Adverse Outcomes

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Background: Patients with chronic kidney disease (CKD) are at increased risk of hyperkalaemia as the kidneys are important in maintaining potassium homeostasis. This study examined the relationships between CKD duration, serum potassium level (K^+) and rates of adverse clinical outcomes.

Methods: This retrospective cohort study used linked primary and secondary care data from that UK Clinical Practice Research Datalink (CPRD) GOLD and Hospital Episode Statistics (HES), respectively. Eligible patients were aged ≥18 years with new or existing CKD stage 3+ (READ code or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 without prior dialysis) between January 2008 and June 2018, or during lookback (2003 to 2007). Index date was 01 January 2008 (prevalent cases) or CKD diagnosis date (incident cases); whichever occurred later. Adverse outcomes were all-cause mortality (ACM) and major adverse cardiovascular events (MACE), a composite of arrhythmia, heart failure, myocardial infarction, and stroke. Crude incidence rates of ACM and MACE were estimated over follow-up from index date to event or end of follow-up (earliest of death, loss to follow-up or study end) based on 1,000 patient years. Published risk equations for ACM and MACE were refitted with adapted coefficient values to include CKD duration (≤5 and >5 years). Reference category for incidence rate ratios was K^+ level 4.5 to <5.0 mmol/L.

Results: Among 297,702 CKD patients, 58.6% were female and mean age was 74.7 years (standard deviation, SD 11.3) at index, with mean follow up of 5.6 years (SD 3.20). Mean eGFR at index was 49.7 mL/min/1.73m^2 (SD 11.6). Crude rates of ACM and MACE in patients with CKD duration ≤5 years were 60.8 per 1,000 patient years (95% confidence interval (CI) 60.3-61.3) and 102.6 (95% CI 102.0-103.3). Rates in patients with CKD duration >5 years were 76.3 (95% CI 75.4-77.2) and 127.4 (95% CI 126.2-128.5), respectively. Irrespective of duration of CKD, K^+ <4.5 or ≥5.0 mmol/L were associated with increased risk of MACE/ACM in comparison with 4.5 to <5.0 mmol/L.

Conclusions: CKD patients with K^+ outside the normal range are at increased risk of ACM and MACE, irrespective of CKD duration. Improved management of K^+ may reduce adverse clinical outcomes in these patients.

Funding: Commercial Support - AstraZeneca

PO1451

Can Potassium Be a Predictor of Cardiovascular Mortality?

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Background: Epidemiologic data demonstrates association between hyperkalaemia and mortality. Patients with ST-segment elevation myocardial infarction (STEMI) often have comorbidities that are associated with hyperkalaemia, such as Chronic Kidney Disease (CKD) and Diabetes Mellitus (DM). The aim of our study was to analyse hyperkalaemia as a prognostic factor in patients with STEMI.

Methods: Retrospective single-center analysis of all patients admitted for STEMI and undergoing primary percutaneous coronary intervention in a two-year period (January 2009 to December 2010). Demographic aspects, comorbidities, potassium level at admission and outcomes were evaluated. Hyperkalaemia was defined as potassium level superior to 5 mmol/l.

Results: Overall, 276 patients were included (mean age 62 ± 14 years, 75% males), 55% had hypertension, 20% diabetes mellitus and 14% previous myocardial infarction. Only 14% were pretreated with renin–angiotensin–aldosterone system inhibitors (RAASi). The median potassium at admission was 4 mmol/l (IQR 3.7 - 4.4mmol/l), and the median creatinine level at admission was 0.88 mg/dl (IQR 0.74 - 1.1mg/dl). 5-year all-cause mortality was 23%. Univariable analysis revealed that age (p <0.001), previous myocardial infarction (p 0.038) and hyperkalaemia at admission (p 0.039) were associated with 5-year all-cause mortality. After adjustment for therapy with RAASi, higher potassium level at admission was associated with 5-year all-cause mortality (adjusted HR 1.55, 95%CI 1,01-2,38; p 0. 045).

Conclusions: In our study, potassium at admission was a predictor of 5-year all-cause mortality. Potassium measurement is an easy tool to help in risk stratification in this population. Further studies are needed to access if pharmacological control of potassium levels will change prognosis.

PO1452

Epidemiology of Hyperkalemia Among Patients Presenting at the Emergency Department in China

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Background: In China, the clinical burden of hyperkalemia (HK) among patients presenting emergency department (ED) is not well described.

Methods: Data containing hospital information system (HIS) records of 157 hospitals, covering 30 provinces in China were extracted from Beijing Data Center for Rational Use of Drugs. Patients presenting ED (aged >=18 years old) with record(s) of serum potassium (S-K) from 2015.1.1 to 2017.12.31 were included. Hyperkalemia were defined as S-K > 5.0 mmol/L. The proportion of patients experience at least one hyperkalemia and the severity of hyperkalemia were calculated among overall outpatients and patients with chronic kidney disease (CKD), heart failure (HF), hypertension (HTN), and diabetes mellitus (DM). The geographic and seasonal distribution of the proportion among overall patients were calculated.

Results: A total of 1,039,245 patients with at least one S-K record each were analysed, in which 36615 (3.52%) patients experienced HK (S-K >5.0 mmol/L), 15059 (1.45%) patients experienced S-K ≥5.5mmol/L. Analysing the index S-K in HK patients, the composition of patients with S-K levels of 5.0-5.5, ≥5.5-6.0, ≥6.0-6.5, ≥6.5-7.0 and ≥7.0 mmol/L were 57.5%, 22.8%, 10.1%, 4.7% and 4.9%, respectively. In patients with CKD, HF, DM and HTN, the proportions of patients who experienced HK were 47.7%, 29.1%, 21.7% and 10.2%, respectively. Analysing the severity of HK in HK patients with CKD, HF, DM and HTN, the proportions of patients with S-K levels ≥5.5 were higher than that in overall ED patients. (Table). Geographic analysis showed that provinces with higher proportions of HK were Tianjin (6.2%), Jiangsu (6.1%) and Jilin (5.7%). Higher proportion of HK were observed in winter (4.1%) than in summer (2.9%).

Conclusions: The proportions of HK in ED patients with CKD, HF, HTN or DM were higher than that in overall ED patients, and the severity of HK increased in patients with CKD, HF, DM and HTN.

The composition of patients at different S-K intervals in hyperkalemia patients with/without CKD, HF, HTN, or DM in ED

S-K (mmol/L)	CKD, N (%)	HF, N (%)	DM, N (%)	HTN, N (%)	Patients without CKD, HF, DM or HTN, N (%)
5.0≤ K <5.5	1165 (38.6)	1786 (49.9)	1832 (49.4)	2018 (54.1)	14755 (65.3)
5.5≤ K <6.0	822 (27.2)	910 (25.4)	955 (25.7)	916 (24.6)	4554 (20.2)
6.0≤ K <6.5	457 (15.1)	471 (13.2)	458 (12.4)	393 (10.5)	1775 (7.9)
6.5≤ K <7.0	257 (8.5)	205 (5.7)	230 (6.2)	196 (5.3)	703 (3.1)
K ≥7.0	320 (10.6)	209 (5.8)	235 (6.3)	204 (5.5)	789 (3.5)
Overall	3021 (100)	3581 (100)	3710 (100)	3727 (100)	22576 (100)

PO1453

Machine Learning Models for Risk Prediction of Adverse Events in Hyperkalemic Patients

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Background: Hyperkalemia is a common electrolyte abnormality in heart failure (HF) and chronic kidney disease (CKD) patients. Although increased risks of adverse events in hyperkalemic patients have been well reported, there is limited information on causality of adverse events. Considering multifactorial conditions of hyperkalemic patients, we aimed to develop predictive models using novel machine learning algorithms.

Methods: We utilized a Japanese hospital claims registry, Medical Data Vision. We extracted hyperkalemic patients with either CKD and/or HF aged ≥18 years, defined as patients with ≥2 serum potassium values ≥5.1 mmol/L; from April 2008 to September 2018. Extracted dataset was split into 80:20 for training and validation. The risk of adverse clinical events including all-cause death, hospitalization for cardiac events, hospitalization for HF, and renal replacement therapy (RRT) introduction over 3 years after hyperkalemic episodes was modeled using gradient boosted tree (XG), neural network (NN), and logistic regression (LR) based on 81 clinical variables collected in 12 months before hyperkalemic episodes.

Results: Of 74,974 hyperkalemic patients, 8,480 patients were included. Mean age was 75.6 years and 53.7% were male. The ROC curve and calibration analyses showed excellent performance for death (AUC=0.841 [XG], 0.815 [NN], 0.838 [LR]), hospitalization for cardiac events (AUC=0.782 [XG], 0.718 [NN], 0.743 [LR]), HF (AUC=0.875 [XG], 0.850 [NN], 0.855 [LR]), and RRT (AUC=0.958 [XG], 0.917 [NN], 0.946 [LR]) (Table). Clinical variables with high importance were identified (Figure).

Conclusions: The machine learning model successfully identified high-risk hyperkalemic patients for adverse events. Despite the need for model validation, these results support the use of predictive models to select high-risk hyperkalemic patients.

Funding: Commercial Support - AstraZeneca K.K.

Calibration analyses for 3-year mortality

Model	# of event	ROC-AUC	Specificity	Sensitivity	PPV	NPV
Gradient boosted tree	1,114	0.841	0.901	0.516	0.504	0.906
Neural network	1,114	0.815	0.902	0.444	0.467	0.893
Logistic regression	1,114	0.838	0.966	0.291	0.625	0.876

Top 20 important clinical variables for predicting 3-year mortality

PO1454

Extracellular Volume and Plasma Potassium Determine Urinary Prostaglandin E2 Excretion in Kidney Disease

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Background: Prostaglandin E2 (PGE2) is the most abundantly produced prostaglandin in the kidney where it plays a key role in renin secretion and electrolyte handling. It is unknown whether urinary PGE2 excretion is a reflection of these functions in patients with kidney disease. Here, our aims were to (1) analyze the changes in urinary PGE2 excretion during interventions modulating extracellular volume (ECV) or electrolyte homeostasis and (2) identify the determinants of urinary PGE2 excretion.

Methods: Urinary PGE2 and PGE2 metabolite (PGEM) excretions were measured in two studies in chronic kidney disease patients: 1) a randomized cross-over trial comparing a low sodium (Na^+) diet (60 mmol/day) with amiloride/hydrochlorothiazide (n=26, each intervention 2 weeks), 2) a 2-week intervention with potassium chloride supplementation (40 mmol day, n=28), and in patients with diabetic kidney disease from a 12-week randomized trial comparing dapagliflozin (n=23) with gliclazide (n=19). The baseline data of these studies were combined (n=96) to identify determinants of urinary PGE2 using multivariable linear regression with correction for age, sex, eGFR, and study.

Results: A low Na^+ diet, amiloride/hydrochlorothiazide, and dapagliflozin reduced ECV and increased plasma renin. Amiloride/hydrochlorothiazide and dapagliflozin increased total urinary PGE2 excretion by 5.3% (95% CI 1.9-8.7%) and 5.8% (95% CI 0.9-10.8%), respectively, while a low Na^+ diet increased PGEM excretion by 5.9% (95% CI 1.2-10.6%). Potassium supplementation had no effect on ECV, plasma renin, or urinary PGE2 excretion. On multivariable linear regression total urinary PGE2 excretion was associated with plasma renin (β 0.3, 95% CI 0.2-0.4), urinary Na^+ excretion (β 0.003, 95% CI 0.0007-0.006), and plasma potassium (β 0.7, 95% CI 0.3-1.0).

Conclusions: Interventions that decrease extracellular volume increase urinary PGE2 excretion. In addition, plasma renin, urinary Na^+ excretion, and plasma potassium are independently associated with urinary PGE2 excretion. Our data suggest that in patients with kidney disease urinary PGE2 excretion not only reflects the kidney's response to changes in extracellular volume but also plasma potassium.

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PO1455

Patient and Clinician Preferences for Hyperkalemia Treatment: A Qualitative Study

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Background: Treatment options for chronic hyperkalemia include the potassium binders Kayexalate®, Veltassa®, and since 2018, Lokelma®. In a qualitative research study, we explored which treatment characteristics are important to patients with hyperkalemia and treating clinicians.

Methods: Adult patients in the US who had received treatment for chronic hyperkalemia in the past 12 months and US clinicians who had treated ≥10 patients with chronic hyperkalemia with potassium binders in the last 3 months participated in focus group discussions consisting of concept elicitation and a ranking exercise, guided by a semi-structured discussion guide, with potential attributes identified through review of product labels.

Results: Twenty-five patients (52.4 ± 14.8 years; 56% male; 32% on dialysis; 20% kidney transplant recipients) and eight clinicians (n=4 nephrologists, n=2 cardiologists, n=2 hospitalists) participated. For patients, the most commonly reported medication side effect was diarrhea (64%), followed by abdominal pain and cramping (56%), nausea and/or vomiting, bloating/flatulence, and cramping in hands and legs (all 36%). The most disliked treatment characteristic was the medication's taste/texture; 58% of patients ranked it among three most important treatment characteristics. Although most patients reported gastrointestinal-related side effects, 54% did not rank diarrhea and 46% did not rank abdominal cramping in the top three characteristics. For clinicians, the most commonly encountered medication side effect was diarrhea (50%), followed by abdominal cramping (25%) and constipation (25%), and the most commonly considered treatment characteristic when prescribing a binder was taste/texture (50%), followed by time before/after taking medications (38%), time to onset (38%) and adherence (38%). Sustained efficacy followed by time to onset were ranked by 88% of clinicians as the two most important characteristics. Medication preparation, medication storage, and constipation were ranked low by both patients and clinicians.

Conclusions: Different potassium binder characteristics are most important to patients (taste/texture and abdominal cramping) and clinicians (sustained efficacy and time to onset). Clinicians should therefore take patient preference into consideration when prescribing a potassium binder.

Funding: Commercial Support - AstraZeneca

PO1456

Patient Palatability and Preference Study of Three Potassium Binders in Patients with CKD and Hyperkalemia: Rationale and Design of the APPETIZE Study

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Background: Patients with CKD are at risk of hyperkalemia (HK) which has been associated with a higher risk of cardiovascular events and mortality. Recently approved K^+ binders provide new treatment options to fulfil the unmet need for HK treatment beyond traditional K^+ binders, which are poorly tolerated by patients and are associated with GI side effects.

Methods: APPETIZE is a cross-sectional, randomised cross-over study with the aim to evaluate the palatability of and patient preference for 3 currently available K^+ binders: Sodium Polystyrene Sulphonate (SPS) or Calcium Polystyrene Sulphonate (CPS), Sodium Zirconium Cyclosilicate (Lokelma®) and Calcium Patiromer Sorbitex (Veltassa®). A single (patient) blind side-by-side, sip and spit taste-test approach will be utilised where patients will be presented with a single full, per label dose of each product to replicate the real-world patient experience. Patient ratings, assessed on a 0-10 scale and emotional response using the AdSAM tool® to evaluate feelings (Appeal, Engagement and Empowerment) will be used to assess patient centric attributes: taste (primary outcome), texture, smell, mouthfeel and likelihood of adherence (secondary outcomes) of each product. Preferential ranking will be performed after all 3 products have been tested. Sixty CKD patients (both dialysis and non-dialysis) with HK per country (480 overall) from US, Canada, Spain, Italy, Germany, France, Sweden and Norway will be included, with equal proportions of patients ever-treated and never-treated with K+ binders.

Results: APPETIZE will describe, compare and rank palatability and preference of 3 currently available K^+ binders by country. Initial results are anticipated towards end of 2020.

Conclusions: Utilizing innovative methodology, APPETIZE will generate evidence intended for patients and physicians (including nephrologists and cardiologists) regarding patient palatability, patient preference and predicted likelihood of adherence for currently available K+ binders.

PO1457

Fixing the Kidneys to Fix the Heart: BRASH Syndrome, a Case Report

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Introduction: BRASH (bradycardia, renal failure, AV-nodal blockade, shock, and hyperkalemia) is a multi-system syndrome. Immediate potassium removal is necessary and will result in resolution of cardiac arrhythmia.

Case Description: A 69 y/o male presented with generalized weakness, oliguric for 2 weeks and subsequence anuric. Lab was significant for hyperkalemia (6.2). EKG showed sinus bradycardia (HR 30), but without pathognomonic features of hyperkalemia. (Fig 1) Medical history significant for nephrectomy from an MVA injury, and IgA nephropathy s/p right renal transplant, hepatitis C, diabetes on insulin, and heart failure on Carvedilol 25mg BID. The patient was admitted to ICU and treated with calcium gluconate and insulin. Cardiology team was consulted for temporary pacers with eventual pacemaker insertion planned. However, upon discussion with the nephrology team, suspicion of BRASH syndrome was raised. Urgent CRRT was started. Rapid correction of potassium resulted in normalization of heart rate immediately. The patient received CRRT for 24 hours, and discharged on scheduled hemodialysis.

Discussion: BRASH syndrome is an uncommon presentation of a vicious cycle in the setting of hyperkalemia from acute kidney leading to the accumulation of AV node blockade medications. This synergizes bradycardia and hypoperfusion. Hypoperfusion, in turn, worsens renal failure leading to a cycle that continues until the patient deteriorates into lethargy, shock, and potentially death. Nowadays, despite commonplace to see patients with chronic kidney injury and cardiac diseases requiring AV nodal blocking medication, BRASH is still an underrecognized syndrome with only a handful of reported cases. Mild hyperkalemia without EKG changes make this diagnosis difficult, as such it is vital to recognize this syndrome from a multi-organ perspective - treatment with immediate correction of potassium via CRRT or hemodialysis can result in resolution without unnecessary transvenous pacing or pacemaker insertion.

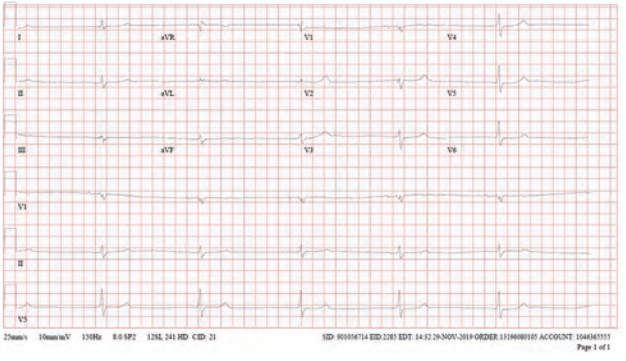

Figure 1: Initial EKG on presentation.

PO1458

Laxative Use and Plasma Potassium Trajectory in Patients with Advanced CKD Transitioning to Dialysis

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Background: Intestinal potassium excretion is increased in patients with advanced CKD. This compensatory mechanism may be enhanced by laxative use; however, little is known about the association of laxative use with longitudinal potassium (K^+) balance in advanced CKD.

Methods: In 34,697 US veterans who transitioned to ESRD from 2007-2015 and with ≥2 K^+ measurements during the last 1-year period before ESRD transition, we examined the association of time-varying laxative use with change in K^+ (slope) over the 1-year pre-ESRD period, using multivariable linear mixed-effects models. The difference in K^+ slope by laxative use status was tested by the interaction of laxative use with time for K^+ slope in the mixed-effects models.

Results: Overall, the mean age was 68 years; 98% were male; 32% were African American; and 76% were diabetic. In the crude model, there was a significant difference in K^+ slope between laxative use and non-use, with declining K^+ slope observed only for laxative use (median, -0.010 vs. 0.008 mEq/L/year, P=0.02; **Table**). Although the magnitude of K^+ slopes was clinically negligible, the between-group difference remained significant even after multivariable adjustment, with laxative use being associated with decline in K^+ (median, -0.013 vs. 0.003 mEq/L/year, P=0.02; **Table**).

Conclusions: Laxative use was modestly and independently associated with decline in K^+ over the last 1-year pre-ESRD period, suggesting enhanced intestinal potassium excretion by laxatives. Further studies are warranted to test whether active interventions with laxatives can improve potassium management in advanced CKD beyond their traditional indication.

Funding: NIDDK Support

Changes in plasma potassium concentration associated with time-varying laxative use status during the last 1-year pre-ESRD period (n=34,697)

	Change in K^+ (median [IQI], mEq/L per year)		P[†]
	Laxative use	Non-laxative use	
Crude model	-0.010 (-0.21, 0.19)	+0.008 (-0.20, 0.20)	0.022
Multivariable-adjusted model[‡]	-0.013 (-0.19, 0.16)	+0.003 (-0.17, 0.18)	0.022

[†]*P* values were for the difference in K^+ slope by time-varying laxative use status.

[‡]Model was adjusted for demographics, smoking status, BMI, comorbidities, length of hospital stay, in-hospital AKI, number of K^+ measurements, last K^+ value, and time-varying medication use and eGFR

PO1459

Effect of Lactated Ringer Solution Use on Serum Potassium in Advanced Kidney Disease

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Background: Lactated Ringer's (LR) solution is a balanced crystalloid containing 4 mEq/L of potassium (K). Its use is restricted in hyperkalemia and in those with advanced kidney disease given potential concerns of exacerbating hyperkalemia. We assessed the effect of LR on serum K levels in patients with advanced kidney disease.

Methods: Retrospective evaluation of 191 patient encounters with advanced kidney disease [defined by estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73m^2 - including patients with acute kidney injury (AKI), chronic kidney disease (CKD), AKI on CKD, and end-stage kidney disease (ESKD) either on dialysis or post renal-transplantation] admitted at the University of Alabama at Birmingham Hospital between 9/1/2017 to 9/1/2018 who received LR for resuscitation and its effect on serum K levels. We stratified patients based on renal function; accounted for concomitant medication use that frequently potentiate hyperkalemia, use of K supplements, blood transfusions immediately prior to LR use, presence of sepsis, and administration of tube feeds.

Results: Average age of patients was 59 years. 19 patients had AKI, 60 patients had AKI on CKD, 20 patients had known CKD, and 61 had ESKD (including 11 who had renal transplantation). Average LR use was 1.9L per patient. Hyperkalemia [defined by serum K ≥ 5.2 mEq/L] was seen in 27 patient encounters (14.1% of the study population). However, 16 of these patients had average K of 5.8 mEq/L prior to LR use. 11 among them were managed with medications alone and 4 patients needed dialysis. Average and highest K levels among all patients within 24-hour post LR use were 4.2 mEq/L and 4.4 mEq/L respectively. 131 patient encounters had sepsis. There was 1 death attributable to hyperkalemia.

Conclusions: 27 out of 191 patient encounters (14.1%) with advanced kidney disease in our cohort had hyperkalemia within 24 hours post-LR administration, and 16 had known hyperkalemia prior to LR use. Our study demonstrates that LR use is not independently associated with hyperkalemia in advanced kidney disease, a population subset who frequently cannot renally excrete K adequately. Further large scale clinical studies are warranted to confirm our findings.

PO1460

Association Between Dyskalemias and Short-Term Hospital/Emergency Department Visits in Patients with Advanced CKD Transitioning to Dialysis

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Background: Patients with advanced CKD may experience immediate hospital/emergency department (ED) visit due to dyskalemia-associated adverse events (e.g. arrhythmias). The association of dyskalemias with short-term hospital/ED visits is understudied amongst those with advanced CKD transitioning to dialysis.

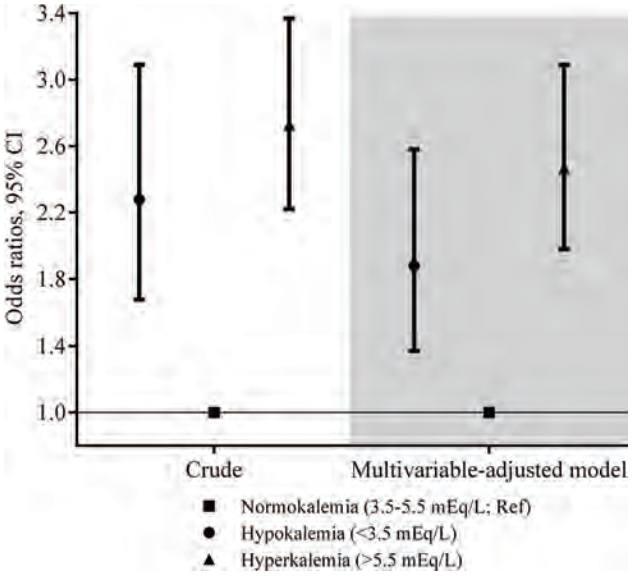
Methods: From among 102,477 US Veterans transitioning to dialysis between 2007-2015, we identified 21,150 patients with pre-dialysis eGFR <30 ml/min/1.73m^2 and a concurrent plasma potassium (K) measurement. We examined the association of hypokalemia [K <3.5], hyperkalemia [K >5.5] and normokalemia [3.5-5.5, reference] with hospital/ED visits within 2 days of plasma K measurement using logistic regressions adjusted for sociodemographics, smoking status, comorbidities, BMI, healthcare encounters, SBP, medications and eGFR.

Results: The mean age of the cohort was 67.3 years; 98% were male; 32% were African American. The mean eGFR and K were 22.3 ml/min/1.73m^2 and 4.6 mEq/L, respectively, and 7% and 3.5% of patients were hyper- and hypokalemic, respectively.

Three % of patients experienced a hospital/ED visit. Both hyper- and hypokalemia were significantly associated with higher risk of a hospital/ED visit in the crude (ORs [95% CIs] 2.73 [2.22-3.37] and 2.28 [1.68-3.09], respectively) and multivariable-adjusted models (2.47 [1.98-3.09] and 1.88 [1.37-2.58], respectively) (Figure).

Conclusions: Hyper- and hypokalemia are associated with higher short-term risk of hospital/ED visits in patients with advanced CKD. Preventing dyskalemias may help in reducing the incidence of short-term hospital/ED visit.

Funding: NIDDK Support



Association between dyskalemias and short-term hospital/emergency department visits in patients with advanced CKD

PO1461

Characteristics of CKD Patients with Hyperkalemia: A Report from the DISCOVER CKD Retrospective Cohort

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Background: Hyperkalemia (HK), defined as serum potassium (sK^+) >5.0 mmol/L, is a potentially fatal condition most often observed in patients with chronic kidney disease (CKD), heart failure (HF) or diabetes and exacerbated by medications that inhibit the renin-angiotensin aldosterone system (RAASi). This real-world study describes characteristics of patients with HK in a large observational international study of CKD patients.

Methods: The DISCOVER CKD retrospective cohort was extracted using the US TriNetX hospital-EMR and Japan Medical Data Vision (JMDV) databases. The study included patients aged >18 years (>20 JMDV) with a diagnostic CKD code (stage 3A to Stage 5 including renal replacement therapy [RRT]) or 2 estimated glomerular filtration rate (eGFR) measures <75 mL/min/1.73m^2 at least 90 days apart between January 2008 and March 2020. The index date was 2nd sK^+ measurement >5.0 mmol/L. Descriptive analyses were used.

Results: Preliminarily, 16436 CKD patients with HK (43% female, mean±SD age 72.2±13.7 years) were identified. Common comorbidities included HF, hypertension and type 2 diabetes, which increased in prevalence with increasing HK severity, Table 1. Mean eGFR was 43.3±24 mL/min/1.73m^2 and mean sK^+ was 5.4±0.5 mmol/L. HK severity, RAASi and diuretic use increased as mean eGFR decreased.

Conclusions: HK was more common in patients with significant comorbidities where RAAS inhibitors have evidence-based indications. Future analyses will determine whether HK limits appropriate management of these comorbidities.

Table 1: Baseline characteristics of CKD patients with HK by severity.

Variable	sK+ 5-<5.5	sK+ 5.5-<6	sK+ ≥6	Overall
Demographics				
N	11580	3268	1588	16436
Female (%)	4915 (42%)	1440 (44%)	703 (44%)	7058 (43%)
Mean Age (SD)	73.0 (13)	71.7 (15)	67.5 (16.9)	72.2 (13.7)
Medical History / Comorbidities N (%)				
Acute Kidney Injury	1965 (17.0%)	951 (29.1%)	696 (43.8)	3612 (22.0%)
Albuminuria	458 (4.0%)	211 (6.5%)	153 (9.6%)	822 (5.0%)
Heart Failure	2809 (24.3%)	1023 (31.3%)	608 (38.3%)	4440 (27.0%)
Hypertension	8636 (74.6%)	2586 (79.1%)	1322 (83.2%)	12544 (76.3%)
Type 2 Diabetes	4680 (40.4%)	1429 (43.7%)	799 (50.3%)	6908 (42.0%)
Mean (SD) Laboratory Values				
eGFR	46.6 (23)	38.3 (24)	30.3 (25.6)	43.3 (24.0)
Serum K+	5.2 (0.2)	5.6 (0.4)	6.3 (0.9)	5.4 (0.5)
Baseline Medication Use N (%)				
RAASi Therapy	1444 (12.5%)	550 (16.8%)	421 (26.5%)	2415 (14.7%)
Diuretics	3317 (28.6%)	1194 (36.5%)	711 (44.8%)	5222 (31.8%)

PO1462

Ambulatory Treatments for RAAS Inhibitor-Related Hyperkalemia and the 1-Year Risk of Recurrence

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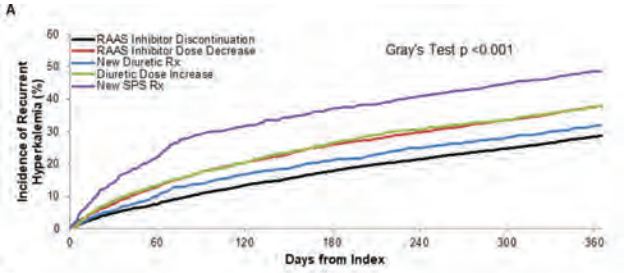
Background: Hyperkalemia commonly occurs with RAAS inhibitor (RAASi) use. The effectiveness of common outpatient interventions in preventing recurrent hyperkalemia has never been directly compared.

Methods: Population-based, retrospective cohort study of Ontario (Canada) residents ≥66 years old on RAASi therapy with ≥1 outpatient hyperkalemia (≥5.3 mmol/L) measurements between 2007-16. RAASi included ACE inhibitors, ARBs, MR antagonists, and ENaC inhibitors. Patients were included if they had one of the following interventions performed within 30 days of the hyperkalemia measurement: a) RAASi discontinuation, b) RAASi dose decrease, c) new K^+ wasting diuretic prescription, d) K^+ wasting diuretic dose increase, or e) sodium polystyrene sulfonate [SPS] prescription. The primary outcome was recurrence of hyperkalemia within 1 year. Secondary outcomes included major adverse cardiovascular events (MACE) and all-cause mortality within 1 year. Multivariable Fine and Gray sub-distribution models accounting for the competing risk of death were used for recurrent hyperkalemia and MACE outcomes. Multivariable Cox proportional hazards models were used for the all-cause mortality outcome.

Results: A total of 21,723 patients were included: RAASi discontinuation (N=13,539), RAASi decrease (N=5,075), new diuretic (N=1,010), diuretic increase (N=1,245), and SPS (N=854). RAASi discontinuation was associated with a lower risk for recurrent hyperkalemia and MACE over 1 year compared with other common hyperkalemia interventions (see **Figure**). However, there was no clear difference in 1-year all-cause mortality among these interventions.

Conclusions: RAASi discontinuation is associated with a lower 1-year risk for recurrent hyperkalemia and MACE compared with other common ambulatory interventions for hyperkalemia.



B

Multivariable Hazard Ratios (95% CIs) for Recurrent Hyperkalemia Within 1 Year

Intervention	Hazard Ratio	Forest Plot
RAASi D/C	– (Ref)	
RAASi Dose Decrease	1.32 (1.25-1.40)	
New Diuretic Rx	1.16 (1.03–1.30)	
Diuretic Dose Increase	1.29 (1.17–1.43)	
New SPS Rx	1.76 (1.58–1.97)	

C

Multivariable Hazard Ratios (95% CIs) for Major Adverse Cardiovascular Events Within 1 Year

Intervention	Hazard Ratio	Forest Plot
RAASi D/C	– (Ref)	
RAASi Dose Decrease	1.37 (1.28-1.46)	
New Diuretic Rx	1.14 (0.97–1.32)	
Diuretic Dose Increase	1.82 (1.65–2.00)	
New SPS Rx	1.36 (1.19–1.55)	

D

Multivariable Hazard Ratios (95% CIs) for Mortality Within 1 Year

Intervention	Hazard Ratio	Forest Plot
RAASi D/C	– (Ref)	
RAASi Dose Decrease	0.97 (0.86-1.08)	
New Diuretic Rx	1.22 (0.98–1.52)	
Diuretic Dose Increase	1.27 (1.08–1.49)	
New SPS Rx	1.08 (0.89–1.32)	

PO1463

Lethal Refractory Hyperkalemia and Metabolic Acidosis in a Patient with Secondary Hemophagocytic Lymphohistiocytosis (HLH)

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Introduction: Renal replacement therapy (RRT) is used as an adjuvant therapy to treat severe electrolyte and acid-base abnormalities. We describe a case of severe metabolic acidosis (lactic acidosis) and hyperkalemia which was refractory to treatment with simultaneous continuous renal replacement therapy (CRRT) and hemodialysis (HD) in a patient with HLH.

Case Description: A 63-year-old female with a history of diabetes mellitus, warm antibody autoimmune hemolytic anemia was admitted to the hospital with hyponatremia and hyperglycemia diagnosed on outpatient labs. Her hospital course was complicated with fevers, severe lactic acidosis, worsening thrombocytopenia and anemia. Infectious and rheumatologic workup was negative. Presumed diagnosis of secondary HLH was made with elevated serum ferritin (100,000 ng/ml), elevated triglyceride levels (346 mg/dl), low fibrinogen levels (70 mg/dl), fevers, bicytopenia and elevated soluble IL-2 receptor levels (34177 units/ml). She was treated with etoposide and dexamethasone for secondary HLH. Nephrology was consulted for hyperkalemia, metabolic acidosis and elevated lactate in our patient with normal renal function. Hyperkalemia was thought to be due to ongoing hemolysis. Despite medical management with intravenous bicarbonate, albuterol and insulin, the hyperkalemia persisted so RRT was initiated. Her potassium levels did not improve despite her serum pH increasing to 7.33. Serum lactate remained persistently elevated to 21 mmol/L. Neither high dialysate flow rates (DFR) up to 7.5 liters per hour with a 2 meq/ dl potassium bath nor hemodialysis which followed, using a zero potassium dialysate bath, lowered the potassium level. The patient continued to have a wide complex QRS interval on her ECG and episodes of ventricular tachycardia and suffered from a cardiac arrest when her potassium was 6.9 meq/dl. Suspected malignancy associated secondary HLH was thought to be the possible etiology of her refractory lethal metabolic problems.

Discussion: HLH has been associated with severe type B lactic acidosis from excessive cytokine overproduction. Often, CRRT with higher DFR than recommended have been used in the past to achieve solute clearance. Our case was unique as the patient continued to have refractory hyperkalemia and elevated lactate despite receiving CRRT and HD and had poor outcomes.

PO1464

Laxative Use and Incidence of Dyskalemia in Patients with Advanced CKD Transitioning to Dialysis

Keiichi Sumida,[1] Ankur A. Dashputre,[1] Praveen Kumar Potukuchi,[1] Fridtjof Thomas,[1,2] Yoshitsugu Obi,[1] Miklos Z. Molnar,[1] Elani Streja,[2] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[1] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA.*

Background: Intestinal potassium excretion is increased in patients with advanced CKD. This compensatory mechanism may be enhanced by laxative use; however, little is known about the association of laxative use with dyskalemias in advanced CKD.

Methods: In 34,697 US veterans who transitioned to ESRD from 2007-2015 and with ≥2 plasma potassium (K^+) measurements during the last 1-year period before ESRD transition, we examined the association of time-varying laxative use with incidence of dyskalemia over the 1-year pre-ESRD period, using generalized estimating equations with adjustment for potential confounders. K^+ levels were categorized as <3.5, 3.5-≤5.5 (reference), and >5.5 mEq/L at each K^+ measurement and treated as a repeated multinomial outcome.

Results: The mean (SD) age of the cohort was 68 (11) years; 98% were male; 32% were African American; and 76% were diabetic. In the crude model, laxative use (vs. non-use) was significantly associated with higher risk of hypokalemia (OR [95% CI], 1.19 [1.13-12.5]) and lower risk of hyperkalemia (0.74 [0.71-0.78]) (**Table**). The associations of laxative use with dyskalemias remained statistically significant even after multivariable adjustment (adjusted ORs [95% CI] for hypo- and hyperkalemia, 1.08 [1.02-1.13] and 0.79 [0.76-0.83], respectively; **Table**).

Conclusions: Laxative use was independently associated with higher and lower risk of hypo- and hyperkalemia, respectively, during the last 1-year pre-ESRD period. Our findings suggest the putative role of constipation in potassium disarrays and the need for careful consideration for the risk-benefit profiles of laxatives in potassium management in advanced CKD.

Funding: NIDDK Support

Adjusted odds ratios (95% CI) for dyskalemia associated with time-varying laxative use (vs. non-use) during the last 1-year pre-ESRD period (n=34,697)

	Time-varying plasma potassium concentration (mEq/L)		
	<3.5 (hypokalemia)	3.5 to ≤5.5 (normokalemia)	>5.5 (hyperkalemia)
% of all repeated values	5.9%	88.6%	5.5%
Crude model	1.19 (1.13-12.5)	1 [reference]	0.74 (0.71-0.78)
Multivariable-adjusted model †	1.08 (1.02-1.13)	1 [reference]	0.79 (0.76-0.83)

†Model was adjusted for demographics, smoking status, BMI, comorbidities, length of hospital stay, in-hospital AKI, number of outpatient medical visits, and time-varying medication use and eGFR

PO1465

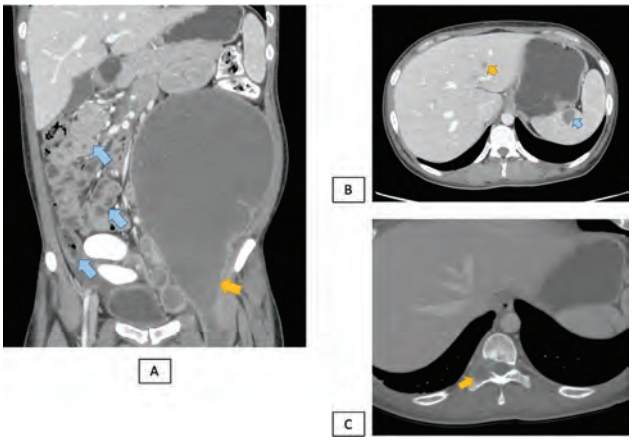
Acquired Bartter-Like Syndrome: An Unusual Presentation of Disseminated Tuberculosis

Isabelle Dominique V. Tomacruz, Anthony Russell Villanueva. *Philippine General Hospital, Manila, Philippines.*

Introduction: Acquired Bartter-like syndrome is a rare renal tubular disorder described to occur in granulomatous disorders such as sarcoidosis; but, its propensity to occur in tuberculosis (TB) is less known.

Case Description: We report the case of a 33-year-old Filipino woman with a 2-week history of lower extremity weakness. She had normal blood pressure and mild weakness on manual muscle testing. Abdominal examination revealed an incidental left lower quadrant mass. Workup revealed hypokalemia with urinary potassium wasting, hypercalciuria, hypomagnesemia, hypochloremia, and metabolic alkalosis, all consistent with Bartter-like syndrome. Abdominal CT scan findings were suggestive of disseminated TB. Ultrasound guided aspiration of the psoas abscess and pigtail insertion were done. Abscess aerobic, anaerobic, and fungal cultures did not isolate any organisms. Histopathology did not reveal any malignant cells. Detection of acid fast bacilli by Ziehl-Neelsen stain and culture confirmed the diagnosis. The patient was started on anti-TB therapy and was maintained on spironolactone, potassium and magnesium supplementation upon discharge. On follow up, electrolyte abnormalities resolved after four months of anti-TB therapy.

Discussion: TB may be a rare acquired cause of Bartter-like syndrome. Management involves treatment of the underlying cause, spironolactone and electrolyte supplementation.



CT images.A: Coronal view shows a left psoas abscess (yellow arrow), & bowel wall thickening (blue arrows)**B:**Axial view shows abscesses in the liver & spleen **C:**Axial view with bone window shows osteolytic lesions with soft tissue components in the right aspect of the T10 vertebra

Serum chemistry	Reference range	Admission	HD 1	HD 3	HD 5	Discharge	4th month of TB treatment (no supplementation)	2 weeks after discontinuation of supplementation	Upon completion TB treatment
Sodium	135-145 mmol/L	136			141	141		138	141
Potassium	3.5-4.5 mmol/L	1.4	1.8	2.3	4	3.9	5.5	4.7	4.9
Chloride	99-110 mmol/L	79			99				
Calcium (corrected calcium)	2.12-2.52 mmol/L	2.1			2.12			2.18	
Magnesium	0.7-1.05 mmol/L	0.61	1.16	0.58		0.57	1.04	0.98	0.97
Bun urea nitrogen	3.2-8.0 mmol/L	9.5			5.4	4.6		4.5	4.6
Creatinine	53-115 umol/L	172	142			102		104	112
Bicarbonate	22-26 meq/L	37.1							25
Random urine electrolytes									
Potassium	mmol/L	6.0							
Chloride	mmol/L	132							
Calcium	mmol/L	4.2							
Creatinine	umol/L	1370							

Blood & urine chemistry results.HD:Hospital Day

PO1466

Curious Case of Bartter Syndrome-Like Phenotype Unmasked by Diuretics

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Introduction: SLC12 A1 mutations have been associated with Bartter syndrome type 1. Here we present a case of severe hypokalemia with diuretics which when investigated led to discovery of a novel SLC12A1 mutation which might have predisposed the patient to Bartter syndrome like phenotype.

Case Description: 68 y/o f with no history of hypokalemia developed heart failure with preserved ejection fraction and was started on low dose loope diuretics which was gradually increased to1-1.5 mg po daily Bumetanide. She developed severe hypokalemia with diuretics which worsened with increasing diuretic doses, needing enormous amounts of potassium supplements. She continued to have persistent hypokalemia (serum potassium 3.0- 3.5 mmol/L) with significant urinary potassium excretion despite being on 260 mEq of oral potassium supplement/day, which improved mildly with addition of Amiloride. She also was hypotensive and was alkalotic secondary to diuresis. Given the significant kaliuresis leading to severe hypokalemia which was out of proportion to the dose of diuretics we did Genetic testing for presence of Bartter's mutation. Genetic testing revealed a novel heterozygous variant mutation in SLC12A1 gene. It showed 1972 C>T transition in exon 16 of SLC12A1 gene. This change converts a codon for leucine (CTT) to a codon for phenylalanine (TTT).

Discussion: Bartter syndrome (BS) type 1 is an autosomal recessive disorder caused by loss of function mutations. Mutations in SLC12A1 gene leading to dysfunction of NKCC2 co-transporter is one of the known mutations associated with Bartter's syndrome. There have been cases of heterozygous mutations of SLC12A1 gene which presented as Bartter syndrome. Our patient is unique as she has a novel heterozygous variant mutation in SLC12A1 gene and this mutation has not been reported to be associated with bartter syndrome. We believe this mutation might cause mild bartter phenotype. Our patient probably has a mild sublicnical Bartter like phenotype secondary to heterozygous variant of the mutation and developed severe hypokalemia when exposed to loop diuretics. Pursuing genetic testing for inappropriately severe hypokalemia needing exorbitant amount of potassium supplementation in a patient due to loop diuretic is a worthy consideration. Further research into this variant is needed to confirm it's pathogenicity.

PO1467

A Case of the Cons: How Contraception Confused Congenital Adrenal Hyperplasia for Conn

Linda-Marie U. Lavenburg, Sanjeev R. Shah, Sandeep Aggarwal. *University of Pennsylvania, Philadelphia, PA.*

Introduction: Drospirenone is a synthetic progestin oral contraception (OCP) with anti-androgen and anti-mineralocorticoid properties. We present a case of hypokalemic alkalosis and hypertension masked by drospirenone use.

Case Description: A 21-year old female with presumed polycystic ovarian syndrome (PCOS) was referred for hematuria, facial rash, and positive ANA concerning for lupus nephritis. Her only medication was drospirenone-ethinyl estradiol for oligomenorrhea, acne and hirsutism. Blood pressure (BP) was 98/67mmhg and heart rate 88 bpm with orthostasis. She had male pattern hair loss and dense comedones on her cheeks. Labs were significant for normal renal function, 2+ hematuria with isomorphic RBCs, negative BHCG and ANA titer 1:64. Glomerulonephritis and rheumatology work-ups were negative. Hematuria was attributed to breakthrough uterine bleeding. Gynecology held her OCP to allow for withdrawal bleeding. At 6-week follow-up, she reported muscle cramps and increased facial hair. BP was 176/98 mmhg. Hypertension was confirmed with ambulatory BP monitoring. Labs were significant for potassium 2.8 meq/L, bicarbonate 37 meq/L, urine sodium 14 meq/L, potassium 54 meq/L, chloride 38 meq/L. Mineralocorticoid excess due to primary hyperaldosteronism (Conn's syndrome) was suspected but plasma renin activity was <1 and aldosterone was <1. Syndrome of apparent mineralocorticoid excess was considered but the presence of hirsutism prompted investigation of congenital adrenal hyperplasia (CAH). Work-up found elevated levels of ACTH (146 pg/ml), DHEA-S (694 mcg/dl), 11-deoxycortisone (452 ng/dl), and testosterone (92 ng/dl), but normal 17-OH progesterone, LH and FSH. Ultrasound showed bilateral adrenal enlargement, normal right and left ovaries with two dominant follicles. She declined genetic testing for 11-beta hydroxylase deficiency (11BHD). Clinical and lab findings were consistent with non-classical CAH due to 11BHD. She started hydrocortisone with suppression of ACTH, decrease in 11-deoxycortisone, and normalization of BP and electrolyte abnormalities.

Discussion: 11BHD is rare form of CAH, which can be confused with PCOS and other syndromes of mineralocorticoid excess. In this case, drospirenone use controlled symptoms but potentially delayed diagnosis of 11BHD. Clinical trials should assess drospirenone in treatment of endocrinopathies.

PO1468

Posaconazole-Induced Hypokalemia in a Hemodialysis Patient

Mital Patel, Minhtri K. Nguyen. *Ronald Reagan UCLA Medical Center, Los Angeles, CA.*

Introduction: Posaconazole is a commonly used antifungal agent that is used for prophylaxis in many transplant recipients. Its side effect profile can vary from cardiovascular effects to metabolic derangements, such as hypokalemia. A prior case report of apparent mineralocorticoid excess (AME) secondary to Posaconazole therapy has been reported in 2017; however, this has not previously been reported in the ESRD patient population.

Case Description: A 68-year-old male with past medical history of idiopathic pulmonary fibrosis who underwent left lung transplant in December 2019 was consulted for acute kidney injury (AKI). Etiology of AKI was attributed to Tacrolimus induced thrombotic microangiopathy that ultimately required initiation of hemodialysis. Posaconazole 200mg PO daily was used for anti-fungal prophylaxis. Throughout the hospitalization, persistent hypokalemia was observed despite dialyzing the patient against a 4K bath. Further hypokalemia evaluation revealed plasma renin level at lower limit of normal (0.5ng/mL/hr), and low plasma aldosterone level at <3.0 ng/dL. 24 hr urinary cortisol-to-cortisone ratio was non-diagnostic likely due to an inadequate collection (creatinine 160 mg/24 hr).

Discussion: We identified a case that mimics apparent mineralocorticoid excess syndrome, where patients receiving Posaconazole behave as if they have increased serum aldosterone levels; however, when serum levels are measured, aldosterone levels are in fact low. Patients are unable to metabolize cortisol to cortisone due to a defect in 11β-hydroxysteroid dehydrogenase. This leads to an accumulation of cortisol, allowing it to bind to the aldosterone receptor and increase sodium entry intracellularly via the epithelial sodium channel (ENaC). Stimulation of the ENaC then leads to potassium secretion and subsequent hypokalemia. Common lab findings include: hypokalemia, low serum renin and aldosterone levels, and elevated urine cortisol/cortisone ratio. Similar presentations can be seen with licorice ingestion, hereditary AME, and carbenoxolone use. This case illustrates the unique presentation of Posaconazole-induced hypokalemia in an ESRD patient (a population that typically experiences hyperkalemia and poor clearance of potassium), who was dialyzed against a 4K bath but persistently remained hypokalemic.

PO1469

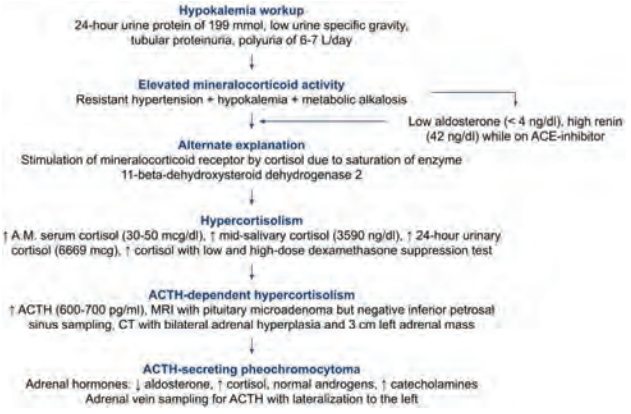
Hypokalemia from ACTH-Secreting Pheochromocytoma

Sana J. Shaikh,[1,2] Anitha Vijayan,[2] Anubha Mutneja.[2] *[1]Barnes-Jewish Hospital, Saint Louis, MO; [2]Washington University in Saint Louis, Saint Louis, MO.*

Introduction: The kidney is the critical effector organ in potassium homeostasis and mineralocorticoids (MC, usually aldosterone), distal sodium delivery and urine flow impact its response. Hypokalemia with HTN and metabolic alkalosis points to high MC activity. This can be classified as (a) ↑renin ↑aldosterone (b) ↑aldosterone despite ↓renin or (c) ↓renin ↓aldosterone. Here we describe an unusual case of hypokalemia due to ACTH-secreting pheochromocytoma.

Case Description: 62-year-old man with resistant HTN, DM, multiple sclerosis was admitted for persistent hypokalemia. Medications were KCL 360 mEq/day, amlodipine, carvedilol, doxazosin, hydralazine and lisinopril. Labs showed hypokalemia (2.4 mmol/L) and metabolic alkalosis (HCO_3 31 mmol/L). Urinary potassium losses were significant. After aldosterone level returned low, focus shifted towards hypercortisolism as a cause of MC activity. Studies confirmed raised cortisol and high ACTH. Pituitary gland workup was negative. Investigation for ectopic ACTH production revealed bilateral adrenal hyperplasia and discrete left adrenal mass. Adrenal hormone workup detected raised catecholamines. Adrenal vein sampling for ACTH showed laterization to the left. After alpha and beta-blockade, laparoscopic left adrenalectomy was done. Intraoperative biochemistry and pathology confirmed ACTH-secreting pheochromocytoma.

Discussion: In the distal nephron, cortisol is inactivated to cortisone by 11-beta-dehydroxysteroid dehydrogenase 2 (11βHSD2). Hypercortisolism causes relative deficiency of 11βHSD2 due to enzyme saturation. Cortisol then stimulates non-selective MC receptor. Systematic workup led to diagnosis of ACTH-secreting pheochromocytoma. After resection of ectopic ACTH source, patient became normokalemic and was discharged with steroid replacement.



Laparoscopic left adrenalectomy

	Left Adrenal	Right Adrenal	Peripheral Blood
Norepinephrine	297607	4423	2528
Epinephrine	160582	23397	1052
Dopamine	4632	150	50
ACTH	> 2000	489	725
Aldosterone	6.2	20	<4
Cortisol	288	800	47

Intraoperative chemistry as noted above.
Biopsy showing adrenal cortical hyperplasia, and a 4.3 centimeter pheochromocytoma confined to the gland and with uninvolved resection margins.

PO1470

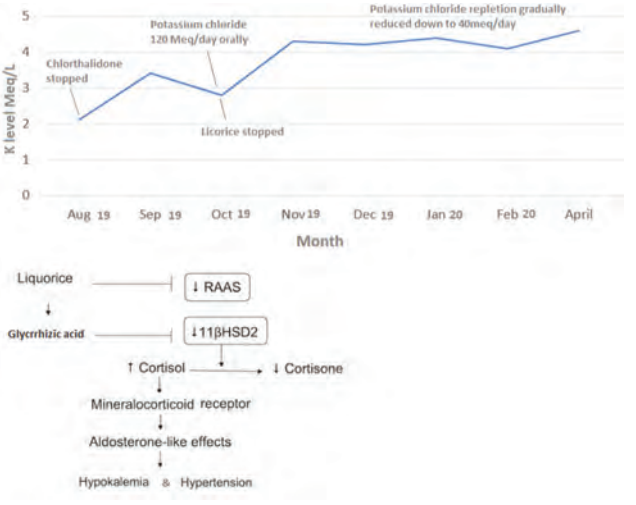
An Interesting Case of Hypokalemia

Adil Ghaffar, Tripti Singh. *University of Wisconsin System, Madison, WI.*

Introduction: Hypokalemia (serum potassium <3.5 meq/L) is one of the most common abnormalities encountered in nephrology practice. With careful history and laboratory investigations, the cause can usually be found.

Case Description: A 68-year-old caucasian male with Hypertension was referred for hypokalemia with level of 2.1 meq/L, serum bicarbonate was 27 meq/L and serum magnesium was 1.7meq/L. His antihypertensives were lisinopril 40mg and chlorthalidone 25mg daily. Despite discontinuation of chlorthalidone, he still required 120 meq of potassium chloride ER tablets daily with potassium levels at 2.8 to 3 meq/L. 24 hr urine potassium was 51 meq/L, denoting renal potassium wasting. Serum cortisol and ACTH levels were normal. Serum aldosterone level was <3 ng/dl and renin activity was 0.1 ng/ml/hr. Upon further exploration, he reported use of licorice for few months. He was advised to stop its use with subsequent improvement of potassium levels to above 4 meq/L and a reduction in potassium repletion.

Discussion: The causes for hypokalemia with hypertension and renal potassium wasting can be differentiated with serum aldosterone, renin activity and cortisol levels. In primary hyperaldosteronism, serum aldosterone is elevated and renin activity suppressed whereas in secondary form, both are elevated. When both are suppressed, it denotes either apparent mineralocorticoid excess, Liddle syndrome, cortisol excess or licorice use. Our patient had normal cortisol level, presented late in adulthood excluding Liddle syndrome and apparent mineralocorticoid excess, and making licorice as a likely cause. He had been chewing black licorice for its taste. Licorice was used in the past for gastric ulcers but it is rarely used nowadays. It inhibits the conversion of cortisol into inactive cortisone, allowing cortisol to act on the mineralocorticoid receptor. The use of licorice should be explored, whenever one encounters renal potassium wasting with suppressed renin and aldosterone.



PO1471

Thyrotoxic Periodic Paralysis: A Stunning Diagnosis

Piotr Starakiewicz, Syed A. Husain. *Columbia University Irving Medical Center, New York, NY.*

Introduction: Thyrotoxic periodic paralysis (TPP), acute hypokalemia and proximal muscle weakness in the setting of thyrotoxicosis, is primarily seen in Asian men with undiagnosed hyperthyroidism in the 2nd-4th decade, often with family history of paralysis and thyroid disease. We describe a case of a young male presenting with acute TPP.

Case Description: A 28year-old white male with no medical history presented with acute onset diffuse weakness with inability to get out of bed, preceded the night prior by leg stiffness. He exercised 2 days prior. He reported marijuana use and a balanced diet. He denied recent travel, medication or supplements. His father had Hashimoto's thyroiditis. Exam showed tachcyardia (106 bpm) and hypertension (132/74 mmHg), and EKG revealed sinus tachycardia with QTc 629. Labs showed: K+ 1.7 mEq/L, HCO3- 22 mmol/L, Cr 0.7 mg/dL, TSH <0.01, fT4 >6ng/dL, and T3 320ng/dL. Fractional excretion of K+ was 3.2%. He was treated with 120mEq KCl with repeat K+ 5.6 mEq/L in 4 hours and symptom resolution. Elevated TSH receptor, anti-thyroglobulin, and thyroid stimulating antibodies with a homogenous radioactive iodine uptake scan [Fig 1] confirmed Grave's disease. He was started on metoprolol and methimazole and discharged home without further episodes.

Discussion: TPP results from acute intracellular K+ shift due to Na/K-ATPase activation in myocytes from a hyperadrenergic state (increased number and sensitivity of β-receptors) and thyroid hormone stimulation. Muscle hyperpolarization and loss of excitability required for contraction results. Body K+ stores remain unchanged. Episodes are associated with high insulin or epinephrine states (eg. mornings, exercise, high-carbohydrate meal). Paralysis, lasting minutes to days, is ascending, symmetrical, and proximal, chiefly affecting legs (bulbar or respiratory involvement is rare). Usually painless, it can be preceded by muscle aches or cramps. Sinus tachycardia is common and life-threatening arrhythmias can occur. Labs demonstrate normal acid-base status and low urinary K. CPK can be elevated. Low TSH, elevated free T4 and T3 confirm the diagnosis. Treatment involves cautious K replacement (due to risk of rebound hyperkalemia), non-selective β-blockers, and therapy for hyperthyroid state

PO1472

CYP24A1-Hypercalcemia in Pregnancy

Sana J. Shaikh,[2,1] Anitha Vijayan.[1] *[1]Washington University in Saint Louis, Saint Louis, MO; [2]Barnes-Jewish Hospital, Saint Louis, MO.*

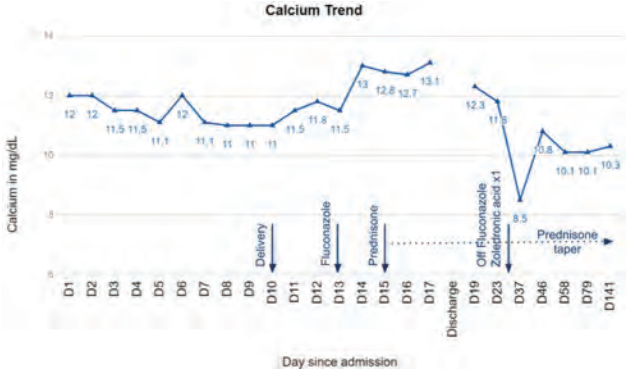
Introduction: Hypercalcemia due to primary hyperparathyroidism and malignancy is common. However, rare genetic mutations in VitD metabolism (CYP24A1 & SLC34A1) are often culprits.

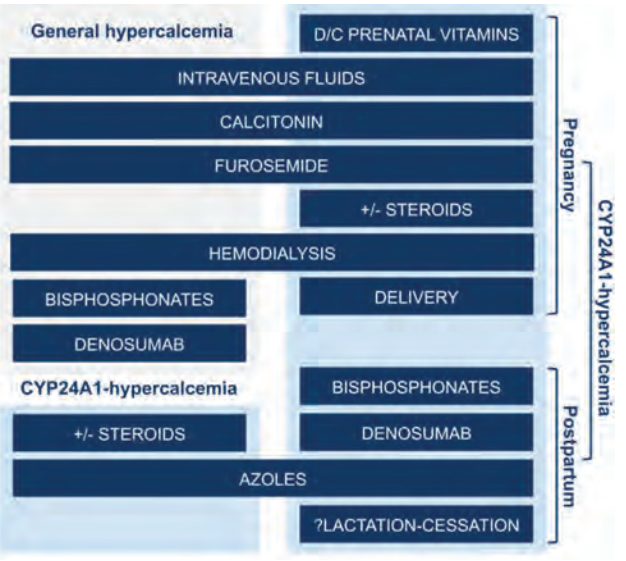
Case Description: 33-year-old woman with chronic hypercalcemia, nephrocalcinosis, CKD 3, HTN was admitted at 34-weeks of gestation for symptomatic hypercalcemia (13.2 mg/dL). Labs showed ↓PTH (9 pg/mL), ↓/↔25-VitD (35 ng/mL) & ↑/↔1,25-VitD (65 pg/mL). Defect in VitD pathway was suspected. 25-VitD:24,25-VitD ratio returned raised (178). Genetic testing confirmed compound heterozygous CYP24A1 mutation.

Discussion: CYP24A1 gene encodes 24-hydroxylase which inactivates 25-VitD and 1,25-VitD to 24,25-VitD and 1,24,25-Vit D. Biochemical profile includes ↑ serum & urinary calcium, ↓PTH, ↑25-VitD:24,25-VitD ratio +/- ↑ 1,25-VitD & 25-VitD. 25-VitD:24,25-VitD > 80 warrants genetic analysis. Azoles inhibit 1-hydroxylase and ↓1,25-VitD, and can be utilized. Steroids ↓1,25-VitD production by activated macrophages, inhibit intestinal calcium absorption and induce CYP24A1, but this cohort is often resistant. Pregnancy upregulates 1-hydroxylase, rendering patients with CYP24A1 mutations sensitive to hypercalcemia. Antepartum therapy options are limited. To limit adverse impact on maternal and fetal health, delivery may be required.

Maternal hypercalcemia with CYP24A1 mutations

Reference	CYP24A1 Mutation	Comments	Pharmacological Treatment
Shah AD et al	Compound heterozygous	Gestational hypercalcemia x4	-
Dinour D et al	Homozygous	Gestational hypercalcemia x3 c/b exogenous VitD + Ca during third pregnancy	D/c VitD + fluids, pamidronate, steroids
Kwong WT et al	Homozygous	Gestational hypercalcemia x2	Fluids, calcitonin
Woods GN et al	Homozygous	Gestational hypercalcemia x2 c/b exogenous VitD + Ca	D/c VitD + fluids, calcitonin
Hedberg F et al	Compound heterozygous	Sister I: gestational hypercalcemia x4 and postpartum hypercalcemia x1; sister II: gestational hypercalcemia x2	Sister I: fluids, furosemide, calcitonin, pamidronate; Sister II: fluids
McBride L et al	Homozygous	Gestational hypercalcemia x2	Fluids, calcitonin, steroids
Arnold N et al	Compound heterozygous	Gestational hypercalcemia c/b exogenous VitD	Fluids, furosemide, steroids during pregnancy + postpartum denosumab
Arnold N et al	Homozygous	Postpartum hypercalcemia in the third pregnancy c/b exogenous VitD + Ca	Fluids, steroids, pamidronate, zoledronic acid, denosumab
Macdonald C et al	Compound heterozygous	Gestational hypercalcemia in 1 of 2 pregnancies c/b exogenous VitD	D/c VitD + short trial of steroids without response





PO1473

A Case of Medication-Induced Hypercalcemia: But It Is Not What You Think

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Introduction: Hyperkalemia is a life-threatening complication of CKD. Patients with diabetes mellitus, congestive heart failure, and those receiving renin angiotensin aldosterone inhibitors are at particularly high risk of developing hyperkalemia. We present a case of hypercalcemia, possibly related to patiromer.

Case Description: A 71-year-old man with past medical history of hypertension, right nephrectomy for renal cell cancer and chronic kidney disease stage GIIIb-IV A3. Serum Cr levels range was 3.5-3.9 mg/dl. Patient was placed on losartan 100 mg to slow the progression of his CKD, and as a result he developed mild to moderate hyperkalemia (5-6.2 mEq/dl). His hyperkalemia persisted despite dietary modification. Patiromer was begun at a dose of 8.4 g/day. Dose was uptitrated to 25.2 g/day to maintain potassium levels < 5.5 mEq/dL. A few months later he developed mild hypercalcemia with serum calcium levels ranging between 10.4- 11.5 mg/dL. The patient was not receiving any oral calcium or vitamin D supplements. His work up included 25 hydroxy Vit D and 1-25 dihydroxy vitamin D levels which were normal at 28 ng/mL and 40 pg/mL respectively. Magnesium levels were normal 1.8-2.0 mg/dL. His PTH level was suppressed for his level of kidney function at 13pg/mL. TSH level was normal at 4 mIU/L. PTH-rp was 13 (normal: 14-27). Urine and serum protein electrophoresis did not reveal paraprotenemia. Given the absence of a clear explanation for his non-PTH mediated hypercalcemia, patiromer was considered as a possible cause. Patiromer was stopped and zirconium cyclosilicate was started. Serum Ca levels began to decline and returned to normal at 9.8 mg/dl two months after the discontinuation of patiromer.

Discussion: Patiromer is a cation exchange resin approved by the FDA in 2015 for the treatment of hyperkalemia. It binds to potassium in exchange for calcium predominantly in distal colon, facilitating increased fecal potassium excretion. Clinical trials that led to the approval of patiromer did not find any increase in serum calcium levels. However, hypomagnesemia was noted. This prompted the recommendation for the need to monitor magnesium levels while receiving the drug. There are only two other reports in the literature of hypercalcemia attributed to patiromer. Our findings call for further investigation and the need for monitoring serum calcium following the initiation of this treatment.

PO1474

An Unusual Source of Hypercalcemia

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Introduction: Hypercalcemia is a common electrolyte abnormality seen in daily practice. This case describes elevated serum calcium from a common cause, but an unexpected source.

Case Description: A 62-year-old female presented with complaints of fatigue, weight loss, and weakness. She was found to have a calcium level of 14mg/dL, acute kidney injury with a creatinine of 2.9 mg/dL from a baseline of 1.6mg/dL, and severe weight loss of 60lbs in the past 6 months. She had been evaluated for malignancy with no concerning findings. Initial workup included: parathyroid hormone (PTH) 8pg/mL, 25, vitamin D 22ng/mL, and creatinine phosphokinase 75u/L. There was concern for occult malignancy so further workup included a serum and urine protein electrophoresis that was negative, parathyroid hormone-related protein (PTHrp), 1,25 dihydroxy vitamin D, and Histoplasma antigen. She had a full-body computed tomography (CT) scan without contrast to look for occult malignancy which was negative for any granulomas, masses, adenopathy, or bony lesions. 1,25 vitamin D was elevated at 238 pg/mL. PTHrp was

elevated at 5.4 pmol/L. It was thought that Positron Emission Testing (PET) was needed and showed extensive skeletal muscle uptake that was nonspecific. With this result, she underwent a biopsy of the quadriceps muscle. She then had electromyography consistent with myositis with a nonspecific pattern. The muscle biopsy showed non-necrotizing intramuscular granulomas consistent with sarcoid-like myositis. She was started on prednisone 60mg daily. Within three days, her serum calcium had decreased to normal.

Discussion: Sarcoidosis is a multisystem disorder of unknown etiology, which is characterized by the accumulation of noncaseating granulomas in involved tissues. The pathogenesis is unclear, but the histopathologic findings of sarcoidosis in the muscles appear as granulomatous inflammation in muscle that leads to muscle fibrosis and tissue injury. The most common is a chronic myopathy with insidious onset of proximal muscle weakness. In our case, the elevated serum calcium and calcitriol guided the diagnosis. Hypercalcemia in granulomatous disease has been described to be secondary to high levels of calcitriol that increase intestinal reabsorption of calcium. Sarcoidosis, though a common entity, can declare itself through extrapulmonary sources and must remain in the differential for all hypercalcemia cases.

PO1475

Amiloride Effects on Urine Calcium in the Setting of Urolithiasis

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Background: Medical management of urolithiasis often targets the biochemical properties of urine to prevent further development of stone burden. Thiazide diuretics are commonly used for recurrent stone formation in patients with hypercalciuria. However, data related to the use of potassium-sparing diuretic amiloride is relatively scarce and the aim of this study is to investigate amiloride's effects on urinary calcium and other properties of urine in prevention of urolithiasis.

Methods: All nephrolithiasis patients who were prescribed amiloride for treatment of hypercalciuria between the years 2011 and 2019 at a single tertiary care center were retrospectively reviewed. Patients met criteria if they had a pre and post treatment 24 hour urine collections. Pre and post urinary calcium levels were compared. Other comparative measures include levels of other stone risk factors measured on urine collections, stone events on treatment and adverse reaction to medication.

Results: A total of 31 patients were started on amiloride. Of those, 15 patients tolerated the medication and completed follow-up urine testing. Amiloride was given due to intolerance of thiazide (11, 73%), persistent hypercalciuria on thiazide (3, 20%), or as combination with thiazide (1, 7%). Maximum treatment dose ranged from 2.5 mg daily to 5 mg BID. Mean duration on treatment was 57.2 months (SD 32.5;9-96). Three (20%) patients stopped due to delayed intolerance and 2 (13%) due to elevated urinary calcium. In the overall cohort, there was no significant difference in urine parameters (Table 1) including urinary calcium (286.3 mg/day pre vs 310.0 mg/day post, p=0.552). Three (20%) had a stone event at a mean of 23.3 months on treatment with 1 surgery, and 2 passage of stones. Six (40%) patients showed metabolic activity with new or growing stones.

Conclusions: In patients that have failed thiazides for treatment of hypercalciuria, switching to or adding amiloride did not result in lower urinary calcium levels.

24 Hour Urine Parameters before and after amiloride treatment

24 urine Parameter	Pre-amiloride (SD)	Post-amiloride (SD)	P-value
Volume (L)	2.37 (0.93)	2.69 (0.86)	0.316
SS Calcium Oxalate	7.15 (3.74)	6.22 (2.8)	0.078
Calcium mg/day	286.3 (103.8)	310.0 (175.6)	0.552
Oxalate (mg/d)	42.5 (16.6)	37.5 (7.94)	0.316
SS Calcium Phosphate	1.52 (1.16)	1.09 (0.80)	0.193
Na (mmol/d)	149.7 (60)	168.5 (89)	0.316

PO1476

Hospital-Acquired Phosphate Derangements and Associated In-Hospital Mortality

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Background: We aimed to report the incidence of hospital-acquired hypophosphatemia and hyperphosphatemia along with their associated in-hospital mortality.

Methods: We included 15,869 adult patients hospitalized at a tertiary medical referral center from January 2009 to December 2013 that had normal serum phosphate levels at admission and at least two serum phosphate measurements during their hospitalization. The normal range of serum phosphate was defined as 2.5-4.2 mg/dL. In-hospital serum phosphate levels were categorized based on the occurrence of hospital-acquired hypophosphatemia and hyperphosphatemia. We analyzed the association of hospital-acquired hypophosphatemia and hyperphosphatemia with in-hospital mortality using multivariable logistic regression.

Results: Fifty-four percent of patients developed new serum phosphate derangements during their hospitalization. The incidence of hospital-acquired hypophosphatemia and hyperphosphatemia was 35% and 27%, respectively. Hospital-acquired hypophosphatemia and hyperphosphatemia were associated with odds of 1.56 and 2.60 for in-hospital mortality, respectively (P-value<0.001 for both). Compared with patients with persistently normal in-hospital phosphate levels, patients with hospital-acquired hypophosphatemia only (OR 1.64), hospital-acquired hyperphosphatemia only (OR 2.74), and both hospital-acquired hypophosphatemia and hyperphosphatemia (i.e., phosphate fluctuations; OR 4.00) were significantly associated with increased in-hospital mortality (all p-value<0.001).

Conclusions: Hospital-acquired serum phosphate derangements affect approximately half of hospitalized patients and are associated with increased in-hospital mortality rate.

Table 2 Association between hospital-acquired serum phosphate derangements and in-hospital mortality

Serum phosphate during hospitalization	N (%)	In-hospital mortality (%)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	p	Adjusted OR (95 % CI)	P
Hospital-acquired hypophosphatemia						
No	10251 (65)	213 (2.1)	1 (ref)	-	1 (ref)	-
Yes	5618 (35)	239 (4.3)	2.09 (1.74-2.53)	<0.001	1.56 (1.25-1.93)	<0.001
Hospital-acquired hyperphosphatemia						
No	11610 (73)	201 (1.7)	1 (ref)	-	1 (ref)	-
Yes	4259 (27)	251 (5.9)	3.55 (2.94-4.29)	<0.001	2.60 (2.08-3.25)	<0.001
Hospital-acquired phosphate groups						
Normal	7405 (47)	97 (1.3)	1 (ref)	-	1 (ref)	-
Hypophosphatemia only	4205 (26)	104 (2.5)	1.91 (1.45-2.53)	<0.001	1.64 (1.23-2.20)	<0.001
Hyperphosphatemia only	2846 (18)	116 (4.1)	3.20 (2.44-4.21)	<0.001	2.74 (2.06-3.66)	<0.001
Both hypo- and hyperphosphatemia	1413 (9)	135 (9.6)	7.96 (6.09-10.40)	<0.001	4.00 (2.88-5.55)	<0.001

Adjusted for age, sex, race, principal diagnosis, Charlson comorbidity score, coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease, cirrhosis, end-stage renal disease, eGFR, acute kidney injury, number of serum phosphate measurements, length of hospital stay, and admission serum phosphate level.

Association between hospital-acquired serum phosphate derangements and in-hospital mortality

PO1477

Pseudohypophosphatemia Caused by Severe Leukocytosis in a Patient with Chronic Lymphocytic Leukemia (CLL) and Tumor Lysis Syndrome (TLS)

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Introduction: TLS is an oncologic emergency, which can cause life-threatening electrolyte derangements. Classic laboratory abnormalities in TLS include hyperphosphatemia, hyperkalemia, hypocalcemia, and hyperuricemia. In cases of severe hyperleukocytosis, false laboratory abnormalities can occur, and can lead to apply inaccurate, potentially harmful treatments.

Case Description: A 71-year-old man with a history of CLL was admitted for dyspnea and volume overload. He had recently started venetoclax one week prior to presentation. Labs revealed a WBC of 79,300/cm^2 (33% blasts), creatinine 1.49 mg/dL (baseline 0.80 mg/dL), serum potassium 7.2 mmol/L, CO_2 8 mmol/L, calcium <5.0 mg/dL, phosphorus 0.5 mg/dL, and uric acid 8.9 mg/dL. He was diagnosed with TLS and treated with rasburicase. Despite aggressive phosphorus repletion, the patient remained severely hypophosphatemic, though he was never symptomatic. Given the incongruence between lab values and clinical status, we suspected a lab error. We ordered STAT labs, sent on ice, which revealed normal serum phosphorus (4.5 mg/dL) on the same day that labs processed by standard protocol revealed a low level (0.9 mg/dL). Other discordant results noted were hyperkalemia (>9.5 mmol/L but 3.7 on a point-of-care arterial blood sample), hypoxemia (pO2 <48 mmHg on ABG but 98% on pulse oximetry room air), and hypoglycemia (serum blood glucose 9 mg/dL but 86 on point-of-care finger testing).

Discussion: This abstract reports the first case of reported pseudohypophosphatemia in a patient with CLL. The pathophysiology of pseudohypophosphatemia is thought to involve a sodium-phosphate co-transporter, though the exact underlying pathophysiology is unknown. Pseudohypoxemia and pseudohypoglycemia, also described in hematologic disorders, are thought to be due to increased metabolic demands by blasts, which decrease oxygen tension and glucose levels in vitro. Increased leukocyte fragility in CLL patients can lead to pseudohyperkalemia. In conclusion, it is crucial to verify lab abnormalities in patients with hyperleukocytosis with point-of-care or deliberate (i.e. arterial blood sample on ice or STAT) sample collection. Failure to recognize psuedohypophosphatemia may result in unnecessary phosphorus repletion, leading to potential harm for the patient.

PO1478

A Deadly Treatment for Opioid-Induced Constipation

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Introduction: Hypermagnesemia is a rare but serious complication of exogenous magnesium (Mg) administration that can occur when GFR is reduced. We describe a case of Mg citrate ingestion for opioid-induced constipation (OIC) and the deadly consequences.

Case Description: A 68-year-old female with history of lumbar spinal stenosis, chronic kidney disease stage IIIA, and hypertension was admitted to our ICU with distributive shock. Over the last month, she had seen physicians 7 times for severe low back pain and was prescribed high quantities of oxycodone and NSAID's. She developed constipation and her rheumatologist instructed she take a bottle of OTC Mg citrate. The next day, she presented to the ED for shortness of breath. Exam: BP 76/52, HR 118, Oxygen sat 86% on room air. She was ill appearing and tachypneic, with a firm/distended abdomen. CT abdomen/pelvis revealed a severe ileus. Labs: acute kidney injury (Creatinine 2 weeks prior 1.1, up to 3.3 mg/dL) and severe hypermagnesemia of 7.5 mg/dL. She was admitted to the ICU, started on pressor support and intubated. Twelve hours later, CVVHD was initiated for severe hypermagnesemia and oliguric AKI; however, her pressor requirements progressively increased until she was on 3 drugs. Eventually, her family decided to withdraw care.

Discussion: Hypermagnesemia is a rare event and occurs in the context of high dose Mg administration (ie. eclampsia treatment) or Mg ingestion in acute or chronic kidney disease. Mg acts as a calcium channel blocker, causing hypotension, bradycardia, muscle paralysis, somnolence, hypocalcemia, respiratory failure, and eventually cardiac arrest. The severity of manifestations is concentration dependent. Management includes IV fluids, loop diuretics, and IV calcium (if the patient is making urine). Hemodialysis is often required for those with severe AKI or ESRD. This case illustrates the challenges of care coordination and duplicate medication prescribing among multiple physicians/practices. OIC was preventable with a bowel regimen. She received 3 different NSAIDs which led to AKI on CKD IIIA. Magnesium citrate was rapidly absorbed systemically in the context of ileus and Mg toxicity developed in the setting of low GFR. Nephrology consultation was delayed, resulting in prolonged severe hypotension, late hemodialysis initiation and ultimately death. These complications were entirely avoidable with a more thoughtful approach to medication prescribing.

PO1479

Constipation to Neuromuscular Deficits: A Case of Hypermagnesemia

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Introduction: Magnesium is a relatively safe over-the-counter cathartic and antacid, but may have dangerous side effects. Hypermagnesemia can be precipitated by renal insufficiency, active gastrointestinal illness, or excessive intake of magnesium. Symptoms, which include neuromuscular and cardiovascular effects, can start when levels exceed 4.8mg/dL.

Case Description: A 60-year-old female with a medical history of bipolar affective disorder, seizures, migraines, type 2 diabetes, and past subarachnoid hemorrhage presented with slurred speech and weakness leading to a fall. She complained of chronic constipation and had taken an unknown amount of milk of magnesia with her docusate. Neurologic exam revealed slowed speech and symmetric muscle weakness. Labs revealed sodium 121mEq/L, creatinine 1.01(baseline 0.5) mg/dL, magnesium 10.0mg/dL, calcium 8.0mg/dL, and phosphate 6.5mg/dL. After imaging ruled out any intracranial pathology, the patient was diagnosed with hypermagnesemia, then started on IV fluids and loop diuretics. Her electrolytes and kidney function continued to correct with hydration, diuretic therapy, and stopping all magnesium-containing medications. It was discovered that she had ingested 52 grams of magnesium by drinking two 26oz bottles. Her weakness improved throughout the second day and returned to full muscle strength by the third. She was discharged with a magnesium level of 2.3mg/dL.

Discussion: This case demonstrates the importance of physician awareness regarding the effects of hypermagnesemia. Although hypermagnesemia is multiple symptoms, "few clinicians associate these symptoms with high levels of serum magnesium, due to an overall unfamiliarity with this condition." An article reported that more than 86% of patients with hypermagnesemia are clinically unrecognized, and in most hospitals, the measurement of magnesium is based on the physician's judgement. Treatment consists of magnesium removal (IV fluids, loop diuretics, or dialysis), stopping magnesium use, and gastrointestinal decontamination. Calcium can also be used as an antagonist by competitively inhibiting magnesium. Prompt recognition is necessary because when magnesium levels are greater than 7.2mg/dL, patients can develop hemodynamic changes (bradycardia, hypotension) and once levels exceed 12mg/dL, symptoms could become fatal (respiratory failure, heart block, cardiac arrest, and flaccid quadriplegia).

PO1480

Clinicopathological Characteristics and Long-Term Prognosis of Monoclonal Immunoglobulin Light Chain-Associated Fanconi Syndrome

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Background: Monoclonal immunoglobulin light chain associated Fanconi syndrome (LC-FS) is a rare disease which involved the proximal tubules. As most of the cases came from western countries, we aimed to analyze the clinicopathological characteristics of Asian LC-FS and its long-term prognosis.

Methods: From January 1998 to February 2019, 26 patients who were diagnosed with both FS and monoclonal gammopathy in Peking Union Medical College Hospital were enrolled. Their clinicopathological and follow-up records were retrospectively reviewed.

Results: At diagnosis, the mean age of the 26 Asian LC-FS patients was 54.7±14.7 years, with females accounting for 57.7 %. The underlying malignancies included monoclonal gammopathy of renal significance (MGRS, n=14, 53.8%), multiple myeloma (MM, n=10, 38.5%), Waldenstrom macroglobulinemia (WM, n=1) and primary plasma cell leukemia (PPCL, n=1). The most common symptoms were fatigue (95.7%), ostealgia (88.5%) and nocturia (61.1%). Their mean eGFR was (68.0 ± 26.4) ml/min/1.73m^2, with different degrees of proximal tubular dysfunctions, including normoglycemic glycosuria (88.0%), hyperphosphaturia (84.2%), aminoaciduria (84.0%), hypouricemia (80.8%), hypophosphatemia (80.8%), RTA (73.1%), and hypokalemia (42.3%). For kidney pathology, some specific features of LC-FS were observed in proximal tubular cells, including k deposition, intracellular crystalline formation and increased lysosomes. A total of 13 patients received chemotherapy, which mainly included bortezomib-based (n=6) and melphalan-based (n=2) regimens. Renal response was achieved in 58.3% cases which was accompanied by the hematological response, and tubular response was acquired in 66.7% cases. The k-LC FS patients presented with more common hypophosphatemia and hyperphosphaturia than the λ-LC group, and no differences were shown in treatment responses between these two groups. Compared to the primary Sjogren's syndrome associated FS patients with increased immunoglobulin G, LC-FS patients had more severe proteinuria, a higher prevalence of ostealgia, and less hypokalemia.

Conclusions: Asian LC-FS patients had mild renal function disorder, with more common hypophosphatemia and hyperphosphaturia in κ-LC patients than in λ-LC patients. The chemotherapy could improve renal function, which was related well to the hematological response.

Funding: Private Foundation Support

PO1481

Metabolic Acidosis in CKD: Time for a New Approach?

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Background: Metabolic acidosis in chronic kidney disease (CKD) is relatively common and increases as renal function declines. More recently, metabolic acidosis has been identified as a key risk factor for the progression of CKD in addition to being linked to increased risk of renal osteodystrophy and muscle wasting. Presently, there are no FDA indicated therapies for the treatment of chronic metabolic acidosis, though sodium bicarbonate is commonly used to try to maintain serum bicarbonate levels in the normal range (22 – 29mEq/L). We sought to understand how prevalent metabolic acidosis is in a real world setting.

Methods: Patient level data was collected online via a HIPAA-compliant form in November 2019 as part of an independent chart audit. A total of 1,008 patient records were submitted by 201 nephrologists. Records were selected based on the most recently seen non-dialysis patients in the outpatient setting with an eGFR<60ml/min/1.73m^2.

Results: At the time of first referral to a nephrologist, 92% of patients had a bicarbonate measure in the chart and 29% initially presented with a level <22mEq/L. At the most recent visit, 14% of the CKD Stage 3 patients, 37% of the CKD Stage 4 patients, and 57% of the CKD Stage 5 (non-dialysis) patients had low levels of serum bicarbonate. Among the patients being treated with sodium bicarbonate, 58% were below 22mEq/L, suggesting that treatment may not be entirely effective. The co-morbidity burden for CKD patients is extremely high. Many patients with serum bicarbonate levels below target have hypertension (80%, 28% classified as uncontrolled), diabetes (46%), heart failure (13%), and coronary artery disease (24%) – conditions that could be aggravated by sodium-containing medications. Furthermore, among those with low serum bicarbonate levels, 33% were notable for edema at the most recent visit. Indeed, overall the rate of edema across all stages of CKD was 22%, but this symptom was significantly higher among patients on sodium bicarbonate.

Conclusions: Metabolic acidosis is highly prevalent in CKD patients. Additionally, the vast majority of patients with metabolic acidosis have co-morbidities that make them not ideally suited for sodium-containing products. New agents that can address metabolic acidosis without a sodium load may provide a better options for these patients.

PO1482

Metformin-Associated Lactic Acidosis and Blindness

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Introduction: Metformin, a first line medication in the treatment of diabetes mellitus, can rarely cause lactic acidosis, usually in patients with acute or chronic kidney disease stage III onwards. We report a case of blindness associated with severe lactic acidosis in a patient with diabetes on metformin and show that the ophthalmologic symptoms may not be a direct result of the severe lactic acidemia alone.

Case Description: A 77 year old female with CKD stage III and type 2 diabetes on 1250 mg of metformin twice daily developed confusion, hypoglycemia and sudden visual loss. Over the prior 3 days, she had nausea, vomiting and diarrhea as well as a reduced urine output. On admission to the hospital, her vitals were stable. She had no other focal neurological deficits. Her creatinine was 4.4 mg/dL(with a baseline of 1.4), potassium 5.9 meq/L, bicarbonate 3 meq/L and blood lactate 23.8 mmol/L. Her arterial blood pH was 6.7. She underwent emergent hemodialysis and mid-way through her 4 hour session, she had complete resolution of her visual loss. By the end of her dialysis, her bicarbonate rose to 18. Ultimately, in a few months, she recovered her renal function back to a serum creatinine of 1.8-1.9, a little higher than her baseline.

Discussion: Some publications suggest vision loss (due to effect on retinal horizontal cell function) and optic nerve ischemia are associated with metformin induced lactic acidosis (MALA) at pH <7.09. It improves after correction of acidosis. But, in our case, the vision improved even before the acidemia corrected. We suggest that, since acute reversible blindness has been described with MALA, but not in patients with hypotension- or sepsis-induced lactic acidosis, this neurologic symptom may be a direct result of abnormal retinal horizontal cell function induced by metformin at a low pH, or the metabolic effects of metformin, rather than due to the acidemia alone. Hemodialysis helps correct electrolyte abnormalities and lactic acidosis. Also, metformin has a large volume of distribution. Its removal by dialysis is uncertain. But there are some case reports suggesting its clearance by HD. Further studies are thus warranted.

PO1483

Metabolic Acidosis Is a Predictive Factor for All-Cause Mortality in Patients with CKD

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Background: The consequences of metabolic acidosis are wide-ranging, consistent with the fact that many critical cell functions require physiologic pH (Salameh AI, *Am J Physiol Regul Integr Comp Physiol*. 2014). The extent to which metabolic acidosis contributes to mortality in patients with chronic kidney disease (CKD) is unknown.

Methods: Optum® de-identified Electronic Health Records dataset 2007 to 2017 was queried to identify patients with non-dialysis CKD Stages 3-5 with ≥2 consistent serum bicarbonate tests 28–365 days apart, ≥3 eGFR values <60 mL/min/1.73 m^2 and ≥2 years of post-index data or who died during that period. Cohorts with metabolic acidosis and normal serum bicarbonate were established based on the baseline serum bicarbonate (12 to < 22 mEq/L or 22 - 29 mEq/L). All-cause mortality was measured at 2 years in patients with metabolic acidosis vs. normal serum bicarbonate at baseline. The impact of baseline serum bicarbonate on 2-year mortality, adjusted for age, sex, race, diabetes, hypertension, heart failure, Charlson Comorbidity Score (index of comorbidity burden), and baseline eGFR and log albumin-to-creatinine ratio (ACR) was evaluated using logistic regression models.

Results: 51,558 patients qualified for analysis; 17,350 with metabolic acidosis, 34,208 with normal serum bicarbonate at baseline. Unadjusted rates of mortality within 2 years were higher among patients with metabolic acidosis vs. normal serum bicarbonate (30.9% vs. 10.2%, respectively, $P< 0.0001$) and within all CKD stages ($P< 0.001$). Each 1 mEq/L lower serum bicarbonate value was independently associated with a 15% higher risk of all-cause mortality, OR: 0.853, 95% CI: 0.846-0.861. These findings were consistent in subgroup and sensitivity analyses.

Conclusions: The presence of metabolic acidosis was associated with a high 2-year risk of all-cause death in patients with CKD. This finding was independent of age, sex, race, pre-existing comorbidities, and baseline eGFR and ACR.

Funding: Commercial Support - Tricida, Inc.

PO1484

SGLT2-Mediated Changes in Urinary Handling of Ketones in Type 1 Diabetes

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Background: Adjunctive therapy with sodium glucose co-transporter 2 (SGLT2) inhibitors have demonstrated clinically meaningful metabolic benefits in type 1 diabetes (T1D), but also represent a component cause of diabetic ketoacidosis. In this *post-hoc* analysis we examined SGLT2-mediated changes in ketone concentrations during clamped euglycemia and hyperglycemia in people with T1D.

Methods: T1D participants enrolled in the ATIRMA trial (NCT01392560) underwent measurement of plasma and urine beta-hydroxybutrate (BHB) and acetoacetate (AA) at baseline and after 8 weeks of empagliflozin 25 mg QD using a novel ZipChip Method developed at the CRPM, during both clamped euglycemia (4-6 mmol/L) and hyperglycemia (9-11 mmol/L).

Results: Forty participants (50% female), aged 24±5 years, HbA1c 8.0±0.9% with diabetes duration of 17.5±7 years, were enrolled. Median [IQR] plasma BHB at baseline was 0.05 [0.02-0.16] mmol/L during euglycemia and 0.06 [0.02-0.17] mmol/L during hyperglycemia. Plasma BHB significantly increased after treatment during both euglycemia (0.20 [0.09-0.40] mmol/L) and hyperglycemia (0.21[0.05-0.40] mmol/L), p<0.05 for both comparisons. Urine BHB at baseline was 1.9 [1.2-4.3] µmol/mmol creatinine during euglycemia and was 3.7 [1.7-10.0] µmol/mmol creatinine during hyperglycemia. Urine BHB significantly increased after treatment during euglycemia (4.1 [1.8-9.7] umol/mmol creatinine), p<0.01. Results were similar for AA.

Conclusions: In people with T1D, ketones were detectable in plasma and urine at baseline during clamped euglycemia and hyperglycemia and ketone concentrations significantly increased after 8 weeks of SGLT2 inhibition under the same study conditions. Further work is needed to establish factors associated with SGLT2-mediated changes in urinary handling of ketones and ketogenesis in people with T1D, which may assist in ketoacidosis prevention strategies.

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PO1485

Lactate Gap as Initial Indicator for Ethylene Glycol Toxicity

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Introduction: Ethylene glycol poisoning is a medical emergency which on initial presentation can be missed if the clinician does not have a high index of suspicion. Treatment of ethylene glycol toxicity is time dependent in preventing morbidity and mortality, thus early recognition and intervention is of critical value. In this case report we aim to focus on the lactate gap as the first indicator of ingestion.

Case Description: 50-year-old female was brought in by EMS after being found unresponsive and covered in vomitus. Vital signs were stable. The patient was thought to have had a seizure causing the lactic acidosis and was post ictal. Labs are shown below. Ethylene glycol toxicity was made the presumptive diagnosis. The patient was transferred to the medical ICU and given a loading dose of fomepizole while hemodialysis was being arranged. The patient then had one session of hemodialysis in the medical ICU and repeat blood gas is displayed below.

Discussion: The diagnosis of ethylene glycol poisoning remains challenging due to non-specific signs and symptoms on presentation. Presentation and lab values may differ depending on the time and amount since ingestion. Access to real-time ethylene glycol serum concentration is uncommon in many health facilities, so the diagnosis relies upon a high index of suspicion. Laboratory studies, specifically the "lactate gap", can be used in aiding the diagnosis. The "lactate gap" is a lab artefact due to a chemical cross reaction. Most POC whole blood analyzers use the enzyme lactate oxidase which cross reacts with the breakdown products of ethylene glycol, specifically glycolate. The lab instrument cannot differentiate between lactate and glycolate because of their structural similarity. Laboratory serum analyzers which are used for routine venous blood samples have less cross-reactivity and thus show a minimal elevation of lactate in comparison. In addition to securing the diagnosis, the lactate gap can be used to monitor clearance of the glycol metabolites.

Laboratory Values

Measurement	On arrival	2 hours later	Post Hemodialysis	Ref Values
pH	7.33	7.22	7.43	7.35-7.45
pCO2	25	40	40	35-45 mmHg
Bicarbonate	12	9	23	23-30 mEq/L
Lactate (POCT)	27	23	2.4	0.5-2.2 mmol/L
Lactate, blood	N/A	8.1	2.1	0.5-2 mmol/L
"Lactate gap"	N/A	14.9	0.3	
Osmolar gap	99	N/A	9	<10 mOsms

PO1486

Anion Gap (AG) and Negative Osmotic Gap (OG) due to Remdesivir's (R) Excipient

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Introduction: The FDA authorized R for COVID-19. Excess Na sulfobutylether (SBE) substituted β-cyclodextrin (CD) solubilizes R (PMID: 32376442). Minute accumulation of SBECD can cause an AG as *n*, its substitution in SBE is 6.5 (Captisol). The FDA advises against using R in adults with eGFR ≤30 mL/min *unless the potential benefit outweighs the potential risks* because SBECB accumulates. We report 2 cases of AG with the FDA protocol.

Case Description: Case A: 77 obese ♀ with bilateral AKA, and initial serum creatinine (Scr) of 1 mg/dL, currently decreasing (0.6 mg/dL). On day 5 R was initiated while a mild ketosis resolved (β OH-butyrate 0.6→0.3→0.1 mmol/L). An AG as high as 16 mmol/L (Alb ~2 g/dL) ensued, wherein the AG of the 1st blood sample after each R infusion correlated inversely with the time elapsed after the infusion. Like ketones, lactate was low throughout R therapy. By the time R started, Scr had risen and plateaued at 1.8 mg/dL and the AG mirrored the subsequent increase and decrease in Scr, and vanished by day 9, when her Scr was < 1.7, after peaking at 2.6 mg/dL, in spite of continuing R, consistent with SBECD cleared by GFR, like cr. Her initial *normal* Scr already meant AKI in this elderly sedentary, bilateral AKA patient. Her OG, only 7 on day 2 of R, further decreased by 11, to a negative OG of –4 mOsm/Kg H_2O the next day, suggesting polyanion accumulation. The calculated osmolarity of a Na_nSBECD solution is $((n + 1)/n)$*[Na] = 1.15*[Na], not 2*[Na] since $n \approx 6.5$, which explains the negative OG. **Case B:** 42 ♀, with morbid obesity and initial Scr of 1 mg/dL. R started on day 2, as Scr rose fast but her AG was 10 mmol/L. Again, the AG rapidly rose to 16 mmol/L (Alb. ~2.5 g/dL), and paralleled the rise and drop in Scr. CRRT was started when Scr was 6 mg/dL. Here again, prior to CRRT the AGs of the 1st samples following each R infusion were inversely related with the time from R infusion. While R was continued, CRRT caused parallel decreases in AG and Scr, since it clears cr and SBECD equally. The R loading dose contains 6 g and the 9 subsequent daily doses 3 g SBECD. Since the mass of $SBE_{6.5}CD$ is 2163.3 D, the initial anion load is ~18 mmol, followed by 9 daily loads of ~ 9-10 mmol.

Discussion: Depending on plasma volume, rate of escape from plasma, GFR, and timing after the infusion, SBECD can cause an AG, and negative OG, when the GFR is low.

PO1487

Anion Gap and Cardiovascular Mortality

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Background: Anion gap has been shown to be independently associated with hypertension, but the association of anion gap and cardiovascular mortality has been unexplored.

Methods: We conducted a prospective cohort study using the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey of the US non-institutionalized population. Anion gap (mEq/L) was calculated as serum sodium (mmol/L) – (serum chloride (mmol/L) + serum bicarbonate (mmol/L). We used weighted Cox proportional hazards models to assess the associations between anion gap with cardiovascular specific mortality, as recorded by the National Death Index. Multivariable models were adjusted for demographics data, BMI, smoking status, diabetes, systolic blood pressure, cardiovascular disease history, ACEi/ARB, diuretics, serum albumin, total cholesterol, total protein, total calorie intake, hemoglobin, cancer diagnosis, eGFR and urine albumin and creatinine ratio.

Results: This study was performed on 39,189 participants [mean (SD) age, 46.86 (19.25) years; 20,194 (51.5%) female. During 875 (4436210 weighted) person-years of follow-up, 936 participants (3169889 weighted participants) died of cardiovascular disease. A history of cardiovascular disease at the time of enrollment was reported in 3875 (9.8%). Figure 1 shows the associations between anion gap in tertiles with cardiovascular related mortality. In analyses restricted to those with a history of cardiovascular disease, results were 116% increased risk for cardiovascular mortality [HR 2.16;95% CI (1.37,3.4)].

Conclusions: Higher anion gap may be a risk factor for cardiovascular-related mortality in adults.

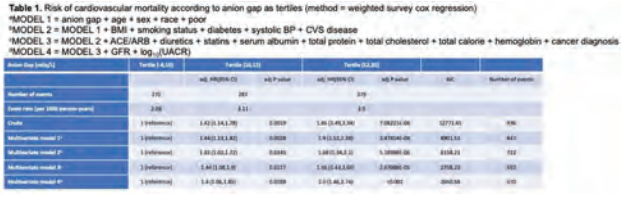

Figure 1. Risk of cardiovascular mortality according to anion gap as tertiles (method = weighted survey cox regression)

PO1488

Profound Lactic Acidosis due to Dextrose Infusion and the Role of Thiamine

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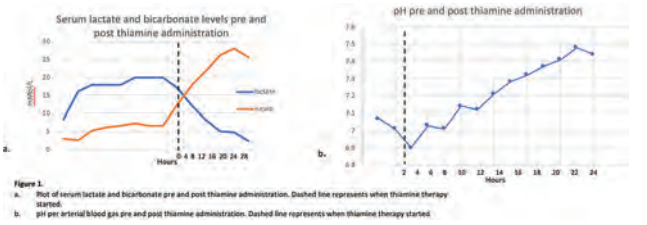
Introduction: Severe metabolic acidosis due to dextrose infusion is a rare but life-threatening complication for which treatment options are poorly described. Normally dextrose is metabolized to pyruvate during glycolysis. Pyruvate is converted to acetyl-CoA via pyruvate dehydrogenase (PDH); this requires abundant oxygen. Thiamine is an essential cofactor for PDH. During anerobic conditions, pyruvate is converted to lactate during a process known as anerobic glycolysis, producing a type A lactate. Pyruvate may also be converted to lactate when oxygen levels are normal via aerobic glycolysis. Aerobic glycolysis produces type B lactate and occurs due to a number of conditions, including thiamine deficiency.

Case Description: A 54-year-old woman with malignant insulinoma was admitted for severe hypoglycemia. The patient was given continuous 20% dextrose infusion; she developed severe lactic acidosis on day seven. Serum bicarbonate was undetectable on blood gas at the time of renal consult; serum lactate was >20. The patient decompensated due to the acidosis, became obtunded, was intubated, and was placed on continuous renal replacement therapy (CRRT). The acidosis failed to improve for 36 hours. Thiamine therapy was begun in an attempt to restore function of the PDH complex and restart the metabolism of pyruvate through the citric acid cycle, halting further type B lactate production. Within hours, lactate levels fell with parallel rise in serum pH. The patient was extubated, alert, and taken off CRRT within 24 hours of beginning thiamine therapy.

Discussion: This patient developed a profound metabolic acidosis secondary to type B lactic acidosis via accelerated glycolysis from dextrose infusion. This case highlights the intricate regulation of dextrose metabolism as well as thiamine as a vital therapy in type B lactic acidosis. Thiamine therapy was key, presumably reinstituting aerobic respiration through the PDH complex and ultimately leading to cessation of lactate production. Given the critical role of thiamine in this case, it is plausible that thiamine could be crucial for other cases of metabolic acidosis, particularly those secondary to type B lactic acidosis.



PO1489

Persistent Lactic Acidosis due to Thiamine Deficiency

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Introduction: Lactic acidosis is one of the most common causes of metabolic acidosis in hospitalized patients. Clinically it is usually associated with obviously impaired tissue oxygenation, but also occurs in situation where systemic impairment in oxygenation does not exist or is not readily apparent. Here we present a case of persistent lactic acidosis found to be due to thiamine deficiency and resolved rapidly after thiamine supplementation.

Case Description: A 38-year old woman presented with 4-day history of abdominal pain, vomiting, diarrhea, and not able to eat. She has a history of alcoholism in remission, vitamin B12 deficiency, PTSD and bipolar disorder. Her medications included cyanocobalamin, disulfiram, lithium, trazodone, and ziprasidone. Vital signs were normal except for mild sinus tachycardia, and the rest of her examination was unremarkable. Laboratory results indicated normal CBC, glucose, BUN, Cr, LFT, and urine analysis. Serum Na, K, Mg, Ca, and PO4 were all low. Serum ethanol and salicylate were not detected, and urine drug screen was negative. Serum HCO3 was low at 14 mmol/L with anion gap of 26. Serum ketone was negative, but serum lactic acid was severely elevated at 9 mmol/L. ABG was consistent with compensated metabolic acidosis. Cardiac echo and other imaging studies did not reveal significant abnormalities. The patient received intravenous fluid replacement and supplementation for various electrolyte abnormalities. While her symptoms of gastroenteritis had improved, the serum lactic acid continued to remain high (7-9s). Since most of the apparent causes of lactic acidosis were excluded in this patient, thiamine deficiency was suspected and thiamine level was confirmed to be low at 59 nmol/L (normal 78-185). Supplementation was initiated with rapid normalization of lactic acidosis.

Discussion: Thiamine is essential for normal aerobic metabolism, and its deficiency may lead to accumulation of pyruvate and conversion to lactic acid. Because thiamine is water soluble, its stores are limited. Thiamine deficiency can occur readily if intake is suboptimal in people who have risk factors, such as long-term heavy alcohol ingestion in this patient. **Teaching points** Thiamine deficiency is a potential cause of lactic acidosis that is reversible with supplementation. A high index of suspicion is necessary for diagnosis in patients with risk factors but no other apparent cause of lactic acidosis.

PO1490

Methanol Intoxication Secondary to Adulterated Cane Alcohol "El Chorrito"

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Introduction: Methanol intoxication is a rare and lethal form of poisoning that may cause severe anion gap and osmolar metabolic acidosis (MA), visual disturbances, neurological dysfunction and death. We present a group of seven unrelated cases with methanol intoxication from cities in southern Mexico of a total of 106 intoxicated patients and 43 deaths reported.

Case Description: Upon arrival to Hospital Civil of Guadalajara a group of seven patients presented with severe MA, high anion and osmolar gap, neurologic and visual deterioration, respiratory failure requiring mechanical ventilation and hemodynamically unstable requiring vasopressor. Intake of methanol was accidental, since a batch of adulterated alcoholic bottles was identified and distributed by "El Chorrito" store. Methanol concentrations is not available in our hospital. CT Scan revealed hemorrhage in basal ganglia and white matter involvement in all of them. Fomepizole is not available in Mexico so an ethanol infusion with vodka was started. All patients initiated hemodialysis (HD) as soon as possible and all underwent at least two sessions. Acid base balance was restored but five (71%) of the seven patients died. The remaining two patients persist in critical conditions requiring mechanical ventilation, no neurologic response and vasopressor dependent.

Discussion: This case series illustrates the poor clinical outcomes suffered by patients with methanol poisoning and the limitations of our public health system. Unfortunately the time lapse upon arrival was prolonged and organ damage irreversible leading to mortality in the majority of the cases.

Table 2.2

Individual values (First-Last)	pH	HCO3	Lactate	Anion Gap	Creatinine
#1	7.24 - 7.29	6.4 - 15.4	7.9 - 4.8	33.2 - 18.57	1.76-1.16
#2	6.8 - 7.47	6.2 - 21.2	10 - 1.2	38.8 - 17.45	1.22-0.83
#3	7.12 - 7.5	7.2 - 24.8	12.7 - 3.1	34.5 - 18.8	1.59-0.56
#4	6.8 - 7.33	6.2 - 23.4	10.2 - 4.4	40.9 - 16.7	2.12-1.3
#5	7.18 - 6.8	10.8 - 16.4	10.5 - 14.4	34.3 - 16.2	1.42-0.73
#6	6.8 - 7.47	6.2 - 30.6	11.8 - 3.2	31.9 - 6.8	1.92-0.64
#7	6.99 - 7.44	6.33 - 26.5	4.4 - 1.1	33.8 - 9.35	0.94-0.51

Baseline characteristics	N=7
Male (%)	6 (85.71)
Female (%)	1 (14.29)
Age (IQR)	49.29 (47-53)
DM (%)	0 (0)
Hypertension (%)	0 (0)
CKD (%)	0 (0)
Invasive ventilation (%)	7 (100)
MAP (IQR)	81.09 (74-88)
Vasopressor drugs (%)	7 (100)
Admission sCr (IQR)	1.67 (1.32-1.84)
AKI KDIGO 3 (%)	7 (100)
Hematuria (%)	0 (0)
Proteinuria (%)	3 (42.86)

PO1491

Starvation Ketoacidosis in a Patient with Muscular Dystrophy

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Introduction: Patients with muscular dystrophy have low muscle mass; thus, they have lower glycogen stores and are more prone to develop ketoacidosis with minimal stress or decreased oral intake. Here we present a rare presentation of ketoacidosis in a patient with muscular dystrophy with concurrent ketoacidosis and hyperchloremic metabolic acidosis who was treated successfully with lactated Ringer's (LR) and dextrose (D5W).

Case Description: A 48 year old woman with a history of muscular dystrophy and chronic, ventilator dependent respiratory failure was referred to our hospital for evaluation of granulation tissue in her trachea. Body mass index was 18 kg/m 2. Laboratory data on admission were significant for sodium of 132 meq /L, potassium of 4.5 meq /L chloride 114 mEq/L, bicarbonate 12 mEq/L, creatinine < 0.1 mg/d, and pH 7.23 (venous blood gas) consistent with non anion gap metabolic acidosis. The following day, laboratory data showed sodium 137 mEq/L, chloride 113 mEq/L, bicarbonate 8 mEq/L, and pH 7.29. The calculated anion gap was 16 mEq/L with albumin 4.2 g/ dL. The urine anion gap was 30 mmol/L. Serum β hydroxybutyrate (BHB) was elevated at 6.6 mmol/L. Because of muscular dystrophy with decreased oral intake, the patient's anion gap metabolic acidosis was attributed to starvation ketoacidosis. The non anion gap metabolic acidosis was attributed to renal tubular acidosis. LR and D5W solutions were administered to treat non anion gap and anion gap metabolic acidosis (starvation ketoacidosis), respectively. After 1-2 days, BHB decreased and electrolytes normalized.

Discussion: Few cases have been reported regarding ketoacidosis in patients with muscular dystrophy, and all of these were treated with dextrose and 0.9% saline. In our case, we used LR and D5W due to concurrent non anion gap and anion gap metabolic acidosis, as 0.9% saline administration was projected to worsen the hyperchloremic acidosis. Anion gap metabolic acidosis in patients with muscular dystrophy and without diabetes should raise suspicion for starvation ketoacidosis requiring D5W. LR should be substituted for 0.9% saline in patients with concurrent hyperchloremic acidosis.

PO1492

Metabolic Acidosis Associated with Linezolid Toxicity

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Introduction: Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis. It can impair mitochondrial ribosomal function leading to severe lactic acidosis, liver toxicity and myelosuppression.

Case Description: A 65-year-old Caucasian woman with PMH of compensated NASH cirrhosis, osteomyelitis diagnosed 4 weeks prior to presentation and now on linezolid, was admitted with abdominal pain. Her vital signs and cardiopulmonary exam were unremarkable. Her abdomen was distended with mild epigastric tenderness. Figure 1 outlines the initial laboratories. Urinalysis was benign and blood cultures were negative. CT abdomen revealed moderate ascites. The anion gap metabolic acidosis (AGMA) were likely explained by Linezolid toxicity. The respiratory alkalosis is related to liver cirrhosis which is associated with increased level of progesterone leading to hyperventilation. Linezolid was stopped and repeat laboratories at 72 hours demonstrated normalization of bicarbonate and lactate values.

Discussion: Our patient has a primary AGMA (Corrected AG = 31) with mild respiratory alkalosis (calculated PaCO2 by Winter's formula = 23). She had an osmolar gap of 5 (The calculated osmolality = 282 mOsm/kg). The AGMA is likely secondary to lactic acidosis (figure 2). The patient does not have signs of hypovolemia. Ethylene glycol (EG) can lead to a false elevation in L-lactate. However, the normal OG makes EG and methanol toxicity less likely. Normal beta hydroxybutyrate level excludes ketoacidosis. Major risk factors for linezolid toxicity include prolonged exposure, administration of relatively higher doses, and baseline chronic liver or kidney disease. Lactic acidosis often resolves rapidly following discontinuation of Linezolid.

Tests	Results	Normal range
Hemoglobin	6.9 g/dL	12-16 g/dL
White Blood cell count	2.5 k/uL	3.70 - 11.00 k/uL
Platelet count	24 k/uL	150-400 k/uL
Sodium	131 mmol/L	132-148 mmol/L
Potassium	5.5 mmol/L	3.5-5 mmol/L
Chloride	94 mmol/L	98-111 mmol/L
Bicarbonate	10 mmol/L	23-32 mmol/L
Blood Urea Nitrogen	29 mg/dL	10-25 mg/dL
Creatinine	0.69 mg/dL	0.7-1.4 mg/dL
Calcium	7.9 mg/dL	8.4-10.5 mg/dL
Albumin	2.3 g/dL	3.5-5.0 g/dL
Glucose	170 mg/dL	65-100 mg/dL
Alanine aminotransferase	7 U/L	0-45 U/L
Aspartate aminotransferase	16 U/L	7-40 U/L
Alkaline phosphatase	256 U/L	40-150 U/L
Bilirubin, total	0.3 mg/dL	0-1.5 mg/dL
PTT	50 seconds	22-32 seconds
INR	1.2	
LDH	125 U/L	0-249 U/L
Lactate	11.5 mmol/L	0.4-1.9 mmol/L
Beta-hydroxybutyrate	0.3 mg/dL	0 – 3 mg/dL
Serum osmolality	287 mOsm/K	275-295 mOsm/K
Serum acetaminophen	< 5.0 mcg/mL	
Serum salicylate	< 0.3 mg/dL	< 20 mg/dL
Serum Ethanol	2 mg/dL	Non-detected
Arterial Blood Gas		
pH	7.34	7.35-7.45
PCO2	19 mm Hg	35-45 mm Hg
PO2	116 mm Hg	75-100 mm Hg
HCO3	10 mmol/L	18-23 mmol/L

Tissue hypoperfusion (Type A)
- Hypovolemia
- Septic shock
- Cardiogenic shock

Decrease Utilization (Type B)- Usually toxin-induced impairment of cellular metabolism
- Diabetic ketoacidosis
- Metformin
- Alcoholism
- Mitochondrial dysfunction (nucleoside reverse transcriptase inhibitors, propofol, linezolid)
- Malignancy
- HIV infection
- Beta-adrenergic agonists (IV epinephrine)

D-Lactate acidosis
- short bowel syndrome
- Propylene glycol

PO1493

The Real Life of Oral Alkalinization by Urologists and Nephrologists on Extracellular Volume: The AlcalUN Study

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Background: Oral alkalinization with sodium bicarbonate ($NaHCO_3$) or citrate is prescribed to treat conditions ranging from metabolic acidosis to nephrolithiasis. While most nephrologists/urologists use these treatments regularly, extracellular volume (ECV) increase is a main feared adverse event for $NaHCO_3$ use. To date, no clinical trial has specifically addressed this aspect in clinical routine.

Methods: AlcalUN (NCT03035812) is a multi-center, prospective, open-label study aiming to assess the impact of a chronic oral alkalinization on ECV. Patients receiving oral alkalinization without $NaHCO_3$ (citrate) comprised the control group. Increased ECV (primary outcome) was assessed based on body weight (BW), blood pressure (BP), and edema at first follow-up visit.

Results: From 02/2017 to 02/2020, 156 patients were enrolled (129 received $NaHCO_3$, 27 citrate). Out of them, 127 (80%) participants had at least one follow-up visit. Normalizing for demographics, patients in the $NaHCO_3$ group had higher incidence of chronic kidney disease (68 *vs.* 30%, p=0.002) and hypertension (75 *vs.* 35%, p=0.001), while patients in the No-$NaHCO_3$ group (citrate) had more nephrolithiasis (95 *vs.* 28%, p<0.001). At baseline, BW, BP, and presence of edema were similar in both groups. After a median of 90 days of treatment, 91 (72%) patients reached the primary outcome, with similar distribution in both groups (71 *vs.* 75%, p=0.79). We found similar results after after propensity score matching.

Conclusions: Chronic oral alkalinization with $NaHCO_3$ does not increase ECV more than citrate, even though it is used in a higher-risk population. These results confirm secondary outcomes from other trials, potentially highlighting the role of chloride load instead of sodium load.

PO1494

Effect of Sodium Bicarbonate on Kidney Injury: A Secondary Analysis of the BASE Pilot Trial

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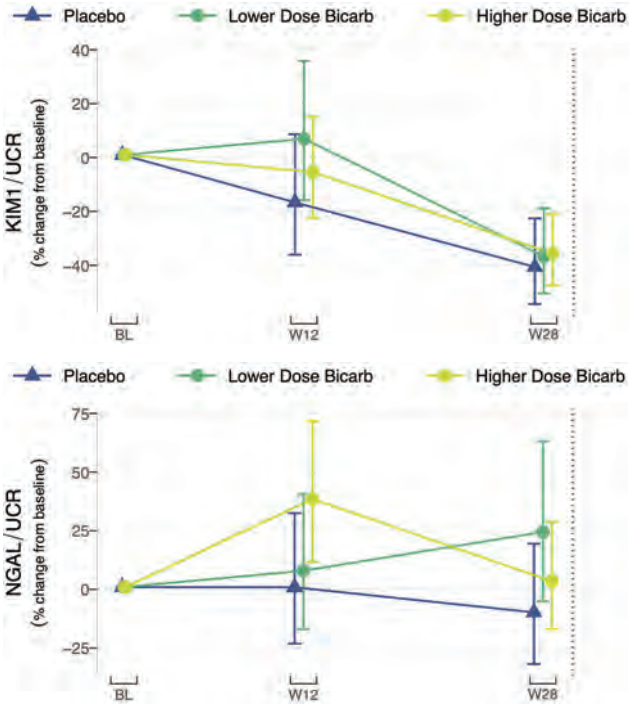
Background: $NaHCO_3$ is used to treat metabolic acidosis in CKD. In the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial, a dose-dependent increase in albuminuria was observed with $NaHCO_3$ over 28 weeks, suggesting that $NaHCO_3$ may promote kidney injury. We investigated the effect of $NaHCO_3$ on kidney tubule injury markers (KIM-1 and NGAL) in BASE participants.

Methods: Urinary KIM-1 and NGAL were measured in 176 BASE participants at baseline, week 12, and week 28. Change in urinary KIM-1/Cr and NGAL/Cr was compared within and between the three treatment groups (Placebo, n=49; Lower-Dose [0.5 meq/kg/d] $NaHCO_3$, n=48; and Higher-Dose [0.8 meq/kg/d] $NaHCO_3$, n=79) using linear mixed models.

Results: Mean±SD baseline values were: age 67±12 years, systolic BP 126±13 mm Hg, eGFR 36±9 ml/min/1.73m^2, serum tCO_2 24±2 meq/L. Median (IQR) urinary values at baseline were: ACR 185 (24, 767) mg/g, KIM-1/Cr 0.88 (0.43, 1.36) ng/mg, and NGAL/Cr 14.3 (6.44, 34.0) ng/mg. At week 12, urinary KIM-1/Cr levels were not different from baseline in any group. However, at week 28, KIM-1/Cr levels were significantly lower in all three groups. NGAL/Cr was significantly higher in the Higher-Dose $NaHCO_3$ group at week 12; however, there were no other significant within group differences at week 12 or 28. In the between group comparisons, there were no significant differences in KIM-1/Cr ($p\geq0.16$) or NGAL/Cr ($p\geq0.07$) at either week 12 or 28.

Conclusions: Among BASE Pilot Trial participants, $NaHCO_3$ had no significant effect on urinary KIM-1/Cr or NGAL/Cr levels over 28 weeks.

Funding: NIDDK Support



PO1495

Re-Evaluation of Renal Bicarbonate Compensation in the Setting of Extreme Chronic Respiratory Acidosis

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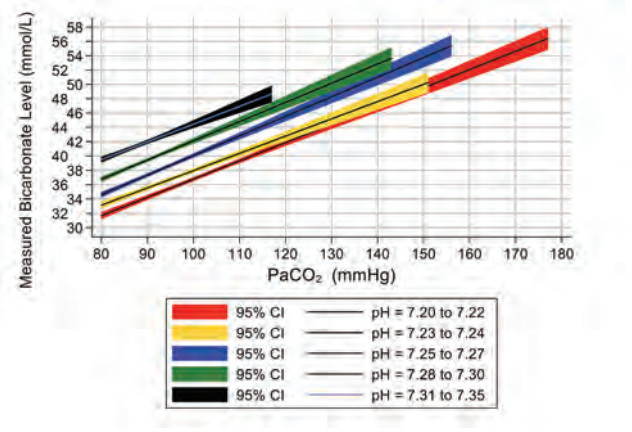
Background: In chronic respiratory acidosis (CRA), the expected renal compensatory increase in serum bicarbonate (HCO3) is 0.35-0.4 mEq/L for every 1 mmHg PaCO2 over 40 mmHg. However, at extreme hypercarbia, at PaCO2 >80 mmHg, limited research dating from the 1960s suggests the HCO3/PaCO2 relationship flattens at a PaCO2 >70 mmHg.

Methods: We analyzed 2840 arterial blood gas (ABG) observations from 761 patients with extreme chronic hypercarbia with PaCO2 > 80 mmHg from 7/2015-7/2017 from a single, US teaching hospital. We included all patients with a pH ranging from 7.20 to 7.35 who had serum bicarbonate levels measured by the main lab autoanalyzer, within 12 hours of the ABG. To reduce the bias of acute respiratory acidosis (RA), we performed a sensitivity analysis on 101 patients who had 603 ABGs 4-10 days apart to assure chronicity of RA. Generalized linear regression models were developed to predict HCO3.

Results: For the 2840 ABGs, the mean (SD) was: pH: 7.27 (0.05), PaCO2: 92.51 (10.95) mmHg (range 80-177), and HCO3 : 37.9 (4.5) mEq/L. In Figure 1. the increase in serum HCO3 was 0.26; 95% CI (0.25, 0.28) for each value of PaCO2 above 80 mmHg after adjusting for pH. The regression equation yielded: HCO3= 88.64*pH +0.34 *PaCO2 - 637.2. The sensitivity analysis produced very similar findings.

Conclusions: At extreme hypercarbia, defined as PaCO2 >80 mmHg, the kidneys have limited ability to retain bicarbonate compared to established formulae for lesser increases in PaCO2. Our new equation predicts this response is a 0.26 mEq/L increase in HCO3 for each 1 mmHg of PaCO2 increase over 80 mmHg.



Measured bicarbonate (Y axis) plotted against measured PaCO2 (X axis) showing an increase of 0.26 mmol/L of bicarbonate for each value of PaCO2 above 80 mmHg, with adjustments for different values of pH (colored lines).

PO1496

It's Not a Bad Trip with This Acid: Sodium Thiosulfate Use in Refractory Metabolic Alkalosis

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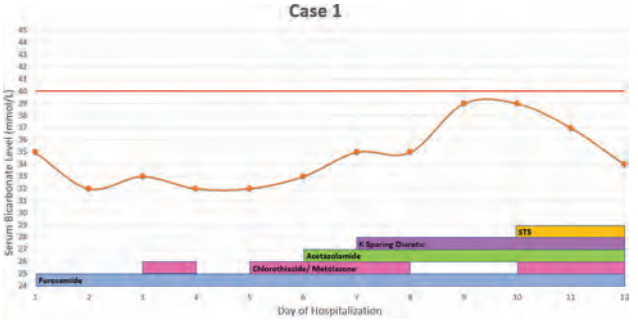
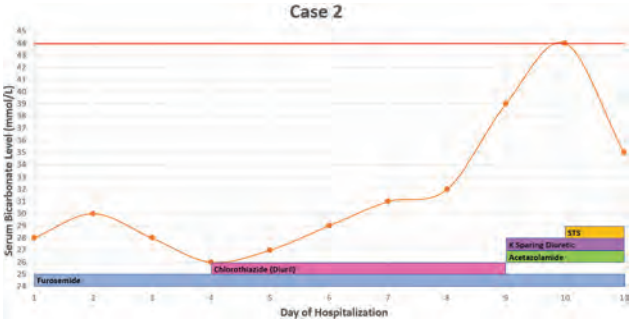
Introduction: Metabolic alkalosis is often a complication of loop diuretic use. It may at times become rate limiting. Serum bicarbonate (HCO3) levels upwards of 30 mmol/L can make even the most eager clinician stop dead in their tracks in the quest for optimal volume control.

Case Description: Here we highlight two patients, a 63 year old female and an 81 year old gentleman, who while on diuretic therapy developed severe metabolic alkalosis, with peak serum bicarbonate levels of 39 and 44 mmol/L respectively. Several strategies were attempted to mitigate the alkalosis. Potassium was aggressively repleted to maintain a normal serum level of 4.5 and 3.6 mmol/L respectively, however, this was unsuccessful. Acetazolamide was employed but ineffective due to its limited efficacy in the setting of low effective circulating volume and renal insufficiency. Advanced measures such as hydrochloric acid and ammonium chloride were not readily available nor feasible to administer. Ultimately, given the known side effect of sodium thiosulfate (STS) to cause metabolic acidosis, STS was administered, resulting in a decrease in the serum HCO3 level and an ability to resume diuresis.

Discussion: When continued diuresis is necessary and correction of metabolic alkalosis cannot be facilitated by potassium repletion or carbonic anhydrase inhibitors, a novel option is to utilize STS and its known ability to generate an acid load to treat the alkalosis. While the mechanism is unclear, a metabolite of STS, hydrogen sulfide, is proposed to be the source of acid. This strategy for correcting metabolic alkalosis has never been reported in the literature before.





PO1497

A Case of Extreme Alkalosis: A Perfect Combination of Perpetuators

Patrícia Valerio,[1] Hugo Ferreira,[2] Teresa Chuva,[2] Ana M. Paiva,[2] Inês Neves,[2] Filomena Faria,[2] José M. Costa.[2] *[1]Centro Hospitalar de Setubal EPE, Setubal, Portugal; [2]Instituto Portugues de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal.*

Introduction: Metabolic alkalosis results from retention of alkali excess. Normally, a physiological response leads to hypoventilation with a secondary increase of $PaCO_2$. The most common cause is H^+ loss, through kidney or gastrointestinal tract, usually with concurrent loss of Cl^- and K^+.

Case Description: 70 y/o caucasian man was admitted for a scheduled surgery due to a stage II urothelial carcinoma. The immediate postoperative period occurred without complications. The patient presented with abdominal distention and gastric stasis. He remained fasting, with gastric tube draining freely. Surgical team performed an exploratory laparotomy with correction of a small bowl internal hernia. In the postoperative period Nephrology collaboration was requested due to acute kidney injury (AKI), with a creatinine (Cr) of 3,39 mg/dL (baseline 1,5 mg/dL) and urea 89,5 mg/dL. On examination the patient was prostrate, severely dehydrated and bradypneic, with oxygen supply FiO_2 28%. He maintained gastric passive drainage for 3 days, around 3 to 3,5 L/day. Blood work showed Cr 4,15 mg/dL, urea 103,9 mg/dL, hypernatremia 147 mEq/L, hypochloremia 78 mEq/L, hypokalemia 3,2 mEq/L, uric acid 16,8 mg/dL, albumin 3,2 g/dL and a total corrected calcium 9,5 mg/dL. Urinalysis revealed a pH of 9,0 and arterial blood gas analysis presented severe metabolic alkalosis (pH 7,63, PaO_2 90 mm Hg, $PaCO_2$ 99 mm Hg, bicarbonate 104,1 mmol/L), low ionized calcium 0,86 mmol/L and lactate 1,9 mg/dL. The patient was immediately admitted in ICU, starting aggressive IV hydration with NaCl 0,9%, IV potassium supplementation and parenteral nutrition.

Discussion: This is an extreme case of metabolic alkalosis where a myriad of contributors gathered in a perfect storm to achieve a bicarbonate concentration above 100 mmol/L, thought to be incompatible with life and, to our knowledge, never reported in the literature. However, the pH value was maintained in life-compatible values by an extreme respiratory compensation which may have saved the patient before treatment initiation. An approach correcting the cause and, at the same time, the perpetuators are the key factors to successfully treat a metabolic alkalosis. Due to severe AKI and alkalosis, dialysis with low bicarbonate dialysate may be indicated.

PO1498

A New Insight into Hyperchloremic Metabolic Acidosis in Kidney Transplant Recipients: Increased Postglomerular Blood Flow Is a Key Condition for Calcineurin Inhibitor-Induced Renal Tubular Acidosis

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Background: Hyperchloremic metabolic acidosis (HCMA) due to renal tubular acidosis(RTA) is a common in kidney transplant recipients(KTR). Calcineurin inhibitor (CNI) have been identified as a cause but have not been fully proven, and whether HCMA is a determinant of poor graft prognosis is controversial.

Methods: HCMA was defined as having a Na-CL (simple strong ion difference) value of 34 or less. All the cases of having diarrhea were excluded. The study group consisted of 26 KTRs who received the renal hemodynamic studies based on urinary clearance of inulin and para-aminohippuric acid 1year post-KT. And glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction(FF) (GFR/RPF) and pre-/post-glomerular vascular resistance (pre-/postVR) were calculated.

Results: The incidence of HCMA was 31%(8/26). The univariate analysis of HCMA compared with non-HCMA significantly showed an increase in RPF(P=0.016), a decrease in post-VR(P=0.003), and a decrease in FF(P=0.0001), suggesting an increase in post-glomerular peritubular blood flow. In addition, the aah lesion score, an indicator of CNI vasculopathy, was significantly higher in the HCMA(P=0.015). All cases with HCMA were classified into low post-VR (Fig.1). Furthermore, in low post-VR alone, the tacrolimus trough level was significantly higher in the HCMA(P=0.002) (Fig.2).

Conclusions: In KTRs, increased postglomerular peritubular blood flow is a key condition for CNI-induced RTA. The presence of HCMA is probably not a serious condition, but rather a desirable hemodynamic state, however, more attention should be paid not to elevate CNI concentration levels in such condition.

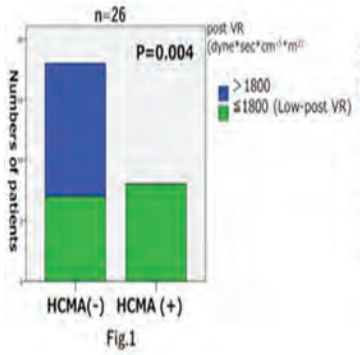


Fig.1

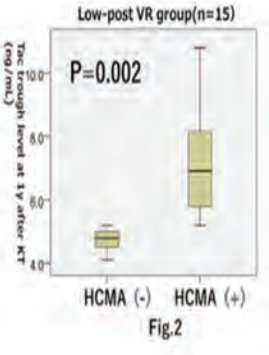


Fig.2

PO1499

Renal Negative Pressure Treatment as a Novel Therapy for Cardiorenal Syndrome

Jennifer L. Asher, Christopher D. Maulion, Olyvia Gleason, Grace Meegan, Juan B. Ivey-Miranda, James H. Fleming, Veena Rao, Jeffrey M. Testani. *Yale University School of Medicine, New Haven, CT.*

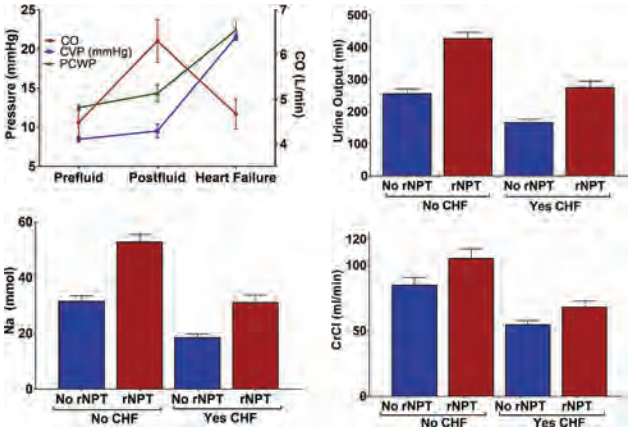
Background: Decongestion is the primary therapeutic objective in acute decompensated heart failure (ADHF). However, congestion itself can worsen renal function and limit diuresis. Renal pelvis negative pressure treatment (rNPT) should reduce tubular pressure, allowing improved kidney function and diuresis. We hypothesized that rNPT would improve diuresis, natriuresis & renal function in a congestion predominate heart failure (HF) model.

Methods: Ten ~80 kg pigs underwent thoracotomy with implantation of a pericardial, Swan Ganz, & bilateral ureteral JuxtaFlow® catheters. High dose furosemide (400mg bolus, then 80mg/hr) was administered since HF clinical use of rNPT will be in conjunction with loop diuretics. Each animal served as its own control with randomization of L vs. R kidney to -30 mmHg rNPT or no rNPT. HF was induced via cardiac tamponade (~200 ml of pericardial 6% hydroxyethyl starch) and IV normal saline. Pericardial pressure was maintained at 20-22.5 mmHg.

Results: Prior to HF induction, rNPT increased urine output (UOP) & creatinine clearance (CrCl) compared to the control kidney during furosemide diuresis ($p<0.001$ for all, Figure). HF induction achieved the target hemodynamic profile with stable cardiac output & elevated filling pressures (Figure). UOP, sodium excretion, & CrCl decreased during HF ($p<0.001$ for all, Figure), but were higher consistently in rNPT kidney vs. control ($p<0.05$ for all, Figure). UOP ($p=0.38$) was the same in rNPT during HF as control prior to HF (Figure).

Conclusions: rNPT increased UO and CrCl, with & without HF. Notably, rNPT rescued the congested cardio-renal phenotype with equivalent diuresis & natriuresis during HF with rNPT compared to the non-HF period without rNPT.

Funding: Commercial Support - 3ive Labs



PO1500

Accurate Estimation of Individual Sodium Intake with Repeated Spot Urine Sampling

Bigina N. Ginos,[1] Liffert Vogt,[1] Petra Frings-Meuthen,[3] Martina D. Heer,[2] Rik H. Olde Engberink.[1] *[1]Amsterdam University Medical Centres, location Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands; [2]Institute of Nutritional and Food Sciences, University of Bonn, Bonn, Germany; [3]German Aerospace Center (DLR), Institute of Aerospace Medicine, Cologne, Germany.*

Background: In clinical practice, individual sodium (Na^+) intake is estimated by measuring Na^+ excretion in one 24-h urine collection (UC), whereas long-term Na^+ balance studies indicate that 7 consecutive 24-h UCs may be needed. To reduce the burden of 24-h UC, single spot urine based alternatives have been suggested, but this approach has been shown to be very inaccurate. Whether the use of repeated spot UCs is an appropriate alternative for (multiple) 24-h UCs to estimate Na^+ intake is unknown.

Methods: We performed a post-hoc analysis of a metabolic ward study in 8 healthy male adults who consumed a 7-d diet with a fixed amount of 200 mmol/d Na^+. Urine was collected in 4 daily intervals (7-13h, 13-19h, 19-23h and 23-7h). After reaching steady state, we estimated Na^+ intake by single and repeated 24-h UCs and repeated spot UCs, using the Kawasaki formula with measured 24-h urine creatinine excretion.

Results: After day 5, mean 24-h Na^+ excretion matched intake, indicating that steady state was achieved (Fig 1A). Mean absolute differences (Δ) between measured Na^+ intake and 3-d spot UC estimates were 18.8 (SD 14.6), 32.3 (SD 18.7), 74.6 (SD 30.0) and 28.2 (SD 19.8) mmol for interval 7-13h, 13-19h, 19-23h and 23-7h, respectively (Fig 1B). With the exception of samples collected between 19-23h, Na^+ intake estimates by 3-d spot UCs did not significantly differ from Na^+ intake estimates by single (Δ 29.8 mmol; SD 23.9) and three 24-h UCs (Δ 22.9 mmol; SD 11.4).

Conclusions: Bias in Na^+ intake estimation did not significantly differ between repeated spot UCs and single and repeated 24-h UCs. Adequately powered studies need to confirm whether repeated spot UCs are an accurate and low burden alternative to 24-h UCs.

Funding: Private Foundation Support

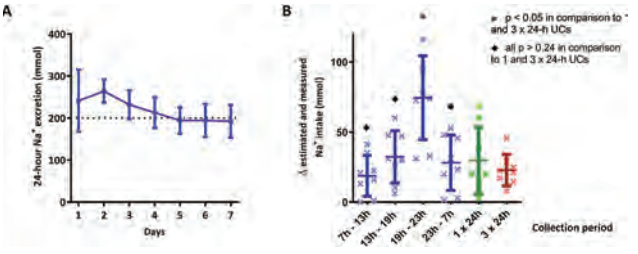


Figure 1. (A) Mean 24-h Na^+ excretion during 7-d diet. (B) Comparison of the performance of three consecutive spot UCs (blue), single 24-h UC (green) and three consecutive 24-h UCs (red) for estimating Na^+ intake (200 mmol/d). Absolute differences between estimated and measured Na^+ intake. Data are mean and SD.

PO1501

Utility of Doppler Ultrasound-Derived Hepatic and Portal Venous Waveforms in the Management of Heart Failure Exacerbation

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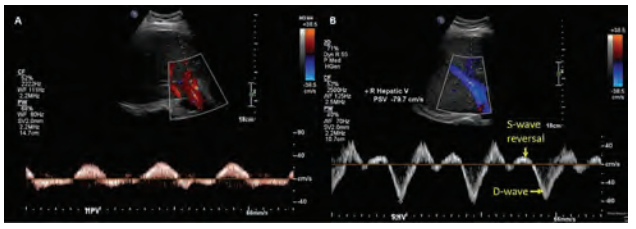
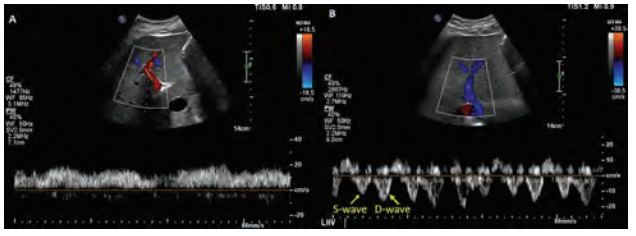
Introduction: Careful evaluation of the fluid volume status and systemic hemodynamics is of paramount importance in patients with heart failure. With growing interest in point of care ultrasonography, non-invasive parameters such as hepatic and portal vein waveforms are assuming importance as markers of systemic venous congestion.

Case Description: 43 year old male was admitted for right lower extremity necrotizing fasciitis requiring below the knee amputation. Postoperatively, he subsequently developed volume overload with pulmonary edema and acute renal injury. Given the patient's sensitive hemodynamic state, volume depletion was driven by doppler ultrasound, specifically portal vein and hepatic vein doppler. After a few days of therapy, the patient had improvement of his renal function, leading to a cessation of dialysis and return of renal function to near baseline.

Discussion: In patients with acute decompensated heart failure, residual clinical congestion at hospital discharge is associated with worse outcomes. A standard assessment of congestion is the measurement of right atrial pressure (RAP) and pulmonary capillary wedge pressures using pulmonary artery catheterization, though its invasive nature precludes routine use. Estimating beside RAP using inferior vena cava (IVC) ultrasound is now common, though it is not without numerous pitfalls limiting its utility. For example, the changes in size of the IVC depend on variations in intrathoracic pressure and lung compliance. Using portal and hepatic vein waveforms can add another piece of information for volume assessment. As shown in our images, the changes initially seen on doppler with hypervolemia can direct management for diuresis/volume removal. These changes seen on doppler waveform aids in management for decongestive therapy.



Portal (A) and Hepatic (B) vein waveforms before decongestive therapy



Portal (A) and Hepatic (B) vein waveforms after decongestive therapy

PO1502

Multiple Spot Urine Sampling Is More Precise and Accurate Than 24-Hour Urine Collection for Estimating Urinary Sodium Excretion

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Background: The estimate of sodium excretion (NaE) is important for the management of hypertension, but 24 hours urinary collection (24-hrsUC), the current standard of care, can be inaccurate, unpractical and poorly representative of the usual Na intake. Multiple spot urine sampling is not affected by any of these errors, so we hypotesized that it can be equally or more precise than 24-hrsUC for estimating NaE.

Methods: 4/subject 24-hrsUC and the related 439 urine samples (1/voiding), were analyzed for uNa and uCr. uNaE (in mEq/Kg/day) of each 24-hrsUC and uNa/uCrR of each voiding were calculated. Individual uNa excretion from 24-hrsUC were compared with all the means of uNa/uCrR derived from 2, 3 and 4 random samples from different days for both precision and accuracy using the mean of all the 24-hrsUC as individual "gold standard". Precision in estimating the gold standard of the 2 methods was measured by comparing the respective coefficient of variations (CV). Accuracy was measured by comparing the P30 and P20 of the 2 methods after transforming uNa/uCrR into uNaE in (mEq/kg/day) by means of the equations (one for children and one for adults) derived from the study data set.

Results: CV of 24-hrs-UCs was 25.7% and that of uNa-to-uCrR as derived from the mean of 2, 3 and 4 samples were respectively 37.1, 28.2 and 22.5%. The CVs were significantly higher in children. Accuracy: P30 and P20 of the 24-hrs-UC were 62.5% and 78.7%, respectively. The corresponding figures obtained from all the 20,258 possible means of 4 samples randomly taken from different days were 73.1% and 94.5%. The internal validation performed by the same subjects 1 year after and the external validation in 8 subjects confirmed the superiority of multiple spot urine sampling.

Conclusions: In real life, with various sources of error systematically affecting 24-hrs-UCs, uNa-to-uCrR will have an even higher precision and accuracy and should be preferred for estimating uNaE.

PO1503

Abnormal Circadian Rhythm of Urinary Sodium Excretion Correlates Closely with Hypertension and Target Organ Damage in Chinese Patients with CKD

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Background: Whether the abnormal circadian rhythm of urinary sodium excretion is associated with hypertension in chronic kidney disease (CKD) is poorly understood. In this study, we assessed the relationship between the circadian rhythm of urinary sodium excretion and hypertension.

Methods: Urinary samples were collected during both the day (07:00 to 22:00) and night (22:00 to 07:00) to estimate night/day urinary sodium excretion ratios. Blood pressure (BP) and clinical data were also measured.

Results: A total of 1,099 Chinese CKD patients were recruited, 308 patients were excluded, and 791 patients were final enrolled in this study. Among them, 291 patients were normotensive and 500 were hypertensive CKD patients. A 1:1 propensity score matching (PSM) analysis was performed with age and estimated glomerular filtration rate (eGFR) matched between 190 normotensive and hypertensive patients. In the full cohort and PSM cohort, multivariate regression analysis showed that the night/day urinary sodium excretion ratio was an independent risk factor for clinical hypertension, whereas 24 h urinary sodium excretion, diurnal and nocturnal urinary sodium excretion were not. When the night/day urinary sodium excretion ratios were further divided into tertiles (tertile 1 < 0.47, tertile 2, 0.47–0.84 and tertile 3 > 0.84), multivariate analysis showed that tertile 3 was independently associated with hypertension in the full and PSM cohorts. In addition, tertile 3 was also independently associated with eGFR ≤ 60 mL/min/1.73 m2 and left ventricular hypertrophy.

Conclusions: These data suggested that an abnormal circadian rhythm of urinary sodium excretion was independently associated with hypertension and target-organ damage. Individualized salt intake and therapeutic strategies should be used to normalize the natriuretic dipping profile in CKD patients.

Funding: Government Support - Non-U.S.

PO1504

Mirabilite External Application for the Treatment of Nephrotic Edema: A Randomized Controlled Study

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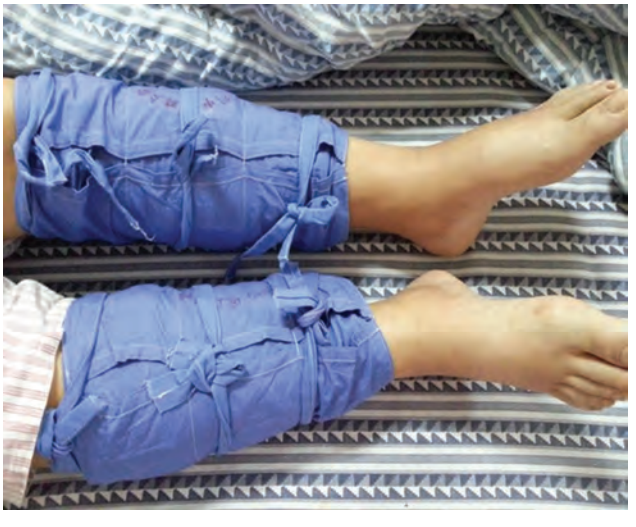
Background: Lower limb edema is the main symptom of nephrotic syndrome (NS). In addition to well established treatment for edema, external mirabilite application (EMA) around swollen areas could potentially benefit patients with NS. Mirabilite is hydrous sodium sulfate mineral that quickly turns into thenardite which is known for its ability to highly absorb water.

Methods: A randomized, single-blinded study included 52 patiennts with NS who were randomly assigned to the experimental group (EMA+diurethic therapy, n=26) and the control group (diurethic therapy, n=26). The study was approved by IRB of the 1st Affiliated Hospital of Guangzhou University of Chinese Medicine. Mirabilite treatment was applied via special cloth bag placed around swollen area on legs, 6 hours per day for 10 days. The primary outcome was the change in leg circumference (LC) and biochemical characteristics of patients. The secondary outcome included body weight and urine output.

Results: Patients from experimental group had significant decrease in LC compared to controls (P=0.000), yet small changes in urine volume output (P=0.436). However, significant correlation of LC with weight gain of mirabilite was observed (r=-0.586, P=0.002). Concentration of electrolytes did not change significantly in the groups. Similar effect was observed regarding liver function markers. However, albumin concentration increased significantly in both experimental and control group. After EMA+diurethic treatment patients had significantly lower body weight (P=0.000). Moreover, weight loss was significantly positively correlated with decrease in LC (r=0.612, P=0.000).

Conclusions: This study suggests that MEA is effective in relieving the symptoms of lower extremity edema in NS patients, but it does not help much in the state of water and sodium storage.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



PO1505

Reappraisal of Urinary Sodium Excretion as a Predictor of Clinical Outcomes in Heart Failure

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Background: Congestion is established as the driver of adverse outcomes in heart failure (HF). Since removal of excess fluid and sodium is often the primary therapeutic objective in this setting, accurate monitoring of the progress of diuretic therapy is of critical importance. While weight change and fluid balance have conventionally been used for this purpose, inconsistent collection, inherent delay in data availability, and lack of distinction between water and sodium balance are among their limitations. We sought to explore the contemporary data on the use of urinary sodium (UNa) as a predictor of outcomes in these patients.

Methods: Articles cited in the PubMed database using keywords "heart failure" and "urine sodium" were searched. Available data from clinical trials published between June 2015 and May 2020 were included. The studies were selected if they prognosticated outcomes in the HF population through use of UNa. Pertinent data on clinical and laboratory parameters (e.g. dose and timing of diuretic therapy, eGFR, serum sodium, and UNa) were extracted and reviewed.

Results: A total of 14 studies with 2,350 participants were included, of which 11 were prospective. The study populations consisted of 12 acute HF cohorts, 1 chronic, and 1 with both. The mean age was 67 years (64% men) with an ejection fraction of 35% and an eGFR of 50 ml/min. Most studies (12 out of 14) used UNa concentration, 2 used fractional excretion and clearance of sodium. Surprisingly, while there was substantial variation across studies in the timing of the applied metric, those exploring clinical endpoints unanimously reported a correlation between low UNa excretion and various adverse outcomes (e.g. worsening renal function, HF readmission, and mortality).

Conclusions: Over the past few years, UNa has been the focus of much investigation as a tool for monitoring of therapy and prognostication in patients with HF. The findings of our study are two folds: 1) Regardless of the applied metric and its timing, contemporary data supports the use of UNa as a potent predictor of clinical outcomes in HF that lacks the limitations of conventional methods. 2) There is no consensus on the optimal cut off and time points for measurement of UNa in this setting. In order for UNa to be applied widely as a consistent and reliable tool, this knowledge gap needs to be addressed in future studies.

PO1506

Defective NAD$^+$ Homeostasis in ADPKD and the Effects of PC1CTT on Redox Modulation and Disease Progression

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in the genes encoding polycystin-1 or 2 (PC1 or PC2). Defective metabolism is a hallmark of ADPKD. The C-terminal cleavage product of PC1 (PC1CTT) can translocate to mitochondria and its expression in Pkd1 KO cells may rescue defective mitochondrial phenotypes. Altered oxidoreductase activity is detected in an ADPKD *in vitro* model. Here we assess the degree of redox imbalance between NAD/NADH in *in vitro* and animal ADPKD models. Moreover, we use an *in vitro* model to express variations of PC1CTT that localize to different subcellular compartments and reveal an association between PC1CTT localization and Redox modulation. Finally, we show that expression of a PC1CTT variant with predominant nuclear as opposed to mitochondrial localization exacerbates the cystic phenotype in a PKD1 KO mouse model.

Methods: We quantified the ratio between NAD+ and NADH in lysates from Pkd1$^{+/-}$ and Pkd1$^{-/-}$ mouse renal epithelial cells. We also assessed the NAD/NADH ratio in kidney lysates from ADPKD mouse models and WT controls. We generated 3 variations of PC1CTT with either an N-terminal HA-tag (2HA-PC1CTT), a C-terminal HA-tag (PC1CTT-HA) or no additional tag, and applied the assay to lysates from HEK cells transfected with these constructs. Finally, we expressed 2HA-PC1CTT in a PKD1 KO mouse model and observed phenotypic differences.

Results: The NAD/NADH ratio was 80% higher in Pkd1$^{+/-}$ cells in comparison to Pkd1$^{-/-}$ cells. Kidney lysates from WT mice had double the NAD/NADH ratio compared to that observed in cystic and pre-cystic animals. Transfection of HEK cells with the PC1CTT constructs revealed distinct patterns: 2HA-PC1CTT localized to nuclei, PC1CTT-HA localized to mitochondria and PC1CTT was found in both. PC1CTT and PC1CTT-HA expressing HEK cells exhibited 40% and 60% higher NAD/NADH ratios than those measured in 2HA-PC1CTT-expressing cells. ADPKD mice expressing 2HA-PC1CTT exhibited a 3-fold increase in kidney-weight/body-weight in comparison to control ADPKD mice.

Conclusions: ADPKD is characterized by defective NAD+ homeostasis. Mitochondrial localization of PC1CTT can potentially rescue this redox imbalance, while nuclear localization of PC1CTT appears to aggravate this imbalance and exacerbate the cystic phenotype in animal models.

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PO1507

Cleavage Fragments of Polycystin 1 Respond to Oxidative Stress and Alter Mitochondrial Dynamics and Function

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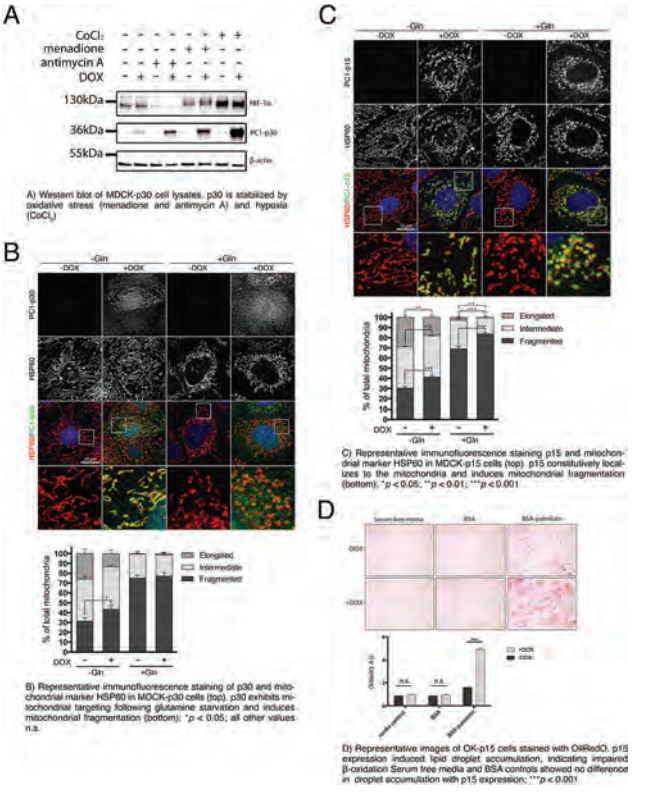
Background: The PKD1 gene, which is mutated in ADPKD, encodes for the PC1 transmembrane protein containing a cytoplasmic C-terminal tail that undergoes cleavage at multiple sites. Two of these C-terminal fragments, a ~30 kDa fragment (p30), and a ~15 kDa fragment (p15) corresponding to the entire soluble C-terminal tail and the extreme end respectively, are overexpressed in patient kidneys. Metabolic reprogramming is a hallmark of ADPKD. We demonstrate that the C-terminal fragments of PC1 respond to oxidative stress and contribute to metabolic reprogramming by altering mitochondrial dynamics.

Methods: MDCK and OK cell lines were generated stably expressing myc-tagged p30 or p15 under a doxycycline-inducible promoter Protein levels of p30 were determined by western blot and localization by immunocytochemistry. Mitochondrial morphology was classified performing immunocytochemistry combined with image analysis. Fatty acid oxidation was assessed performing OilRedO staining and quantified by measuring the number of lipid droplets

Results: p30 normally undergoes rapid degradation and is stabilized in response to oxidative stress. Following glutamine starvation, p30 targets mitochondria and results in fragmentation. p15 does not undergo degradation and constitutively targets to the mitochondria where it induces mitochondrial fragmentation. Further, expressing p15 results in accumulation of lipid droplets indicative of impaired mitochondrial β-oxidation.

Conclusions: Our data unmasks p30 as a sensor of metabolic stress. We speculate that p30 stabilization and subsequent p15 cleavage are involved in metabolic reprogramming in ADPKD by altering mitochondrial morphology and function. Elucidating the exact underlying mechanisms is of major importance to understanding disease progression in ADPKD.



PO1508

Cardiac Dysfunction in Pkd1-Deficient Mice Is Associated with Metabolic Rewiring

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Background: Myocardial abnormalities are associated with significant clinical burden in ADPKD but the underlying pathogenesis is still largely unclear.

Methods: We investigated the metabolic basis of the ADPKD-associated cardiac phenotype using a mouse homozygous for a *Pkd1* hypomorphic allele that prevents PC1 cleavage (VV) with early cardiac dysfunction.

Results: VV hearts displayed metabolome and lipidome signatures associated with lower levels of glucose and amino acids (aa) and higher levels of lipid species than wild-type (WT) hearts. This VV profile also included decreased *Cpt1b* (-28±12%, p<0.05, *Pparα* (-26±12%, p<0.05), PGC1α (-22±8.4%, p<0.05), phospho-AMPK (-46±12%, p<0.01) and phospho-ACCβ (-35±15%, p<0.05) expression, indicating downregulation of fatty acid oxidation and lipotoxicity. Mitochondrial density was higher in VV than WT hearts (49.5±1.8% *vs* 41.3±3.0%, p<0.01) and size was smaller, but shape descriptors and MFN2 and DRP1 expression did not differ. Structural changes were followed by increased cardiac oxygen consumption in response to glucose (928±157 *vs* 762±104pmolO_2/min/mg, p<0.05). Notably, VV neonate cardiomyocytes showed higher mitochondrial maximal respiration than WTs (327±24 *vs* 216±64pmolO_2/min, p<0.01) and a trend of increased basal respiration (p=0.09). These data suggest that glucose and aa may be preferably used as energy substrate in VV hearts. Cardiac expression of fetal genes *Nppa* and *Acta1* were also increased (3.35±1.54 *vs* 1.10±0.54 AU, p<0.01 and 2.26±0.94 *vs* 1.07±0.38 AU, p<0.01, respectively), revealing inappropriate transcriptional transition to the mature state. Unlike *Pkd1*-deficient kidneys, phospho-RPS6 is downregulated in VV hearts (-58±15%, p<0.01) and glucose is not targeted for aerobic glycolysis, since lactate levels were reduced. These metabolic changes correlated with increased cardiac apoptosis and inflammation but not with hypertrophic remodeling.

Conclusions: Our findings uncover a cardiac metabolic rewiring associated with *Pkd1* deficiency, revealing a pattern only partially similar to the metabolic profile observed in the cystic kidney phenotype. These data conceptually expand the understanding of heart dysfunction associated with *Pkd1* deficiency and likely ADPKD.

Funding: Government Support - Non-U.S.

PO1509

Elevated Expression of CaMK4 Contributes to mTOR-dependent Cell Proliferation and Cyst Growth of ADPKD Cells

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Background: Mammalian target of rapamycin (mTOR), a central integration site for pathways involved in cell growth, is abnormally activated in renal cyst-lining cells in human ADPKD and PKD mice. mTOR inhibition reduces cell proliferation and cyst growth in PKD mice. A better understanding of the pathways responsible for elevated mTOR activation is important for the development of new therapies. Calcium/calmodulin-dependent kinase type IV (CaMK4) was recently identified as an important upstream regulator for mTOR activation in multiple cells. CaMK4 is fully activated by binding of Ca^{2+}/Calmodulin(CaM) and phosphorylation by Ca^{2+}/CaM-dependent kinase kinases β (CaMKKβ). However, the role of CaMK4 on mTOR signaling and cyst growth in ADPKD remains unclear.

Methods: We stained tissue sections of human ADPKD kidneys and normal human kidneys (NHKs) with an antibody to CaMK4. We also analyzed levels of CaMK4 in primary human ADPKD and NHK cells, 30-weeks old *Pkd1*$^{RC/RC}$ (BALB/c background) and *Pkd1*$^{RC/+}$ (normal) mouse kidneys. We determined the effects of W7, a calmodulin inhibitor, STO-609, a CaMKKβ inhibitor, and KN-93, a CaMK4 inhibitor, on mTOR signaling, cell proliferation, and *in vitro* cyst growth of ADPKD cells. To confirm a role of CaMK4 on mTOR regulation, we knocked down CaMK4 using a lentiviral shRNA approach in human ADPKD cells.

Results: We found moderate levels of CaMK4 in nuclei of tubule cells in NHK; by contrast, there were elevated levels of CaMK4 in the cytosol and nuclei of cystic epithelial cells of human ADPKD kidneys. CaMK4 level was 2.5-fold higher in human ADPKD cells compared to NHK cells. We also found a 2.8-fold increase of CaMK4 expression in *Pkd1*$^{RC/RC}$ kidneys compared to normal kidneys. Inhibition of CaMK4 using KN-93 caused a remarkably decreased in levels of P-S6K and P-S6 in a dose-dependent and time-dependent manner. Inhibition of CaMK4 activation using W7 and STO-609 reduced P-S6 in ADPKD cells. CaMK4 knock down decreased levels of mTOR, P-S6K and P-S6 confirming regulation of CaMK4 on mTOR signaling in ADPKD cells. W7, STO-609, and KN-93 significantly inhibited cell proliferation and *in vitro* cyst growth of ADPKD cells within a collagen matrix.

Conclusions: The aberrant expression of CaMK4 appears to contribute to elevated mTOR-dependent proliferation of cystic cells and may be a potential target to slow cyst growth in PKD.

Funding: NIDDK Support

PO1510

Mechanisms of Tethered-Ligand Mediated Polycystin 1 GPCR Signaling

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Background: Polycystin-1 (PC1) is the most commonly mutated protein in autosomal dominant polycystic kidney disease (ADPKD) thought to function as an atypical GPCR. *In vivo* studies have demonstrated PC1-regulated G protein signaling is a critical function for preventing renal cystogenesis. Like the Adhesion class of GPCRs, PC1 undergoes auto-catalyzed cleavage at a GPS motif which generates an extracellular N-terminal fragment and a membrane-embedded C-terminal fragment (CTF) composed of 11 transmembrane domains preceded by an N-terminal extracellular stalk of 25 residues. We previously reported that CTF-mediated signaling to an NFAT promoter-luciferase reporter is dependent on the presence of the stalk, is reduced by ADPKD-associated missense mutations within the stalk, and can be rescued by synthetic, stalk-derived peptides, supporting a tethered ligand mechanism of PC1-G protein signaling. In this study, we have utilized a combination of computational molecular dynamics (MD) simulations and mutation-function analyses to investigate the mechanism of PC1 signaling.

Methods: A computer model of the human PC1 CTF was generated using the cryo-EM structure of the PC1-PC2 complex (Su et al, 2019) and the I-TASSER protein structure prediction tool. All-atom enhanced simulations (> 900 ns) using a robust Gaussian accelerated molecular dynamics (GaMD) technique were performed followed by calculation of residue correlation matrices and free energy profiles for residue-residue interactions.

Results: All-atom simulations with the wildtype, ADPKD mutant and stalk-less versions of the PC1 CTF model were consistent with the previous functional signaling data. Key residue interactions between different domains of the CTF predicted from the GaMD simulations suggest an allosteric mechanism for PC1-G protein activation for which mutagenesis and functional signaling and expression assays are underway.

Conclusions: Complementary experiments and simulations have provided important insights into a mechanism of PC1 GPCR signaling at an atomic level and support an important role of the stalk region as a tethered ligand. This in-depth knowledge is expected to facilitate future drug design efforts targeting this function of PC1 for more effective treatments of ADPKD.

Funding: NIDDK Support, Other NIH Support - NIGMS, Other U.S. Government Support, Private Foundation Support

PO1511

Role of Polycystin 2 in Endoplasmic Reticulum Calcium Release and Pathogenesis of Polycystic Kidney Disease

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Background: The prevailing view is that PKD is a ciliopathy. Yet, polycystin-2 contains an ER retention signal, is most abundantly expressed in ER. Early studies showed that PC2 is involved in agonist-induced ER Ca2+ release. Decrease in ER Ca2+ release in PC2-deficient cells is believed to contribute to cAMP overproduction and cystogenesis, the foundation for treatment by tolvaptan. Recent patch-clamp recordings reveal that PC2 conducts predominantly monovalent cation with ~40X more selective to K+ than Ca2+. The low selectivity for Ca^{2+} raises the question regarding the role of PC2 in Ca2+ release in ER and thus the role of ER-localized PC2 in PKD pathogenesis. Cation exchange and/or parallel anion movement across ER membrane is imperative for Ca2+ release. TRIC-B (trimeric intracellular cation-B) is a known ER resident K+ channel mediates counterion exchange for IP3R and RyR-mediated Ca2+ release.

Methods: For in vitro studies PC2-deleted renal epithelial cell line and HEK cells with CRISPR-Cas9-mediated gene knockout of TRICB channel are used. ER Ca2+ release stimulated by carbachol or ATP is assayed by increases in the intracellular Ca2+ measured by using Fura-2 calcium imaging. Zebrafish is used as in vivo PKD model. Gene specific antisense morpholinos are used for targeted knockdown of PC2 and TRICB in zebrafish embryos. Dorsal curvature and pronephric cystic phenotypes are analyzed.

Results: Agonist-stimulated ER Ca2+ release is blunted in PC2-null epithelial cells. Expression of WT PC2 restores ER Ca2+ release. Expressing WT TRIC-B channel, but not LOF mutant, rescues ER Ca2+ release in PC2-null cells. Similarly, ER Ca2+ release is blunted in cells deleted of TRIC-B, and expression of WT PC2 partially rescues defective ER Ca2+ release in TRIC-B-null cells. Zebrafish embryos injected with PC2 antisense morpholino develops dorsal curvature and enlarged pronephric cyst, which can be rescued by co-injecting WT, but not LOF mutant, PC2 RNA. Co-injecting WT, but not LOF, TRIC-B RNA rescues defects in PC2-morphant fish.

Conclusions: PC2 is a monovalent cation channel facilitates ion exchange for IP3R-mediated Ca2+ release. Loss of this function of PC2 in ER plays a critical role in the cystogenesis of PKD.

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PO1512

Ca^{2+}-Permeable TRPV4 Channel Modulates Cystogenesis in ARPKD PCK453 Rats

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Background: PKD is a cohort of monogenic disorders that result in the development of renal cysts filled with fluid. Deficient flow-mediated $[Ca^{2+}]_i$ responses have been linked to the development of PKD. We showed that mechanosensitive TRPV4 channel is preferentially expressed in the distal nephron where its activity is imperative for flow-dependent $[Ca^{2+}]_i$ elevations. We also found that TRPV4 activity was dramatically decreased in primary cells cultured from ADPKD patients thus contributing to their impaired $[Ca^{2+}]_i$ dynamics.

Methods: We tested how manipulation of TRPV4 activity with pharmacological or dietary means affects cystogenesis in PCK453 rats, a model of ARPKD using a combination of metabolic studies, biochemistry, and $[Ca^{2+}]_i$ imaging in freshly isolated cyst monolayers.

Results: Treatment with TRPV4 activator, GSK1016790A for 1 and 2 months attenuated ARPKD progression manifested as a significant decrease in kidney to total body weight ratio, reduced cyst numbers and area when compared to the control. TRPV4 blocker, GSK2193874 exacerbated ARPKD progression leading to a larger kidney volume and more pronounced cystogenesis. We showed that high K^+ intake increased renal TRPV4 expression and activity. Consistently, high K^+ diet (10% KCl) had similar to GSK1016790A beneficial actions on ARPKD progression. GSK2193874 reversed these effects suggesting their TRPV4-dependent nature. Unexpectedly, high K^+ high alkali diet

(10% K Bicarbonate/Citrate) dramatically accelerated cystogenesis despite augmented renal TRPV4 expression. TRPV4 activity (estimated as a GSK1016790A-dependent rise in $[Ca^{2+}]_i$ in freshly isolated cyst monolayers from PCK453 rat kidneys) was approximately 2 fold larger in cyst cells from high K^+ diet treated compared to control. Basal $[Ca^{2+}]_i$ and flow-induced $[Ca^{2+}]_i$ levels were also larger on this condition. In contrast, TRPV4 activity was more than 2 fold lower in rats on high K^+ high alkali diet.

Conclusions: We show a positive correlation between TRPV4 functional status and the time course of ARPKD progression in PCK 453 rats. Chronic alkali load renders TRPV4 to an inactive state, which contributes to exacerbated cystogenesis in PCK453 rats. We also posit that stimulation of TRPV4 with GSK1016790A or high K^+ but not high K^+ high alkali diet will be instrumental to attenuate the rate of PKD progression in clinic.

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PO1513

Abstract Withdrawn

PO1514

Somatic Tubular Epithelial Cell Model of Type II Polycystic Kidney Disease Reveals Phenotypes of Altered Ciliary Length and Polycystin-Intraflagellar Complex Degradation

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Background: Autosomal dominant polycystic kidney disease (PKD) is a life-threatening monogenic disorder affecting 12 million people worldwide, commonly due to loss-of-function mutations in *PKD1* or (type II) *PKD2*, encoding polycystin-1 (PC1) and polycystin-2 (PC2), respectively. These form a receptor-channel complex in the primary cilium whose molecular function remain uncertain, making it difficult to develop targeted therapeutics. Mice and organoids can express PKD phenotypes, but are slow and complex, posing challenges for mechanistic analysis.

Methods: To establish a somatic cell model of PKD, we generated five clones of porcine proximal tubule cell line (LLCPK1) completely lacking PC2 using the CRISPR-Cas system, alongside five isogenic control lines. Mutations were verified for each allele by TOPO cloning and clones were derived from a single subclone to minimize heterogeneity. Cells were evaluated for PC1 steady-state levels, ciliary defects, and cyst formation in low adhesion plates in the presence of cyst activators. Forskolin, 8-Br-cAMP and the myosin inhibitor blebbistatin promoted cystogenesis. Transcript analysis indicated that the effects of altered PC1 steady-state levels was post-transcriptional. Exogeneous *myc*-PC2 rescued PC1 in the PC2 null cells.

Results: In the absence of PC2, PC1 was thoroughly degraded, similar to findings in human and distinct from mouse. Notably, intraflagellar transport components including ARL13B and IFT88 were also reduced. Cilia in 2D cultures appeared short while in the cystic cells was lengthened. Pharmacologic agents that inhibit the proteasome and the lysosome stabilize PC1 in these cells and rescues the ciliary phenotype. Additionally, the drugs reduce cyst size in human PKD organoids lacking *PKD2*.

Conclusions: We have established a somatic tubular epithelial cell model for PKD, which can be rapidly assessed for molecular and cellular phenotypes. This reveals the necessity of PC2 for proper ciliary structure and to prevent the degradation of a protein complex containing PC1 and intraflagellar transport components. Overall the porcine lineage appears more similar to human cells compared to mouse. Targeting degradation pathways rescues this novel complex and may represent a useful therapeutic approach for PKD.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences

PO1515

Heterozygous Loss of Pkd2 Accelerates Cystogenesis in Pkd1$^{RC/RC}$ Mice

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in *PKD1* (~85% of cases) or *PKD2* (~10% of cases), which encode polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively. The sporadic nature of cyst formation led to the hypothesis that cystogenesis requires a two-hit mechanism, involving a germline mutation (first hit) and somatic mutation (second hit) in the PKD gene. More recent evidence indicates that reducing normal PC-1 expression below a critical threshold is sufficient to initiate cyst formation. To further investigate the role of gene dosing, we evaluated the effect of knocking out one allele of *Pkd2* on the onset and progression of cystogenesis in the *Pkd1$^{RC/RC}$* (R3277C) hypomorphic mouse model that develops mild cystic disease over several months (Hopp, *et al.* J CIin Invest., 2012).

Methods: *Pkd2$^{+/-}$* mice (Wu *et al*. Cell, 1998), which have normal kidneys, were crossed with *Pkd1$^{RC/RC}$* mice to generate *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mice. Body weight (BW), two kidney weight (KW), KW/BW, and cystic index were compared between *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* and *Pkd1$^{RC/RC}$* littermates from 1 week to 9 months. Cystic index and blood urea nitrogen (BUN) were also measured.

Results: There was no difference in BW between the *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* and *Pkd1$^{RC/RC}$* mice. We found that *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mice developed early cystogenesis with rapid increases in KW and cystic index up to 8 weeks of age. The KW/BW of *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mice was twice that of *Pkd1$^{RC/RC}$* mice at 8 weeks (3.0 ± 0.2 *vs.* 1.5 ± 0.1%) and cystic index was also significantly higher (32.0 ± 3.8 *vs.* 5.6 ± 3.7%). At 9 months, KW/BW of the *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mice remained elevated compared to *Pkd1$^{RC/RC}$*mice (3.2 ± 0.2 *vs.* 1.7 ± 0.1%). Cystic index was 21.0 ± 0.7 and 6.4 ± 2.1% for the *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* and *Pkd1$^{RC/RC}$* kidneys, respectively. *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mice also had elevated renal fibrosis and BUN levels at 9 months, consistent with a decline in renal function.

Conclusions: This study demonstrates that heterozygous loss of *Pkd2* accelerated the onset of cystogenesis in *Pkd1$^{RC/RC}$* mice, supporting the hypothesis that PC-1 and PC-2 function in a common pathway and that lowering the expression of the polycystins is sufficient to initiate cystogenesis. We think that the increased progression of cystic disease in *Pkd1$^{RC/RC}$*; *Pkd2$^{+/-}$* mouse makes it a promising model for evaluating therapeutic interventions.

Funding: NIDDK Support

PO1516

FPC, TFAP2B, and MCM3 Function in a Species-Specific Regulome That Modulates Myc/MYC Expression: Implications for ARPKD

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Background: Mutations in *PKHD1* cause human ARPKD (MIM 263200), but mouse *Pkhd1* mutants have limited or no renal cystic disease. We previously showed that MYC is overexpressed in human ARPKD kidneys but not in mouse *Pkhd1* mutant kidneys, and that mouse FPC C-terminal domain (FPC-CTD) activates *Myc* (ASN 2018). Trudel (2019) has reported that Myc is a central driver in *Pkd1*-induced pathogenesis. Relevant to the current study, mice express three TFAP2B isoforms while humans express only one, which is most similar to mouse isoform TFAP2B1. Here, we describe a species-specific regulatory framework (regulome) in which FPC-CTD, TFAP2B, and MCM3 regulate *Myc/MYC* in renal collecting duct (CD) cells.

Methods: Human and mouse CD cell lines, *Myc*-tagged *TFAP2B*, *Tfap2b1*, and *Tfap2b2*, V5-tagged human and mouse FPC-CTD constructs, and *Cys1*, *Pkhd1* and *Myc/MYC* promoter constructs were used to perform dual luciferase and co-IP assays.

Results: In mouse cells, TFAP2B1 & 2 positively regulated expression of *Pkhd1* and *Cys1* while *Myc* was positively regulated by TFAP2B2 but negatively regulated by TFAP2B1. TFAP2B1 negative regulation of *Myc* was epistatic over FPC-CTD activation. MCM3, previously identified as a FPC-CTD binding partner, positively regulated *Myc* promoter activity. Human *MYC* was activated by FPC-CTD and negatively regulated by TFAP2B.

Conclusions: We show that in both mouse and human, FPC-CTD and TFAP2B regulate *Myc/MYC* expression. Notably, mouse TFAP2B isoforms differentially regulate *Myc* expression, while humans lack a *MYC* activating isoform. Based on our data, we propose a model in which a regulome that includes FPC-CTD, TFAP2B, and MCM3 modulates *Myc/MYC* expression in CD cells in a species-specific fashion. Species-specific renal phenotypes could be attributable to differences in constituent proteins, isoform diversity, and epistatic interactions within the proposed regulome. We speculate that this model may explain the differential effects of *PKHD1*/*Pkhd1* deficiency on renal cystogenesis and provide initial clues for putative renoprotective mechanisms in *Pkhd1* mutant mice.

Funding: NIDDK Support, Private Foundation Support

PO1517

Characterization of Porcine Models of Autosomal Recessive Polycystic Kidney Disease

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Background: Autosomal recessive polycystic kidney disease (ARPKD), a relatively common form of mainly infantile PKD, is caused by biallelic mutations to *PKHD1*. The missense change, p.T36M, is the most common pathogenic allele (~15% of the total) and associated with severe disease. Mouse and rat models do not display the classical ARPKD presentation of early onset, enlarged, echogenic kidneys. Therefore, to better understand the pathomechanism, we developed and characterized porcine ARPKD models. The pig has a similar anatomy (multi-papillary structure) and physiology to humans, and thus it makes an ideal model system to study disease progression and test treatment options in this disorder.

Methods: Using the CRISPR/Cas9 methods and homology directed repair (HDR), we genetically engineered pigs with the p.T36M or null *PKHD1*alleles. The following genotypes were breed (WT, T36M/T36M, T36M/KO, KO/KO) and characterized longitudinally to 5-months old (where possible) using MRI and a blood chemistry panel, and analyzed histologically.

Results: Two KO/KO pigs were sacrificed at one and two days of age with a phenotype of greatly enlarged cystic kidneys with severe functional loss as well as fibrotic, cystic livers, matching classical human ARPKD. Four T36M/KO pigs were imaged monthly to five months but they only developed a few kidney cysts that did not grow significantly during follow up, and without a decline in function. Similar analysis of two T36M/T36M pigs revealed only occasional kidney cysts.

Conclusions: Through gene editing, an authentic porcine model of early onset ARPKD kidney and liver disease was developed that will be valuable for understanding the pathomechanism of neonatal ARPKD. MRI and biochemical assays enabled detailed

evaluation of functional and morphological changes in the kidneys, liver, and heart of the milder genotypes. Analysis of the p.T36M allele indicates it more functional in pigs, and so associated with a milder phenotype than in humans.

PO1518

Cystin Deficiency in Cys1$^{cpk/cpk}$ Cells Leads to Marked Reduction in Fibrocystin/Polyductin (FPC)

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Background: Human ARPKD (MIM 263200) is caused by mutations in *PKHD1* (which encodes FPC), yet mouse *Pkhd1* mutations cause minimal renal cystic disease. By contrast, *Cys1$^{cpk/cpk}$ (cpk) mice* exhibit an ARPKD-like renal phenotype. The function of cystin (encoded by *Cys1*) is not fully understood, but the protein is found in the cytoplasm, primary cilium, and nucleus. Its N-terminal myristoylation enables membrane-association, and the AxEGG motif is necessary for ciliary targeting, suggesting a function for cystin in vesicular trafficking. To examine whether cystin is a trafficking adaptor for transmembrane ciliary proteins, like FPC, we evaluated FPC expression in *wild-type (WT)* and *cpk* mouse kidney cell lines.

Methods: Cell lines: Wild-type (WT) and *cpk* mouse kidney cortical collecting duct cells were developed using mTERT immortalization. We used qRT-PCR, western blotting, morphometry (ImageJ), and protein colocalization with fluorescent confocal microscopy.

Results: While *Pkhd1* mRNA levels were similar, FPC protein levels were reduced by 75% in *cpk* cells relative to WT. In contrast, PC2 protein levels were only reduced by 25% and no differences in acetylated tubulin or other ciliary proteins, e.g. Ift88 or Arl13b, were observed. In *cpk* cells, both cystin and FPC were absent from primary cilia, but the percentage of *cpk* cells with primary cilia, ciliary length and thickness were identical to *WT* cells. These observations suggested that cystin deficiency specifically influenced FPC protein expression and localization. Elevated levels of p62/*SQSTM1* expression suggest that enhanced, selective autophagy could explain reduced FPC levels in *cpk* cells. In support of this proposed mechanism, we observed that proteasome inhibition, which activates autophagy, reduces FPC levels in both *WT* and *cpk* cells.

Conclusions: Our studies reveal a patho-mechanistic connection between renal phenotypes in human ARPKD and *cpk* mice, wherein cystin deficiency is linked to reduction in FPC. Current studies are focused on elucidating mechanisms by which cystin deficiency induces autophagy and loss of FPC. The recent identification of an ARPKD patient with a homozygous *CYS1* mutation (bioRxiv 2020 doi.org/10.1101/2020.02.18.946285) highlights the significance of these studies for human disease.

Funding: Private Foundation Support

PO1519

Tsc2 Mutation Induces Renal Tubular Cell Nonautonomous Disease

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Background: Tuberous sclerosis complex is associated with both renal tumors and cysts in most affected patients. The renal cystic disease is poorly understood and has no approved treatment. Using a new principal cell-targeted murine model of the Tsc cystic disease, we found that the renal cystic epithelium was mostly composed of type A intercalated cells with an intact *Tsc2* gene by sequencing, though they exhibited a *Tsc*-mutant disease phenotype. We posited that extracellular vesicles were involved in promoting the intercalated cell phenotype and disease expression.

Methods: We used lineage tracing experiments to understand the tubular cell fate, and dynamic light scattering, tunable resistive pulse sensing, transition electron microscopy and western blot analysis to characterize the extracellular vesicles. We used microarray analysis to characterize the effects of the extracellular vesicles on target tubule cells.

Results: Using lineage tracing experiments, we find that while principal cells are involved and undergo clonal expansion, they contribute a surprisingly small number of cells to the cyst. We identify that cystic kidneys contain more interstitial extracellular vesicles than noncystic kidneys, excrete fewer extracellular vesicles in the urine, and contain extracellular vesicles in the cyst fluid. We demonstrate that the loss of the *Tsc2* gene in the cells producing the extracellular vesicles greatly changes the effect of extracellular vesicles on renal tubular epithelium, such that they develop increased secretory and proliferative pathway activity. mTORC1 activity is not the only controller of extracellular vesicles production, but mTORC1 inhibition does reduce the extracellular vesicle production and greatly changes the effect of extracellular vesicles from treated cells. This may be, at least in part, why mTORC1 inhibitors have a beneficial effect in patients.

Conclusions: Taken together, these results contribute to the mechanistic understanding of how genetically intact cells contribute to the disease phenotype.

Funding: Other U.S. Government Support

PO1520

Tsc Gene Locus Disruption and Differences in Renal Epithelial Extracellular Vesicles

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Background: The severity of tuberous sclerosis complex (TSC) manifestations seem to be different depending which TSC locus is affected. This is a puzzling finding, given that the gene product of both loci heterodimerize to regulate mTORC1 activity, so loss of either one releases the repression and results in constitutive mTORC1 activation.

Methods: To begin to understand possible mechanisms for this difference, we have used mouse inner medullary collecting duct (mIMCD) cells with either the *Tsc1* or the *Tsc2* gene disrupted by a CRISP/CAS9 strategy. We have previously characterized the *Tsc2*-mutant cell line derived EVs, and present here intriguing differences between the extracellular vesicles (EVs) derived from cells with mutant *Tsc1* or *Tsc2* genes. To characterize the EVs, we used tunable resistive pulse sensing, dynamic light scattering, transition electron microscopy and mmunoblot analysis.

Results: To characterize the size of the EVs, we used tunable resistive pulse sensing and dynamic light scattering. The parental cell line had an average size of 123.5 ± 5.7 nm and mutant *Tsc1*-derived EVs had an average size 131.5 ± 8.3 nm. The surface charge for the two cell lines were -16.3 ± 2.1mV and -19.8 ± 2.7mV respectively. The isolated nanosized vesicle had excellent purity as assayed using transmission electron microscope. Both cell lines had a heterogenous population of EVs based on size, and more than 90% of the EVs were smaller than 150nm. Immunoblot analysis revealed by the presence of the cilial Hedgehog signaling protein Arl13b and the intercellular proteins TSG101 and Alix, as well as the transmembrane proteins CD63, CD9, and CD81. *Tsc1* deletion resulted in less EVs production and synthesis rate compared to *Tsc2* deletion. RNA and protein transfection studies were done to evaluate the role of EVs in disease pathology. Quantitative PCR analysis showed the downregulation of miR-212a-3p and miR-99a-5p in EVs derived from *Tsc2* which are sought to contribute the more TS severity as compared to TSC1. In addition, miR-212-3p/mTORC1 and mIR-99a-5p/mTORC1 axis are could be a novel therapeutic and biomarker strategy for TSC disease.

Conclusions: We have found that the intercellular communication of EVs has significant differences depending upon which TSC locus is affected, and this difference may be involved in the different phenotypes expressed.

Funding: Other U.S. Government Support

PO1521

Rapamycin and Dexamethasone in Pregnancy Prevents Tuberous Sclerosis Complex-Associated Cystic Kidney Disease

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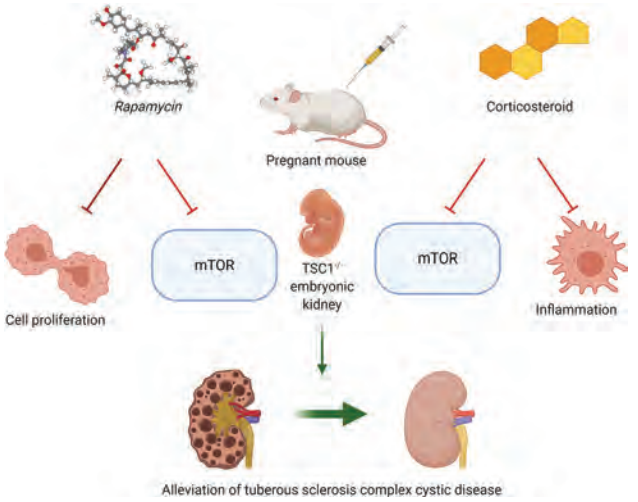
Background: Renal cysts appear in the majority of tuberous sclerosis complex (TSC) patients and lead to a gradual loss of renal parenchyma. Chronic kidney disease is the leading cause of morbidity and mortality in adult TSC patients. The molecular pathways responsible for cyst formation and progression are not known and medical therapy is not available.

Methods: Homozygous deletion of *TSC1* in Six2+ nephron progenitor cells was generated by mating *TSC1$^{f/f}$* females with Six2 Cre$^{tg/+}$ males. Kidneys were harvested at different embryonic ages for histopathology and western blotting for phosphorylated S6, F4/80, P65, c-Myc, and Ki-67. Proximal tubular cells were FACS-sorted using CD133 antibody for RNA sequencing and immunological phenotyping by F4/80. Rapamycin or dexamethasone was injected intraperitoneally during pregnancy.

Results: *TSC1* deletion in nephron progenitor cells induced proximal tubule cell damage and cyst formation, starting as early as E15.5. mTORC1 hyperactivation, as well as macrophage infiltration in TSC null proximal tubules, led to tubular cell damage and cyst formation. Rapamycin prolonged survival by inhibiting mTORC1 and c-Myc activity in the embryonic kidneys and reducing the proliferation rate of PTCs. Administration of steroids during pregnancy prevented cyst formation in TSC offspring, not only by hindering the inflammatory process but also by downregulating mTORC1 activity.

Conclusions: TSC cystic kidney disease can be ameliorated during pregnancy by inhibiting mTOR activity and inflammation.



PO1522

Description of a Multidisciplinary Model of Care in a French Cohort of Tuberous Sclerosis Complex Adult Patients

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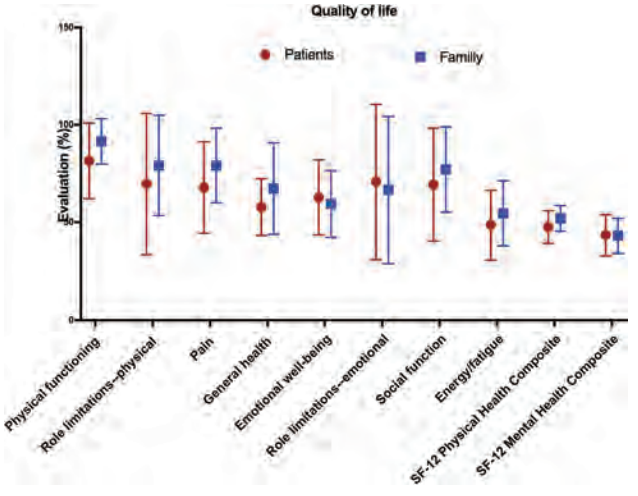
Background: Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder. Due to the various manifestations of TSC and their potential complications, a multidisciplinary care approach is recommended by consensus guidelines. Our study aimed to give a complete description of our TSC adult cohort and to evaluate the multidisciplinary and interdisciplinary management model.

Methods: Data on each adult patient diagnosed with TSC, including disease manifestations, interventions and outcomes, were collected at baseline and updated annually. A multidisciplinary TSC approach with all the recommended explorations was carried out annually. Quality of life was evaluated by SF36 score.

Results: 90 patients were enrolled in a french hospital, between January 2000 and September 2018. Median age of patients at inclusion was 37 years (range, 27-47). Regarding the occurrence of TSC manifestations, 97% of the patients had cutaneous lesions, 89% had neurological manifestations, 83% had renal manifestations and 100% had dental lesions with pits. More than half the patients had sclerotic bone lesions (68%), TAND (64%) and lymphangioleiomyomatosis (LAM) (59%). A TSC multidisciplinary approachin day hospital was developed including a global follow-up and an evaluation of TSC targeting organs, according to the recommendations. A satisfaction survey revealed global and entire TSC patient satisfaction (100%). The assessment of physical health and mental health indicated considerable deterioration (47.52% and 43.46%, respectively). The patient's family's quality of life was evaluated and the results were similar to those found for patients, for each variable (figure).

Conclusions: We obtained an accurate description of a cohort of adult patients with TSC. Our multidisciplinary approach model allowed us to provide optimal management of TSC patients with a high level of patient satisfaction.

Funding: Clinical Revenue Support



PO1523

Whole-Exome Sequencing in 97 Families with Renal Ciliopathies Reveals a Causative Mutation in a Known Kidney Disease Gene in 62% and Identifies Potential Novel Causative Genes

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Background: Nephronophthisis-related ciliopathies (NPHP-RC) represent the most frequent genetic cause of end-stage renal disease in the first three decades of life. Affected children present with increased echogenicity and/or cysts on renal ultrasound. As mutations in 96 recessive genes have been identified as disease-causing (*Kidney Int* 95:914, 2019), whole exome sequencing (WES) represents the best approach for the identification of the causative mutation (*Nephrol Dial Transplant* 31:1802, 2016). In a previous study of consanguineous or familial cases of NPHP, we identified causative mutations in 63% of all patients (*Kidney Int* 89:468, 2016) by WES.

Methods: To reveal the percentage of causative mutations in NPHP-RC and to identify potential novel disease genes, we evaluated WES data from 97 families with childhood-onset NPHP-RC for causative mutations in 178 monogenic chronic kidney disease genes. Clinical inclusion criteria were increased renal echogenicity or identification of ≥ 2 renal cysts on renal ultrasound.

Results: In 60 out of 97 families (62%), we identified a mutation in a known monogenic kidney disease gene as causative for the phenotype. Out of these, 47 families harboured mutations in one of the known ciliopathy genes. 13 families were diagnosed for a disease that phenocopies NPHP-RC. Amongst these, CAKUT represented the most frequent phenocopy disease (7/13 families), followed by Alport syndrome, metabolic diseases and nephrocalcinosis (2/13 families each). In 10 families, in which a mutation in known disease genes was excluded, we identified a biallelic mutation in a potential novel causative gene candidate.

Conclusions: By whole exome sequencing we identified a disease-causing mutation in 62% of families with a diagnosis of NPHP based on renal ultrasound and identified 10 potential novel causative gene candidates.

Funding: NIDDK Support

PO1524

Using Whole-Exome Sequencing to Identify PKD1 and PKD2 in 50,000 UK Biobank Participants

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Background: Studies have demonstrated that genetic testing using whole-exome sequencing (WES) detects undiagnosed monogenic kidney disease in up to 2% patients with predefined clinical phenotypes and/or strong family histories of kidney disease. We aimed to take advantage of newly available datasets with WES and medical information on 50,000 people from UK Biobank (UKBB) to identify *PKD1* and *PKD2* variants in a sample not selected for kidney disease, to compare their phenotypic features to people with ICD 10 codes for *PKD* in UKBB.

Methods: We analysed data from the subset of 50,000 individuals from UK Biobank (n=500,000) who have had WES data released. We looked for mutations in *PKD1* and *PKD2*. Our primary analysis involved looking for a subset of mutations, protein-truncating variants, that had a very high likelihood of being disease-causing. We performed standard quality control which included visual inspection and assessing individual mutation on genome databases.

Results: We found 53 protein truncating variants (44 in *PKD1* and 9 in *PKD2*). The Average age for those with mutations was 57, the same as the UKBB population. We excluded 33 variants on the basis that they were either very common in GNOMAD therefore unlikely to be pathogenic or did not pass visual inspection on IGV plot. This left 20 likely pathogenic mutations (13 *PKD1* and 7 *PKD2*). An ICD 10 code for PKD on hospital records was found in 8 of those with mutations. The 8 individuals with mutations and a PKD ICD 10 code had a more severe phenotype; 7/8 (88%) were hypertensive compared with 6/12 (50%) in those with mutations but without a PKD ICD10 code. Their renal function was worse (63% v 15% had CKD, eGFR 53 v 80, p=0.01) and 1 individual received a renal transplant.

Conclusions: We were able to find disease causing mutations in *PKD1* and *PKD2* and link this to phenotype in UKBB. People with protein truncating mutations and hospital codes for *PKD* had independent evidence of kidney disease however those without an ICD 10 code of *PKD* could either have milder undiagnosed *PKD*, or non-pathogenic mutations. The genetic complexity of *PKD1* and 2, and the difficulty of ascertaining mutations with exome sequencing means that further work needs to be done to see if prevalence of *PKD*, and in particular undiagnosed mutations, could be assessed using WES from the complete UKBB dataset when available.

PO1525

PKD1 Compared with PKD2 Genotype and Cardiac Hospitalizations in the HALT-PKD Studies

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Background: Polycystin 1 and 2 are expressed in vascular endothelial and vascular smooth muscle cells. While the hallmark of autosomal dominant polycystic kidney disease (ADPKD) is the development and continued growth of multiple renal cysts that ultimately result in loss of kidney function, cardiovascular complications are the leading cause of death. Although hypertension occurs earlier and more frequently in *PKD1* vs. *PKD2*, both genotypes seem to confer equal risk of developing intracranial aneurysms. It is currently unknown if *PKD1* vs. *PKD2* confers a different risk of cardiovascular events.

Methods: 864 individuals with ADPKD who participated in the 5-yr HALT-PKD study A or B and had genotype data with either a *PKD1* or *PKD2* mutation were included in this analysis. Since the number of cardiac events in the HALT-PKD studies was limited, we determined the association of genotype with the adverse cardiac event with the highest frequency (cardiac hospitalization; defined according to the Common Terminology Criteria for Adverse Events v.4.0 of the National Cancer Institution and adjudicated by an endpoints committee). The association of genotype with cardiac hospitalization was determined using logistic regression.

Results: Among the 864 included participants, individuals with the *PKD1* genotype (84%) were slightly younger (42±10 vs. 46±10 yrs, p<0.0001) and had a slightly lower baseline estimated glomerular filtration rate (eGFR; 70±26 vs. 75±26 ml/min/1.73m^2, p=0.06) vs. *PKD2*. Cardiac hospitalization (n=43) was more common in individuals with a *PKD2* genotype (9.2%) compared to a *PKD1* genotype (4.1%; p=0.01). After adjustment for age, sex, race, and study randomization, *PKD2* was associated with an increased odds of cardiac hospitalization (OR; 2.14, 95% CI: 1.04-4.41 vs. *PKD1*). This association was slightly attenuated after further adjustment for cardiac history, systolic blood pressure, body mass index, and baseline estimated glomerular filtration rate (OR: 2.12, CI: 0.99-4.52).

Conclusions: In early- and late-stage participants in the HALT-PKD studies, *PKD2* genotype was independently associated with increased odds of cardiac hospitalization.

Funding: NIDDK Support

PO1526

A Novel Case of Turner Syndrome and Autosomal Dominant Polycystic Kidney

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Introduction: Turner Syndrome (TS) is a sex chromosome disorder resulting from the complete or partial loss of one of the X chromosomes. Short stature is common feature of TS and is commonly treated with growth hormone (GH). Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disease that has bilateral renal cysts and is an important cause of end stage renal disease (ESRD).

Case Description: A 5-y/o girl with TS with 45 XO, treated with GH since the age 2 yr with good clinical response. She presented to nephrology clinic for evaluation of bilateral large kidneys for age (RK 10.0 cm, LK 9.7 cm) per recent renal ultrasound (US). No hypertension was found on her exam. Family History was negative for polycystic kidney disease (PKD), hypertension, renal disease, hemodialysis, renal transplant or intracranial aneurysms. On follow up US 1 year later, a few small bilateral cysts measuring < 1cm and persistent renal enlargement was noted. Due to concerning findings of progressive renal cysts with further growth of the kidneys potentially secondary to GH treatment, her GH treatments was stopped. After 6 months off GH therapy, renal enlargement was unchanged with more enlargment of her cysts. Patient got genetic studies for PKD and was found to be heterozygous for pathogenic variant in the *PKD1* gene consistent with the diagnosis of ADPKD. Parents both tested negative for *PKD1* mutation suggestive of de novo mutation.

Discussion: Patients with TS often have short stature requiring GH treatment in order to achieve improved adult height. TS has multi-organ system manifestations including an increased risk for renal anomalies like simple renal cyst, horseshoe, duplicated, or absent kidney. This case highlights the potential increased risk for patients with TS who are on GH treatment to develop kidney disease. To the best of our knowledge, the association of TS and ADPKD has not been described yet. The current clinical practice guidelines state that patients with known TS should receive a renal US at time of diagnosis with no further follow up renal imaging has been recommended at this time. Given the potential role of GH in cyst proliferation and frequency of GH therapy in this patient population, we recommend reevaluation of current renal screening guidelines for patient with TS. Early diagnosis and treatment could potentially reduce morbidity associated with renal disease and growth hormone.

PO1527

CYP24A1 Mutations Are Associated with Renal Cystic Disease

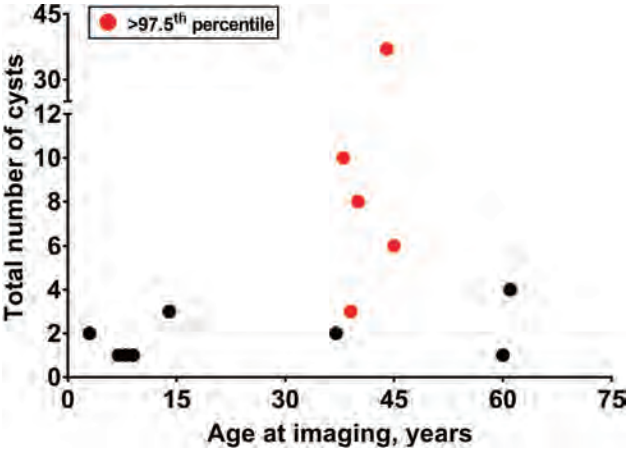
Christian Hanna, Theodora A. Potretzke, Peter Tebben, Vicente E. Torres, Peter C. Harris, John C. Lieske, David J. Sas, Dawn S. Milliner, Fouad T. Chebib. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Loss-of-function mutations in the *CYP24A1* gene cause a rare hereditary disease leading to reduced 24-hydroxylase enzyme activity, characterized by increased serum 1,25-dihydroxyvitamin D_3 levels, hypercalcemia, hypercalciuria, nephrocalcinosis, and/or nephrolithiasis. Renal cysts in *CYP24A1* mutations were first reported in a single case study from our institution. However, to date a possible association between *CYP24A1* mutations and renal cysts has not been examined.

Methods: Retrospective review of all patients with confirmed *CYP24A1* mutations and complete renal imaging studies at a tertiary academic center between 2010 and 2020. Cyst location, number, and diameter were measured by contrast-enhanced computed tomography (CT), non-contrast CT, ultrasound or magnetic resonance imaging.

Results: Among the 13 patients with *CYP24A1* mutation, 46% were male and 38% children. The mean age at diagnosis was 24.7 ± 18.8 years (range 1-60). Medullary and/or corticomedullary junction renal cysts were present in all 13 cases (5 with unilateral and 8 with bilateral cysts). The mean age at imaging with first detected cyst was 31.1 ± 20.5 years (range 3-61). The median number of cysts per patient was 3 (IQR 1.5-7). The mean size of the smallest and largest cyst were 3.6 ± 2.2 mm (range 2-8) and 11.9 ± 6.9 mm (range 2-30) respectively. All 13 had normal age-adjusted renal size and none had a family history of polycystic kidney disease. The number of cysts (≥ 5 mm in size) in 63% of adult patients was above the 97.5th percentile of an age- and sex-matched control population (Figure 1).

Conclusions: This study suggests an association between *CYP24A1* mutations and cystic kidney disease. Further studies are needed to evaluate the role of *CYP24A1* and vitamin D metabolism in renal cyst formation, and whether cysts enhance CKD risk in patients with *CYP24A1* deficiency, or modify nephrocalcinosis/urinary stone risk.



PO1528

Collagen Changes Suggestive of a Primary Defect in pkd2$^{+/-}$ Adult Zebrafish Kidney

Mohamed A. Addani, Deema A. Anaam, Diana Alzamareh, Abdalla A. Modawi, Nicole Ho, Kevin L. Webb, Heather L. Holmes, Michael F. Romero, Slobodan Macura, Timothy L. Kline, Vicente E. Torres, Caroline R. Sussman. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Zebrafish are a valuable model for studies of PKD, with conservation of pathways and phenotypes including renal cysts. *Pkd2* mutant zebrafish develop dorsal tail curvature (*pkd2*$^{-/-}$), which prevents survival. No phenotype has been described in *pkd2*$^{+/-}$ zebrafish embryos or adults. MRI is useful for analysis of PKD kidney and collagen changes characterize PKD. In this study, we examined collagen changes in *pkd2*$^{+/-}$ adult zebrafish kidney and MRI *in vivo*.

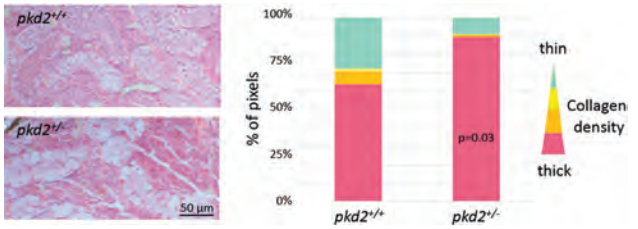
Methods: Zebrafish *hi4166 pkd2*$^{+/-}$ were compared to sibling *pkd2*$^{+/+}$ (males). Total kidney volume and texture were quantified from MRI *in vivo* (16mo, n=3). Collagen density was quantified from picrosirius red (PSR) stained sections using polarized light microscopy and ImageJ for color thresholding (19m, n=3). Integrity of the collagen triple helix was assessed in kidney frozen sections labeled with collagen hybridizing peptide in zebrafish (18m, n=4) and mouse *Pkd1*$^{RC/RC}$ (10m).

Results: Kidney volumes were not different; however, texture analysis showed *pkd2*$^{+/-}$ kidney was more heterogeneous. This was not explained by cysts, as none were visible by H&E staining, nor were tubule diameters different. PSA staining showed significantly

more dense collagen, and collagen hybridizing peptide labeling showed more denatured collagen in *pkd2*$^{+/-}$ zebrafish kidney. Preliminary data from *Pkd1*$^{RC/RC}$ mice show similar patterns of collagen density and denaturation.

Conclusions: To our knowledge, this is the first report of any phenotype in *pkd2*$^{+/-}$ zebrafish (adult or embryo). The presence of a dominant phenotype and a collagen defect suggests conservation of disease etiology. A collagen defect in the absence of cysts indicates independence of collagen changes from cyst formation, suggesting collagen changes may be a primary defect in PKD pathophysiology.

Funding: NIDDK Support



Increased collagen density in kidney of *pkd2* mutant zebrafish visualized by staining with picrosirius red and imaging using polarized light (left) quantified using image thresholding in ImageJ (right). Pixels are binned by color indicating density as shown.

PO1529

Cystic Kidney Disease in Patients with Thin Basement Membrane Disease (TBMD)

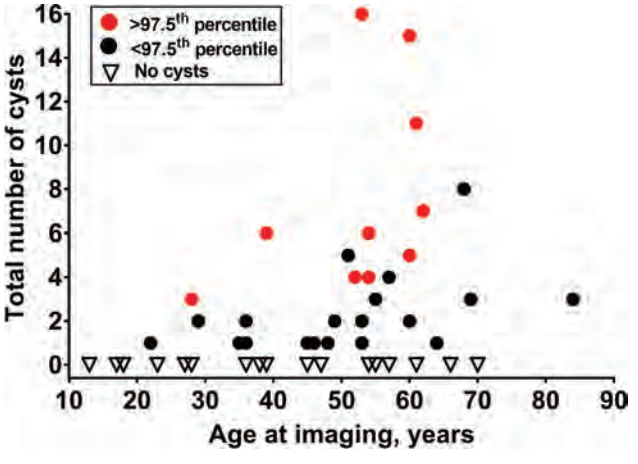
Janina Paula T. Sy-Go, Samar M. Said, Jing Miao, Theodora A. Potretzke, Prince Singh, Reem M. Neal, Peter C. Harris, Vicente E. Torres, Samih H. Nasr, Fouad T. Chebib. *Mayo Clinic Minnesota, Rochester, MN.*

Background: TBMD is a benign glomerular disease typically manifesting as microscopic hematuria with/without minimal proteinuria and with preserved kidney function. A few reports described the finding of kidney cysts in TBMD patients, but this association remains uncertain.

Methods: A retrospective study of patients seen at a tertiary academic center (2009-2019) and had a kidney biopsy with reported diffuse glomerular basement (GBM) thinning was done. The diagnosis of TBMD was confirmed by a careful review of the biopsy findings, including EM images. Patients with clinical and/or pathologic features of Alport disease or with unavailable abdominal imaging were excluded. Cyst number and size were recorded on the first available imaging.

Results: Among 49 TBMD patients, 29 (59%) had kidney cysts (cystic), and 20 had no cysts (noncystic). Both cystic and noncystic groups were mostly females (69% vs. 80%). Cystic patients were older at time of biopsy (51 vs. 38 yrs) and imaging (51 vs 39 yrs). Hematuria was the major indication for biopsy. Hematuria and dysmorphic RBCs were found in 72% and 41% of cystic patients respectively vs. 80% and 10% in noncystic patients. Cystic patients had lower mean eGFR at time of biopsy (69 vs. 93 mL/min/1.73 m^2), higher mean 24-h proteinuria (968 vs. 172 mg/d), and comparable mean GBM thickness (193 vs. 206 nm). 18 (62%) patients had bilateral cysts. Median number of cysts was 3 (IQR 1-5.5). Average sizes of the smallest and largest cysts were 5.1 (± 4) and 19.6 (± 24) mm respectively. The number of cysts (≥5 mm) in 34% of cystic patients was above the 97.5th percentile of an age-/sex-matched control population (Figure 1).

Conclusions: Bilateral kidney cysts were found in a large percentage of biopsy-proven TBMD patients. COL4A mutations could be a potential etiology of mild cystic kidney disease with hematuria or mild proteinuria.



No. of cysts at imaging.

PO1530

COL4A3/COL4A4 as a Cause of Multicystic Kidney Disease

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Background: Thin basement membrane nephropathy (TBMN), the most common cause of persistent microhaematuria (mH), is due to mutations in genes codifying alfa-3 and alfa-4 collagen IV chains *(COL4A4/COL4A3*). Initially considered as a benign condition, subsequent studies have shown that an important number of patients develop proteinuria and CKD. We reported in a previous small study the presence of multicystic kidney disease (MCD) in some TBMD patients. In this study we aimed to evaluate the presence of MCD in a larger cohort of TBMD patients and analyze its association with renal outcomes.

Methods: We collected 50 patients with a diagnosis of TBMD based on the presence of persistent mH (>5 erythocytes per high power field in more than 90% of urinary sediments and radiological examinations to exclude other causes of mH) and at least one first-degree relative with persistent mH. TBMD diagnosis was confirmed by renal biopsy (glomerular basement membrane thickness less than 150nm) in 18 patients and by genetic test (pathogenic mutations in *COL4A3/COL4A4*) in 6 patients. MCD was diagnosed by the presence of uncountable cysts on renal ultrasonography.

Results: Mean age at diagnosis was 43.7 years, 34% were males and 18% had hypertension. At baseline, serum creatinine (SCr) was 0.9 mg/dL, proteinuria 0.48 gr/24h and 9 patients (18%) had CKD (estimated glomerular filtration rate -eGFR- lower than <60 mL/min/1.73m^2). 7 patients (14%) had CKD G3 and 2 (4%) CKD G4. Kidney cysts were found in 34 patients (68%) and 19 (38%) met MCD criteria. After a mean follow-up of 14.7±11.5 years, 23 patients (46%) had CKD. Among them, 17 patients (34%) had CKD G3, 2 (4%) CKD G4, and 4 (8%) CKD G5. Hypertension was more frequent among CKD patients as compared with no-CKD patients (39 vs 0%, p 0.00), proteinuria was higher (0.58±0.68 vs 0.39±0.58 g/24h, p 0.05) and MCD more frequent (65.2% vs 14.8%, p 0.00). Patients with MCD had higher SCr (2.1 vs 1.1 mg/dL, p 0.004) and lower eGFR (41.7 vs 77.2 mL/min/1.73m^2, p 0.00) at the end of follow-up, and MCD was the only risk factor for the occurrence of CKD (OR 6.49, 95% CI 1.3-31.6) by multivariable analysis that included age, hypertension and proteinuria.

Conclusions: MCD is frequently observed in TBMD patients and is a risk factor for the progression of CKD.

PO1531

Genotype-Phenotype Correlations in Pediatric Patients with HNF1B Mutations

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Background: *HNF1B* is one of the most common disease-causing genes of CAKUT, especially renal cysts. *HNF1B* mutations also manifest various renal and extra-renal phenotypes. Faguer S, et al. proposed *HNF1B* scoring system in 2014 to screen patients with *HNF1B* mutations clinically.

Methods: A total of 14 patients, who were diagnosed as having *HNF1B* mutations in the Department of Pediatrics, Seoul National University Children's Hospital during the period from 1990 to 2019, were recruited in this study, and the phenotypes of the patients were analyzed retrospectively.

Results: All 14 patients were male. Initial symptoms of patients revealed incidental azotemia(36%), abnormal prenatal USG(29%), etc. The median ages at the onset, at the genetic diagnosis, and at the last follow-up were 0.1 years, 12.8 years, and 20.3 years, respectively. *HNF1B* genotyping revealed total heterozygous mutation in 43%, truncating mutations in 36%, and missense mutations in 21% patients. The renal image studies revealed multiple renal cysts in 93% patients, renal parenchymal hyperchogenecity in 79%, and unilateral/bilateral renal hypoplasia in 50%. The other renal or extra-renal phenotypes included hyperuricemia in 79% patients and hypokalemia in 57%. During follow-up, 86% patients progressed to CKD, including 36% patients to ESRD. The mean *HNF1B* score at the time of diagnosis was 14.4±5.8, and all patients except one had a score higher than 8. The score at the last follow-up in ten patients except for 4 patients with transplantation was highest in patients with missense mutations (22.5±3.5) and lowest in those with truncating mutations (14.0±2.9, *P*=0.040). Hypokalemia was most common in patients with total deletion mutations (83%) and least common in those with missense mutations (0%, *P*=0.027).

Conclusions: *HNF1B* mutations manifest various renal and extra-renal phenotypes. Most patients (86%) progressed to CKD or ESRD during follow up. The *HNF1B* scoring system showed high sensitivity, although specificity was not evaluated.

PO1532

Identifying and Assessing the Phenotypic Features of HNF1B Deletions and Duplications in UK Biobank

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Background: Heterozygous mutations of hepatocyte nuclear factor 1β (*HNF1B*) are the most common known monogenic cause of developmental kidney disease. Renal cysts are the most frequently detected feature. Other features include early-onset diabetes and abnormal liver function. It is thought that duplications of *HNF1B* do not result in strong phenotypic features. The true pathogenicity and penetrance of many rare putative disease-causing copy number variants (CNVs) is uncertain and may be over-estimated by clinical ascertainment. We aimed to assess the pathogenicity and penetrance of *HNF1B* deletions and duplications in UK Biobank (UKBB) and to describe any associated phenotype.

Methods: We used data from 388,714 UKBB participants to assess CNVs of HNF1B in a population-based setting using SNP chip intensity data. We tested the association of these CNVs with diabetes and other clinically-relevant traits. We assessed the UKBB phenotype and biomarker information and correlated these with the deletions and duplications.

Results: We identified 11 individuals with large deletions relating to *HNF1B* and 106 with duplications. There were no significant difference in the average ages of deletion (53), duplication (56) and UKBB population (57). Of the 11, 3 were reported to have glomerular disease, 1 had haematuria, 1 had a renal transplant, and 6 had diabetes (55% vs. 5% amongst the rest of UKBB; P=2x10-6). The penetrance of diabetes was 30% and average eGFR was 71 (45% with eGFR<60) compared to average GFR 91(p<0.0001) in UKBB population. Their liver function is comparatively different. Gamma GT 110 v 37.4 (p<0.0001) and ALP 186.5 v 83.5 (p<0.0001) in UKBB population. Average eGFR was lower in people with a duplication (80 v 91 in UKBB population, p<0.0001). We found no association between *HNF1B* duplication and diabetes (4.4% vs. 5.3%; P=0.8) or liver function.

Conclusions: *HNF1B* deletions and duplications can be detected in a large unselected dataset. Deletions are more pathogenic than duplications. However, *HHF1B* duplications do appear to affect renal function, which has not been previously described. The frequency of both *HNF1B* deletions and duplications may be higher than previously estimated.

PO1533

Late-Onset Hepatocyte Nuclear Factor 1β-Associated Kidney Disease

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Introduction: Hepatocyte Nuclear Factor 1β (HNF1β) is an important transcription factor for kidney development. HNF1β mutations are rare, associated with multisystemic disease and heterogeneous kidney involvement. HNF1β-associated kidney disease may not manifest until adulthood. We present a case of an older female with chronic hypomagnesemia and kidney cysts due to a heterozygous deletion in the HNF1β gene.

Case Description: 66 y/o Puerto Rican female with a history of recurrent urinary tract infections, pre-diabetes, hypertension, arthritis, congenital absence of left ovary and baseline SCr 0.9 mg/dL was referred for evaluation of bilateral kidney cysts and chronic hypomagnesemia. Review of magnetic resonance imaging and ultrasound going back to 2003 showed normal sized kidneys and presence of more than 4 cysts in each kidney, some of which were mildly complex. No extrarenal cysts were noted and she denied family history of kidney cysts. Chronic symptomatic hypomagnesemia was present since at least 2015 with serum magnesium ranging from 1.1-1.6 meq/L, resulting in emergency room visits and hospitalizations. Fractional excretion of magnesium was 29%, consistent with renal magnesium wasting. Serum potassium and bicarbonate were normal. Intact parathyroid hormone ranged from 83-112 pg/mL but serum calcium, phosphorus, 25 dihydroxyvitamin D were normal. Urinalysis was bland. She was sent for genetic testing and underwent whole exome sequencing. Results demonstrated a heterozygous deletion in the HNF1β gene consistent with HNF1β nephropathy. She was started on amiloride and slow release magnesium supplementation with near normalization of her serum magnesium.

Discussion: HNF1β-associated kidney disease is a challenging diagnosis given extreme variability in phenotypes. De novo mutations occur in up to half of patients leading to diagnosis later in life. Our patient's constellation of medical problems including glucose intolerance, mild hyperparathyroidism, hypomagnesemia, unilateral ovary agenesis and genitourinary (GU) tract abnormalities are all features of HNF1β-associated kidney disease. This diagnosis should not be overlooked in patients with GU abnormalities, electrolytes disturbances and/or signs of tubulointerstitial kidney disease. Additionally, these patients should be monitored for progressive kidney disease and undergo periodic screening for renal cell carcinoma.

PO1534

A Post Hoc Analysis of Tolvaptan (TOL) Efficacy and Safety in Slowing Rate of Renal Function Decline in Subjects with Very Late-Stage Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a progressive disease that causes end-stage renal disease in ~50% of the affected individuals by age 60. TOL, a selective vasopressin V2-receptor antagonist, has been shown to slow the progression of renal function decline in ADPKD subjects with an eGFR of 25 mL/min/1.73m^2 or higher. The efficacy and safety of TOL in subjects with lower eGFR remain understudied. This post-hoc analysis evaluated the efficacy and safety of TOL in subjects with stage 4 CKD (eGFR of <30 mL/min/1.73m^2).

Methods: This is a retrospective analysis of a subgroup of ADPKD subjects who enrolled in the TOL open-label extension (OLE) trial (NCT02251275). Included subjects had a baseline eGFR of <30 mL/min/1.73m^2, received ≥ 1 TOL dose, and were randomized to the placebo group in the REPRISE trial (NCT02160145). Two subgroups of subjects were analyzed, one with baseline eGFR of 25-30 (Subgroup 1) and one <25 (Subgroup 2). The variables evaluated included demographics, adverse event (AE) profile, and intra-subject comparison of change in annualized eGFR decline during the OLE trial to that during placebo use in the REPRISE trial. Annualized eGFR change slopes in the treatment period were calculated using eGFR values between Month 1 and 12 visits to compensate for the acute hemodynamic effect of tolvaptan. Comparison was made by linear mixed model.

Results: Of 1,803 subjects enrolled, 159 (8.8%; 76 in Subgroup 1 and 83 in Subgroup 2) met the selection criteria. Annualized eGFR change slopes for all subjects (n=148) were -5.28 in the REPRISE trial and -3.16 in the OLE trial with a treatment effect of 2.11 (95% CI 1.56, 2.66), p<0.0001). The treatment effects were 1.99 and 2.17 for Subgroups 1 and 2, respectively (p<0.0001 for both subgroups). The 5 most common AEs were thirst (32%), polyuria (30%), renal pain (25%), blood creatinine increase (23%) and nocturia (22%); the rates were similar between the 2 subgroups. One incidence of hepatic enzyme increase, one of hemodialysis and one death (unrelated to TOL) was only observed in Subgroup 2.

Conclusions: This post-hoc analysis demonstrated that TOL significantly decreases the rate of eGFR decline in ADPKD subjects with stage 4 CKD, including those with an eGFR of <25 mL/min/1.73m^2.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc

PO1535

Tolvaptan and Renal Function in Autosomal Dominant Polycystic Disease: A Two-Center Experience of 186 Cases

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Background: TEMPO and REPRISE trials demonstrated that tolvaptan slows the decline in the estimated glomerular filtration rate (eGFR) in patients with autosomal dominant polycystic kidney disease (ADPKD). However, the real-world data of the change in eGFR in patients with ADPKD taking tolvaptan is lacking. Also, comparison of the slopes of the change in eGFR before and after starting taking tolvaptan in a same patient has not been reported.

Methods: Patients who started taking tolvaptan for ADPKD between June 2014 and June 2019 at Toranomon Hospital and Toranomon Hospital Kajigaya were retrospectively analysed for the change in eGFR before and after starting taking tolvaptan. Note that approved indication of tolvaptan for ADPKD patients in Japan includes total kidney volume larger than 750 mL and eGFR greater than 15 mL/min/1.73 m^2. The eGFR at 1, 2, 3, 4, 5 years before and after starting tolvaptan were collected from the medical record. Patients with none of these values were excluded from the study.

Results: 186 patients were included in the study. 43% were men. Average age was 50.2 ± 10.2 (mean ± standard deviation). Total kidney volume was as follows when stratified by chronic kidney disease (CKD) stages: stage 1, 1119 ± 266; stage 2, 1521 ± 600; stage 3a, 1659 ± 787; stage 3b, 2106 ± 1330; stage 4, 2847 ± 1976 mL. 139 patients had eGFR data before and after starting tolvaptan, whereas 24 patients only had data before and 23 patients only had data after starting tolvaptan. The eGFR slope after starting taking tolvaptan was -3.7 ± 2.3 mL/min/1.73 m^2 (n=162), and was as follows when stratified by CKD stages: stage 1, -5.9 ± 4.3 (n=4); stage 2, -4.5 ± 2.8 (n=47); stage 3a, -3.1 ± 2.1 (n=38); stage 3b, -3.5 ± 1.8 (n=40); stage 4, -3.3 ± 1.8 mL/min/1.73 m^2/year (n=33). The change in eGFR slope after starting tolvaptan was -1.2 ± 5.4 in stage 1-3a patients (n=76) and +0.8 ± 2.3 mL/min/1.73 m^2/year in stage 3b-4 patients (n=63), which showed statistically significant difference (p=0.003).

Conclusions: Real-world data from our institution observed the eGFR slope of -3.7 ± 2.3 mL/min/1.73 m^2 after starting taking tolvaptan. The eGFR slope in patients with CKD stage 3b-4 improved on average after taking tolvaptan. The same was not observed in patients with CKD stage 1-3a.

PO1536

Impact of Long-Term Tolvaptan Treatment for Autosomal Dominant Polycystic Kidney Disease: A Single-Centre Retrospective Japanese Cohort Study

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Background: Several clinical trials have revealed the efficacy of the tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) in recent years. Our objective is to verify the impact of tolvaptan in our Japanese ADPKD cohort.

Methods: We retrospectively investigated the efficacy of tolvaptan for ADPKD patients who initiated tolvaptan from June 2014 to March 2020 in Hokkaido University Hospital. Patients treated with tolvaptan for more than 1 year were included for analyses. Patients never treated by tolvaptan were set as control. Patients in CKD stage 5 or 5D at baseline or postkidney transplantation were excluded from analyses. We stratified patients by Mayo classification (Class 1A-1E). Analyses included the comparison of the annual changes of eGFR(ΔeGFR (mL/min/1.73m^2/year)) and total kidney volume (ΔTKV (%/year)) between pre and post-treatment, and ΔeGFR or ΔTKV between tolvaptan-treated and control.

Results: 109 tolvaptan-treated and 139 control patients were included. 24 patients in each group were excluded. About 40% of tolvaptan-treated patients belonged to advanced CKD stage (CKD3b-4). Duration of tolvaptan treatment was 3.3±1.3 years. eGFR of tolvaptan group were lower and htTKV of tolvaptan group were higher compared to those of control group at baseline (eGFR: 53.7±22.8 vs 65.7±30.0, p=0.16. htTKV: 1193.9±649.6 vs 829.5±799.5 mL/m, p<0.0001). There was no significant difference in ΔeGFR between (tolvaptan -2.95±2.86 vs control -3.09±3.31, p=0.33), however in tolvaptan group ΔeGFR improved compared to pre-treatment (-2.95±2.86 vs -4.33±5.72, p=0.027) and this improvement lasted at least for 36 months in 50 patients. ΔTKV of tolvaptan group was lower than that of control (2.19, 95%CI(0.33-4.05) vs 5.10(4.00-6.19), p<0.01) and this trend was also found in Mayo class 1B-1D. ΔTKV also decreased compared to pre-treatment (2.19(0.33-4.06) vs 4.67(2.57-6.76), p<0.01).

Conclusions: Tolvaptan dramatically reduced ΔTKV, while there was no beneficial effect for ΔeGFR compared to control. However tolvaptan improved ΔeGFR compared to that of pre-treatment. The discrepancy between our results and previous reports might arise from the fact that our cohort mainly comprised advanced CKD stage patients or limited sample size. Further long-term observation is required to validate the effect of tolvaptan.

PO1537

Canadian Real-World Assessment of Tolvaptan in ADPKD: C-MAJOR Study and Safety Monitoring and Distribution Program

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Background: Tolvaptan is the only approved treatment in Canada for slowing renal function decline and kidney enlargement in ADPKD patients. As per Health Canada requirement, a patient registry evaluating long-term clinical outcomes (C-MAJOR study) and a hepatic safety monitoring and distribution program (HSMDP) to mitigate risk of liver injury were implemented and have been ongoing for 5 years. The aim of this interim analysis is to describe baseline characteristics of patients at initiation of tolvaptan through the C-MAJOR study and to report on treatment persistence and liver transaminases elevation rate through the HSMDP.

Methods: C-MAJOR is a non-interventional, multi-centre study of ADPKD patients treated with tolvaptan. HSMDP ensures tolvaptan is dispensed under controlled liver function monitoring.

Results: As of April 2020, 398 patients, 51% female, were enrolled in C-MAJOR. At baseline, mean (SD) age was 45.1 (11.5) years, BP was 129.4 (13.4)/83.1 (10.0) mmHg and eGFR was 63.6 (27.8) mL/min/1.73 m^2. Total kidney volume was 1949 (1562) mL, 80.7% of patients had a family history of ADPKD and 39.4% had a family history of early end-stage renal disease. As per Mayo classification, 90.2% were at high risk of disease progression (1C-D-E). The most common ADPKD clinical manifestations were hypertension (83.2%), hepatic cysts (69.6%) and kidney pain (24.1%). Over a mean (SD) follow-up of 2.0 (1.0) years, adverse events were reported in 82.7% of patients, most common being polyuria (19.6%), fatigue (18.6%), and nocturia (15.1%). Over a mean (SD) follow-up of 23.0 (17.6) months in the HSMDP, 2.4% (39) of the 1,600 patients who received at least one shipment of tolvaptan reported an elevation of transaminases >3x ULN. There were 0.3% (5) of patients meeting the guidelines for permanent discontinuation. No cases of drug-induced liver injury were reported. Treatment discontinuation rates at 12, 24 and 36 months were 14%, 21% and 26%, respectively.

Conclusions: This analysis provides Canadian real-world evidence of high-risk disease progression at tolvaptan initiation, 3-y persistence data similar to phase III study and the HSMDP showing tolvaptan was permanently discontinued in 0.3% of patients because of hepatic effects.

Funding: Commercial Support - Otsuka Canada Pharmaceutical Inc.

PO1538

Early Findings of Patients with Autosomal Dominant Polycystic Kidney Disease Initiating Tolvaptan in the United States: A Claims-Based Analysis

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. Tolvaptan (Jynarque®), the first and only approved treatment for ADPKD in the United States (US), has been shown to slow kidney function decline in clinical trials. An understanding of characteristics of the real-world patients initiating treatment with tolvaptan in the US is needed.

Methods: An observational, retrospective analysis assessing baseline measures was conducted among patients with ADPKD who had initiated treatment with tolvaptan from 14 May 2018 through 9 January 2020 in the US. Data were obtained by linking the Symphony Health Integrated Dataverse (IDV), a nationally representative billing database, with Specialty Pharmacy (SP) data from the tolvaptan Risk Evaluation and Mitigation Strategy (REMS), which is a mandatory program for patients prescribed tolvaptan to treat ADPKD. The study index date was the date of first shipment of tolvaptan. Descriptive analyses were conducted on the following baseline measures: demographics, comorbidities, and disease characteristics. All measures were identified within the 6-month period prior to the index date in the Symphony Health IDV. For patients with more than 1 CKD stage diagnosis during the baseline period, the CKD stage closest to the index date was captured.

Results: The study sample included 4,355 patients. The mean age at tolvaptan initiation was 48.8 years (Standard Deviation: 12.3), with 51.7% (n=2,251) female. Hypertension was the most commonly observed comorbidity (n=3,520, 80.8%), followed by diabetes (n=273, 6.3%). The distribution of CKD stage, available for 1,566 (36.0%) patients during their baseline period, was: 6.2% (n=97) in CKD Stage I, 13.4% (n=210) in CKD Stage II, 55.2% (n=864) in CKD Stage III, 22.9% (n=359) in CKD Stage IV, and 2.3% (n=36) in CKD stage V.

Conclusions: This is one of the first real-world studies to describe comorbidities and disease characteristics in patients with ADPKD initiating tolvaptan in the US. Stage III was the most commonly reported CKD stage among patients with a known CKD stage during their baseline period. Additional analyses evaluating the real-life impact of tolvaptan on clinical outcomes, healthcare utilization, and quality of life are needed.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization Inc.

PO1539

Early Real-World Descriptive Findings on Tolvaptan-Treated Patients with Autosomal Dominant Polycystic Kidney Disease in the United States

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Background: Tolvaptan is the first and only treatment for autosomal dominant polycystic kidney disease (ADPKD) approved in the United States (US). The Food and Drug Administration (FDA) required a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of severe liver injury potentially associated with tolvaptan. This study aims to characterize patient demographics and treatment patterns among patients enrolled in the REMS in the US.

Methods: A descriptive analysis of patients with ADPKD enrolled in the tolvaptan REMS from 14 May 2018 through 3 February 2020 was conducted. Only patients enrolled in the REMS with at least 1 tolvaptan prescription dispensed were included in the analysis. The observational period began from a patient's first shipment date of tolvaptan (index date) and ended on 3 February 2020 or patient death, whichever occurred earlier. Descriptive analyses provided baseline patient characteristics and follow-up measures on a subset of patients eligible for treatment pattern assessment. Additionally, medication possession ratio (MPR) (number of days supplied over a 1-year period) and persistency (length of time taking tolvaptan allowing for ≤59 days between refills) were measured.

Results: A total of 5,366 patients who initiated tolvaptan in the REMS comprised the study population. Mean age at tolvaptan initiation was 46.8 years (standard deviation [SD]: 11.6); 2,751 (51.3%) were female. Of the patients with a known race (n=2,705, 50.4%), the majority were white (n=2,153, 79.6%). Of those with known ethnicity (n=2,682, 50.0%), 2,352 (87.7%) were non-Hispanic or non-Latino. Overall, 2,366 (44.1%) tolvaptan initiators had at least 1 year of follow-up after the index date and were included in the treatment pattern analysis. The most frequent dose of tolvaptan was 45/15 milligrams daily (47.5%). The mean MPR was 0.74 (SD: 0.32); mean persistency was 325.9 days (SD: 173.2).

Conclusions: This is the first descriptive demographic report of real-world ADPKD patients in the US initiating tolvaptan. Based on the data currently available, most patients were between 35-55 years, equally male or female, and were non-Hispanic or non-Latino whites. The patients included in the treatment pattern analysis remained on tolvaptan close to 1 year.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization Inc.

PO1540

Benefit of Tolvaptan on Time to ESRD for Patients with Rapidly Progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Disease Progression Model

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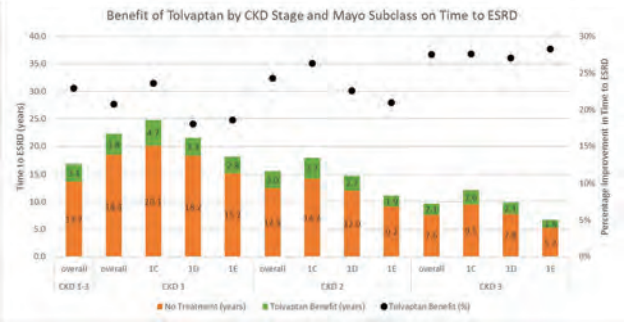
Background: The efficacy and safety of tolvaptan in adults with ADPKD was initially established in a 3-year phase 3 clinical trial (TEMPO 3:4; NCT00428948). Tolvaptan was approved in the United States in 2018 for patients with ADPKD at high risk of progression. A published ADPKD progression model predicted longer-term outcomes including eGFR decline and time to ESRD. The model incorporated an equation used to predict eGFR based on Mayo subclasses 1C, 1D, and 1E as indicators of rapid progression. To estimate treatment benefit, long-term outcomes were modelled for patients treated with and without tolvaptan based on the TEMPO 3:4 cohort.

Methods: In the base case, the annual absolute reduction in eGFR decline for tolvaptan versus placebo of 1.2 ml/min/1.73m^2 was applied to the predicted rates of eGFR decline in the absence of treatment. Additionally, in a sensitivity analysis based on a post-hoc analysis of TEMPO 3:4, the effect on eGFR decline by subclass 1C, 1D, and 1E was applied. CKD progression and time to ESRD were estimated for both cohorts.

Results: The predicted time to ESRD was longer for all patients in CKD stages 1-3 treated with tolvaptan, with greater estimated absolute benefit when treatment was initiated for patients in early CKD stages (Image).

Conclusions: The model estimates that patients treated with tolvaptan versus no treatment spend more time in earlier CKD stages and later onset of ESRD. Results were consistent across CKD stages and Mayo subclasses. Findings highlight the potential long-term value of early intervention with tolvaptan in patients at risk of rapid ADPKD progression.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.



PO1541

Global Real-World Evidence of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a rare, hereditary, systemic kidney disease characterized by progressive renal damage. Patients frequently develop end stage kidney disease, requiring renal replacement therapy. Tolvaptan is the first and only treatment shown to slow kidney function decline in adults who are at risk of rapidly progressing ADPKD. The goal of this literature review was to understand real-world effectiveness and safety data currently available on tolvaptan treatment.

Methods: A review of the literature was conducted in January 2020 in Embase (including Medline) with no language, timeframe, or geography restrictions. Observational studies of ADPKD patients receiving tolvaptan were identified; outcomes of interest included clinical effectiveness and safety, healthcare resource utilization and costs, and quality of life (QoL).

Results: A total of 43 relevant publications were identified. Studies were conducted in Canada, Japan, and across Europe with sample sizes ranging from a single case report to registry analyses of more than 1,000 patients. Clinical results from 6 studies reported a slowing of total kidney volume (TKV) growth and no significant changes in annual decline of estimated glomerular filtration rate (eGFR) over a range of 3 months to 2 years following tolvaptan initiation. Commonly reported adverse events included polyuria (~10%) and liver function-related events (~9%). Reported in 6 studies, 15.6% of patients discontinued tolvaptan treatment, primarily for aquaretic symptoms. Two studies reported that tolvaptan treatment did not appear, over a 1-year period, to negatively impact QoL, with more than 75% of patients reporting little impact on daily activities. No eligible economic studies were identified.

Conclusions: Patients with ADPKD receiving tolvaptan in the real-world experienced improved clinical outcomes without negative impact on QoL. Additional studies assessing real-world evidence supporting tolvaptan treatment in this population are needed.

Funding: Commercial Support - Otsuka Pharmaceuticals Development & Commercialization, Inc.

PO1542

Urinary Lithogenic Risk Profile in ADPKD Patients Treated with Tolvaptan

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Background: Nephrolithiasis is a common health problem in autosomal dominant polycystic kidney disease (ADPKD) and significantly contributes to patient morbidity. Recently, Tolvaptan has been introduced for the treatment of ADPKD, but if it is associated with alterations of the urinary lithogenic risk profile remains unknown.

Methods: We conducted an analysis of participants enrolled in the Bern ADPKD registry, a prospective observational cohort study. 24 hour urine analyses were performed at baseline and then at yearly follow-ups. Relative supersaturation ratios for calcium oxalate, brushite and uric acid were calculated with the program EQUIL2. Unadjusted and multivariable mixed-effects linear regression models, adjusted for age, sex, body mass index, estimated glomerular filtration rate, net acid excretion and height-adjusted total kidney volume were used to assess the association of Tolvaptan with urinary parameters relevant for kidney stone formation. Maximum individual follow-up time was 3 years, median follow-up time 1.9 years and cumulative follow-up time was 169 years.

Results: 125 participants (38 with and 87 without Tolvaptan treatment) were included in the analysis. In multivariable analysis, Tolvaptan treatment was associated (adjusted estimate of the difference Tolvaptan vs. no Tolvaptan; 95% CI) with lower urine relative supersaturation ratios for calcium oxalate (-0.56; -0.82 to -0.3, $p < 0.001$), brushite (-0.33; -0.54 to -0.11, $p = 0.004$) and uric acid (-0.62; -0.88 to -0.37, $p < 0.001$) and with increased urine citrate in mmol/mmol creatinine per day (0.25; 0.050-0.46, $p = 0.02$) and calcium in mmol/mmol creatinine per day (0.31; 0.090-0.53, $p = 0.006$) excretion. In addition, Tolvaptan treatment was associated with decreased net acid excretion in mEq/mmol creatinine per day (-0.54; -0.90 to -0.17, $p = 0.004$) and increased net gastrointestinal alkali absorption in mEq/mmol creatinine per day (0.57, 0.26-0.88; $p < 0.001$).

Conclusions: Tolvaptan treatment is associated with a significantly improved urinary lithogenic risk profile in ADPKD patients.

PO1543

The Effect of Trichlormethiazide in Patients with Autosomal Dominant Polycystic Kidney Disease Using Tolvaptan: A Randomized Cross-Over Controlled Trial

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Background: The vasopressin V2 receptor antagonist tolvaptan has been shown to slow the progression of autosomal dominant polycystic kidney disease (ADPKD). However, some patients discontinue tolvaptan due to severe adverse aquaretic events. This open-label, randomized, controlled, counterbalanced, crossover trial investigated the effects of trichloromethiazide, a thiazide diuretic, on reducing urinary volume and improving tolvaptan tolerability in patients with ADPKD on high-dose tolvaptan, based on the effects of thiazides in patients with nephrogenic diabetes insipidus.

Methods: A total of 10 patients with ADPKD on high-dose tolvaptan (median age, 49 years; 4 males) received antihypertensive therapy with or without trichloromethiazide in random order for 12 weeks. The starting doses for trichloromethiazide were 2 and 4 mg in patients with estimated glomerular filtration rates of ≥30 and <30 mL/min/1.73 m^2, respectively. Target blood pressure range was 110/70–130/80 during the study period. Primary outcomes were 24-h urine volume and urine osmolarity. Secondary outcomes were health-related quality of life (HRQOL) assessed by the Kidney Disease Quality of Life-Short Form questionnaire, rate of decline in renal function, serum/urinary electrolytes, serum/urinary biomarkers associated with chronic kidney disease and ADPKD progression, and office blood pressure.

Results: The urine volume was significantly reduced (3324 ± 614 vs. 4169 ± 729 mL; $P < 0.001$) along with an increase in urinary osmolarity (179.0 ± 26.6 vs. 139.1 ± 39.6 mOsm; $P = 0.001$) in patients on antihypertensive therapy with trichloromethiazide. Moreover, trichloromethiazide improved several HRQOL subscales including effects of kidney disease, sleep, emotional role functioning, social functioning, and role/social component summary. There were no significant differences in the slope of estimated glomerular filtration rate assessed by creatinine and cystatin C or serum/urinary biomarkers between the patients on antihypertensive therapy with and without trichloromethiazide. Office blood pressure was not significantly different between the treatment groups.

Conclusions: In patients with ADPKD treated with high-dose tolvaptan, trichloromethiazide may improve tolvaptan tolerability and HRQOL by reducing urinary volume without affecting ADPKD-related parameters.

PO1544

Predictors for Suppressing Polycystic Liver Progression of ADPKD by Tolvaptan

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Background: Polycystic liver disease (PLD) is one of the fatal complications of ADPKD, which leads to abdominal compression, cyst infection, and liver failure. Although PLD progresses after reaching ESKD, few drugs can effectively inhibit its growth. Tolvaptan (TVP), V2 receptor antagonist, has been known to suppress the growing rate of polycystic kidney disease, but the effect on PLD has not been studied yet. In order to evaluate the tolvaptan's effect on PLD, an observational cohort study was conducted.

Methods: ADPKD patients with PLD taking tolvaptan were enrolled in this study. Total liver volume (TLV) was measured by CT and calculated by automated calculated application, VINCENT®. Annual change of TLV (ΔTLV) was defined by the approximate slope estimated from more than two points. If the patients had some interventions including cyst drainage, surgical fenestration, and transcatheter trans-arterial embolization, the observational period was excluded for one year after such interventions. We compared ΔTLVs before and after TVP initiation, and defined "responder" as patients whose post-ΔTLV were smaller than pre-ΔTLV. Factors associated with "responder" were analyzed by the logistic regression model, adjusting sex, age, BMI, blood pressure, height adjust total kidney volume(htTKV) and ΔTLV before taking TVP(preΔTLV), by using R version 3.4.3.

Results: 85 patients were eligible to this study. Median observational periods were 1.98 and 2.19 year in pre-prescription period and post-prescription period respectively. Median age was 53 years old and 31 cases were female. Median htTLV and htTKV before taking TVP was 1747[557-7432] (ml/m) and 909[226-4152] (ml/m), respectively. The reduction of ΔTLV were observed in 46 cases, who were significantly older, had higher preΔTLV and had higher rate of taking ursodeoxycholic acid. Logistic regression analysis showed older age (OR 2.60[1.36-5.72],$p<0.01$) and higher preΔTLV (OR 1.25[1.12-1.46], $p<0.01$) were the predictors of the reduction of ΔTLV.

Conclusions: In this study, more than half of ADPKD patients experienced reduction of ΔTLV after taking TVP. Our study suggests that elder age and higher pre-ΔTLV would predict the reduction of the progression of PLD after TVP use, though it was reported younger female tend to have larger PLD.

PO1545

Use of Lixivaptan in a Patient with Autosomal Dominant Polycystic Kidney Disease (ADPKD) Who Previously Experienced Liver Toxicity with Tolvaptan

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Introduction: Blockade of the vasopressin V2 receptor has beneficial effects on the renal manifestations of ADPKD, the most prevalent inherited renal cystic disease in humans. Tolvaptan, a vasopressin V2 receptor antagonist, is the only approved pharmacologic therapy for the treatment of ADPKD patients; however, it is associated with potentially serious idiosyncratic liver toxicity. Lixivaptan is a novel, potent antagonist of the V2 receptor in Phase 3 development for the treatment of ADPKD. Evidence from non-clinical and in silico studies predicts that lixivaptan will have a safer liver toxicity profile in patients with ADPKD. Here we provide the first clinical evidence of lixivaptan's superior liver safety compared to tolvaptan.

Case Description: A female patient with ADPKD presented with severe bilateral, intractable flank and abdominal pain. The patient had been treated with tolvaptan previously in an attempt to improve her pain; however, tolvaptan therapy had to be permanently discontinued after the patient developed clinically-meaningful alanine aminotransferase (ALT) elevations on each of three sequential attempts to treat her. The patient was screened and enrolled in an open-label study of lixivaptan under a US IND expanded-access protocol (PA-103). After treatment with therapeutic doses of lixivaptan for 12 months, there have been no elevations of ALT or other liver chemistry tests. Improved pain control has allowed resumption of more normal daily activities and the cessation of use of opioid pain medications. Pharmacodynamic effects including decreases in total kidney volume and liver volume were demonstrated as well as expected changes in eGFR with a vasopressin antagonist. Treatment with lixivaptan continues.

Discussion: This is the first report of successful treatment with lixivaptan of a patient who had previously experienced liver toxicity on tolvaptan. These clinical data highlight the potential for improved liver safety with lixivaptan in a patient at high risk for developing liver toxicity. A larger study (PA-ADPKD-303: The ALERT Study) is starting up to treat ADPKD patients with lixivaptan who previously discontinued tolvaptan because of liver chemistry test elevations.

PO1546

Generation of Collecting Duct Kidney Organoids from Human Induced Pluripotent Stem Cell

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Background: Polycystic kidney disease (PKD) is one of the most common human genetic disorders without effective therapy. During its progression, fluid-filled cysts displace normal collecting duct (CD) tubules causing end-stage renal failure. The lack of disease-relevant in vitro models of PKD has hampered early drug discovery and needs more efficient and robust tools.

Methods: Here we modified a previously published protocol [1] and established a high-throughput and highly efficient method for the generation of CD kidney organoids from human induced pluripotent stem cells (hiPSC). We employed a dynamic modulation of cell signaling pathways in combination with 3D extracellular matrix support to induce CXCR4+/cKit+ ureteric bud (UB) cell progenitors and further UB branching.

Results: The UB gives rise to renal collecting ducts and the lower urinary tract. We observed the development of UB-like cytoarchitecture including, bifurcated ureteric tip expressing specific markers (RET, WNT9B, HOXB7). Using single-cell RNA sequencing (scRNAseq) we identified two major cell populations in differentiated CD organoids – collecting duct cells and stromal cells. CD cells express typical markers of UB trunk (CK19), the ureteric epithelium (CDH1, CK8), as well as mature markers (AQP2, CALB1, MUC1) including principal (AQP3) and intercalated cells (AQP5). Moreover, we identified cilia formation on the inner surface of the luminal cavity of CD tubules which mimics normal kidney development. Using pharmacological approaches, we were able to induce cysts formation in response to forskolin and cholera toxin treatment, thus, simulating the abnormal CD response to excess cAMP in PKD or normal rodent embryonic kidneys [2].

Conclusions: In conclusion, we provide a robust and highly efficient method for collecting duct marker expressing organoids that may contribute to elucidating the mechanisms of kidney development, disease modeling of the lower urinary tract (polycystic kidney disease), and drug discovery. 1. Taguchi A, Nishinakamura R. (2017) Higher-order kidney organogenesis from pluripotent stem cells. *Cell Ste Cell*. 21: 730-746 2. Magenheimer BS et al. (2006). *J Am Soc Nephrol.* 17(12): 3424-3437

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PO1547

A Fluidic Model of ARPKD Using Vascularized Kidney Organoids Identifies HIF-1 as a Potential Therapeutic Target

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Background: We have recently reported a method to generate vascularized kidney organoids using fluidic chips. Vascularized kidney organoids derived from PKHD1 mutants demonstrated clinically relevant phenotypes that recapitulate cystogenesis in distal nephrons unlike static models with forskolin which induces cysts in proximal tubules. Here, we utilized this new PKD model to elucidate pathomechanisms and identified potential therapeutic targets for ARPKD patients.

Methods: PKHD1-mutant hPSCs were generated by CRISPR/Cas9 genome editing and differentiated into kidney organoids by following our reported protocol. Cystogenesis was stimulated by either fluidic flow on fluidic chips or forskolin in static culture. Cystic phenotypes were quantitatively determined by immunostaining. Gene expression was evaluated by 3D-gene microarray, and signal pathways were assessed by Metacore. Based on signal pathway results, candidate compounds were tested, and phenotypic improvement was evaluated by measuring tubular/cyst diameters using whole-mount immunostaining.

Results: Fluidic flow altered 407 signal pathways in PKHD1-/- organoids when compared to PKHD1+/- organoids while 63 pathways were changed by forskolin treatment in conventional static culture. In those pathways, 32 were involved in both flow- and forskolin-induced signal changes. In the common 32 pathways, HIF-1 pathway was top ranked with lowest p value of 3.71×10^{-14}, suggested as a potential pathomechanism of ARPKD. To validate the result, we treated vascularized kidney organoids with HIF-1 inhibitor from day 16, the earliest stage of nephron differentiation. The distal nephron diameter was increased from 36.2 ± 7.7 μm (n=96) to 54.4 ± 21.8 μm (n=59) by fluidic flow ($p=8.65\times10^{-12}$), which was decreased to 46.1 ± 16.8 μm (n=158) by a HIF-1 inhibitor ($p=0.004$).

Conclusions: We identified HIF-1 as a potential therapeutic target for ARPKD patients. PKD organoids using an organ-on-a-chip platform might serve as a better model to elucidate disease developing mechanism and discover disease-specific new therapeutic targets *in vitro*.

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PO1548

The Effect of Trehalose on Autophagy-Related Proteins and Cyst Growth in a Hypomorphic Pkd1 Mouse Model of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: There is growing attention on understanding the role of impaired autophagy in ADPKD. Trehalose (TRE) is a natural sugar that is used as a food additive. TRE increases protein stability, aggregate clearance and autophagy in neurodegenerative diseases. TRE treatment in wild type (WT) mice resulted in increased expression in the kidney of Atg12-5 complex and Rab9a (Table), autophagy-related proteins that play a role in the formation of autophagosomes. Thus, the aim of the study was to determine the effect of TRE on cyst growth and autophagy-related proteins, in the Pkd1$^{RC/RC}$ (RC) mouse model.

Methods: Autophagy proteins determined by immunoblot analysis. Male RC mice were treated with TRE from 50-120 days of age.

Results: In RC kidneys, expression of the Atg12-5 complex was inhibited by TRE resulting in increased free Atg12. TRE was unable to rescue the deficiency of the Atg12-5 complex. Rab9a was decreased in RC and unaffected by TRE. The TRE-induced increase in p62, a marker of autophagic cargo, that was seen in WT was blocked in RC kidneys. In RC kidneys, there were decreases in autophagy-related proteins (Atg12-5 complex, Atg5, Atg16L1), decreased Rab9a and increased mTORC1 (pS6, p-mTOR) proteins. 2 kidney/body weight ratio (2K/BW), cyst index/count, BUN were not different in TRE vs. Veh treated RC kidneys.

Conclusions: The autophagy phenotype in RC kidneys was characterized by decreases in essential autophagy related proteins. TRE increased Atg12-5 complex, Rab9a and p62 in WT kidneys, but was unable to rescue the deficiency in autophagy proteins or suppress mTORC1 in RC kidneys and did not protect against cyst growth.

Funding: Veterans Affairs Support, Other U.S. Government Support

Densitometry units/GAPDH *P<0.05, **P<0.01. ***P<0.001

	WT	WT+TRE	RC	RC+TRE
ATG12-5	0.4	0.9	0.05**	0.05**
Free ATG12	0.1	0.1	0.8***	0.9***
Rab9a	0.7	1.0	0.3*	0.3*
p62	0.4	1.0**	0.1	0.1
ATG16L	1.5	1.5	0.8*	0.5*
ATG5	1.4**	1.4**	0.8	1.0
pS6	0.6	0.7	2.1**	2.4**
p-mTOR	1.1	1.1	1.9**	2.3**
2K/BW (%)			2.7	3.0
Cyst index/number			14/330	16/300
BUN (mg/dL)			23	24

PO1549

Suppressed Autophagic Flux in the Heart in a Hypomorphic Pkd1 Mouse Model of ADPKD

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Background: Heart disease is largely unexplored in mouse models of ADPKD. The aim of the study was to determine mTOR signaling and autophagy in the heart in Pkd1$^{RC/RC}$ (RC) mice

Methods: Proteins were determined by immunoblot analysis. Mice were treated with autophagy inducers 2-deoxyglucose (2-DG) or Tat-Beclin1 peptide (Tat).

Results: There was increased heart weight/body weight ratio (HW/BW) in 180 d old RC mice. In 70 day old RC hearts, there was no increase in mTOR but a large increase in p-AMPK^{Thr172}, a known autophagy inducer. In 150 day old RC hearts, there was an increase in p-S6, p-Akt^{Thr308}, p-GSK3β, p-AMPK, p-Beclin, an autophagy regulator and activating molecule in Beclin-1-regulated autophagy (AMBRA1). There was suppressed autophagic flux (lack of an increase in LC3-II, a marker of autophagosomes, with the lysosomal inhibitor bafilomycin-Baf), in 70 and 150 d old RC hearts compared to an increase in wild type (WT) hearts. In 120 d old RC hearts there was no increase in proliferation (PCNA) or apoptosis (TUNEL). Both 2-DG and Tat treatment increased heart weight and had no effect on kidney weight

Conclusions: There was a large increase in p-AMPK and suppressed autophagy in RC hearts. Unexpectedly, autophagy inducers increased heart weight

Funding: Veterans Affairs Support, Other U.S. Government Support

	Age (days)	WT	RC
HW/BW (%)	150	0.49	0.52
HW/BW (%)	180	0.57	0.71***
Densitometry			
p-S6	120	0.7	1.3*
p-Akt	120	0.6	1.5*
p-GSK3B	120	1.1	1.4*
p-AMPK	70/120	0.5	1.5**
p-Beclin	120	0.3	0.7*
AMBRA	120	0.3	0.8**
		WT Veh	WT Baf
LC3-II	70	0.9	1.7*
LC3-II	120	0.6	1.3*
		RC Veh	RC Baf
LC3-II	70	0.2	0.3
LC3-II	120	0.9	0.9
HW/BW (%)		RC	RC+Tx
2-DG	150-350	0.54	0.59
Tat	70-120	0.53	0.62**
2K/BW (%)			
2-DG	150-350	2.8	2.7
Tat	70-120	2.4	2.3

*P<0.05, **P<0.01. ***P<0.001

PO1550

Ferroptosis Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: Ferroptosis is a newly discovered form of non-apoptotic cell death which is dependent on accumulation of lipid reactive oxygen species (ROS). Recent studies have shown that ferroptosis is involved in the pathophysiological processes of many diseases, such as cancer. However, the roles of ferroptosis in ADPKD remain unknown.

Methods: To evaluate whether ferroptosis occurs in ADPKD, we detected the levels of ROS with C11-BODIPY and 4-HNE staining, and the expression of glutathione peroxidase 4 (GPX4), a key protein in the ferroptotic pathway, by western blot and qRT-PCR in cystic cells and kidneys. To understand the role of ferroptosis in ADPKD, we treated *Pkd1* mutant mice with erastin, a ferroptosis inducer, and Ferrostain-1, a ferroptosis inhibitor.

Results: We found that the levels of free radical-induced oxidation and 4-HNE, a biproduct of lipid peroxidation, were increased in *Pkd1* mutant renal epithelial cells and tissues as examined by C11-BODIPY and 4HNE staining. Erastin treatment resulted in smaller-than-normal mitochondria with increased density, a morphological feature of ferroptotic cells, in *Pkd1* mutant renal epithelial cells under electronic microscopy. We further found that treatment with erastin promotes cyst growth as seen by increased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and lipid peroxidation in *Pkd1*$^{RC/RC}$ mice (all $p < 0.01$). In contrast, treatment with Ferrostain-1 delayed cyst growth in early stage *Pkd1*$^{flox/flox}$;*Pkhd1*-Cre mice and *Pkd1*$^{RC/RC}$ mice as seen by decreases in all the parameters observed in erastin treated mice. Treatment with erastin increased the activation of ERK, Stat3, Akt and Rb in *Pkd1* mutant renal epithelial cells and tissues. Activation of Stat3 increased the expression of DNA methyltransferase 1 (DNMT1), leading to the binding of DNMT1 to the *GPX4* promoter and decreased expression, resulting in the accumulation of ROS species to promote cystic renal epithelial cell ferroptosis. Treatment with Ferrostain-1 reversed all these processes in *Pkd1* mutant renal epithelial cells and tissues.

Conclusions: *Pkd1* mutation induced the downregulation of GPX4 via Stat3-DNMT1, resulted in accumulation of ROS species, and the induction of ferroptosis to promote renal cyst growth. Inhibition of ferroptosis may be a viable new therapy for ADPKD.

Funding: NIDDK Support

PO1551

Cux1 Regulates Cilia Length in Polycystic Kidney Disease

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Background: Renal cyst development in ADPKD results from mutations in the PKD1 or PKD2 genes, which encode the proteins polycstin1 (PC1) and polycystin2 (PC2). PC1 and PC2 proteins are localized to primary cilia where they are proposed to form a receptor channel complex that detects flow transmitting a calcium-mediated signal. Primary cilia are critical to the pathogenesis of ADPKD, which is one of many ciliopathies that exhibit renal cystic disease. Cux1, a murine homolog of the Drosophila gene Cut, is a cell cycle dependent transcriptional repressor that regulates the cyclin kinase inhibitor p27. Cux1 is highly and ectopically expressed in mice carrying a collecting duct (CD) specific mutation of Pkd1 (Pkd1 knockout) and in human ADPKD cells. Mice carrying mutations in both Cux1 and Pkd1 have reduced cystic disease and an increased life span. A role for Cux1 in regulating genes involved in cilia assembly and function has recently been identified in the Galapagos cormorant, however the role of Cux1 in cilia in the mammalian kidney is not known.

Methods: To begin to determine whether Cux1 regulates ciliogenesis we evaluated cilia morphology and the expression of the ciliary protein, OFD1 (oral-facial-digital-1),

identified as a Cux1 target in the Galapagos cormorant. Cilia analysis was performed on kidneys isolated from wild type, Cux1 transgenic, Pkd1 knockout, and Pkd1/Cux1 double knock out mice. Cilia morphology was assessed by immunofluorescence labeling of alpha-tubulin, a major component of cilia, and the collecting duct marker dolichos biflorus agglutinin (DBA) to identify cells in which Pkd1 was deleted.

Results: Cilia in Pkd1/Cux1 double knockout kidneys were significantly shorter than cilia in the Pkd1 knockout kidneys alone, consistent with previous studies showing that decreased cilia length corresponds to decreased cystic disease. OFD1 is an inhibitor of ciliogenesis and OFD1 expression in the various mouse models demonstrate that OFD1 expression corresponds to Cux1 expression. OFD1 protein levels were the lowest in the kidneys of mice constitutively expressing Cux1 and were highest in mice with deletions of Cux1.

Conclusions: Taken together, our results suggest a novel role for Cux1 in regulating ciliogenesis in the kidney and that reduced cystic disease in the Pkd1/Cux1 double mutant mice results from reduced cilia length.

PO1552

Low-Dose Repeated Cisplatin-Induced Renal Injury Promotes Cyst Formation in Both Cilia Mutant and PC2 Mutant Mouse Models

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Background: Multiple renal cystic diseases, including PKD, are caused by dysfunction of the primary cilium on the tubule epithelium. Links between cilia dysfunction, cyst formation, and renal injuries have been reported. In animal models, injury (e.g. ischemia reperfusion) exacerbated the rate of cyst formation. Cisplatin is an antitumor drug used widely in treatment of varieties of malignancies that also has severe nephrotoxicity side effects. Here we evaluate whether a second form of renal injury induced by a low dose of Cisplatin also leads to mal-repair of the kidney and to increased cyst formation in mouse models with cilia function perturbation.

Methods: To test the effects of cisplatin-induced renal injury on cyst formation, we utilized a low-dose repeated cisplatin protocol (5.0mg/kg BW; IP once a week for 4 weeks) on adult-induced conditional Ift88 and PC2 mutant mice. We preformed IF staining for the injury marker kim1 and flow cytometry analysis of immune cells from WT and cilia dysfunctional kidneys 3 days after 2° cisplatin treatment to evaluate renal injury. Cyst index were analyzed at 5 weeks in PC2 mutant and at 9 weeks in Ift88 mutant after the final dose.

Results: Low-dose repeated cisplatin treatment resulted in increased kim1 expression, mainly in the cortex, compared to vehicle treatment group in both Ift88 mutant and PC2 mutant mice compared to control. Analysis of flow cytometry data showed that there was minimal immune cell accumulation, including macrophages, NK, B or T cells, at 3 days after 2° cisplatin injection, similar to that in controls. Additional time points are currently being evaluated. While we did not observe major changes in immune cell response at the earlier time point prior to cyst formation, in both PC2 and Ift88 mutants there was a marked increase in cyst severity, accompanied with massive immune cell accumulation compared to vehicle treated mutants at 5 and 9 weeks after the final cisplatin injection, respectively.

Conclusions: These data indicate cilia function is important in regulating repair processes following injury, defects in which contribute to more aggressive rates of cystogenesis. Additionally, it suggests multiple forms of injury induce cyst formation and that the cisplatin protocol could be used as an alternative approach to IRI to accelerate cyst formation in PKD animal models.

Funding: NIDDK Support

PO1553

Primary Cilia Defects Reflect Specific Bone Cell Activity in Human ADPKD Osteoblast Cells

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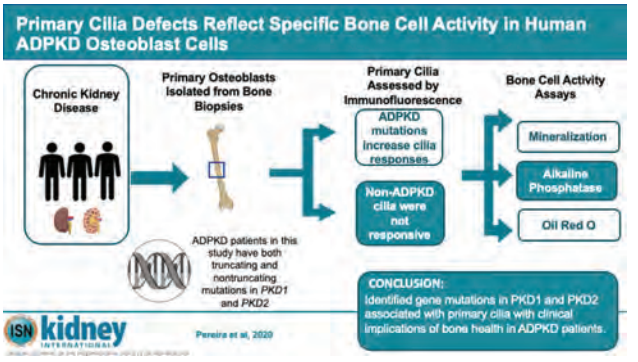
Background: Autosomal dominant polycystic kidney disease (ADPKD) is predominately caused by mutations in primary cilium genes polycystic kidney disease *PKD1* and *PKD2*. Recent studies show that ADPKD is associated with abnormal bone health with decreased bone formation and low bone serum alkaline phosphatase, even when kidney function is preserved. Knowledge of the regulatory links between ADPKD, cilia, and human bone health is lacking.

Methods: We assessed primary cilia in cultured pre-osteoblasts derived from ADPKD patients with *PKD1* or *PKD2* mutations, relative to healthy controls and non-ADPKD chronic kidney disease (CKD) patients. Cilia were quantified by immunofluorescence staining of pericentrin and acetylated-α-tubulin. Cilia responsiveness was examined following treatment with lithium chloride (LiCl), an activator of the canonical Wnt signaling pathway that is known to induce cilia elongation. Biochemical osteoblast analyses included bone turnover by alkaline phosphatase (ALP) activity and mineralization assays.

Results: Compared to healthy control cells, ADPKD osteoblasts displayed longer cilia at baseline and were significantly more responsive to elongation with LiCl. In contrast, non-ADPKD CKD osteoblasts had shorter cilia and lacked LiCl responsiveness. Despite similar histological features and adynamic bone characteristics, ADPKD osteoblasts mineralized faster than osteoblasts from non-ADPKD CKD. The ALP activity levels were decreased in ADPKD osteoblast cells, which is consistent with the lowered circulating bone ALP levels.

Conclusions: Together, these data support a model whereby altered cilia responsiveness in ADPKD osteoblasts is linked to bone cell activity and mineralization defects that are distinct from adynamic bone of non-ADPKD CKD patients.

Funding: NIDDK Support



PO1554

Pathobiology of Cyst Progression in Nbce1A and Pkd1 (RC/RC) Mouse Models

Deema A. Anaam,[1] Heather L. Holmes,[2] Adriana Gregory,[1] Ka Thao,[3] Alison Stiller,[2] Peter C. Harris,[3,4] Timothy L. Kline,[1,2] Michael F. Romero.[2,3] *[1]Radiology, Mayo Clinic Minnesota, Rochester, MN, Rochester, MN; [2]Physiology & Biomedical Engineering, Mayo Clinic Minnesota, Rochester, MN, Rochester, MN; [3]Nephrology & Hypertension, Mayo Clinic Minnesota, Rochester, MN, Rochester, MN; [4]Biochemistry & Molecular Biology, Mayo Clinic Minnesota, Rochester, MN, Rochester, MN.*

Background: The *Pkd1(RC/RC)* mouse is a hypomorphic model of autosomal polycystic kidney disease (ADPKD) characterized by renal cortical and medullary cysts which increase in size and number with age. The nature of these cysts and how this epithelium differs from normal collecting duct epithelia is currently unknown. Moreover, as the phenotype is variable, the disease progression of any individual mouse is unknown. We also generated an isoform specific Na^+ bicarbonate cotransporter knockout (*Nbce1A*-KO) mouse using TALENs. As with the whole gene knockout, these mice are severely acidotic but also present with cortical renal cysts. The nature of these cysts and their connection to NBCe1A protein expression is currently unknown.

Methods: We measure mouse (Bk6J) total kidney volume (TKV) using MRI (7T/16T) and ultrasound (US; SonoVol Vega). The Vega system allows 3D renal imaging and cardiac analysis (e.g., heart rate, ejection fraction, cardiac output). We follow renal function using transdermal GFR measurements. Lastly, kidneys are harvested, fixed, followed by immunofluorescence (IF) of cryosections with nephron segment specific markers or picrosirius red (collagen stain) of paraffin sections.

Results: A longitudinal study of *Nbce1A-KO* and *RC/RC* mice shows both models increased TKV (Fig A) measured by MRI or US (Fig B,C). Both show lower GFR [WT: 558±40, *nbce1A-KO*: 420±144, RC/RC: 276±63 μL/min/(100g-bw)]. Ejection fraction and stroke volume were preserved, while heart rate and cardiac output decreased in *Nbce1A-KO* and *RC/RC* mice (Fig A). Both *Nbce1A-KO* (Fig E) and *RC/RC* mice (Fig F) have collecting duct cysts, positive for AQP2 and cKit. Picrosirius red staining shows that these cystic structures have increased collagen thickening.

Conclusions: Taken together these data imply that cystogenesis in the *RC/RC* and *nbce1A-KO* models have similar pathobiology. Potentially this means that understanding how and why cysts develop in nbce1A-KOs may provide additional mechanistic information in ADPKD.

Funding: NIDDK Support, Private Foundation Support

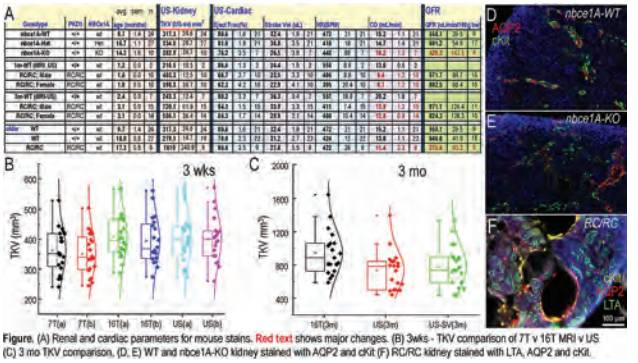


Figure. (A) Renal and cardiac parameters for mouse stains. Red text shows major changes. (B) 3wks - TKV comparison of 7T v 16T MRI v US (C) 3 mo TKV comparison, (D, E) WT and nbce1A-KO kidney stained with AQP2 and cKit (F) RC/RC kidney stained with LTA, AQP2 and cKit.

PO1555

Characterization of the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Response in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive development and enlargement of bilateral renal cysts. Abnormal epithelial cell proliferation, along with the inability to maintain planar cell polarity, underlies cyst formation and enlargement. Therefore, processes that stimulate renal cell proliferation have the potential to generate the cystic phenotype. Interestingly, an increased nuclear factor erythroid 2-related factor 2 (Nrf2) response has been shown to direct cancer cells into an anabolic mode that favors cellular proliferation, and has been associated with renal cyst formation in experimental and human fumarate hydratase deficiency. However, the Nrf2 response has not been described in ADPKD. We hypothesized that early ADPKD presents with an elevation in the Nrf2 response that favors cellular proliferation and contributes to cystogenesis.

Methods: We sought to longitudinally characterize the Nrf2 response and association with cystogenesis and fibrosis in a slow progressive mouse model of ADPKD (*Pkd1*$^{RC/RC}$) and its wildtype controls (n=6 males, 6 females per group). Urine and plasma samples were collected at 30, 60, 120, and 180 days for chemistries and metabolic profiles, and cystic index (CI), and total kidney volume (TKV) were determined from abdominal MRI. Nrf2 levels and related response enzymes, as well as cell proliferation and fibrosis were analyzed using western-blots, immunofluorescence, and assay kits.

Results: At 30 days, *Pkd1*$^{RC/RC}$ mice presented increased CI and TKV/BW. However, serum creatinine and fibrotic markers were not different compared to controls. *Pkd1*$^{RC/RC}$ mice exhibited elevated Nrf2 expression and immunoreactivity early on that declined as ADPKD progressed from 30 to 180 days and correlated directly with cell proliferation (R^2=0.693, $p<0.05$) and inversely with fibrotic markers (R^2=0.672, $p<0.05$).

Conclusions: Our study shows longitudinal changes in the Nrf2 response in *Pkd1*$^{RC/RC}$ mice that are associated with cystogenesis early on and renal fibrosis at later stages of the disease. These findings have significant implications for the treatment of human ADPKD, and suggest that Nrf2 modulators might represent an advantageous intervention for the disease.

Funding: NIDDK Support

PO1556

Dietary Protein Load Increases Kidney Macrophage and Accelerates Polycystic Kidney Disease

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Background: The disease severity for autosomal dominant polycystic kidney disease (PKD) is highly variable even among families with the same gene mutation, suggesting factors other than genetics may affect cystogenesis. One factor that accelerates cyst growth in PKD mouse is compensatory renal hypertrophy triggered by unilateral nephrectomy or a high protein diet. We recently reported that unilateral nephrectomy increases kidney macrophages, cytokines and accelerates cystogenesis in *Pkd1*-knockout mice. We hypothesize that *Pkd1*-knockout mice fed a high protein diet, similarly increases kidney macrophages and accelerates cyst growth.

Methods: We used adult tamoxifen inducible *Pkd1*$^{flox/flox}$ mice with or without CAGG-cre. After cre induction, mice were fed either a high protein (HP: 60%), a normal protein (NP: 18%) or a low protein (LP: 6%) diet for a total of 1 or 6 weeks. Some mice fed a HP diet were treated with liposomal clodronate (to deplete macrophage) or phosphate buffer saline (intraperitoneally twice a week) for a total of 6 weeks. Mice were euthanized at the end of the experiment for kidney histology, measurements of cytokine and macrophages by FACS.

Results: *Pkd1*-knockout mice fed a HP diet for 6 weeks resulted in increased number of kidney resident macrophage (CD11b^{lo}, F4/80 ^{hi}) and infiltrating macrophages (CD11b^{hi}, F4/80^{lo}) compared to *Pkd1*-knockout mice fed a NP or LP diet. HP diet fed mice resulted in increased kidney pro-inflammatory cytokines, chemokines and severe kidney cysts growth compared to NP or LP diet fed mice. Early after dietary protein modification (1 week), *Pkd1*-knockout mice fed a HP diet had larger kidneys, higher cystic index and kidney mTOR level compared to LP diet fed *Pkd1*-knockout mice but there were no differences in the number of macrophages, chemokine and cytokine levels in the kidney. HP diet fed *Pkd1*-knockout mice treated with liposomal clodronate, resulted in decreased number of macrophages, cytokine and fewer cysts compared to PBS treated *Pkd1*-knockout mice.

Conclusions: Dietary protein load increases kidney macrophages, inflammatory cytokine production and accelerates cyst growth in adult *Pkd1*-knockout mice. HP diet stimulates kidney cyst expansion prior to the recruitment of macrophages early on, but subsequent macrophage depletion therapy slowed the acceleration of cyst growth.

Funding: NIDDK Support, Private Foundation Support

PO1557

Cyst-Lumen Renal Stones in Mice Compound Heterozygous for Hypomorphic Pkd1^{V} and Pkd1^{RC} Alleles

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Background: Autosomal dominant polycystic kidney disease (ADPKD) patients exhibit a ~2.5-fold higher propensity for renal stone formation compared to that of the general population. However, there are no good mouse models for the analysis of stone formation in ADPKD. We previously reported the presence of cortical renal stones in cystic mice compound heterozygous for hypomorphic alleles *Pkd1*^{V} and *Pkd1*^{RC} (Parnell *et al.* 2018 J Am Soc Nephrol 29:295). In this present study, the composition and location of the renal stones in this PKD model were determined.

Methods: *Pkd1*^{V} and *Pkd1*^{RC} mice on a C57 background were crossed to produce cystic *Pkd1*$^{V/RC}$ mice. Mice were sacrificed at 3-26 weeks and their kidneys analyzed by Alizarin Red and von Kossa staining. Individual stones were microdissected from cysts and analyzed by μCT and infrared spectroscopic analysis to determine their composition.

Results: Although *Pkd1*$^{V/RC}$ mice were noticeably cystic by 3-weeks of age, stone formation was not obvious until ~13-weeks. Histological sections from 13- and 26-week old mice had regions that stained positive by Alizarin Red and von Kossa in a generally overlapping pattern. In contrast, there were no obvious staining patterns by Alizarin Red or von Kossa in kidneys from 3-week old mice. When kidneys were dissected it became evident that the stones were found almost exclusively within the lumens of cysts (see microdissected cyst with internal stone in Figure 1). μCT and infrared spectroscopic analysis confirmed that dissected stones were comprised of calcium phosphate in the mineral form of apatite, and also rich in protein.

Conclusions: *Pkd1*$^{V/RC}$ mice develop mineralized stone deposits comprised of apatite and protein within the renal cystic lumen. To our knowledge this is the first known instance of renal stones in a mouse model of ADPKD.

Funding: NIDDK Support

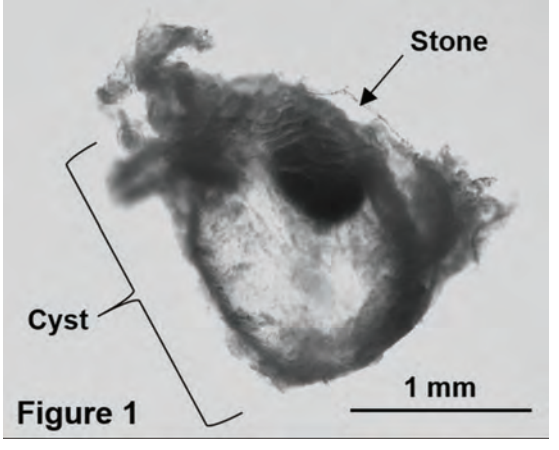

Figure 1

PO1558

Small-Molecule Allosteric Activators of Long-Form PDE4 Enzymes Suppress Cystogenesis in Models of ADPKD

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Background: In ADPKD, mutations in either *PKD1* or *PKD2* perturb intracellular calcium signalling and drive a chronic elevation of intracellular cAMP through de-suppression of calcium inhibited adenylyl cyclase 5/6. This elevation of cAMP signalling underpins the molecular pathology of ADPKD, promoting widespread cyst formation within the nephron epithelium, ultimately leading to renal failure. Phosphodiesterase 4 (PDE4) enzymes degrade intracellular cAMP in a localised manner, and their activity contributes to the compartmentalisation of sub-cellular cAMP dynamics. By modulating or terminating cAMP mediated signalling events, PDE4 isoforms are placed as a central regulator of many cAMP mediated biological processes. We have previously described the discovery and characterization of novel small-molecule compounds which allosterically activate long isoforms of PDE4, and here we further describe their therapeutic potential in suppressing the core cAMP drive behind the pathogenesis of ADPKD.

Methods: Biochemical assay, gene expression profiling and genetic manipulation of cell models were undertaken alongside primary human cell 3D-culture experiments and

Mouse *Pkd1*$^{RC/RC}$ metanephric organ culture to investigate the effects of pharmacological long-form PDE4 activation on intracellular cAMP and cyst dynamics.

Results: Our data show that within murine kidney epithelial cells PDE4 long-form variants from Pde4c and Pde4d predominate and that allosteric pharmacological activation of long-form Pde4 enzymes suppresses intracellular cAMP. We show that the PDE4 mediated suppression of cAMP signalling results in the suppression of cystogenesis in translational models of ADPKD, such as in *Pkd1*$^{RC/RC}$ metanephric organ culture and primary human ADPKD cyst culture. This further supports the potential therapeutic benefit of allosteric activation of PDE4 in treating ADPKD.

Conclusions: Small-molecule activators of long-form PDE4 enzymes suppress aberrantly elevated cAMP signalling and exhibit potential utility as therapeutics in ADPKD.

Funding: Commercial Support - Mironid Limited

PO1559

Probenecid Inhibits Cyst Development in Pkd1$^{RC/RC}$ Mice

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Background: ADPKD cysts contain high levels of ATP that contribute to cyst enlargement. Among other effects, ATP excess leads to a reduced reabsorption in cyst-lining cells and cyst fluid accumulation. We demonstrated that Pkd1$^{RC/RC}$ mice, a model of ADPKD, exhibit increased expression of pannexin-1, a membrane channel capable of ATP release. Probenecid, a uricosuric agent, is also used as a pannexin-1 blocker reducing ATP release. We studied therapeutic potential of probenecid in Pkd1$^{RC/RC}$ mice and its effect on sodium reabsorption.

Methods: Pkd1$^{RC/RC}$ mice, a hypomorphic model of ADPKD, were aged till 10.5 months and osmotic minipumps were implanted to deliver probenecid for 42 days. After treatment, 1 year old conscious mice were subjected to glomerular filtration rate (GFR) measurements and kidneys were collected for histomorphological studies. Effect of probenecid on Na^+ reabsorption was tested on mpkCCD cells seeded onto permeable supports with open-circuit current measurements.

Results: In vivo inulin clearance study demonstrates that Pkd1$^{RC/RC}$ mice have normal GFR 1.05±0.09 ml/min/100g at the 6 months old age (n=15) whereas GFR in C57BL/6 mice - 0.94±0.1 ml/min/100g (n=8). With disease progression GFR in Pkd1$^{RC/RC}$ mice reduces to 0.36±0.08 ml/min/100g at 12 months age. 42 days long probenecid treatment (15.9 mg/kg/day) significantly improves GFR to 1.43±0.11 ml/min/100g ($p<0.001$). Probenecid treatment also reduced kidney hypertrophy: kidney/TBW ratio in vehicle group was 2.54±0.17% vs 1.76±0.05% probenecid ($p<0.05$). Histological study on sectioned kidneys revealed that probenecid significantly reduces cyst size. Cyst to total slice area ratio was 13.9±2.7% (vehicle) vs 3.4±0.8% (probenecid) (n=5 each group). Earlier we have shown that probenecid decreases luminal ATP release in immortalized CD cell culture. As ATP is cable of downregulating Na^+ reabsorption via the epithelial sodium channel we tested if probenecid increases ENaC activity. We applied probenecid to mpkCCD cell monolayer and found that the drug causes a bell-shaped dose-dependent increase of amiloride-sensitive transepithelial flux with maximal effect at 50 μM.

Conclusions: Probenecid demonstrates therapeutic potential against ADPKD cyst progression in a Pkd1$^{RC/RC}$ mouse model by reducing cyst size, renal hypertrophy and supporting GFR and reabsorption from the cyst space. Support: ASN Carl W. Gottschalk Award

Funding: Private Foundation Support

PO1560

Pharmacological Inhibition of β-Catenin-Activated Transcription Slows Cystogenesis in a Postnatal Mouse Model of ADPKD

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Background: The Wnt signaling pathway has an important role in nephron development and elevated expression of β-catenin, master regulator of the Wnt signaling pathway, has been shown to correlate with cystogenesis in autosomal dominant polycystic kidney disease (ADPKD). Here we provide evidence that pharmacological inhibition of β-catenin-activated transcription slows cystogenesis in a postnatal model of ADPKD.

Methods: To understand the pathological contribution of Wnt signaling to ADPKD, we measured expression of Wnt genes and β-catenin *in vivo* using a postnatal murine model of ADPKD. We also tested the effect of a selective β-catenin-CBP inhibitor on cyst formation.

Results: We observed both increased expression of *Wnt 7a* and higher levels of β-catenin in cystic kidneys of *CAGG-CreER^{T2};Pkd1$^{flox/flox}$* mice. In addition, fibronectin, a known transcriptional target of β-catenin was significantly overexpressed in murine cystic kidneys and also in kidneys from humans with ADPKD. To test whether increased β-catenin transcriptional activity was required for cystogenesis, we treated *CAGG-CreER^{T2};Pkd1$^{flox/flox}$* mice with a small molecule, ICG-001, that blocks the interaction of β-catenin with CBP. We detected significant reduced cyst formation as measured by the kidney/body weight ratio (0.047g ±0.004 vs 0.022g ±0.001) and the cyst area per kidney area (37.8% ±3.1 vs 13.7% ±3.1) and also observed a significant reduction in fibronectin after ICG-001 treatment. Interestingly, cysts that may have formed prior to the start of the treatment remained large suggesting that ICG-001 may primarily act on inhibiting cyst initiation, rather than inhibiting the enlargement of pre-existing cysts. Importantly, ICG-001 treatment did not affect the growth of the mice.

Conclusions: Our study demonstrates that increased β-catenin transcriptional activity has an important role in cystogenesis and inhibition of the β-catenin-CBP complex by ICG-001 may serve as a new therapeutic modality to decrease cyst formation.

Funding: NIDDK Support

PO1561

Glucosylceramide Synthase Inhibition Preserves Mitochondrial Function and Reduces Reactive Oxygen Damage in the Jck Mouse Model of Polycystic Kidney Disease

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Background: Glucosylceramide synthase inhibitor (GCSi) treatment blocks disease progression in PKD mouse models. Defective mitochondrial morphology and function are observed in kidneys of ADPKD patients and murine models. We assessed the impact of GCSi treatment on mitochondrial function in the *jck* mouse model of PKD and *jck* derived kidney epithelial cells.

Methods: Twenty-six-day old WT or *jck* mice were treated with vehicle or 60 mg/kg GCSi (Genz667161) in feed for 38 days prior to tissue harvest. mRNA expression was measured using RT-PCR. protein levels were measured by western blot. Mitochondrial DNA content was measured using real-time PCR. Oxidized DNA was detected using anti-8OHdG antibodies. Oxidized proteins were measured using the Oxyblot system (Millipore).

Results: Reductions in electron transport chain and mitochondrial membrane proteins, as well as mitochondrial DNA were observed in control *jck* mouse and ADPKD patient samples. Decreased antioxidant gene expression was also observed in *jck* kidneys as were increased levels of oxidized DNA and protein; these changes were mirrored in ADPKD samples. Reduced cystic burden following treatment of *jck* mice with GCSi was associated with increased levels of mitochondrial DNA, mitochondrial proteins, and induction of mitochondrial biogenesis pathways. GCSi treatment partially reversed antioxidant gene downregulation and normalized oxidized DNA and protein levels in *jck* tissues. *Jck* cells exhibited decreased mitochondrial number, defective mitochondrial function, and increased protein oxidation consistent with *in vivo* and ADPKD patient data. GCSi treatment alleviates these defects. This suggests that reduced mitochondrial function and increased oxidative stress are primary cellular defects and not a result of cystogenesis.

Conclusions: Mitochondrial dysfunction and increased oxidative stress were observed in *jck* mouse tissues, *jck* cell lines, and ADPKD patient samples. GCSi treatment inhibited disease progression in *jck* mice, reducing oxidative stress and correcting mitochondrial dysfunction. Reduced kidney cyst growth following GCSi treatment correlates with preserved mitochondrial function.

Funding: Commercial Support - Sanofi-Genzyme

PO1562

Oral Delivery of Nanoparticles for Renal Disease

Jonathan Wang, Kenneth R. Hallows, Eun ji Chung. *University of Southern California, Los Angeles, CA.*

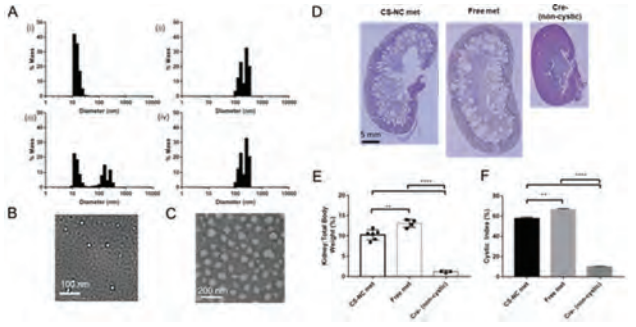
Background: Nanomaterials are promising for drug delivery, but few have been successful for oral delivery, the optimal route for chronic diseases like polycystic kidney disease (PKD). Drug candidates that slow cyst growth require high dosages leading to side effects like hepatoxicity. To limit this, we previously developed kidney targeting micelles (KM) and found they accumulated in the kidneys. To augment this system for oral delivery, herein, we load KMs and metformin (met), a diabetes drug with PKD promise, into chitosan nanocapsules (CS-NC) to overcome the barriers of the gastrointestinal (GI) tract. We hypothesize that CS-NC will deliver met across the GI tract and show efficacy in PKD mice models. Furthermore, we characterize KMs loaded into CS-NC to serve as a platform for future oral delivery of targeted therapeutics.

Methods: CS-NC were synthesized via ionic gelation. To confirm KM loading into CS-NC, dynamic light scattering (DLS) was performed for the following: KMs loaded into CS-NC, KMs mixed with CS-NC, CS-NC, or KM. To assess the oral delivery performance, we orally gavaged 300 mg/kg met loaded in CS-NC or free met to Pkd1$^{fl/fl}$; Pax8 rtTA;Tet-O cre mice. On P22, kidneys were excised to assess kidney morphology.

Results: DLS of CS-NC showed diameters of 148.5 ± 0.3 nm, while KMs are 14.9 ± 1.5 nm (Fig. 1 Ai, ii). DLS results of the mixed conditions show both populations of particles (Fig. 1 Aiii), whereas loading KMs within CS-NCs removes free KMs (Fig. 1 Aiv), demonstrating encapsulation within CS-NCs. TEM of KMs (Fig. 1 B) and CS-NC (Fig. 1 C) show spherical morphology. Upon oral gavage of CS-NC met, a lower kidney to body weight ratio (10.3 ± 1.1 vs. 13.1 ± 1.0) and (b) cystic index (57.6 ± 1.2 vs. 66.5 ± 0.8) was seen in the CS-NC met group vs. free met (Fig. 1 E,F) ($N \geq 4$, $^{**}p \leq 0.01$, $^{****}p \leq 0.0001$).

Conclusions: These initial studies show promise that KMs can be loaded within CS-NCs and can function as an orally delivered targeted nanotherapeutic. To our knowledge, our studies represent the first nanomedicine strategy for PKD therapy.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute (NHLBI) R00HL124279 and NIH New Innovator Award (DP2–DK121328), Other U.S. Government Support



PO1563

Long-Term Effect of Novel Morphometric 3D Capsule Device to Constrain Growth in Polycystic Kidney: Comparison Between Wild-Type, Cy/+, and PCK Rat Models

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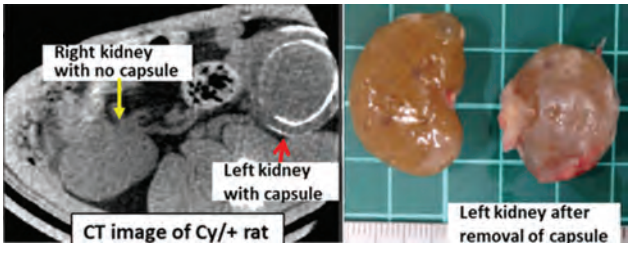
Background: As a potential therapeutic method to halt the progression of polycystic kidney disease, we developed and implanted a computed tomography (CT) image-derived morphometric 3D capsule device to encase a kidney. In this study, the long-term effect of the capsule device on size, function, and histology of polycystic kidneys were assessed using wild-type, Cy/+ and PCK rat models.

Methods: Kidney capsule devices were designed from CT images of rats and surgically implanted on left kidneys, while sham operations performed as controls, in wild-type (n=2), Cy/+ (n=2) and PCK (n=3) rats. After operation, rats were followed to grow. Monthly CT scans were performed and used to measure kidney volume. At the final follow-up, rats were sacrificed and kidney weight, serum BUN and creatinine (Cre) were measured. Histological analyses including cystic area measurement and immunohistochemistry were performed.

Results: In wild-type rats, kidney weights in sham and encapsulated (Enc) rats were similar (Right [R]: 2.2g, Left [L]: 2.1g sham vs. R 2.3g, L 2.2g Enc). In Cy/+ rats survived over 6 months, kidney weights, BUN, and Cre were all lower in Enc rats than those in sham rats (Weight: R 4.7g, L 4.6g sham vs. R 3.6g, L 2.9g Enc (Figure); BUN mg/dL: 113.8 sham vs. 44.9 Enc; Cre mg/dL: 2.06 sham vs. 0.71 Enc). In PCK rats survived over 3 months, kidney weights, BUN, and Cre were all lower in Enc rats than those in sham rats (Weight: R 5.6g, L 6.0g sham vs. R 4.5g, L 3.8g Enc; BUN: 30.6 sham vs. 22.9 Enc; Cre: 0.43 sham vs. 0.36 Enc). Encapsulated kidneys of polycystic rats showed smaller histologic cystic area with reduced cell proliferation and macrophages than unencapsulated kidneys.

Conclusions: Both Cy/+ and PCK rats in long-term follow-ups showed considerable reductions in size of the kidneys that were encapsulated with morphometric 3D capsule devices as well as reduction in BUN and creatinine, demonstrating proof of concept toward a novel potential therapeutic avenue for halting progression of polycystic kidney disease.

Funding: Government Support - Non-U.S.



PO1564

Quantifying Murine Total Kidney Volume with Robotic 3D Ultrasound

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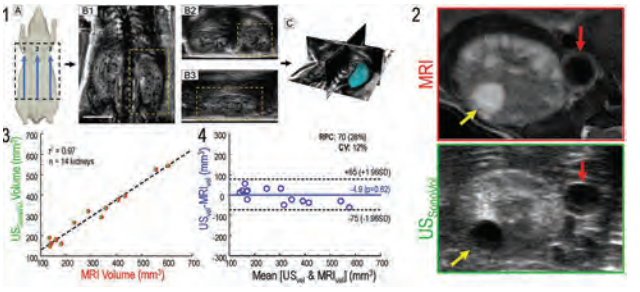
Background: Polycystic kidney disease (PKD) is a genetic disorder characterized by renal cyst formation and kidney enlargement. Noninvasive staging of PKD can be accomplished by measuring total kidney volume (TKV). While TKV has been readily implemented in the clinic, its adoption in preclinical research with small animals has lagged. In this study, a new high-throughput imaging device, based on robotic ultrasound (US), was evaluated as a complementary approach for measuring TKV in murine models and validated against *in vivo* and *ex vivo* gold standards (MRI and Vernier calipers).

Methods: Two cohorts of mice were evaluated in a cross-sectional study. Cohort 1 included a range of mature *Pkd1* mice (N = 14 kidneys) that were imaged in 3D with both US and MRI. Cohort 2 included healthy mice (N = 16 kidneys) spanning both sexes and two ages (4&16 wks). Mice from Cohort 2 were imaged with 3D US *in vivo*, euthanized, and TKV measured *ex vivo* with Vernier calipers (length/width). Agreement was assessed with correlation and Bland-Altman (BA) analysis. US images were segmented by 4 independent readers and inter-reader reliability was assessed via intraclass correlation coefficient (ICC).

Results: US-TKV correlated strongly with both MRI and caliper measurements (r^2 = 0.97 and 0.93, respectively). Against MRI, BA-analysis demonstrated no significant bias and a limit of agreement (LOA) of 70 mm^3 between the techniques. Against calipers, a small but statistically significant overestimation was detected of kidney length/width by *in vivo* US imaging (0.87 mm). Inter-reader agreement for TKV was strong with an ICC of 0.93 (95%CI: 0.83–0.97).

Conclusions: These results show that robotic 3D US, performed by a novice operator, can produce rapid, accurate, and consistent *in vivo* measurements of TKV in murine models. Future studies will include larger cohort sizes and additional models of kidney disease (e.g. fibrosis) making this approach ideal for therapeutic screening.

Funding: NIDDK Support



(1) 3D US orthoslice views. (2) Matched US and MRI slices. (3) Linear regression. (4) Bland-Altman analysis.

PO1565

Rapid, Quantitative Measures of ARPKD Kidney Disease with Novel Magnetic Resonance Fingerprinting

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a rare but potentially lethal genetic disorder characterized by diffuse collecting tubule microcysts. There are currently no disease-specific treatments, although several therapies have shown promise in ARPKD animal models. Clinical trials for ARPKD patients have not been possible due to the lack of sensitive measures of ARPKD kidney disease progression. We previously identified renal T1 and T2 relaxometry as potential imaging biomarkers of ARPKD. The goal of this study was to evaluate a novel, rapid magnetic resonance imaging (MRI) technique, magnetic resonance fingerprinting (MRF), in kidneys of healthy volunteers and pediatric ARPKD patients.

Methods: MRF is a quantitative MRI technique that simultaneously generates maps of multiple MRI parameters (e.g., T_1,T_2), while also showing resistance to motion artifact, allowing for more rapid and comprehensive assessment of tissue composition and pathology. We developed a kidney MRF acquisition protocol to generate T_1 and T_2 maps in a single breath-hold (~15 seconds/slice). This MRF method was first validated *in vitro* using standardized T_1 and T_2 phantoms. *In vivo* kidney T_1 and T_2 maps were then obtained from 10 healthy volunteers and 3 ARPKD patients.

Results: MRF-based T_1 and T_2 maps demonstrated good agreement with reference values in standardized phantoms. MRF experiments in healthy volunteers further showed repeatable assessments of the renal cortex (T_1:1318±91 ms; T_2:71±6 ms) and medulla (T_1:1592±63 ms; T_2:73±5 ms), consistent with literature values. Repeated kidney MRF scans for 3 ARPKD patients (age 7-13 yrs, estimated glomerular filtration rates 52-97 ml/min/1.73m^2) on 2 successive days demonstrated good reproducibility (< 3% differences for T_1 and T_2). Significant differences were seen between the volunteer and ARPKD patient populations for both mean kidney T_1 ($p<0.007$) and T_2 ($p<0.04$).

Conclusions: This novel kidney MRF acquisition provides fast, accurate, and repeatable kidney T_1 and T_2 maps in pediatric ARPKD patients. The short acquisition times, coupled with resistance to motion artifact, suggest that MRF could allow rapid, quantifiable imaging assessments of ARPKD kidney disease even in younger children, which could be used to identify high risk patients and/or to assess therapeutic efficacy in clinical trials.

Funding: NIDDK Support, Commercial Support - Siemens Healthineers

PO1566

Automated Instance Cyst Segmentation of Polycystic Kidneys in MRIs

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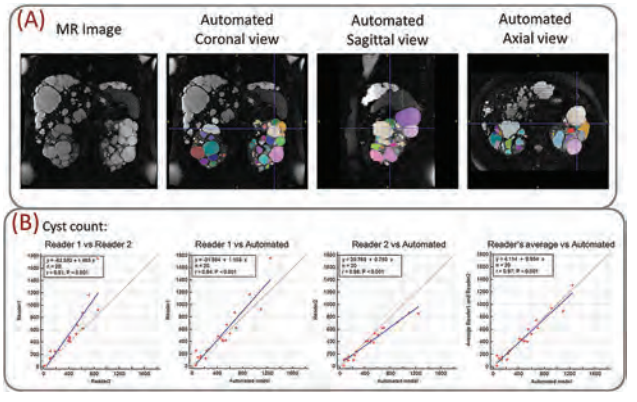
Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development of multiple cysts in the kidneys. Currently, total kidney volume (TKV) is used as the only imaging biomarker to monitor disease progression. However, the ADPKD phenotype can vary widely among patients presenting with similar TKVs. In this study, we developed an MR image analysis method that automatically segments and differentiates individual cysts (i.e. instance-based segmentation) within the kidneys of patients affected by ADPKD.

Methods: A total of 60 T2-weighted MR images representative of different ADPKD stages and phenotypes were identified from our database (TKV range: 296mL-9690mL). The automated 3D instance cyst segmentation model was developed using a convolutional neural network. We reformulated the instance segmentation task by training the model to learn cyst edges and cores separately. The instance labeling was later generated by a combination of connected components and the watershed algorithm. The network was trained on 30 images and validated on 10 images using a 4-fold cross validation technique. The remaining 20 images were used for testing and were compared to manual tracings from two independent readers.

Results: An example of the automated method performance is shown in figure 1A. Quantification of the automatically generated cysts (Fig. 1B.) showed strong correlation with the number of cysts detected by readers 1 and 2 with an R^2 of 0.96 and 0.88, respectively. The cystic index showed high correlation with an R^2 of 0.92 and 0.90 for the comparisons between the automated method and readers 1 and 2, respectively.

Conclusions: We developed and tested the first fully automated instance cyst segmentation method for patients affected by ADPKD. The results demonstrate the feasibility and high accuracy of performing cyst counting and measuring total cyst volume and cystic index automatically.

Funding: NIDDK Support, Clinical Revenue Support



PO1567

Human Factors Impact on the Development of Software as a Medical Device (SaMD): A Case Study Using the System Usability Scale (SUS)

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an inherited, progressive, cystic kidney disease and is the fourth leading cause of end-stage renal disease (ESRD). Total kidney volume (TKV) is the most relevant imaging biomarker for tracking and predicting the natural course of ADPKD. Accurate prognostic tools may help predict outcomes and optimize clinical management to slow the loss of renal function. The ADPKD Progression Management (APM) System is a web-based, clinical-decision support software that offers a consistent method for estimating TKV and aids in the prediction of likely risk of progression. The system helps health care providers (HCPs) automatically calculate TKV, project likely TKV growth, and track eGFR and TKV changes over time. The APM System was evaluated for perceived ease-of-use and user satisfaction utilizing the industry standard System Usability Scale (SUS). The SUS is a simple, reliable tool consisting of 10-items with five response options, anchored by "Strongly Disagree" and "Strongly Agree"; the calculated score ranges from 0-100.

Methods: The SUS was used in 4 human factors studies of the APM System. Participants included nephrologists and radiologists who completed test cases using mock data. Participants had no prior experience with the software and received no training on the system. Participants entered clinical information, utilized the automated image measurement to calculate TKV, and generated the automated statistical calculation of predicted growth of TKV, a marker of disease progression. Participants then completed a SUS questionnaire. In each study, a global SUS score was calculated; a total of 79 participants contributed to the global SUS scores: 37 nephrologists, 28 radiologist and 14 nephrologist/radiologist support staff.

Results: APM System received the following SUS scores in studies one through four: 72, 77, 70*, and 80. The SUS score showed an 8 point increase from the first study to the fourth study. *New functions (e.g. Consultation workflow) introduced.

Conclusions: The SUS results demonstrate the impact of iterative improvements in the design and usability of the APM System. The SUS global scores provide evidence that the perceived usability is above average and comparable to the average SUS score for the top 10 apps across iPhone, Android and tablets.

PO1568

Correlation of Baseline Urinary Metabolic Biomarkers with ADPKD Severity in the TAME-PKD Study Participants

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Background: Recent work suggests that dysregulated cellular metabolism plays a key role in autosomal dominant polycystic kidney disease (ADPKD) pathogenesis, with increased glycolytic metabolism (Warburg effect) and impaired oxidative metabolism. The TAME-PKD double-blind, placebo-controlled RCT is underway, testing the safety, tolerability and efficacy of metformin, a regulator of cell metabolism and activator of AMP-activated kinase, in ADPKD patients. The purpose of this study was to analyze the degree to which various baseline urinary biomarker values of key metabolites and metabolic enzymes correlate with ADPKD disease severity parameters in this study population.

Methods: Concentrations of total protein, key metabolites (creatinine, lactate, pyruvate, succinate, and cAMP), and key glycolytic enzymes (pyruvate kinase M2 (PKM2), lactate dehydrogenase A (LDHA), and pyruvate dehydrogenase kinase 1 (PDK1)) were measured by ELISA, enzymatic assays and immunoblotting in baseline urine specimens of 95 TAME-PKD participants. These analytes normalized by creatinine were correlated with patients' baseline height-adjusted total kidney volumes (htTKV) by MRI and estimated GFR (eGFR) by CKD-EPI in unadjusted analyses. Additional analyses were performed adjusting for participants' age and sex.

Results: As expected, a very significant negative correlation was found between htTKV and eGFR ($r = -0.385$; $p = 0.0001$) in this population, with a modest positive correlation between urinary total protein excretion and htTKV ($r = 0.201$; $p = 0.052$). None of the metabolites correlated with htTKV or eGFR. Among metabolic enzymes, PKM2 and LDHA both positively correlated with htTKV ($r = 0.286$; $p = 0.005$ and $r = 0.233$; $p = 0.025$, respectively). All of these correlations remained generally consistent in multivariable regression models adjusting for patient age and sex.

Conclusions: To varying degrees, proteinuria, lactate, PKM2, and PDK1 urinary concentrations correlated with ADPKD severity at baseline in the TAME-PKD study population, consistent with the idea that upregulated glycolytic flux is a feature of ADPKD severity. Future analysis will reveal how treatment with metformin may affect both disease progression and the various urinary metabolic biomarkers in patients throughout the study.

Funding: Other U.S. Government Support

PO1569

Urine NAG Is an Effective Clinical Parameter to Presume Disease Activity of Autosomal Dominant Polycystic Kidney Disease

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Background: Patients with ADPKD are mixed with those who progress to ESRD and those who maintains stably, and should be assessed separately from disease activity shown in rate of kidney volume progression (RKVP), disease progression shown in total kidney volume (TKV), and also renal function shown in eGFR. This is also crucial in considering indication of tolvaptan. However, the evaluation of RKVP requires multiple imaging studies, and problems with costs and complexities. Considering that ADPKD is a disorider primarily affecting tubulo-interstitium, we aimed to examine the clinical potential of urine NAG to evaluate RKVP by retrospective obseration.

Methods: Among ADPKD patients treated in our hospital between January 2010 and June 2019, 62 patients who met the conditions of no tolvaptan use, GFR≧30, duration of treatment in our hospital≧1 year, and multiple TKV measurement by CT scanning were included in the analysis.

Results: The mean age was 46.3 years, 62.9% men, the mean baseline eGFR was 60.1±18.5 ml/min/L, the median TKV was 1137 mL, and the median urine NAG index (NAG-to-Cr ratio) was 4.64 U/mg Cr. In the reduced renal function group (30≤eGFR< 60 mL/min, n=32), we observed a correlation between NAG index and RKVP in single-regression analyses ($R^2 = 0.330$, $p = 0.003$), but not with eGFR, TKV. However, there was no significant correlations between all parameter and RKVP, including NAG index, in the normal renal function group (eGFR≥60 mL/min, n=30). Multiple regression analysis showed that NAG index was a predictor of RKVP in the reduced renal function group ($p = 0.005$). Based on the approximate equation in the single-regression analyses of NAG index and RKVP (RKVP=1.511 X NAG index-2.869), the 95% confidence interval for NAG index (5.98-9.40 U/mgCr) in the reduced renal function group, and the corresponding RKVP values (6.16-11.33%/year), reasonable cut-off value of NAG index to predict RKVP≥5% per year might be considered to be 6.0 U/mgCr.

Conclusions: In ADPKD patients with renal dysfunction (CKD stage≤3), it was considered that NAG index may be useful as a predictor of the disease activity shown by RKVP and, if it is 6.0 U/mgCr or greater, may be presumed to be associated with higher disease activity.

PO1570

Overweight and Obesity Are Predictors of Pain in the HALT-PKD Studies

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Background: Pain is a frequent complication of autosomal dominant polycystic kidney disease (ADPKD) and includes back and abdominal pain. Level of pain was previously found to be unrelated to kidney size in participants in the 5-yr HALT-PKD studies. We hypothesized that overweight and obesity would be independently associated with greater self-reported back, abdominal, and radicular pain at baseline and that weight loss would be associated with reduced pain over the follow-up period.

Methods: 835 individuals with ADPKD who participated in the 5-yr HALT-PKD study A or B were included in a cross-sectional analysis. The association of baseline BMI with pain was evaluated using multivariable ordinal logistic regression (likert-scale responses). In a longitudinal analysis, the association of annual change in BMI as a time-varying predictor with annual change in pain was evaluated using a generalized estimating equation analysis.

Results: Participants were 43±10 years old and baseline estimated glomerular filtration rate (eGFR) was 71±26 ml/min/1.73m^2. Back, abdominal, and radicular pain were reported more frequently in individuals with overweight/obesity ($p<0.05$). After adjustment for demographics, exercise, pain medications, eGFR, and mutation class, overweight/obesity were associated with increased odds of greater back pain and radicular pain, but not abdominal pain. Associations remained similar after further adjustment for baseline height-adjusted kidney and liver volume (Study A only; n=436); back pain: overweight OR: 1.66 [1.02, 2.68], obese OR: 1.77 [1.03, 3.03]; radicular pain: overweight: 2.28 [1.13, 4.60], obese OR: 2.68 [1.25, 5.76]. Longitudinally (n=823), weight loss (annual BMI decrease >3%) was associated with decreased odds of worsening back pain (OR: 0.87 [0.76, 1.00]) over time vs. weight gain (annual BMI increase >3%).

Conclusions: In early- and late-stage participants in the HALT-PKD studies, overweight and obesity were associated with greater back and radicular pain, independent of total kidney/liver volume. Weight loss was associated with reduced risk of worsening back pain, thus may be an effective strategy to reduce pain symptoms in individuals with ADPKD.

Funding: NIDDK Support

PO1571

Asymptomatic Pyuria as a Prognostic Factor in Autosomal Dominate Polycystic Kidney Disease

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Background: Urinary tract infection (UTI) in patients with autosomal dominant polycystic kidney disease (ADPKD) is linked to faster disease progression. The effect of asymptomatic pyuria on ADPKD disease progression is not known.

Methods: Retrospective study of ADPKD patients seen at a tertiary academic center with available urinalysis (UA) and abdominal CT/MR imaging, and without infection or other cause of pyuria. Clinical characteristics of patients with asymptomatic pyuria (AP) (> 10 urinary WBC/hpf without UTI) were compared to the group with no pyuria (NP) (WBC 0-3/hpf). First and last available eGFR and height-adjusted total kidney volume (HtTKV) were obtained to calculate the rate of eGFR and HtTKV change with time.

Results: Female and male patients with AP had similar mean age at UA and baseline eGFR as compared to their counterpart with NP (Table 1). Median baseline HtTKV was similar in NP and AP females (596 vs 550 ml/m, respectively) but higher in AP males as compared to NP males (1132 vs 898 ml/m, respectively). There was no difference between females NP and AP in the median rate of eGFR decline (-2.2 vs -2.0 ml/min/1.73m^2/yr) or HtTKV growth (4.4 vs 4.0 %/yr). Compared to males NP, males AP had a higher median rate of eGFR decline (-3.8 vs -2.6 ml/min/1.73m^2/yr, p= 0.04) and a faster median rate of Ht-TKV growth (12.9 vs 6.7 %/yr, p= 0.03).

Conclusions: Asymptomatic pyuria is associated with a faster decline in kidney function and growth of kidney volume in male patients with ADPKD. This could be used as an additional negative prognostic marker.

Table 1: Kidney Function and Height-adjusted Total Kidney Volume by Subgroup

	Females No pyuria (N=317)	Females Asymptomatic pyuria (N=189)	Males No pyuria (N=259)	Males Asymptomatic pyuria (N=67)
Age at UA, years, mean + SD	46.5 ± 13.7	49.5 ± 16.1	50.1 ± 16.1	47.3 ± 16.3
eGFR1, ml/min/1.73m2, mean + SD	66.5 ± 29.3	65.2 ± 29.7	59.9 ± 32.8	58.3 ± 35.5
Age at eGFR1, years, mean + SD	44.3 ± 13.0	45.7 ± 15.4	46.8 ± 15.4	43.3 ± 16.6
eGFR2, ml/min/1.73m2, mean + SD	51.7 ± 32.1	47.5 ± 32.7	42.3 ± 32.1	32.3 ± 25.8
Age at eGFR2, years, mean + SD	51.0 ± 13.4	54.9 ± 15.3	54.4 ± 16.0	51.0 ± 15.7
Time between eGFR1 and eGFR2, years, mean + SD	6.6 ± 6.9	9.2 ± 7.6	7.5 ± 7.3	7.6 ± 7.3
Ht-TKV1, ml/m, median (IQR)	595.7 (343.1 – 1029.9)	550.2 (319.5 – 974.0)	898.0 (475.5 – 1621.2)	1132.2 (6509.4 — 2507.7)
Age at Ht-TKV1, years, mean + SD	45.2 ± 13.2	47.3 ± 15.5	48.6 ± 15.9	44.0 ± 20.1
Ht-TKV2, ml/m, median (IQR)	692.4 (400.9 – 1295.0)	705.0 (349.8 – 1172.6)	1060.2 (572.2 – 2090.5)	1850.5 (819.6 – 2865.6)
Age at Ht-TKV2, years, mean + SD	49.1 ± 13.0	51.9 ± 15.1	52.0 ± 15.5	49.4 ± 15.4
Time between HtTKV1 and HtTKV2, years, mean + SD	3.8 ± 4.7	4.5 ± 5.2	3.4 ± 5.1	5.3 ± 12.6
eGFR rate of decline, ml/min/1.73m2 per year median (IQR)	-2.2 (-4.1 — -0.7)	-2.0 (-3.3 – -0.8)	-2.6 (-4.3 — -1.1)	-3.8 (-5.7 — -2.2)
HtTKV rate of growth, % per year, median (IQR)	4.4 (0.7 – 8.4)	4.0 (1.2 – 8.0)	6.7 (3.1 – 13.1)	12.9 (1.7 – 15.4)

PO1572

Volume Progression and Imaging Classification of Polycystic Liver in ADPKD

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Background: While polycystic liver in ADPKD is common and affects significantly the quality of life, volume progression of liver cysts is not well understood. This is in part because previous longitudinal studies focused on the progression of liver volume not liver cyst volume. Thus, the purpose of the study is to evaluate and classify polycystic liver progression in patients with ADPKD based on patient's age, sex, height-adjusted liver cystic volume (htLCV) and height-adjusted liver volume (htLV) measurements.

Methods: Longitudinal MRI data (CRISP and HALT studies) from 695 patients with ADPKD over a maximum follow-up of 14.23 years were evaluated to measure LCV and LV. Among them, 258 patients with LCV > 50mL and at least 2 time-points were included in the analysis. Linear mixed models on log-transformed htLCV and htLV were fitted as a function of participant's age and study as well as a random intercept and slope. The slope coefficient was used to approximate the mean annual rate of change (MAROC) for each outcome. Using the age of 15 years as the hypothetical initial age for LCV=0, differential growth trajectories were plotted to categorize the participants according to their LCV growth rate and age.

Results: Overall, the MAROC was 10.8% for htLCV and 1.8% for htLV ($P<0.0001$). 232 participants had net-increases (last measurement > first) on htLCV, while 26 participants had net-decreases (or values remained the same) on htLCV. For the net-increase group, MAROC was 12.7% for htLCV and 2.2% for htLV ($P<0.0001$). For the net-decrease group, MAROC was -7.3% for htLCV ($P=0.0168$) and -2.1% for htLV ($P=0.1116$). According to the annual growth rate, 5 classes (A <5%, B 5-<10%, C 10-<15%, D 15-<20%, E ≥20%) were defined. The numbers for female and male participants in each class were (F,M): A (31,7); B(48,15); C (49,51); D (27,16); E (9,5).

Conclusions: The mean volume growth rate of the liver cyst was 6 times greater than that of the liver. Similar to the kidney imaging classification, the severity of polycystic liver may be categorized on the basis of patient's age and liver cyst volume.

Funding: NIDDK Support, Other U.S. Government Support

PO1573

Baseline Characteristics and Associations with Renal Function in a Greek Cohort of Polycystic Kidney Disease

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Background: Recent advances in the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD) highlight the interplay between the clinical and the laboratory profile of the disease. This study aims to present the baseline characteristics of patients followed in a large ADPKD cohort from a single center in Greece, and explore possible associations between demographic, clinical and laboratory parameters

Methods: Patients followed in a specialized outpatient PKD clinic from December 2018 up to December 2019 were recruited in this study. At enrollment, demographics, medical and family history and laboratory data were recorded using a standardized form. Estimated glomerular filtration rate (eGFR) was calculated and Magnetic Resonance Imagining for total kidney volume (TKV) measurement was performed

Results: One-hundred three females and 83 males with a mean age±SD of 41.4 ± 13 years (18.8 % < 30 years) were enrolled. Overall, 60.8% of them were classified as Chronic Kidney Disease, (CKD) stage 1 and 2. The ADPKD was diagnosed at a mean age±SD of 26.5±12.5 years. Thirty four percent out of 186 patients were diagnosed before the age of 20 and 9% of them before the age of 10. A positive family history was present in 89% of patients. In this subgroup, the median age of the affected parent that reached end stage renal disease (ESRD) was 55 (range 28-87) years. Hypertension was diagnosed in 89% at a mean± SD age of 37.2 ± 10.5 years. Hepatic cysts were present in 79.3% of patients, urinary tract infections, nephrolithiasis, macroscopic hematuria and pain in 44.3%, 42.5%, 24.8% and 54.4% respectively. A history of intracranial bleeding in family was positive in 21.5%. In multivariable analysis, lower eGFR was associated with younger age at the time of APKD diagnosis ($p < 0.002$), younger age at hypertension diagnosis ($p < 0.08$) and greater values of TKV ($p < 0.001$), height adjusted TKV ($p < 0.001$) and Body Mass Index (BMI) ($p = 0.02$)

Conclusions: In this study, patients with ADPKD were diagnosed at a young age and hypertension developed early on the course of the disease. Both these factors together with higher values of BMI and TKV were independently associated with low eGFR

PO1574

Identification of Factors Associated with Progression, Prognosis, and Tolvaptan Indication in Polycystic Kidney Disease Patients

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Background: The identification of risk factors for the progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an emerging field. The present study explores the associations between epidemiological, clinical and imagining data in a large cohort of ADPKD patients

Methods: All patients included in the study had a Magnetic Resonance Imaging (MRI) for measurement of Total Kidney Volume (TKV). For all patients, the Mayo Clinic Imaging Category (MCIC) and the respective prediction for End Stage Renal Disease (ESRD) were calculated. Patients eligible for tolvaptan treatment (MCIC 1C,1D,1E, age <55 years old and estimated-GFR (e-GFR) ≥25ml/min) were identified. Individual medical history, clinical and laboratory data were examined for associations with renal and imaging parameters using linear regression models

Results: 158 patients in total were included. Based on measurements of height-adjusted TKV (ht-TKV) and age, 5% of the patients were classified as 1A, 20% as 1B, 34% 1C, 25% 1D and 16% 1E, MCIC. In multivariable analysis, patients' age ($p=0.01$), male sex ($p<0.001$), parent's age at time of ESRD ($p<0.001$) and proteinuria ($p=0.04$) were associated with ht-TKV. Parent's age at ESRD differed significantly between the MCICs of the offspring (mean±(SD)), 70.83 (12.90) in 1A, 63.79 (11.39) in 1B, 57.32 (10.42) in 1C, 51.42 (9.18) in 1D and 47.94 (5.73) years old in 1E, ($p<0.001$). Similarly, there were differences in the presence and age of hypertension onset ($p=0.004$ and $p=0.003$, respectively). In 104 patients eligible for tolvaptan treatment, age at ADPKD diagnosis, age at hypertension onset and parent's age reaching at ESRD were all significantly lower ($p<0.001$ for all) when compared to non-eligible patients. Finally, factors associated with the prediction score of ESRD (e-GFR 10ml/min) were hypertension, uric acid and the age at ESRD of the affected parent ($p=0.001$, 0.02, 0.01, respectively)

Conclusions: The age at which an affected parent had reached ESRD, as heritability estimator, was significantly associated with a worst phenotype, prognosis and tolvaptan indication. Early diagnosis of the disease, hypertension and its early onset, proteinuria and male sex are also possible risk factors for the progression of ADPKD

PO1575

Design and Basic Characteristics of a National Patient Registry in ADPKD

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Background: Most patients with autosomal dominant polycystic kidney disease (ADPKD) do not participate in clinical research. To empower ADPKD patients in the US to participate in research and to encourage the development of optimal prognostic and treatment strategies, the PKD Foundation designed a national ADPKD Registry of patient-reported data.

Methods: The ADPKD Registry is hosted on a secure, online platform (IQVIA, oc-meridian.com/pkdcure). Participants are registered and consented through the online system and asked to complete a series of modules quarterly. The Core Questionnaire asks about diagnosis, latest kidney function lab values, current symptoms, and comorbidities. Participants are also asked about family history, diet and lifestyle, and quality of life.

Results: The ADPKD Registry was launched on September 4, 2019. As of May 2020, 1023 ADPKD patients across the US have registered and completed the Core Questionnaire. Participants have a median age of 52 years, and are 72% female, 94% Caucasian, 4% self-identifying as Hispanic/Latino and 2.4% as African American. 76% have not reached end stage renal disease, 4% are treated with dialysis, and 21% received a renal transplant. A family history of the disease was reported in 79% of participants, 12% have had a genetic test for PKD, with a vast majority (94%) reporting diagnosis by imaging. At the time of entering the registry, 78% reported having hypertension and 62% had liver cysts (although only 28% reported a diagnosis of polycystic liver disease(PLD)).

Conclusions: The ADPKD Registry is a longitudinal research tool intended to capture patient-reported data with respect to ADPKD and is designed to impact research in multiple ways. All participants have consented to be contacted about future clinical trials for which they will likely qualify and a process has been established to enable researchers to submit content for new outcome modules. Thus far modules addressing extra renal complications such as PLD and vascular aneurysms have been developed. In addition, the variety of disease stages reported by participants will allow for a range of research questions related to the clinical management of ADPKD from early stage disease through dialysis outcomes and post-transplant complications.

Funding: Private Foundation Support

PO1576

First in Canada: A Comprehensive Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patient Registry in British Columbia (BC)

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Background: Early identification, assessment of renal progression and implementation of appropriate treatments are key components of modern ADPKD care. Existing BC Renal programs focus on patients in later disease stages when they access chronic kidney disease clinics, renal replacement modalities, or renal formulary drugs, but data capture of early stage ADPKD patients is limited. A comprehensive ADPKD patient registry was created to enhance identification and understanding of ADPKD in BC.

Methods: The registry was created within PROMIS, the dedicated BC Renal database. A specific focus was registration of patients seen in nephrologists' private offices, prior to enrollment in other BC Renal administered services. Minimum registry data set included basic patient name, date of birth, provincial healthcare number and diagnosis. Laboratory and outcome data are captured via existing PROMIS infrastructure. A streamlined registration process was developed with stakeholder feedback. Time-limited reimbursement was provided to nephrologists' office to support the new workflow of identifying and registering patients.

Results: With the ADPKD registry, the number of ADPKD patients registered in PROMIS has increased from 545 to 1065 between January 2015 to January 2020. The increase in patient registration has been most prominent in early stage patients not on dialysis or transplant (increased from 237 to 703). In those not on dialysis or transplant increase in patients registered was most pronounced in those at earlier CKD stages; from 2015 to 2020, in those with eGFR<15ml/min, registration increased from 27 to 34 patients, with eGFR 15-30ml/min registration increased from 97 to 98, with eGFR 30-45ml/min registration increased from 43 to 117, with eGFR 45 to 60ml/min registration increased from 19 to 109, and in those with eGFR >60ml/min, registration increased from 32 to 237 patients.

Conclusions: Through creation of a comprehensive ADPKD registry, greater numbers of ADPKD patients have been identified in BC, particularly patients earlier in their disease course. The registry will continue to build on this with next steps including enhancements to clinical data, patterns of treatment use, quality metrics for care delivery, and clinical outcomes.

Funding: Commercial Support - Creation of the registry was assisted via an unrestricted grant from Otsuka Canada Pharmaceuticals Inc.

PO1577

STAGED-PKD: An Enriched, Seamless, Two-Stage Study for Venglustat Assessment in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) occurs due to cyst formation and growth, resulting in increased total kidney volume (TKV) preceding kidney function decline by decades. The natural history of ADPKD complicates testing of new therapies. Venglustat, a glucosylceramide synthase inhibitor, inhibits cyst growth and reduces kidney failure in PKD mouse models. STAGED-PKD determines venglustat safety and efficacy and was designed using enrichment for progression to ESRD and extensive modeling from prior ADPKD trials.

Methods: STAGED-PKD is a two-stage (Phase 2/3), international, double-blind, randomized controlled trial in adults with ADPKD with increased TKV (Mayo Imaging Class 1C–1E) and eGFR 45–90 mL/min/1.73 m^2. Target enrollment in Stages 1 and 2 is 240 and 320 patients, respectively. Stage 1 randomizes patients 1:1:1 to venglustat dose 1, dose 2 or placebo. Stage 2 randomizes patients 1:1 to placebo or venglustat preferred dose based on Stage 1 safety data. Primary endpoints are TKV growth rate over 18 months in Stage 1 and $eGFR_{CKD-EPI}$ slope over 24 months in Stages 1 and 2 (n=560).

Results: Baseline characteristics for Stage 1 are shown (Table; n=225). Mean patient age is 42.7 years; mean $eGFR_{CKD-EPI}$ is 65.5 mL/min/1.73 m^2. Overall, 55.1%, 30.7% and 14.2% are of Mayo Imaging Class 1C, 1D and 1E, respectively.

Conclusions: STAGED-PKD enables optimal dose selection and evaluation of venglustat safety and impact on TKV growth and eGFR slope in ADPKD. Stage 1 TKV assessment via a nested approach allows early efficacy evaluation, increasing trial design efficiency.

Funding: Commercial Support - Sanofi Genzyme

Characteristic	N=225
Male, n (%)	128 (56.9)
Age, years ± SD	42.7 ± 6.3
Race, n (%)	
White	145 (64.4)
Asian	75 (33.3)
Other	5 (2.2
Stratification factors, n (%)	
Mayo Imaging Classification	
1C	124 (55.1)
1D	69 (30.7)
1E	32 (14.2)
Region	
North America	48 (21.3)
Europe	99 (44.0)
China	12 (5.3)
Japan	29 (12.9)
Republic of Korea	28 (12.4)
Rest of the World	9 (4.0)
Medical history (pre-specified), n (%)	
Hypertension	202 (89.8)
Hepatic cyst	143 (63.6)
Back pain	63 (28.0)
Hematuria	48 (21.3)
Nephrolithiasis	43 (19.1)
Urinary tract infection	38 (16.9)
Proteinuria	35 (15.6)
Abdominal pain	28 (12.4)

Characteristic	N=225
Prior medication, n (%)	
ACEI	68 (30.2)
ARB	95 (42.2)
ACEi, ARB, or both	179 (79.6)
Beta blocker	41 (18.2)
Calcium channel blocker	47 (20.9)
Diuretic	30 (13.3)
Blood pressure, mmHg ± SD	
Systolic	126.0 ± 11.2
Diastolic	83.4 ± 9.2
Total kidney volume, mL ± SD (n=212)	1903 ± 861
Height-adjusted total kidney volume, mL/m ± SD (n=212)	1094 ± 491
Serum creatinine, mg/dL ± SD	1.24 ± 0.28
$eGFR_{CKD-EPI}$, mL/min/1.73 m^2 ± SD	65.5 ± 12.7

Stage 1 Baseline Characteristics

PO1578

STAGED-PKD: Patient Enrichment and Modeling-Driven Efficient ADPKD Trial Design

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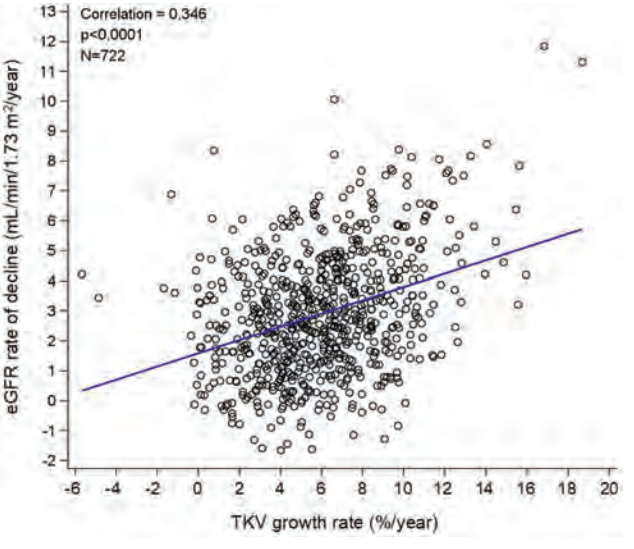
Background: Total kidney volume (TKV) and eGFR slope are key endpoints in autosomal dominant polycystic kidney disease (ADPKD) trials, indicative of cyst growth and kidney function decline. To date, unequivocal demonstration of drug effect on these endpoints required two trials. STAGED-PKD assesses the effect of glucosylceramide synthase inhibition with venglustat on both endpoints in one efficient, short-duration trial.

Methods: Retrospective analysis of TKV and eGFR slope data from CRISP (3-yr) and HALT-A combined identified rapidly progressing patients for enrichment. A statistical relationship between TKV growth vs eGFR slope was derived by modeling. Meta-analysis was conducted of randomized clinical trials assessing treatment impact on both TKV and eGFR. These analyses enabled study powering for both endpoints. Comparison of design efficiency was performed vs prior trials.

Results: Retrospective analysis of CRISP and HALT-A confirmed a significant correlation between TKV growth and eGFR slope (correlation 0.346, p<0.0001; Figure). Different statistical approaches showed that in rapidly progressing ADPKD patients, 50% reduction in TKV growth is associated with a ~30% reduction in eGFR slope. Thus, STAGED-PKD is powered to detect 50% reduction in TKV growth and 30% reduction in eGFR slope. STAGED-PKD is highly efficient vs HALT-A and -B, TEMPO 3:4, and REPRISE.

Conclusions: Modeling allowed the design and powering of a two-stage study to assess venglustat impact on TKV growth and eGFR slope. STAGED-PKD improves study efficiency via modeling and patient enrichment to reduce patient number and trial duration.

Funding: Commercial Support - Sanofi Genzyme



Modeling of the Relationship Between TKV Growth Rate and eGFR Decline

PO1579

Biological Efficacy and Safety of Niacinamide in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cyst enlargement, leading to kidney failure. Sirtuin-1 is upregulated in ADPKD and accelerates disease progression by deacetylating p53. Niacinamide is a dietary supplement that inhibits sirtuins at high doses.

Methods: We conducted an open-label, single arm intervention trial (Study 1, N=10), and a randomized, double blinded, placebo-controlled trial (Study 2, N=36) to assess the biological activity and safety of niacinamide. Patients with ADPKD were given 30 mg/kg oral niacinamide or placebo, for 12 months. Primary endpoint was ratio of acetylated p53 to total p53 protein in peripheral blood mononuclear cells. Secondary outcomes were change in height-adjusted total kidney volume (ht-TKV) and overall pain and quality of life scores. Other biomarkers of efficacy included serum creatinine, CRP, urine protein/creatinine and urine MCP1/creatinine ratios.

Results: There were no statistically significant differences in the baseline characteristics between treatment arms. There was no sustained effect of niacinamide on acetylated/total p53 ratio in either study. In study 1, the ratio was higher at 1 month (p= 0.003) but not at 6 and 12 months and no difference was noted between placebo and niacinamide arms in study 2 (p=0.51). There was no difference in the change of ht-TKV from baseline to 12 months between niacinamide and placebo. Ht-TKV increased slightly from 1049 to 1082 ml/m (p=0.71) with small eGFR decline from 83.6 to 81 ml/min/1.73 m^2 (p=0.84) in niacinamide treated patients (combined study 1+2). Furthermore, there was no statistical difference in urine MCP1/creatinine, urine protein/creatinine and quality of life scores over time. Niacinamide was generally well-tolerated. Most common adverse effects were nausea, diarrhea, gastroesophageal reflux (combined GI symptoms:70% in study 1,78% in study 2 niacinamide treatment arm and 58% placebo), headache and acneiform rash with no difference in their incidence between niacinamide and placebo.

Conclusions: Niacinamide is safe and well-tolerated in ADPKD patients. However, we were unable to detect a sustained inhibition of sirtuin activity over 12 months of treatment, and there was no signal to suggest a beneficial effect on any efficacy measure.

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PO1580

Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Design and Baseline Characteristics of Participants

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Background: Complications of ADPKD begin in childhood. While the hallmark of the disease is the development and continued growth of multiple renal cysts that ultimately result in loss of kidney function, cardiovascular complications are the leading cause of death. Vascular dysfunction (endothelial dysfunction and large elastic artery stiffness) is evident from a very young age and appears to involve increased oxidative stress and inflammation. Treatment options to prevent cardiovascular disease in adults with ADPKD are limited; thus, childhood may represent a key therapeutic window.

Methods: Curcumin is a safe, naturally occurring polyphenol found in the Indian spice turmeric, with a unique ability to activate transcription of key antioxidants, suppress inflammation, and reduce proliferation. We are conducting an ongoing randomized, placebo-controlled, double-blind clinical trial to assess the effect of curcumin therapy (25 mg/kg/d) on vascular function (brachial artery flow-mediated dilation [FMD_{BA}] and aortic pulse-wave velocity [aPWV]; co-primary outcomes) and kidney growth (change in height-adjusted total kidney volume [htTKV]) in children/young adults 6–25 yrs with ADPKD.

Results: The study is fully enrolled. Of the 68 screened participants, all 68 were randomized to receive either the curcumin or placebo. Participants ranged in age from 6-25 yrs, n=25 (37%) were children <18 yrs, and mean±S.D.estimated glomerular filtration rate was 117±16 ml/min/1.73m^2. FMD_{BA} was 9.3±0.5%, aPWV was 510±95 cm/sec, and median (IQR) htTKV was 333 (234, 475) ml/min. In the sub-group of young adults who received a supraphysiological infusion of ascorbic acid to inhibit vascular oxidative stress (n=24), FMD_{BA} improved vs. isovolumetric saline (13.6±5.2% vs. 11.3±4.3%), indicating baseline vascular oxidative stress. Greater baseline aPWV was independently associated with larger baseline htTKV.

Conclusions: The trial will be completed in December of 2020. This study has the potential to establish a novel, safe, and facile therapy for the treatment of arterial dysfunction, and possibly renal cystic disease, in an understudied population of children and young adults with ADPKD.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences, Commercial Support - Verdure Sciences (provided curcumin and placebo), Private Foundation Support

PO1581

End-of-Study Results from ACQUIRE: A Study Measuring Quality of Life, Treatment Preference, and Treatment Satisfaction of Autosomal Dominant Polycystic Kidney Disease Patients in Europe

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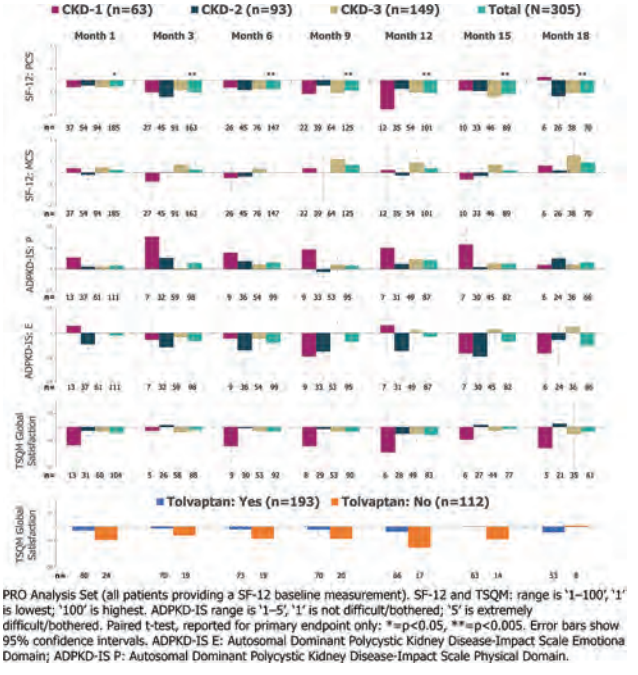
Background: Little is known about health-related quality of life (HRQoL) and patient (pt) reported outcome (PRO) measures in early autosomal dominant polycystic kidney disease (ADPKD), and longitudinal studies are lacking.

Methods: ACQUIRE (NCT02848521) was a prospective, non-interventional, real-world observational study in pts with early and rapidly progressing ADPKD (chronic kidney disease [CKD] stages 1–3) across 7 European countries. The primary objective was to measure changes in Physical Health Composite Scale (PCS) scores of the 12-item Short Form Health Survey (SF-12) over 18 months. Other objectives included changes in SF-12 Mental Health Composite Scale (MCS) scores, ADPKD-specific PROs including the ADPKD-Impact Scale (IS), -Urinary Impact Scale (UIS) and -Pain & Discomfort Scale (PDS), and treatment satisfaction questionnaire (TSQM-9).

Results: Patient demographics were previously reported. Overall 305/403 (75.7%) were included in the PRO analysis set. Changes from baseline in SF-12 (PCS and MCS), ADPKD-IS (Physical and Emotional domains) and TSQM-9 (Global Satisfaction) through Month 18 are presented in **Figure 1.** CKD-1 pts and pts not receiving tolvaptan reported the lowest treatment satisfaction. No consistent changes were observed for ADPKD-UIS and ADPKD-PDS (not shown).

Conclusions: Over an 18-month timeframe, pts reported reduced scores in the PCS component of SF-12, deterioration in the physical components of ADPKD-IS and reduced treatment satisfaction. These data suggest that continued disease progression negatively impacts the HRQoL of pts with early stages of ADPKD and implies there may be current unmet treatment needs in this pt population.

Funding: Commercial Support - Otsuka Pharmaceutical Europe Ltd.



PRO Analysis Set (all patients providing a SF-12 baseline measurement). SF-12 and TSQM: range is '1–100', '1' is lowest; '100' is highest. ADPKD-IS range is '1–5', '1' is not difficult/bothered; '5' is extremely difficult/bothered. Paired t-test, reported for primary endpoint only: *=p<0.05, **=p<0.005. Error bars show 95% confidence intervals. ADPKD-IS E: Autosomal Dominant Polycystic Kidney Disease-Impact Scale Emotiona Domain; ADPKD-IS P: Autosomal Dominant Polycystic Kidney Disease-Impact Scale Physical Domain.

Figure 1. Change from Baseline in PROs

PO1582

Mortality Risk in Elderly ESRD Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Study Findings Using Data from the United States Renal Data System

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Background: Mortality rates may be different for patients in end-stage renal disease (ESRD) with ADPKD compared with patients with other etiologies of ESRD. While mortality estimates have been published by USRDS (2018) for elderly ESRD patients in general (220 per 1,000 patient-years using data from 2012) little has been published reporting national estimates for patients with ADPKD specifically. This analysis sought to estimate ADPKD-specific mortality rates among ESRD patients aged 65 years or older.

Methods: ESRD patients treated with dialysis or transplant with at least one ADPKD diagnosis code and a reported ESRD service date from January 1, 2014, to December 31, 2016, in the US Renal Data System (USRDS) were included. Mortality rates were estimated overall, by sex, by race, and by age group (with a patient's follow-up potentially spanning two age groups). Both unadjusted mortality and adjusted mortality by 2016 US population age distributions for 65 years and older were estimated.

Results: Of 3,208,884 ESRD patients in the USRDS database, 76,428 patients (2.4%) had ADPKD and of those 14,756 were aged 65 years and older in the study period. Among elderly ADPKD patients, mean age was 70.8 years and overall mortality was 99.8 per 1,000 patient-years (129.6 age-adjusted).

Conclusions: These findings fill an important gap in the literature on ADPKD mortality in the US.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Mortality (Deaths per 1,000 Patient-Years) Among Elderly Patients with ADPKD in ESRD

Population	Number of Patients (%)*	Mortality (95% CI)	Age-adjusted Mortality
Overall	14,756 (100%)	99.8 (96.4, 103.3)	129.6
Overall, by sex	7,433 (50.4%)		
Male	7,323 (49.6%)	104.4 (99.5, 109.6)	134.4
Female	11,413 (77.3%)	95.3 (90.6, 100.2)	124.8
Overall, by race			
White	11,413 (77.3%)	101.7 (97.8, 105.8)	136.1
Black	1,610 (10.9%)	104.7 (94.2, 116.0)	123.3
Hispanic	1,186 (8.0%)	80.0 (69.6, 91.5)	100.3
Asian	422 (2.9%)	91.4 (73.1, 112.9)	102.9
Other or unknown	125 (0.8%)	86.1 (55.1, 128.1)	94.2
Overall, by age group			
65 to 74 years	11,183 (75.8%)	68.8 (65.5, 72.2)	
75 to 84 years	3,060 (20.7%)	158.9 (150.1, 168.2)	
85 years and older	513 (3.5%)	340.6 (307.6, 376.2)	

*Patient demographics at study entry.

PO1583

Risk of Severe Herpes Zoster Infection in Patients with Polycystic Kidney Disease: A Nationwide Cohort Study with Propensity Score-Matching Analysis

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Background: Polycystic kidney disease (PKD) should be considered as a systemic disorder rather than only a kidney disease. Significantly lower lymphocyte cell counts, including B and T lymphocyte counts, is noted in patients with PKD. This lymphopenia poses a risk of viral infection. Data to elucidate the herpes virus infection risk in patients with PKD are lacking; therefore, we conducted a national-wide population-based cohort study to investigate the herpes virus risk in PKD patients.

Methods: Patients who were hospitalized at least once with a diagnosis of autosomal dominant PKD were defined as PKD patients; patients without any diagnosis of PKD during the study period were grouped into the non-PKD cohort. The index date was set as the date when the patients were newly diagnosed with PKD. All study patients were followed up until the occurrence of herpes zoster infection, herpes simplex infection, death, withdrawal from the National Health Insurance Research Database for other reasons, or until December 31, 2013.

Results: We included 4358 PKD patients and 4358 non-PKD patients. The incidence rate and the risk of developing herpes zoster and herpes simplex were estimated using multivariate stratified analyses. PKD patients had an overall 2.43-fold risk of herpesvirus infection (aHR = 2.43, 95% CI 1.47–4.04) and 2.36-fold risk of herpes zoster (aHR = 2.36, 95% CI 1.34–4.13) in subgroup analysis compared with the non-PKD cohort. PKD patients without any comorbidities had a significantly higher risk of herpes zoster or herpes simplex (aHR = 3.38, 95% CI 1.51–7.56).

Conclusions: This is the first study to reveal the severe risk of herpes zoster infection in patients with PKD. High index suspicion of severe herpes zoster infection should be maintained in clinical professionals. Whether patients with PKD should be prophylactic universally with anti-varicella-zoster virus vaccine needs to be investigated in the future.

PO1584

The Use of a Visual Four-Score Scale Improves the Yield of ^{18}F-FDG PET-CT Imaging in the Diagnosis of Cyst Infection in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: [^{18}F]FDG PET/CT proved useful in the diagnosis of renal and hepatic cyst infection (CyI) in patients with autosomal dominant polycystic kidney disease (ADPKD). However, the definition of CyI by [^{18}F]FDG PET/CT is subjective. Here, we infer a diagnostic threshold of [^{18}F]FDG uptake in case of CyI based on a visual 4-point scale.

Methods: All ADPKD patients who were hospitalized between January 2007 and March 2019 for suspected CyI and who underwent an [^{18}F]FDG PET/CT were retrospectively identified. CyI was defined upon 5 concomitant criteria: (i) fever ≥38°C; (ii) abdominal pain; (iii) peak plasma C-reactive protein levels ≥70 mg/L; (iv) no other cause of inflammation; and (v) favorable outcomes after antibiotics for ≥21 days. First, all [^{18}F]FDG PET/CT images were qualitatively interpreted by 2 blinded board-certified physicians in nuclear medicine. CyI was diagnosed in case of (i) homogeneous or (ii) heterogeneous [^{18}F]FDG accumulation in cyst wall, or (iii) diffuse [^{18}F]FDG accumulation within the cyst. Next, the uptake of [^{18}F]FDG of the suspected CyI was scored in comparison to blood pool and liver activities. An accumulation of [^{18}F]FDG around the cyst equivalent or inferior to the blood pool was scored as 1. If it was superior to the blood pool but inferior or equal to the hepatic [^{18}F]FDG background, it was scored as 2. If it was slightly superior to the liver, it was scored as 3. If it was largely superior to the hepatic [^{18}F]FDG activity, it was scored as 4.

Results: Sixty [^{18}F]FDG PET/CT (man/woman ratio of 54.1%) were performed for suspected CyI in 38 ADPKD patients: 29 episodes met the gold-standard criteria for CyI. The visual assessment of PET/CT images reached a sensitivity of 73.1% and a specificity of 70.6%. The pattern of [^{18}F]FDG accumulation around or within the suspect cyst was not discriminant. By contrast, the 4-point scale improved the diagnostic yield (specificity of 85.3%), with a diagnostic threshold of [^{18}F]FDG uptake ≥3, i.e. higher than the hepatic background.

Conclusions: [^{18}F]FDG PET-CT imaging helps in the diagnosis of CyI in ADPKD patients, and the use of a 4-point scoring of [^{18}F]FDG uptake improves its yield, with positive and negative predictive values of 78.3% and 78.4% respectively.

PO1585

Liver Cyst Infection After Hepatic Transcatheter Arterial Embolization in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Hepatic transcatheter arterial embolization (TAE) is a non-surgical treatment to reduce the volume of enlarged liver in patients with autosomal dominant polycystic kidney disease (ADPKD). The incidence of liver cyst infection after hepatic TAE is not known.

Methods: Patients with ADPKD who underwent hepatic TAE between January 2014 and July 2019 in Toranomon Hospital Kajigaya to reduce the volume of enlarged liver were retrospectively analyzed for their history of liver cyst infection before and after hepatic TAE.

Results: 107 patients were included in the study. The mean ± standard deviation (SD) of age and height-adjusted total liver volume was 53.9 ± 9.6 years and 5,048 ± 2,124 mL, respectively. 26 patients (24%) were men, and 36 patients (34%) were on renal replacement therapy. Seven patients (7%) had a history of liver cyst infection before hepatic TAE. During the follow-up period, 16 patients (15%) experienced 20 liver cyst infections in total after hepatic TAE, and only one of them had a history of liver cyst infection before hepatic TAE. The mean ± SD of the follow-up period was 714 ± 601 days, while median [interquartile range] was 467 [225-1,078] days. 10 out of 16 patients were on renal replacement therapy, which were all hemodialysis. Four out of 20 liver cyst infections occurred within three months of hepatic TAE. The incidence rate of liver cyst infection after hepatic TAE was 96 cases per 1,000 person-years.

Conclusions: This is the first report on the incidence of liver cyst infection after hepatic TAE. Although comparison with a control group without hepatic TAE is necessary to evaluate the risk of liver cyst infection caused by hepatic TAE, setting a control group with a similar background is difficult and remains a research question.

PO1586

3D Facial Gestalt Analysis of Individuals with Mutated PKD1 and PKD2 Genes in Polycystic Kidney Disease: Results of a Czech Pilot Study

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Background: Pathogenic variants in *PKD1* and *PKD2* genes cause autosomal dominant polycystic kidney disease (ADPKD) that can also manifest in the liver, pancreas or cardiovascular system. Nonetheless, association of ADPKD with 3D facial gestalt has not been studied SO far. Here we present our first results of 3D facial morphometry in a Czech ADPKD patients.

Methods: Thirty ADPKD cases were enrolled and analyzed by the 3dMD Face System. Morphometric analyses were performed using the Morphome3cs software by comparing cases versus age and sex matched controls.

Results: We observed that 3D facial gestalt in ADPKD patients differs from controls. ADPKD patients have more prominent nasal region, most significantly in the area of the tip of the nose. In addition, there is retrusion of the eyebrows area, midface-zygomatic prominence and retrusion of the lateral buccal region. Most of the ADPKD cases have thin upper lip (red part of lip) in opposition to a prominent lower lip.

Conclusions: The preliminary results of this pilot study suggest that there could be a distinct 3D facial gestalt in ADPKD. ADPKD is an ideal candidate for "phenotype-driven variant prioritization", where molecular genetic analysis could be linked to 3D morphometry. In ADPKD families, where molecular genetics failed to identify a causative variant, 3D morphometry could be used as a predictive marker of the risk of disease in presymptomatic patients. Supported by Charles University Grant Agency, project number 44120.

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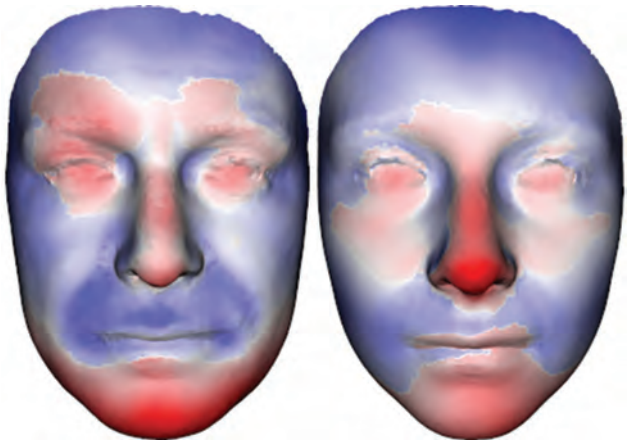

Average face of men (right) and woman (left) with PKD1 or PK2 pathogenic mutationRed-protrusion, blue- retrusion areas (comparing with controls)

PO1587

Increased Phosphorylation of ACTN4 Leads to Podocyte Dysfunction and Focal Segmental Glomerulosclerosis Mimicking Disease-Causing Mutations

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Background: Genetic mutations in ACTN4 have been linked to focal segmental glomerulosclerosis (FSGS) in humans through cytoskeletal disruption and impairment in podocyte response to mechanical stress. ACTN4 is phosphorylated at S159 in podocytes, but the effect of this post-translational modification on podocyte and kidney function is not known.

Methods: We used phosphomimetic ACTN4 to investigate the effects of this phosphorylation *in vitro* and *in vivo*. The effect of phosphorylation on the interaction between ACTN4 and F-actin was assessed through F-actin bundling assays, and the effect on F-actin alignment was assessed by immunofluorescence staining and quantified using autocorrelation analysis. Microfluidic organ-on-a-chip technology was used to measure the rate of podocyte detachment when simultaneously exposed to fluid flow and cyclic strain. A phosphomimetic mouse model was generated, subjected to subtotal nephrectomy (to simulate glomerular hyperfiltration), and assessed for renal injury. Targeted mass spectrometry was used to determine whether injurious stimuli to podocytes increased ACTN4 phosphorylation.

Results: Compared to wild type (WT) ACTN4, phosphomimetic ACTN4 led to increased F-actin bundling activity and higher spatial correlation of F-actin alignment in podocytes. When subjected to mechanical stress in organ-on-a-chip culture devices, phosphomimetic podocytes demonstrated nearly a 3-fold higher rate of detachment (28/154 podocytes, 18.2%) in comparison with WT (12/170 podocytes, 7.1%, $p<0.05$). Phosphomimetic Actn4 mice developed proteinuria and glomerulosclerosis after subtotal nephrectomy. Finally, phosphorylation of ACTN4 at S159 in podocytes was stimulated by high extracellular glucose and TGF-b.

Conclusions: Increased phosphorylation of ACTN4 at S159 leads to biochemical, cellular, and renal pathology that is similar to pathology resulting from human disease-causing mutations in ACTN4. Stimulation of this phosphorylation by glucose and TGF-B suggests potential mechanisms of ACTN4-mediated kidney disease that extend beyond its original genetic etiology.

Funding: NIDDK Support

PO1588

Toward a Molecular Mechanism for Low-Molecular-Weight Proteinuria in Dent Disease

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Background: Dent disease is a progressive X-linked disorder caused by loss of function of the Cl^-/H^+ exchanger CLC-5. Early symptoms include low molecular weight (LMW) proteinuria resulting from inefficient recovery of filtered proteins by megalin and cubilin receptors in the proximal tubule (PT). Knockout of Clc-5 in mice recapitulates the LMW proteinuria observed in human disease and decreases protein (but not mRNA) levels of megalin and cubilin. How loss of CLC-5 leads to reduced receptor expression remains unknown. Previous gene expression studies in *Clcn5* KO mice suggest there are alterations in cholesterol and lipid metabolism. Elevated cholesterol levels have been demonstrated to alter the organization of the endocytic pathway and impair receptor recycling in cultured cells. We hypothesize that altered cholesterol metabolism impairs megalin traffic through the recycling pathway and promotes its degradation.

Methods: We used siRNA knockdown (KD) and CRISPR/Cas9 knockout (KO) and rescue approaches in an opossum kidney (OK) cell culture model that recapitulates morphologic and functional features of the PT *in vivo* to study the role of Clc-5 in the endocytic pathway. Additionally, we assessed PT function, megalin/cubilin expression, and cholesterol distribution in newly generated CRISPR/Cas9 Clc-5 KO mice.

Results: KD or KO of Clc-5 resulted in significantly decreased endocytic uptake of fluorescently labeled albumin that was fully rescued by heterologous expression of wild-type human CLC-5. Additionally, the half-life of megalin was reduced in Clc-5 depleted cells. We confirmed LMW proteinuria in the KO mice. Heterozygous females also have reduced PT albumin uptake and megalin expression. We observed an accumulation and a redistribution of cholesterol in PTs of heterozygous mice and in Clc-5 KD OK cells.

Conclusions: Our new cellular models for Dent disease should enable us to identify the molecular mechanism that results in reduced megalin/cubilin expression and determine whether altered cholesterol metabolism contributes to the LMW proteinuria observed in Dent disease.

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PO1589

Super-Resolution Imaging of the Filtration Barrier Suggests a Role for Podocin R229Q in Genetic Predisposition to Glomerular Disease

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Background: Breakdown of the three-layered glomerular filtration barrier is a leading cause of end-stage kidney disease. Whereas extensive research led to a growing understanding of hereditary glomerular diseases in children, most adult patients lack a genetic diagnosis. p.R229Q is a common missense variant in *NPHS2*, the gene encoding podocin, and it is associated with albuminuria in the general population. However, epidemiological studies suggest that p.R229Q is only disease causing in trans-association to additional genetic alterations.

Methods: We assessed the predisposition of p.R229Q to glomerular disease by introducing the equivalent point mutation in mice using CRISPR/Cas9-mediated genome editing. By applying super-resolution STED microscopy and functional measurements, we characterized the phenotype of Pod^{R231Q} mice. Additionally, we evaluated the $podocin^{R231Q}$ protein stability in human cultured podocytes.

Results: Although $Pod^{R231Q/wildtype}$ mice do not develop overt glomerular disease, super-resolution microscopy and morphometric analyses revealed ultrastructural alterations that have recently been linked to disease predisposition. Ultrastructural alterations were even more prominent in homozygous $Pod^{R231Q/R2321Q}$ mice eventually resulting in microalbuminuria in aged mice. Consistent with a recently published study, the slit diaphragm length correlated significantly with levels of albuminuria. $Podocin^{R231Q}$ protein levels were decreased in $Pod^{R231Q/R231Q}$ mice and human cultured podocytes expressing the variant. Mechanistically, increased proteasomal degradation resulted in a decreased protein stability of $podocin^{R231Q}$ in human cultured podocytes.

Conclusions: Collectively, our data suggest that podocin R231Q may contribute to genetic predisposition in adult patients.

PO1590

Reduced Glomerular and Nephron Injury due to Albumin Knockout in the Heavily Nephrotic, Polymerization-Defective GBM Laminin B2-Del44 Mutant Mice

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Background: Increased proteinuria is associated with adverse outcomes in chronic renal disease. Much evidence indicates that increased albumin filtration through the glomerular filtration barrier exacerbates nephron injury, but in vivo evidence is conflicting. Although it was previously shown that Nagase analbuminemic rats exhibit little or no increase in renal injury following multiple insults, Alport mice lacking albumin were previously shown to have dramatically increased lifespan with delayed injury to glomeruli and nephron epithelium.

Methods: We mated CRISPR-mediated, albumin-knockout mice with laminin B2-Del44 mice, which exhibit heavy albuminuria, but delayed foot process effacement and fibrosis. Mice were monitored until their natural deaths or euthanized at 9, 3, or 10 months for analyses. Plasma was analyzed for BUN. Glomeruli were analyzed by electron microscopy to determine foot process effacement. Nephron epithelium was analyzed by immunofluorescent microscopy to determine status of injury markers.

Results: Albumin-Del44 double mutant mice exhibited a significantly increased lifespan (6-month vs 9-month average), with significantly reduced BUN at all ages. Similar to Alport mice, foot process effacement in albumin-Del44 double mutant mice

was decreased at yonger ages. Nephron tubule epithelium exhibited reduced KIM-1 expression at early ages, indicating delayed injury.

Conclusions: Similar to Alport mice, the absence of albumin in *Lamb2*-Del44 mice resulted in increased lifespan with delayed renal injury. These data support a significant role of albumin in nephron injury in murine models of nephrotic syndrome.

Funding: NIDDK Support

PO1591

Klotho Improves Renal Function in Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD-UMOD)

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Background: Heterozygous Uromodulin (UMOD) mutations cause ADTKD but no therapies are available. We tested if Klotho improves renal function in a murine model for ADTKD-*UMOD*.

Methods: To generate a stronger phenotype we crossed homozygous mutant Umod ($Umod^{C93F/C93F}$) mice with Klotho-overexpressing (TgKl) mice. We studied wild-type (WT), TgKl, $Umod^{C93F/C93F}$ and TgKl/$Umod^{C93F/C93F}$ mice at 6 and 13 months. For quantitative proteome analysis (LC-MS/MS) we harvested kidneys at 3 months.

Results: 1. Compared to $Umod^{C93F/C93F}$ mice, TgKl/$Umod^{C93F/C93F}$ animals had significantly lower serum BUN, creatinine, cystatin C (see Figure 1), PTH, FGF23 values, and less renal fibrosis. 2. Mutant UMOD is retained in the endoplasmic reticulum but relative urinary UMOD secretion was higher in TgKl/$Umod^{C93F/C93F}$ vs. $Umod^{C93F/C93F}$ (relative UMOD protein expression 0.27±0.15 vs 0.13±0.06, p<0.05). 3. Compared to $Umod^{C93F/C93F}$, TgKl/$Umod^{C93F/C93F}$ animals had significantly lower systolic (mean 118±5 vs. 137±5 mmHg, p<0.05) and diastolic blood pressures (56±4 vs. 83±7 mmHg, p<0.01), and lower mRNA expression of markers of cardiac hypertrophy. 4. To identify the mechanism for better renal outcome in TgKl/$Umod^{C93F/C93F}$, we performed an unbiased proteomics approach. We identified downregulation of Transforming growth factor-beta-induced protein (TGFBI) together with multiple collagens, prolargin, biglycan, and osteoglycin/mimecan in TgKl/$Umod^{C93F/C93F}$ vs. $Umod^{C93F/C93F}$ animals. We confirmed lower mRNA expression of TGFBI and collagens.

Conclusions: Klotho improves renal outcome in ADTKD-*UMOD* mice by increasing urinary UMOD secretion and ameliorating renal fibrosis by downregulation of TGFBI and collagens.

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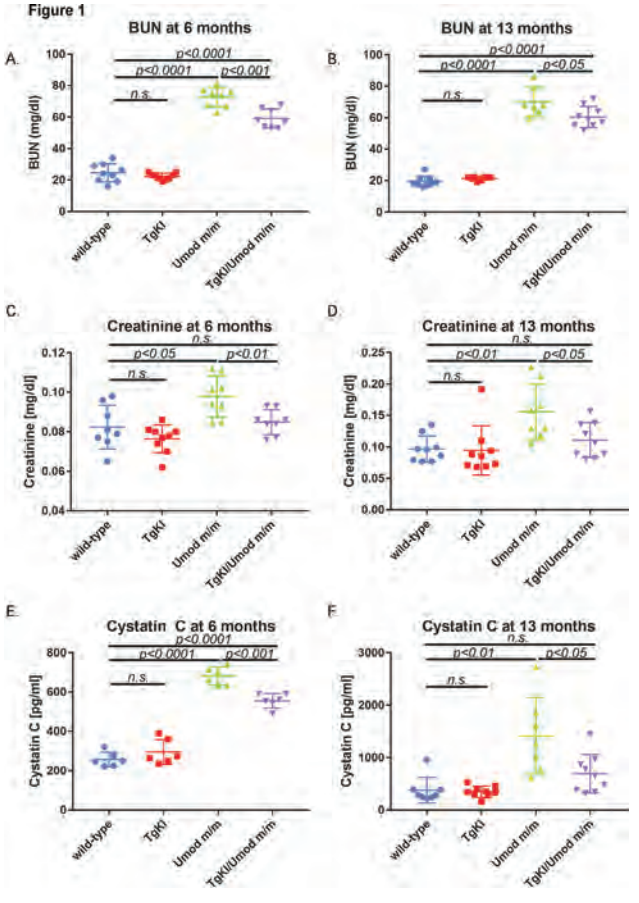

TgKl/$Umod^{C93F/C93F}$ mice show significantly lower BUN, creatinine, and cystatin C values.

PO1592

Spectrum of Mutations in 106 Chinese Patients with Gitelman Syndrome

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Background: Gitelman's syndrome (GS) is an rare, autosomal recessively inherited salt-losing tubulopathy(SLT) characterized by hypokalemic metabolic alkalosis. GS is caused by the mutations in *SLC12A3* gene encoding for the thiazide-sensitive NaCl cotransporter (NCC). However, the sensitivity of genetic sequencing was low. No large genomic rearrangements in Chinese patients with GS was previously identified.

Methods: Targeted gene sequencing (TES) by next generation sequencing associated with SLTs was performed for patients suspected of GS. Then, a search for large genomic rearrangements by ligation-dependent probe amplification(MLPA) assay was performed in patients with heterozygous for point mutations and patients with homozygous mutations without consanguinity history.

Results: Fifty-nine patients(55.67%) were female, the age was (34.87±15.36)years, serum potassium level was (2.68±0.36)mmol/L, serum magnesium level was (0.58±0.13)mmol/L, ninty-four patients(88.68%) had hypomagnesemia, seventy-nine patients(81.44%,79/97) had hypocalciuria. Eighty-three different mutations in *SLC12A3* were identified within these 106 GS patients, including 32 novel mutations and 4 recurrent ones,5 large genomic rearrangements. Recurrent mutations were p.T60M (22.86%),c.965-1_976delGCGGA CATTTTTGinsACCGAAAATTTT(6.19%),p.D486N(4.76%), p.N359K(4.76%). Triple mutations was identified in 8 patients, compound heterozygous mutations were identified in 70 patients, homozygous mutations were identified in 18 patients, whereas 10 patients had only one heterozygous mutation. The 5 large genomic rearrangements were exon deletion, including E7,E8 deletion, E8,E23 deletion, E20-E24 deletion, E8 deletion,E4-E6 deletion. The sensitivity of genetic testing sequencing was 90.57%.

Conclusions: We identified 83 mutations related to GS, containing 32 novel variants and 4 high-frequency ones, 5 large genomic rearrangements. TES combined with MLPA significantly increased the sensitivity of genetic sequencing and facilitate more accurate diagnosis of GS.

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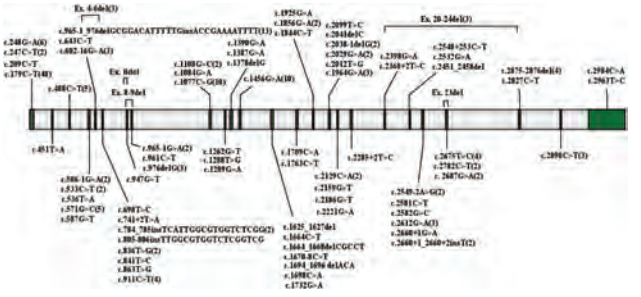

Schematic diagram of mutations in 106 ChineseGS patients

PO1593

Glucosylceramide Synthase Inhibition with Venglustat in Classic Fabry Disease Patients Leads to Progressive Reduction of Endothelial Cell Globotriaosylceramide Inclusion Volume

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Background: Fabry disease (FD) is a rare disorder caused by mutations in the gene for the lysosomal enzyme alpha-galactosidase A (αGal-A). Progressive accumulation of globotriaosylceramide (GL-3) in vascular endothelial and other cell types leads over decades to renal, cardiovascular, and other severe clinical manifestations. In a phase 2 study, glucosylceramide synthase inhibition with venglustat led to reduction in microscopic (LM) scores of lysosomal GL-3 inclusions in skin capillary endothelial cells (EC) after 3 years, although not after 6 months. We applied quantitative unbiased stereological methods to better characterize the effect of venglustat on skin EC GL-3 inclusions.

Methods: Skin biopsies were obtained from classic male Fabry disease patients (N = 11) at baseline and during daily treatment with venglustat (NCT02228460, NCT02489344). Images from at least 50 randomly selected superficial skin capillaries per biopsy were obtained using transmission electron microscopy (EM) at 7,500 X magnification. The fraction of the volume (Vv) of EC cytoplasm occupied by GL-3 inclusions [Vv(Inc/Endo)] was estimated using point counting by a masked reader. Two-sided paired t tests were used to evaluate changes from baseline to post-treatment values at each time point.

Results: Venglustat therapy led to a significant reduction from baseline in Vv(Inc/Endo) of 0.062 (21.1%; p=0.001) after 6 months and 0.119 (38.7%; p=0.001) after 3 years of treatment.

Conclusions: Treatment with venglustat led to reduction in skin capillary GL-3 inclusion fractional volume which was detectable after 6 months using precise quantitative EM methods, but not by LM scoring. This was followed by further reduction over the next 2 1/2 years. We posit that, in the absence of αGal-A activity, inhibition of GL-3 production with venglustat allowed other enzymatic or non-enzymatic mechanisms to progressively reduce EC lysosomal GL-3 content. Long-term venglustat therapy may therefore prevent or reverse progressive tissue injury in Fabry disease.

Funding: Commercial Support - Sanofi Genzyme

PO1594

The Role of Claudin Variants in the Formation of Kidney Stones

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Background: Genetic risk factors contribute to the formation of calcium-based kidney stones. The majority of calcium is reabsorbed via paracellular transport through tight junctions along the human nephron epithelium where Claudin proteins are expressed. Claudins determine the selectivity and permeability of different nephron segments. Studies have shown that *CLDN* gene sequence variants are associated with kidney stones. I hypothesize that sequence variants in Claudin genes that regulate paracellular renal transport of calcium. will be associated with the formation of kidney stones.

Methods: Patient DNA was analyzed by Fluidigm Next Generation Sequencing and confirmed by sanger sequencing. Rare variants (MAF<1%) were compared to the gnomAD database. *In silico* prediction software was used to predict the impact of the amino acid change. Human claudin variants were generated by site-directed mutagenesis and cloned into a mammalian expression vector, pEGFP. Immunofluorescence was performed on HEK293 cells that were transiently transfected with both variant and WT sequences.

Results: Ninety adult patients (45 females, 45 males) with recurrent calcium-based kidney stones were recruited from one urologist's kidney stone clinic. Seventy-two percent (65/90) of the patients self-defined as Canadian-European. Sixty-two percent (56/90) of the patients presented with the first kidney stone less than 40 years of age. Four novel heterozygous missense variants were identified in the following: *CLDN11* S157F, *CLDN16* K29E, *CLDN17* A94V, and *CLDN18* H212D. Nine rare variants include *CLDN*4 A82T, *CLDN*4 A113T, *CLDN7* V55I, *CLDN*8 A94V, *CLDN*8 M97T, *CLDN*12 M98V, *CLDN*23 A90T, and *CLDN*24 V97I. *CLDN4* A82T, *CLDN8* A94V, *CLDN11* S157F, and *CLDN17* A94V are predicted to be deleterious. HEK293 cells were transiently transfected with *CLDN4* A82T and the mutant protein was unable to localize to the tight junction, unlike the WT *CLDN4* protein which did co-localize with ZO-1 by immunofluorescence as expected (n=3 independent experiments). Other claudin variants are under evaluation.

Conclusions: The rare heterozygous variant, *CLDN4* A82T is located at the second transmembrane domain and predicted to be deleterious. Functional analysis showed that *CLDN4* A82T has an impact on the localization of the protein to the tight junction.

Funding: Private Foundation Support

PO1595

Elucidation of Molecular Pathogenesis of Lowe Syndrome and Dent Disease Type 2

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Background: Lowe syndrome and Dent disease-2(Dent-2) are both X-linked kidney diseases caused by *OCRL* gene abnormalities. However, the severity of these diseases are quite different. Genetic studies have shown that patients with truncating mutation in exon 1-7 of *OCRL* gene were diagnosed with Dent-2, and those with truncating mutations in exon 8-24 were diagnosed with Lowe syndrome. OCRL protein encodes a 5-phosphatase that acts on phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) and is related to cellular functions by the regulation of inositol phospholipids. The molecular mechanism by which different phenotypes of Dent-2 and Lowe syndrome are caused by the same gene variant has not been clarified until now, but it is suspected that an isoform consisting of exon 8-24 exists and it works partially as a 5-phosphatase. However, such isoform has not been identified yet.

Methods: We extracted mRNA from cultured urine derived cells of healthy controls and Dent-2 patient with truncating mutation in Exon4 of *OCRL* gene and then examined 5 'end of mRNA of these cells by using rapid amplification of cDNA ends (5' RACE) method. We also prepared three types of OCRL protein expression vector: wild type model, Dent-2 models harboring truncating mutation in exon 4 and exon 7, and Lowe syndrome models harboring truncating mutation in exon 16 and exon 22. These vectors were transfected into Hela cells and analyzed the protein expression and 5-phosphatase activity.

Results: As a result of 5' RACE, the 5' end starting from Exon 6 was detected in both cells of healthy control and Dent-2 patient. In fluorescent immunostaining of transfected Hela cells, strong protein expression was observed in the wild type model, relatively weak expression was observed in Dent-2 models and no expression was observed in Lowe syndrome models. Western blot analysis detected two bands of 105kDa and 80kDa in the wild type model, single band of 80kDa in Dent-2 models, and no band in Lowe syndrome models. 5-phosphatase activity of Dent-2 models was 50-85% of that of wild type model, whereas that of Lowe syndrome models was less than 20% of that of wild type model.

Conclusions: An isoform OCRL protein with 5-phosphatase activity is synthesized by alternative transcription of *OCRL* gene. This isoform contributes to the mild clinical phenotype in Dent-2.

Funding: Government Support - Non-U.S.

PO1596

Atypical Histological Abnormalities in Patients with Nephronophthisis Diagnosed with NPHP1 Deletion

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Introduction: Nephronophthisis (NPHP) is a chronic tubular interstitial disorder that exhibits autosomal recessive genetic forms, causing progressive renal failure in children. It is rare to show urinary abnormalities, edema and hypertension in patients with NPHP. Thus, it is often detected only when the renal failure becomes advanced. NPHP is divided into three types leading to the age of end-stage renal failure, *i.e.*, infant type (around five years old), juvenile type (around 13-14 years old), and adolescent type (around 19 years old). In present study, we report a case of NPHP diagnosed at twenty-six years old who was detected renal dysfunction by annual medical check-up.

Case Description: A 26-year-old woman has not been recognized any growth disorder, and has never been pointed out any urinary abnormality in a school checkup. She was detected renal dysfunction (sCr 2.2mg/dL) by annual medical check-up at 26 years old. Urine test indicated low specific gravity urine, but not proteinuria and microscopic hematuria. However, urinary β2-MG was high (805μg/L), and renal biopsy was performed for definitive diagnosis. Histological findings showed no significant findings in glomeruli. However, moderate fibrosis was observed in the interstitial area, and moderate atrophy was observed in the tubules. There was no significant finding in the immunofluorescence analysis, and no electron dense deposits was detected by electron microscopy. Although cyst-like expansion of the tubules was not clear, tubular atrophy was dominantly found in the distal tubules by CK7 staining. Then, we performed genetic analysis of *NPHP1* gene, and found complete deficiency of *NPHP1* gene, leading to definitive diagnosis of juvenile NPHP.

Discussion: NPHP is often progress to ESRD at an average age of 13-14 years old. Thus, it is exceedingly rare to find NPHP in adult. Although present case did not show the typical histological abnormalities, such as cyst-like expansion of the tubular lesion, we could diagnose by genetic analysis of NPHP1 gene. In patients with renal failure with tubular interstitial disease dominantly in distal tubule, it is necessary to discriminate NPHP even in the adult case.

PO1597

Biobank of Urinary Cells and Human Kidney Organoids Reveals Nephropathic Cystinosis Phenotypes and Gene Therapy Strategy

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Background: Cystinosis is a rare disorder caused by mutations in *CTNS* encoding a cystine transporter, leading to renal Fanconi syndrome and kidney failure. Cysteamine treatment slows, but does not prevent these outcomes and animal models fail to exhibit Fanconi syndrome. Stem cell derived kidney organoids exhibit structures with segmented, nephron-like segments, providing an *in vitro* platform to study nephropathic cystinosis. As a monogenic disorder, gene therapy is an attractive therapeutic approach which can be optimized in kidney organoids. However, cystinosis patients are rare, and iPS cells representing this population are needed.

Methods: Cells from the urine of 16 patients with cystinosis and control subjects were reprogrammed into iPS cells via Sendai virus. CRISPR gene editing was applied to non-cystinotic iPS cells generating 8 *CTNS*$^{-/-}$ lines with isogenic controls. Patient-derived and CRISPR-derived *CTNS* mutant and control iPS cell cohorts were differentiated into kidney organoids and propagated in suspension culture to assess cystinotic phenotype. Organoids were transduced at different stages of differentiation with lenti and adeno-associated viruses with fluorescent reporters to assess efficacy of gene transfer.

Results: Patient-derived and CRISPR-derived stem cells exhibited >100 fold increased intracellular cystine content and vacuole-like structures, compared to controls. Both patient and CRISPR iPSCs differentiated into kidney organoids with proximal and distal tubules and podocyte segments. However, cystinotic organoids developed lobular cyst-like structures in suspension culture over multiple weeks, which were reduced with cysteamine treatment. Lentiviral and AAV transduction successfully entered kidney organoid structures and co-localized with nephron markers when transduced at early stages of differentiation.

Conclusions: We have established a biobank of urinary and iPS cells representing over 20 cystinotic genotypes, with phenotypes in both patient- and CRISPR-derived *CTNS* mutant lines that show improvement with cysteamine. Viral transduction of kidney organoids can be timed to produce high levels of entry. This biobank provides a comprehensive resource for patient-specific development of more efficacious therapeutics for cystinotic nephropathy, including gene therapy.

Funding: Other NIH Support - Somatic Cell and Genome Editing Consortium, Private Foundation Support

PO1598

Clinical and Genetic Features of Autosomal Dominant Alport Syndrome

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Background: Alport Syndrome is the second most frequent genetic kidney disease, accounting for around 2% of patients with end-stage kidney disease. It is caused by pathogenic variants in *COL4A3*, *COL4A4* and *COL4A5* genes. The aim of this study was to evaluate the clinical and genetic spectrum of patients with autosomal dominant Alport syndrome.

Methods: Retrospective cohort study of 82 families (252 patients) with autosomal dominant Alport Syndrome. Clinical, genetic, laboratory and pathological data were collected. Renal survival, estimated glomerular filtration rate (eGFR) decline, genotype-phenotype correlation and extrarenal features were analyzed.

Results: A pathogenic DNA variant in *COL4A3* was identified in 106 patients (34 families) while 134 harbored a pathogenic variant in *COL4A4* (44 families). Complex/digenic inheritance was observed in 12 patients without clear genotype–phenotype correlation. Overall median renal survival was 67 years [95% CI, 58–73], without significant differences related to gender, causative gene or type of variant ($p = 0.85$, $p = 0.28$ *and* $p = 0.81$ *respectively*). Microhematuria was the most common renal manifestation (93%) while extrarenal features were rare. The results of kidney biopsies ranged from normal to focal segmental glomerulosclerosis. Hypertension was common and the age at its diagnosis correlated with age at end-stage kidney disease ($p < 0.01$). The slope of eGFR decline was -1.66 mL/min/1.73m^2 per year (-1.9 to -1.42) for the overall group, with no significant differences between *COL4A3* and *COL4A4* genes (P=0.60).

Conclusions: This study shows that autosomal dominant Alport Syndrome patients present a wide spectrum of symptoms ranging from asymptomatic to end-stage kidney disease, regardless of the affected gene or type of variant. This broad phenotype contributes to underdiagnosis in clinical practice and makes autosomal dominant Alport Syndrome diagnosis very challenging.

Funding: Government Support - Non-U.S.

PO1599

Beneficial Effect of Oxalobacter formigenes Treatment on Nephrocalcinosis in a Rat Model of Primary Hyperoxaluria

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Background: Hyperoxaluria leads to urinary calcium-oxalate supersaturation and crystal retention in renal tissue (nephrocalcinosis). In case of primary hyperoxaluria (PH), increased hepatic oxalate production because of a rare genetic defect often leads to severe nephrocalcinosis and early ESRD. Secondary hyperoxaluria is generally less severe, however more common and often related to intestinal oxalate hyperabsorption. Current therapy is often unsatisfactory. Oral administration of *Oxalobacter formigenes* (OxF), an oxalate-degrading bacteria, is thought to reduce intestinal oxalate absorption and to derive oxalate from systemic sources by inducing enteric oxalate secretion. Here, the ability of OxF treatment to prevent or reduce PH induced nephrocalcinosis, by using an ethylene glycol (EG) rat model to mimic increased hepatic oxalate production, was investigated.

Methods: Eighteen rats were administered EG (0.75% in drinking water) for 6 weeks, of which 9 were treated by oral gavage with OxF and 9 received vehicle. Five control rats did not receive EG/OxF. Plasma and urinary oxalate levels, calcium-oxalate crystalluria, urinary volume, fluid intake, and serum creatinine were monitored during the study period. At sacrifice, nephrocalcinosis was quantified.

Results: Vehicle treated EG animals showed clear hyperoxalemia, hyperoxaluria, calcium-oxalate crystalluria and nephrocalcinosis. In OxF treated EG animals the plasma oxalate levels were lower compared to vehicle-treated ones (significant at week 4: 47.6±20.9 vs 20.8±8.9 μM). Nephrocalcinosis was completely absent in the EG/OxF group. Urinary output of oxalate (crystals) was similar in OxF and vehicle treated EG animals which indicates that, taking into account the absence of crystals in renal tissue of OxF treated EG animals, the amount of oxalate offered to the kidney for excretion was higher in the EG/vehicle group. EG administration significantly increased urinary volume, renal mass and fluid intake, most probably due to osmotic diuresis and partially reversed by OxF. Serum creatinine levels of EG animals (both vehicle/OxF) stayed at baseline levels throughout the study.

Conclusions: This study shows a beneficial effect of OxF treatment on the development of PH-induced hyperoxalemia and nephrocalcinosis, pointing to OxF induced enteric oxalate elimination.

Funding: Commercial Support - Oxthera

PO1600

The Knockdown of RPL36A Downregulates GLA Expression Associated with Fabry Disease In Vitro Model

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Background: Mutations in the galactosidase alpha (*GLA*) locus can cause Fabry disease. The *GLA* locus is mapped in the reverse strand of *the RPL36A-HNRNPH2* readthrough locus. The study aimed to show the influence of the siRNA downregulation of the *RPL36A* expression (the first gene in the *RPL36A-HNRNPH2* locus*)* on the *GLA* expression.

Methods: The siRNA method was used to downregulate the expression of *RPL36A* in HEK293 cells. The expression of the two genes *RPL36A* and *GLA in vitro* was analyzed by RT qPCR. The protein products of the two genes were analyzed by ELISA and Western blot.

Results: The RT qPCR results of the *RPL36A* knockdown by siRNA showed a significant decrease not only for *RPL36A* expression but also for *GLA* expression ($p<0.05$) compared with the results of the untreated HEK293 cells. ELISA and Western blot assays showed a decrease in the GLA protein following knockdown of *the RPL36A* gene, but the two assays did not show a decrease in the expression for RPL36A protein. Alignment analysis by EMBOSS Matcher showed RPL36A protein amino acid sequence (Length: 106, Mass (Da): 12,441) is 99.1% like RPL36AL protein amino acid sequence (Length: 106, Mass (Da):12,469). Intriguingly, the sequence of mRNA transcripts of both genes showed an 85.3% similarity. The designed siRNA was specific to *RPL36A* transcript NM_021029.6 and not to *RPL36AL* transcript NM_001001.5, which may explain the RT qPCR results.

Conclusions: The data provided evidence that malfunction in the expression of *the RPL36A* locus located at the start of the *RPL36A-HNRNPH2* readthrough locus can cause an error in the expression of *GLA*. These findings revealed the importance of the *RPL36A-HNRNPH2* readthrough region in Fabry disease. The work was supported by Sanofi-Genzyme Project GZ-2017-11708.

Funding: Commercial Support - Sanofi-Genzyme Project GZ-2017-11708.

PO1601

Focal Segmental Glomerulosclerosis with Glomerular Basement Membrane Abnormalities Caused by Compound Heterozygous Myosin 1E Gene Mutations

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Introduction: Nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) in children is often associated with genetic mutations in podocyte structural proteins. This clinical case report highlights a pediatric patient with nephrotic syndrome and FSGS found to have two genetic mutations in myosin 1E gene (MYO1E) encoding the motor domain of the protein. While both of these mutations have previously been identified as variants of unknown significance individually, we report a case of compound heterozygous mutations resulting in FSGS.

Case Description: An 11-year old white male presented with proteinuria and hematuria. Family history of kidney disease included a paternal cousin with hematuria that spontaneously resolved. The patient had no history of recurrent urinary tract infections, kidney stones or excessive NSAID usage. Kidney biopsy revealed FSGS with basket-weaving, splitting and segmental thickening of glomerular basement membranes (GBM) on electron microscopy. Genetic testing was negative for Alport mutations but identified two variants in MYO1E gene (Table). Parental testing revealed each had one variant inherited by the patient, resulting in compound heterozygous mutation in the patient.

Discussion: Both missense mutations in this patient encode the motor domain of myosin 1e protein (residue 19-692), essential for podocyte motility and structural integrity. Hereditary mutations at other locations encoding the motor domain of MYO1E have been described and associated with FSGS. Functional studies showed that MYO1E motor domain variants led to protein mis-localization and disruption to the podocyte structural integrity (Mele et al. NEJM, 2011). MYO1E depletion in mice causes GBM abnormalities similar to lesions in this patient (Chase et al. Am J Physiol Renal Physiol, 2012). While each individual mutation inherited by the patient is not known to be pathogenic, we hypothesize that the combination of non-conservative mutations in the patient resulted in abnormal myosin-1e protein function that caused GBM abnormalities and FSGS.

Genetic diagnostic testing results for proband and parents

	Gene	Variant Location	Allelic Inheritance	Encoded location of myosin-1e
Mother	MYO1E	1684 G>A (Gly562Arg)	Heterozygous	Motor domain, missense mutation
Father	MYO1E	275 C>A (Ala92Glu)	Heterozygous	Motor domain, missense mutation
Patient	MYO1E	275 C>A (Ala92Glu) and 1684 G>A (Gly562Arg)	Double heterozygous	2 Motor domain mutations

PO1602

Metabolic State Modeling of Kidney Single Nuclei Data Reveals Cell-Specific Signatures at Baseline and in Disease

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Background: The kidney is a metabolically active and cellularly diverse organ. Perturbations in metabolic pathways, such as lipid metabolism, is a well-established sequelae of chronic kidney diseases, such as diabetic nephropathy. Single cell RNA sequencing has allowed for an unprecedented understanding of the kidney's transcriptomic complexity. However, until now, understanding the diverse metabolic states of the kidney has been limited to either expression analysis of single metabolic enzymes or bulk metabolomics experiments. Given the highly interconnected nature of metabolic networks and the kidney's cellular complexity, integrating a systems-level understanding of metabolic perturbations with single cell sequencing has the potential to reveal previously unappreciated metabolic cell states and disease perturbations.

Methods: We have applied the newly developed Flux Balance Analysis (FBA) algorithm for single cell sequencing data, Compass (doi: 10.1101/2020.01.23.912717), to a dataset of 36,560 single nucleus transcriptomes from mouse kidney comprised of three healthy mice and three mice with CoQ-deficiency proteinuric kidney disease.

Results: First, Compass correctly predicted well-established cell-specific kidney transport processes. Next, when comparing proximal tubule clusters, corresponding to S1, S2 and S3 segments, the S3 segment was found to have both high activity of branched chain amino acid (BCAA) metabolism and high activity of fatty acid oxidation (FAO). This previously unknown link between BCAAs and FAO in the kidney is of particular interest, given the known relationship between BCAA metabolism, FAO and metabolic disease. Finally, when comparing transcriptomes between disease and healthy mice, podocyte-specific changes in FAO and steroid metabolism were observed which correlated with podocyte cytoskeletal regulation, a hallmark of podocyte injury.

Conclusions: In summary, the combination of an enhanced resolution of single nucleus transcriptomics with a systems-level analysis of metabolic networks in the kidney have revealed cell-specific metabolic states at baseline and in disease. Future application of this analysis to human data will provide important validation for the generalizability of these findings and further insight into metabolic perturbations in human disease.

Funding: NIDDK Support

PO1603

Metabolic Dysfunction of Glomerular Endothelial Cells in Alport Syndrome

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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD), but its impact on Alport syndrome (AS, characterized by mutations in collagen IVα3α4α5) is unknown. We have previously shown that glomerular endothelial cells (GEC) are damaged in AS mice, manifested by enlarged fenestrations and alteration of the glycocalix in the early stage of disease. In the present study we report the early transcriptional changes in AS GEC as an indication of endothelial dysfunction and a contributing factor to Alport progression.

Methods: We generated endothelial *td*Tomato reporter AS mice and isolated GEC at 4 month of age by FACS. We studied *tdT* specificity in GEC by flow cytometry, WB, and by multiphoton and confocal microscopy, and their transcriptome by RNA-seq analysis. Data were analyzed and AS-GEC were compared to WT-GEC in terms of their morphology and differential gene expression. Tissue samples from patients with AS were used to confirm out findings from mice to that of in human by immunohistochemistry.

Results: Comparative transcriptomics showed high enrichment of differentially expressed genes associated with cellular metabolism, with lipid metabolism being among the top five most highly enriched biological processes in GEC. In particular, genes associated with fatty acid uptake, synthesis and oxidation were significantly downregulated. Among the differentially regulated genes, PGC-1α, which acts as a master regulator of cellular metabolism, was the most highly downregulated. Downstream of PGC-1α, genes associated with fatty acid transport, (CD36, FATP-1, FATP-2, Fabp3), fatty acid synthesis (fatty acid synthase), fatty acid oxidation (Acox1, Bdh2, Eci3, Abcd2), and antioxidant enzymatic scavenger proteins (Gpx3, Gpx6, Gsta3, sod2) were also downregulated. We observed similar findings in human biopsy samples from AS patients by histology.

Conclusions: In sum, we report for the first time a lipid metabolic dysfunction in Alport glomerular endothelial cells. Therefore, better understanding of the functional role of the glomerular endothelium in AS could lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

Funding: Private Foundation Support

PO1604

NPHS1 Variants Can Cause Persistent Asymptomatic Proteinuria: Genetic and Clinical Characteristics of Patients with NPHS1 Variants in Japan

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Background: *NPHS1* gene, which encodes nephrin, is known as a causative gene of congenital nephrotic syndrome (CNS). In addition, recently, it had been recognized that *NPHS1* variants present with childhood steroid resistant nephrotic syndrome (SRNS) or focal segmental glomerular sclerosis (FSGS). However, it is not well known that this gene variants account for more milder phenotypes such as asymptomatic proteinuria.

Methods: 347 unrelated patients with CNS, infantile nephrotic syndrome, FSGS and asymptomatic proteinuria were screened for podocyte related genes including *NPHS1* by using targeted exome sequencing. A retrospective review of clinical information was conducted for the cases with pathogenic variants in *NPHS1*.

Results: We identified 15 *NPHS1* autosomal recessive pathogenic variants in 15 cases including 2 siblings. Regarding clinical manifestation, 6 cases showed CNS, 5 cases showed SRNS and 4 cases showed only asymptomatic mild to moderate proteinuria. The median age developing proteinuria in cases with SRNS and asymptomatic proteinuria was 6 years old. Pathological evaluation for 12 cases revealed that 11 cases showed minor glomerular abnormality and 1 case showed findings resemble membranous nephropathy. Genetic analysis revealed the variants c.2464G>A p.(V822M) and c.2515del were variantal hot spots in the Japanese population and all 6 cases having V822M showed milder phonotypes such as SRNS (n=2) or asymptomatic proteinuria (n=4) and no one showed CNS.

Conclusions: In this study, *NPHS1* variants were detected not only in cases with CNS and SRNS, but also in cases with asymptomatic proteinuria. Shono et al. have previously reported that V822M was a causative variant in cases with familial nephrotic syndrome who showed complete remission and functional analysis revealed that this variant leads to milder phenotype through mechanisms of (1)mild reduction of cell surface expression, (2)motion and trafficking restriction on surface and (3)interfering with assembly of microdomain on surface (Hum Mol Genet. 2009). Our study confirmed this variant leads to very mild phenotypes of SRNS or even the asymptomatic proteinuria and broadened the understanding of clinical manifestations of cases with *NPHS1* variants.

PO1605

Ckd. Qld fabRy Epidemiology (aCQuiRE) Study: Fabry Disease Prevalence Among Patients with CKD

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Background: Fabry disease (FD) is a rare, genetic disorder resulting in absence or deficiency of alpha-galactosidase A (α-Gal A), leading to accumulation of globotriaosylceramide (GB3) in cells and tissues. Associated mortality and morbidity are due to renal, cardiac, and cerebrovascular manifestations. General population prevalence is ~0.0025%. Dialysis population prevalence is estimated at 0.12-0.36%. Little is known about the prevalence of FD amongst wider chronic kidney disease (CKD) populations. Although FD is X-linked, affected females can have variable disease manifestations. Prevalence amongst women is unclear.

Methods: A prospective cross-sectional study of FD prevalence amongst CKD patients in public Queensland nephrology services was undertaken across 7 sites Oct 2017-Aug 2019. Patients with all stages of CKD including Stage 5D/5T were eligible to participate, irrespective of prior CKD aetiology or diagnosis.3,000 CKD patients were screened using dried blood spot (DBS) testing. Repeat DBS and/or Lyso-GB3 testing was employed where results were inconclusive. FD was confirmed through diagnostic *GLA* genetic sequencing. All biochemical and genetic testing was undertaken in an accredited clinical laboratory.

Results: 6 unrelated cases (0.20%) of FD were identified. 3 were patients with a previously identified diagnosis of FD (100% sensitivity). 3 were patients with a new diagnosis of FD as a result of study participation. Of these 6 identified cases, 5/6 were male and 1/6 was female. This represented 0.3% and 0.08% of all male and female participants respectively. All newly diagnosed cases were male with two being CKD Stage 5T, and one being CKD Stage 5D. One case was in a participant who identified as Indigenous, the first known case in this population. In total, an additional 28 at-risk family members were identified who may benefit from family screening. No readily identifiable pattern of symptoms was identified.

Conclusions: Our results support the potential feasibility and utility of a cascade testing strategy principally using DBS, as a primary screening method for FD in adult patients with CKD. Further, we confirm that a significant proportion of prevalent cases of FD amongst those with CKD remains undiagnosed.

Funding: Commercial Support - Sanofi-Genzyme

PO1606

Systems Analyses of Renal Fabry Transcriptome and Response to Enzyme Replacement Therapy (ERT) Identifies a Cross-Validated and Druggable ERT-Resistant Module

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Background: Fabry nephropathy (FN) is caused by mutations in the α-galactosidase A gene and can be managed with ERT. Via understanding the molecular basis of FN and long-term ERT impact, we aim at a framework for selection of biomarkers/drug-targets.

Methods: Obtained from normal controls and two independent FN-cohorts, mRNA-isolates from archival kidney biopsies (n=41) taken prior and up to 10 years of ERT were subjected to RNAseq and partly IHC. Combining pathway-centered analyses with network-science allowed computation of transcriptional landscapes from glomeruli, proximal/distal tubuli & arteries and integration with existing proteome and drug::target data.

Results: Despite inter-cohort heterogeneity, FN seemed well controlled, esp. via early introduced ERT. Pathways consistently altered in both FN-cohorts pre-ERT vs. controls were limited to glomeruli and arteries and commonly pertained to same biological themes. While glomerular keratinization-related processes were ERT sensitive, a majority of alterations, such as transporter activity and responses to stimuli, remained dysregulated or remerged despite ERT. Inferring an ERT-resistant genetic module on this basis identified targets suitable for drug repurposing **(Figure 1)**.

Conclusions: Transcriptional landscapes of kidney compartments reflected differences in FN-cohorts. ERT can revert FN molecular state to closely match controls. We identified and cross-validated ERT-resistant modules, when leveraged with external data, allowed estimating their suitability as biomarkers and targets for adjunct treatment.

Funding: Government Support - Non-U.S.

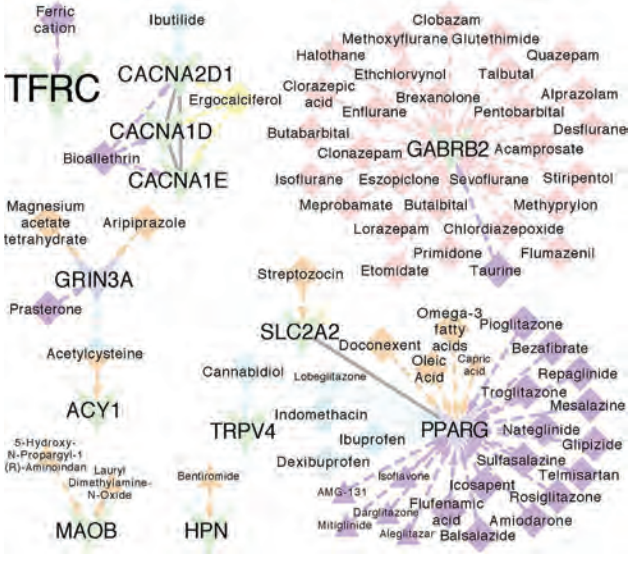

Figure 1. Target::Target::Drug interactome. Node color target: green=glomerular target, blue=arterial target.

PO1607

Circular RNA-Based Biomarker Profile of Patients with Fabry Disease

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Background: Fabry disease is a rare X-linked lysosomal storage disease, caused by mutations in the galactosidase α gene. Deficient activity of α-galactosidase A leads to glycosphingolipid accumulations in multiple organs. Circular RNAs represent strong regulators of gene expression. Their circular structure ensures high stability in blood. We hypothesized, that blood-based circular RNA profiles improve phenotypic assignment and therapeutic monitoring of Fabry Disease.

Methods: A genome-wide circular RNA expression analysis was performed in blood of 58 genetically diagnosed patients with Fabry Disease and 14 age- and sex matched healthy controls. Most highly increased circular RNAs were validated by quantitative real-time PCR. A disease control cohort of 109 patients with acute kidney injury was included. Linear regression analyses were performed for validated circular RNAs and clinical patient characteristics.

Results: A distinct circular RNA transcriptome signature identified patients with Fabry Disease. Circular RNAs *hsa_circ_0006853, hsa_circ_0083766* and *hsa_circ_0002397* distinguished patients with Fabry Disease from healthy controls and patients with acute kidney injury. *Hsa_circ_0002397* demonstrated, furthermore, a female-specific circular RNA expression pattern. Circular RNA level were significantly related to galactosidase α gene mutations, early symptoms, phenotypes, disease severities, specific therapies and long-term complications of Fabry Disease.

Conclusions: The discovery of circular RNA-based and Fabry Disease specific biomarker may advance future diagnosis and therapeutic monitoring to diminish long-term complications of Fabry Disease.

Funding: Commercial Support - Shire

PO1608

Outcome of Primary Hyperoxaluria Type 3: Clinics, Diagnostics, and Follow-Up

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Background: Primary hyperoxaluria type 3 (PH3) is said to be the most benign form of PH and the risk of chronic kidney disease (CKD) and even end stage renal disease (ESRD) is reported to be low. We collected clinical, diagnostic and follow up data from our PH3 patients to evaluate the true disease characteristics.

Methods: We retrospectively screened the OxalEurope Registry for data of PH3 patients known to the German Hyperoxaluria Center and analyzed them for clinical and laboratory parameters.

Results: From the 90 PH3 patients enrolled in the OxalEurope Registry, 45 had all laboratory analysis done at the Hyperoxaluria Center (3-45 years of age, 23 males). Genetically confirmed diagnosis revealed 21 different biallelic mutations in *HOGA1*. The main symptom was recurrent urolithiasis, most prominently found in the first 3 years of life (>25% of patients). Nephrocalcinosis was seen in 7 patients. Mean follow up for all patients was 7.76 (0.25-34) years, median age at first symptom was 0.96 (0.17-10) and median age at diagnosis (based on genetics) was 4.57 (0.25-16.86) years. Not all patients experienced clinical remission: 3/6 patients > 20 years of age have ongoing kidney stone development. A high amount of stone removal procedures during the first years of life, but also later in life was observed. Urinary oxalate (Uox) excretion was significantly and continuously elevated over time. There was no significant difference in Uox between PH1 (1.37 mmol/1.73m^2/24h), PH2 (1.4 mmol/1.73m^2/24h) and PH3 (1.13 mmol/1.73m^2/24h) with the exception of a lower Uox in PH1 patients sensitive to B6 medication (0.94 mmol/1.73m^2/24h, $p<0.05$). A decline in kidney function was observed, which was related to a decreased clearance of oxalate. Nine patients had CKD stages 2 or 3. One patient showed a significant decline in eGFR over a period of 15 years (134 to 68.1 ml/min/1.73m^2), which we would relate several lithotripsy procedures (n=16), but also ongoing hyperoxaluria.

Conclusions: Our analysis from a subgroup of European PH3 patients provides additional information on clinical outcome. PH3 patients seem to have the highest kidney stone burden during the first years of life, but they do not stop producing stones. Some PH3 patients progress to CKD and to loss of kidney function over time. Uox is comparable to non B6 responsive PH1 and also to PH2 patients.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc., Private Foundation Support

PO1609

Patient Journey in Alport Syndrome

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Background: Patients with Alport Syndrome(AS) experience difficulties in diagnosis. Misdiagnosis remains frequent even after detailed clinical and pathological assessment. Qualitative interviews were conducted with patients diagnosed with AS and caregivers, to better understand the patient experience.

Methods: Thirty-nine Interviews (16 male and 23 females >18 years) from the United States, United Kingdom, France, Japan, and Germany were conducted with patients and caregivers. Respondents were recruited by each country's Alport advocacy groups. Responses were summarized and presented quantitatively and qualitatively.

Results: Thirty-nine participants (20 patients, 4 caregivers, 15 respondents being patients themselves and caregivers) completed the interview; and shared their experience as patients, or that of the patients they care for (interviews reflect 32 firsthand patient experiences, and 7 patient experiences from caregivers; mean age=34). Thirty-four patients experienced their first symptoms as children (mean=9 yrs). Seventy-nine percent experienced hematuria before diagnosis. Despite early signs, diagnosis was delayed.

Males recorded hearing loss more than females (2/3 vs. 1/3 respectively) and at earlier ages (adolescent for males vs. females in 20-30s). Males consulted a nephrologist earlier than females (median age: 12 vs. 28) and were diagnosed ~15 years earlier than females (median age=16, female=31). The median delay in diagnosis from first symptom onset was 15 years (males=11, females=26). Two-thirds of patients were diagnosed with genetic testing and/or renal biopsy. The remainder were diagnosed by an array of treatment criteria (16 genetic, 16 biopsies, 9 others). Patients on delayed diagnosis sometimes receive inconclusive or no biopsy results. Based on current standard of care, dialysis or transplant is seen as inevitable future outcome. The same population included patients with dialysis (n=7) and transplant (n=5) experience. Participants perceived transplant as an improvement of renal symptoms compared to dialysis.

Conclusions: Diagnosis can take years. Initial symptoms such as hematuria alone would not raise the suspicion for AS. Delays in diagnosis have significant psychosocial impact on patients and caregivers. While dialysis and transplant are considered inevitable outcomes of the disease, patients and caregivers recognize the unmet need for future disease specific treatments.

Funding: Commercial Support - Sanofi Genzyme

PO1610

Multidisciplinary Renal Genetics Clinics: Family Perspectives and Preferences

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Background: Multidisciplinary renal genetics clinics (RGC) comprising nephrologists, clinical geneticists, and genetic counsellors operate in 15 public hospitals across Australia with the goal of providing family-centred care and definitive molecular diagnoses to patients. However, little is known about family perspectives of multidisciplinary clinics or of undergoing genomic testing in this context.

Methods: Patients having genomic testing were surveyed following initial RGC attendance and after results disclosure. We explored patient experiences of the clinic, perceived impact of the disease on the family and reproductive planning, understanding of the test, and hopes and expectations relating to testing. Surveys included the Decision Regret, and Genetic Counselling Outcome scales.

Results: Of 221 respondents to the baseline survey (RR=72%), most preferred the multidisciplinary clinic model to seeing specialists in separate clinics (n=145, 70%). A better understanding of the condition and implications for relatives were most commonly ranked as the most important advantages of the multidisciplinary clinic (n=27, 47%). Respondents agreed they received enough information during pre-test counselling (n=180, 92%) and had the opportunity to ask questions (n=181, 94%). The majority of respondents understood that the test analyses many genes (n=115, 59%), causative variant(s) may not be identified (n=143, 73%), and results may be of uncertain significance (n=142, 73%). Despite this, 44% of respondents thought the test was likely / highly likely to identify the cause of the condition (n=85).

Conclusions: Understanding patient and family experiences and opinions, and the short- and long-term impacts on families will guide the design and delivery of RGCs and associated genomic testing programs. A full author list is available online at www.kidgen.org.au.

PO1611

Autosomal Recessive Renal Tubular Dysgenesis Caused by a Founder Mutation of Angiotensinogen (AGT)

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Background: Autosomal recessive renal tubular dysgenesis (ARRTD) caused by inactivation mutations in *AGT, REN, ACE*, and *AGTR* is a very rare but fatal disorder with incomplete knowledge about pathogenesis and a lack of therapeutic options.

Methods: We report six Taiwanese with ARRTD from six unrelated families diagnosed by renal histology. Clinical features, prevalence of carrier heterozygosity, pathogenesis, and potential rescue therapy were examined.

Results: All patients exhibited antenatal oligohydramnios, postnatal anuria, pulmonary hypoplasia, and profound hypotension refractory to interventions. AGT (Angiotensinogen) protein levels were diminished in the liver along with reduced serum AGT, angiotensin I (Ang I) and II (Ang II) levels. Neonatal demise occurred in all but one. All carried the same homozygous E3_E4 del:2870bp deletion+9bp insertion in *AGT*. The allelic frequency of this heterozygous *AGT* mutation was approximately 1.2% (6/500), suggesting that ARRTD may not be exceedingly rare in Taiwan. This mutation results in skipping of exons encoding the serpin domain of AGT, which is important for renin interaction and the generation of truncated protein (1-295 amino acids). *In silico* modeling revealed a diminished interaction between mutant AGT and renin, and proximity ligation assay demonstrated a significant decrease in the amount of this truncated protein.

Conclusions: This *AGT* mutation leads to the diminished interaction with renin and decreased Ang I and II generation. Hydrocortisone may potentially rescue the cases of ARRTD caused by this truncated AGT.

PO1612

KIDNEYCODE: A Genetic Testing Program for Patients with CKD

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Background: The International Society of Nephrology recommends the adoption of genetic testing with a goal of providing precision medicine based on individual risk. A recent whole-exome sequencing study showed that genetic inheritance may be responsible for up to 10% of CKD diagnoses. We designed a gene panel to prospectively provide genetic testing in a subset of patients with CKD.

Methods: Reata Pharmaceuticals is partnering with Invitae on KIDNEYCODE, a US program that provides no-charge genetic testing using next generation sequencing (NGS) to enable diagnosis of a subset of rare monogenic causes of CKD: Alport syndrome (AS), autosomal dominant polycystic kidney disease (ADPKD) due to *PKD2* variants, focal segmental glomerulosclerosis (FSGS), and autosomal recessive PKD due to *PKHD1* variants. Invitae's renal disease panel includes 17 genes (*ACTN4, ANLN, CD2AP, COL4A3, COL4A4, COL4A5, CRB2, HNF1A, INF2, LMX1B, MYO1E, NPHS1, NPHS2, PAX2, PKD2, PKHD1*, and *TRPC6)*. Patients at risk for hereditary CKD (eGFR ≤ 90 mL/min/1.73m^2 plus hematuria or a family history of CKD) or known or suspected AS or FSGS are eligible. Family members of those with known or suspected AS or FSGS are also eligible.

Results: Of 455 test results, a genetic variant was reported in 278 patients. Of those, 206 patients had 219 variants in *COL4A3, 4, or 5* genes [112 Pathogenic/ Likely Pathogenic (P/LP), 107 Variants of Uncertain Significance (VUS)], 87 patients had 95 variants in genes associated with FSGS (22 P/LP, 73 VUS), 40 patients had 44 variants in *PKHD1* (5 P/LP, 39 VUS), and 8 patients had variants in *PKD2* (4 P/LP, 4 VUS). Of the 109 patients with P/LP *COL4A* variants, 51 reported a previous diagnosis of Alport syndrome. Other diagnoses in patients with P/LP *COL4A* variants included FSGS, thin basement membrane disease, familial hematuria, hereditary nephritis, IgAN, diabetic CKD, hypertensive CKD, and ADPKD. Hearing loss was reported in 34, and eye disease was reported in 2 of the 109 patients with P/LP *COL4A* variants.

Conclusions: Initial results with the KIDNEYCODE panel demonstrate the utility of NGS. Combining genetic testing with clinical presentation and medical history can improve the accuracy of diagnosis of hereditary CKD.

Funding: Commercial Support - Reata Pharmaceuticals

PO1613

Very Rare Mutation Identified in Female Patient with Multisystemic Fabry Disease in the United States

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Introduction: Fabry disease is an X-linked lysosomal storage disorder characterized primarily by kidney, cardiac and central nervous system dysfunction. Over a 1000 mutations have been identified to be associated with disease. We describe a patient with biopsy confirmed Fabry disease identified to have very rare mutation not listed in genetic databases.

Case Description: A 48 year old female with past medical history of chronic kidney disease G4A3 (previously biopsy proven Fabry disease), dilated cardiomyopathy, atrial fibrillation, previously treated breast cancer, was referred to our clinic by a nephrology group given progressive worsening of kidney function and consideration for migalastat. Patient was diagnosed with Fabry disease at the age of 32 (normal renal function at the time), and subsequently received agalsidase beta for a period of 3 years thereafter. However, therapy was ceased due to insurance issues. In the interim, patient has progressive decline in renal function (creatinine 2.5 mg/dL on referral), worsening proteinuria, along with development of dilated cardiomyopathy and neuropathy. We proceeded with genetic testing to identify mutation of galactoside A (GLA) gene and kidney biopsy(image 1). Genetic testing revealed a novel mutation variant c.820G>C(p.Gly274Arg) deemed to be heterozygous and of unknown significance by the laboratory. Kidney biopsy revealed classic finding of glomerular inclusions (podocyte and mesangium) with diffuse renal parechymal scarring. Patient was eventually prescribed agalsidase beta, given non amenability to migalastat.

Discussion: This case highlights identification of a very rare mutation of the GLA gene that appears to have late onset manifestations. Pursuing genetic testing in patients with Fabry disease has become more important with the introduction of novel therapy migalastat, which may not be compatible with numerous pathogenic mutations.

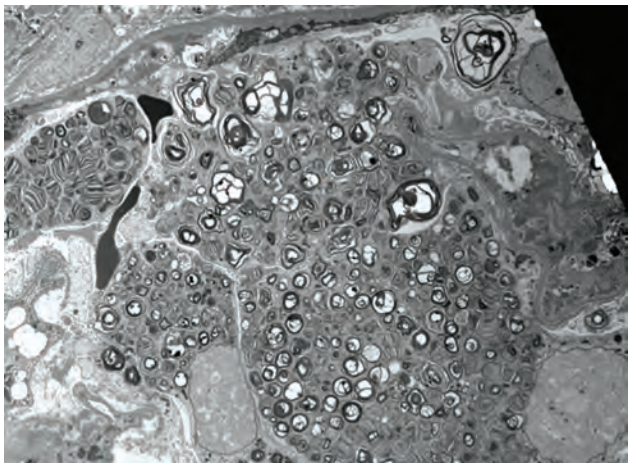

Image 1

PO1614

A Unique Case of COL4A3/4 and ACTN4 Mutations Combined

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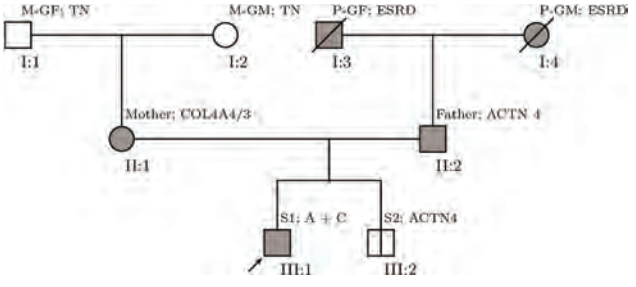
Introduction: Alport syndrome is due to mutations of the COL4A gene. Males with COL4A5 mutations present with proteinuria and CKD, hearing impairment and anterior lenticonus. Disease in women ranges from mild hematuria and proteinuria to a syndrome similar to that of X-linked males. Patients in families with mutations of the Alpha-actinin-4 gene (ACTN4; autosomal dominant inheritance) present histologically and clinically with focal segmental glomerulosclerosis. We present the first ever-reported case of a patient with both COLA4 and ACTN4 mutations

Case Description: Family pedigree is shown in the figure. Subject II:1 is a female with Alport's syndrome diagnosed by kidney biopsy, CKD3 (in her 50's) had genetic testing showing a COL4A3 mutation. Her husband (II:2, in his 50's), had ESRD presumed to be secondary to diabetes (DKD). Given concerns for possible disease in their 2 sons, genetic testing was performed. The oldest son (III:1; in his 30's) showed the same COL4A3 mutation as II:1 but an additional ACTN4 mutation. He has microalbuminuria (90mg/g) and GFR >90 ml/min. The younger son (III:2; in his 20's) showed the ACTN4 mutation but no COL4A mutation (clinical tests are pending). Given the ACTN4 mutations in the sons, subject II:2 was tested, showing an ACTN4 mutation (suggesting DKD was not the single etiology of his ESRD). Family history showed both paternal grandparents had ESRD, unknown etiology for I:4 (died in her 50's) and presumed to be due to DKD for I:3 (died in his 80's)

Discussion: ACTN4 and COL4A mutations have not been reported in a single patient before. The identification of 2 mutations known to be associated with CKD will allow for early intervention with management of comorbid conditions like hypertension, obesity and diabetes and use of RAAS inhibitors. Distinct disease patterns may emerge associated with specific genetic abnormalties allowing a more personalized treatment. Genetic testing should be considered for all patients presenting with proteinuria as findings may dictate changes in management



PO1615

Kidney Tubuloids Model Cystinosis and Allow Drug Screening

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Background: Cystinosis causes progressive damage to the kidney and other organs. In cystinosis, a *CTNS* mutation causes lysosomal cystine accumulation and other metabolic abnormalities including alfa-ketoglutarate (aKG) accumulation in patient cells and serum. Excess KG associates with aggravated apoptosis, abnormal autophagy and proximal tubule dysfunction, suggesting a key role in cystinosis pathology (*Jamalpoor et al. BioRXiv 2020*). Current treatment with cysteamine reduces cystine and delays, but does not stop, progression of renal insufficiency nor restores tubular dysfunction. Therefore, new therapies are needed. Here, we use patient kidney tubuloids to model cystinosis and to test the efficacy of a novel drug combination.

Methods: Tubuloids were grown from primary renal cells from the urine of two cystinosis patients and compared with two healthy controls. Tubuloid origin and composition were assessed by qPCR and stainings. The effect of cysteamine and/or bicalutamide treatment was studied by a large-scale metabolic screen using LC-MS. Potential toxicity of bicalutamide was tested by measuring ATP levels as proxy for tubuloid viability at increasing doses.

Results: Urine-derived tubuloids consisted of kidney cells (PAX8+p63-) and not urothelium (PAX8-p63+). Tubuloids contained proximal tubule, loop of Henle, distal tubule and collecting duct epithelium. Patient tubuloids showed hallmark cystine accumulation (1.25 ± 0.12 *vs.* 0.16 ± 0.01 nmol/mg protein in controls, $p<0.05$). Although cysteamine normalized cystine levels, it failed to restore aKG accumulation. The novel combination of cysteamine with bicalutamide more potently lowered cystine and reduced aKG in tubuloids (aKG peak area reduction of 16-28% with bicalutamide and 21-37% with the combination, both $p<0.05$). Finally, the used bicalutamide dose did not compromise the viability of cystinotic tubuloids.

Conclusions: Tubuloids model cystinosis *in vitro* and allow personalized drug screening. Moreover, tubuloids show that the combination of cysteamine and bicalutamide is more effective in normalizing the metabolic abnormalities in cystinosis than cysteamine alone. **Acknowledgements** This work is supported by the partners of RegMedXB, powered by Health Holland, Top Sector Life Sciences & Health and the Dutch Kidney Foundation (grant 150KG19).

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PO1616

Case Report: Familial FSGS Associated with a Novel Variant of WT1

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Introduction: The underlying causes of Familial FSGS are currently being elucidated by exome sequencing. WT1 has been reported in association with Frasier Syndrome, Denys-Drash syndrome and isolated nephrotic syndrome. WT1 variants have emerged as a common cause of autosomal dominant FSGS.

Case Description: We report a case of a 22 year old male who presented at age 17 with nephrotic range proteinuria progressing to ESRD over 4.5 years. His renal biopsy at that time revealed FSGS andExome sequencing (Next Generation Sequencing) demonstrated a WT1 variant of uncertain significance. Family history was significant for the following: mother with microalbuminuria (229mg/24hr on spot protein) and hypertension (onset 2 years prior to proteinuria); maternal uncle with congenital unilateral renal agenesis and later End Stage Kidney Disease requiring transplant at age 29 years; and maternal grandfather who died in his 60s on dialysis for unknown reasons. Genetic analysis in the patient and mother revealed the same heterozygous variant in WT1 (c.1078G>T, p.Gly360Cys).

Discussion: WT1-related renal disease is associated with autosomal dominant inheritance. We strongly suspect the WT1 variant described was pathogenic, as evidenced by a family history of both FSGS and genitourinary tract malformations. We review the association of WT1 with nephrin and postulate a potential interaction with XY karyotype, similar to other WT-1 associated disease. Disclosure: The views expressed are those of the authors and do not reflect the Department of Army or U.S. Government.

PO1617

Positive Identification of Genetic Causes of FSGS Increases with Proper Patient Selection

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Background: FSGS is a histological lesion with diverse pathogenesis, commonly divided into primary, secondary (maladaptive, virus or drugs), and genetic forms. Differentiation of these forms is challenging but important for management and prognosis. We aimed to identify clinicopathologic factors that could be predictive of finding a genetic diagnosis in individuals with unknown forms of FSGS.

Methods: Cohort study included 51 FSGS patients with either a "secondary" form of FSGS without an identifiable cause or with presumed "primary" FSGS who failed to respond to immunosuppressive therapy (IS). Seven patients with primary FSGS in remission following IS served as negative control. Patients were classified as having pathogenic/likely pathogenic variants (Group 1a), relevant variants of uncertain significance (relevant VUS; Group 1b), and no relevant variants (Group 2). Clinicopathologic characteristics are presented in Table 1.

Results: A pathogenic/likely pathogenic genetic variant or relevant VUS was found in 41.2% (n=21/51) and in 11.8% (n=6/51) of the patients, respectively. 55.6% were in *COL4A* (*A3/A4/A5/A1*), 33.3% in podocyte genes (*INF2/NPHS2/TRPC6/NPHS1*), and 11.1% in other genes (*DLC1/SMARCAL1/UMOD*). Family history of kidney disease was present in 75% (n=15/20) of the patients in Group 1a, 16.7% (n=1/6) in Group 1b, 20.8% (n=5/24) in Group 2 and 0% (n=0/7) in the negative control. There was a negative correlation between proteinuria and the probability of finding a genetic variant. Severe foot process effacement on EM and nephrotic syndrome were significantly more common in the negative control group compared to Group 1a.

Conclusions: Over 50% of adult patients with FSGS who could not be categorized into primary or known secondary forms were found to have a genetic diagnosis. Positive family history and absence of nephrotic syndrome increased the likelihood of identifying a pathogenic/likely pathogenic variant. Genetic testing is therefore highly recommended in such population.

Table 1 Clinicopathologic characteristics of the patients

	Negative control (NC; n=7)	Group 1a (n=21)	Group 1b (n=6)	Group 2 (n=24)	*P value (NC vs. Group 1a)*
Age at biopsy	30.43±25.70	41.95±15.46	46.83±20.33	45.29±15.31	0.297
% of patients with family history	0/7 (0%)	15/20 (75%)	1/6 (16.7%)	5/24 (20.8%)	0.017
eGFR (ml/min/BSA)	53.60±17.81	58.15±31.52	38.67±20.84	57.97±26.41	0.677
Serum creatinine (mg/dL)	1.48±0.62	1.34±0.47	3.04±2.55	1.50±0.55	0.608
Albumin (g/dL)	2.30±0.62	3.62±0.64	3.53±0.82	3.33±1.01	0.001
total Cholesterol (mg/dL)	409.2±188.6	215.1±60.1	249.2±158.5	219.2±90.9	0.053
Proteinuria (g/24h)	9.78±2.42	3.13±1.18	5.85±2.21	7.53±1.13	<0.001
% of patients with nephrotic syndrome	7/7 (100%)	1/21 (4.8%)	1/6 (16.7%)	7/24 (29.2%)	<0.0001
>80% foot process effacement on EM	6/7 (85.7%)	5/19 (26.3%)	1/5 (20%)	9/24 (37.5%)	0.021

EM: electron microscopy. Unpaired t-test and Chi-square or Fisher test were used for statistical analysis.

Table 1

PO1618

A Rare Case of Nephrotic Syndrome Associated with Dent Disease

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Introduction: Dent's disease is a rare X-linked condition caused by a mutation in *CLCN5* and *OCRL* gene, which impair the megalin-cubilin receptor-mediated endocytosis in kidney's proximal tubules. Thus, it may manifest as nephrotic-range low-molecular-weight proteinuria (LMWP). On the other hand, glomerular proteinuria, hypoalbuminemia and edema formation are the key features of nephrotic syndrome (NS) that rarely found in Dent's disease.

Case Description: A man in his 30s with Dent's disease presented with leg edema for five days. The laboratory results revealed hypoalbuminemia and a decreased of urine β2-microglobulin/urine protein ratio (Uβ2/UP), indicating that the primary origin of proteinuria shifted from LMWP to glomerular proteins. The kidney biopsy revealed no glomerular abnormality, and calcium deposition in the renal medulla. Electron microscopy indicated extensive foot-process effacement of the glomerular podocytes. After a combination of treatment with prednisolone and cyclosporine, the nephrotic syndrome was remitted.

Discussion: This report describes a first case of adult-onset NS in Dent's disease. Given the atypical clinical presentation and the shift of LMWP to glomerular proteinuria in this patient, glomerulopathy and the Dent's disease existed separately in this patient. In such a case of combind LMWP and glomerular proteinuria, the Uβ2/UP can be used to monitor the relapse of NS. We should perform renal biopsy in patients with sudden onset of edema and hypoalbuminemia even those who have a congenital proteinuria.

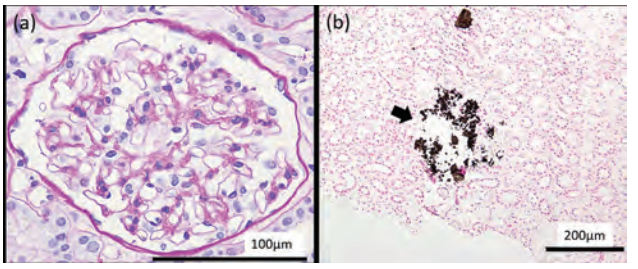

Figure1(Left)A glomerulus in PAS staining showed there were no cellular crescents and no proliferation of mesangial cells. (Right) Von Kossa staining showed renal medulla with calcifications (arrows) was observed in the medullary interstitium.

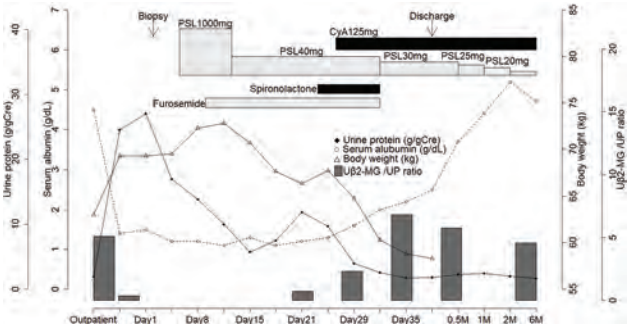

Figure 2 The patient treatment course

PO1619

Mitochondriopathy Manifesting as Inherited Tubulointerstitial Nephropathy Without Symptomatic Other Organ Involvement

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Introduction: Mitochondrial dysfunction has been previously described in cases of human chronic kidney disease (CKD), and subjects affected by primary systemic mitochondrial disease develop CKD. Importantly, examples of mitochondrially inherited tubulointerstitial kidney disease in subjects with no other symptomatic organ involvement have been recently reported, suggesting the possibility of a single-organ mitochondrial disease.

Case Description: A 12-year-old boy presented with short stature, low body weight, increased serum creatinine (1.9 mg/dL) and increased blood urea nitrogen (30 mg/dL). Blood analysis showed anemia, vitamin D deficiency, hyperparathyroidism and negative antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA). Ultrasound showed small kidneys (< 5th percentile). A kidney biopsy showed mild, non-specific, chronic tubulointerstitial nephropathy on light microscopy. Immunofluorescence was negative. Electron microscopy showed markedly enlarged and dysmorphic mitochondria. Given this striking histopathologic finding, genetic testing was performed. Next generation sequencing of mitochondrial DNA from the tissue biopsy showed the presence of a homoplasmic, single, missense mutation in position 616 (m.616T>C) of the mitochondrially encoded transfer RNA phenylalanine (*MTTF*) gene. Analysis of blood derived mtDNA from mother and maternal uncle, who were on dialysis since their 30s, confirmed the same homoplasmic mitochondrial mutation, supporting our hypothesis. The renal biopsy findings, genetic findings, and pattern of inheritance were strongly suggestive of a diagnosis of mitochondrially inherited tubulointerstitial kidney disease. Notably, no additional symptomatic organ involvement was present in these subjects.

Discussion: Our case supports and reinforces the possibility of a single organ-limited mitochondrial disease, regardless of the systemic mitochondrial DNA mutation status, potentially radically changing management and prognosis of these patients. Careful analysis of mitochondria by electron microscopy should be performed in patients with tubulointerstitial nephropathy and family history of kidney failure.

PO1620

Discovery of CHK-336: A First-in-Class, Liver-Targeted, Small Molecule Inhibitor of Lactate Dehydrogenase for the Treatment of Primary Hyperoxaluria

Jennifer H. Cox,[1] Marc-Olivier Boily,[1] Alex Caron,[1] Amandine Chefson,[1] Oliver Chong,[1] Jim Ding,[1] Valerie Dumais,[1] Samuel Gaudreault,[1] Robert Gomez,[1] James Guthrie,[1] Ross P. Holmes,[2] Andrew J. King,[1] John Knight,[2] Jeff Lester,[1] W. T. Lowther,[3] Renata Oballa,[1] Michael D. Percival,[1] Tao Sheng,[1] Jayakumar Surendradoss,[1] Joyce Wu,[1] David A. Powell.[1] *[1]Chinook Therapeutics Inc., Vancouver, BC, Canada; [2]University of Alabama at Birmingham, Birmingham, AL; [3]Wake Forest University, Winston-Salem, NC.*

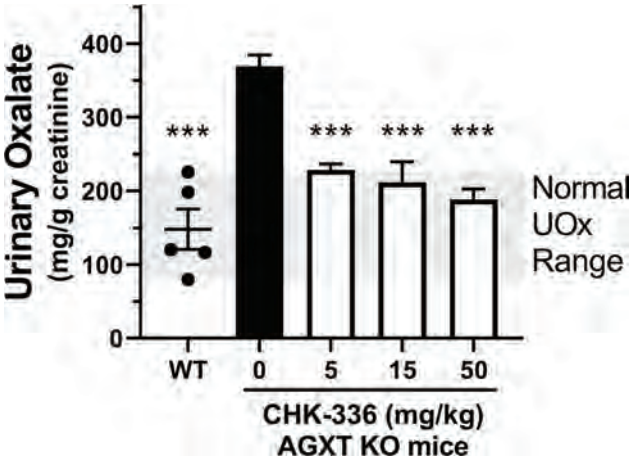
Background: Primary hyperoxalurias (PH) 1-3 are autosomal recessive disorders involving excess hepatic oxalate production resulting in frequent kidney stones, progressive CKD and ESRD. Few therapeutic options currently exist for these patients. Lactate dehydrogenase (LDH) catalyzes the final and only committed step in hepatic oxalate synthesis and represents a potential therapeutic target for all forms of PH. Herein we describe the profile of a potent and selective LDH inhibitor.

Methods: CHK-336 was evaluated in LDH activity assays and in an AGXT knockout PH1 mouse model. Additional characterization of drug properties was performed.

Results: CHK-336 demonstrates potent and selective inhibition of LDH in enzyme assays (IC_{50} = 0.4 nM) and hepatocyte assays (IC_{50} = 80-142 nM). To minimize the potential for extra-hepatic LDH inhibition, a liver-targeted tissue distribution profile was engineered into the molecule. CHK-336 demonstrates exceptional liver-targeting across species mediated by OATP-uptake into hepatocytes and tight binding to LDH resulting in a long liver half-life that supports once-daily oral dosing. In a PH1 mouse model, CHK-336 produced significant and dose-dependent reductions in urinary oxalate to levels observed in wild-type mice. Wide safety margins were established in rodent toxicity studies to support continued development of CHK-336.

Conclusions: By potently blocking LDH, the terminal step in hepatic oxalate synthesis, along with engineering of liver-targeted tissue distribution, CHK-336 is a promising oral small molecule development candidate with the potential to treat patients with hyperoxaluria.

Funding: Commercial Support - Chinook Therapeutics Inc.



CHK-336 reduces UOx in AGXT-KO mice

PO1621

Disease Manifestations, Treatment, and Healthcare Resource Use (HRU) in Primary Hyperoxaluria Type 1 (PH1): An International Online Chart Review Study

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Background: Few multinational studies have examined the clinical burden of PH1. This online retrospective chart review evaluated disease manifestations, treatments, and HRU in a large international sample of PH1 patients.

Methods: Nephrologists in the US, Canada, UK, France, Germany, and Italy provided data from PH1 patients in their care via an online platform. Eligible patients had PH1 confirmed by genetic testing or liver biopsy and ≥2 office visits from 2016-2019. Data on disease manifestations, treatment and HRU were collected.

Results: Overall, 86 patients (56% from North America; 63% female) from 41 unique providers were analyzed. Mean age at diagnosis was 21.2±11.6 yrs, with a mean of 6.7±9 yrs to diagnosis from first symptoms. Mean age at index (first office visit in past 3 yrs) was 25.3 yrs; 71% had stage ≥3 CKD at index (median eGFR: 44mL/min/1.73m^2). Mean follow-up was 1.6±1 yrs. The most common PH1 manifestations during follow-up were uro-/nephrolithiasis (57.1%) and urinary tract infection (UTI; 56.0%). Additionally, 29.8% of patients had ≥1 acute renal decline episode, of which 53% resulted in lasting renal function loss. In total, 11.6% of patients had ESKD at or before index, and 8.1% developed ESKD post-index; 2.3% had ESKD with timing not noted. Dialysis and transplant (liver and/or kidney) at any time were reported in 22.2% and 17.1%, respectively. In terms of HRU during follow-up, 51% of patients required ≥1 stone removal procedure (lithotripsy: 38%; ureteroscopy: 28%; percutaneous nephrolithotomy: 9%). Hospitalization and ER visits were required by 85.9% and 84.6% of patients, respectively, where data was reported (n=73).

Conclusions: There is significant delay between PH1 presentation and diagnosis. Patients with PH1 suffer progressive renal function decline, with many progressing to ESKD. During follow-up, almost all patients required ER visits and hospitalization, and most had stone episodes and UTIs and required stone removal procedures. These findings highlight an ever-present risk of acute events that contribute to ongoing morbidity, HRU and impaired quality of life, underscoring the need for early intervention with effective PH1 treatment.

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PO1622

Recurrent SLC12A3 Mutations in Taiwanese Families with Gitelman Syndrome: A Rapid Detection for the Higher Prevalence

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Background: Recurrent mutations in *SLC12A3* gene responsible for autosomal recessive Gitelman syndrome (GS) are reported to be common with uncertain prevalence. Rapid detection of the recurrent hotspots may help early diagnosis of GS but remain challenging. We aim to investigate the prevalence of recurrent *SLC12A3* mutations in a large Taiwan cohort of GS families and develop a simple, novel, and rapid method to detect recurrent *SLC12A3* hotspots.

Methods: One hundred and thirty independent families with genetically-confirmed GS referred from different regions of Taiwan were consecutively enrolled to define recurrent *SLC12A3* hotspots and determine their prevalence. Using Taqman MGB probe-based real time primer chain reaction (RT-PCR), hotspots-based mutational detection plate was designed and optimized to recognize all hotspots. We validated this mutation detection plate and also tested the feasibility in 12 newly-diagnosed GS patients.

Results: A total of 57 mutations in *SLC12A3* gene were identified from our cohort and 22 different mutations including two deep intronic mutations were found in at least two unrelated families, comprising 85.7% of all allelic mutations including biallelic triple mutations. These 22 hotspots-based detetion plate was fully validated with excellent sensitivity and specificity in GS patients carrying biallelic *SLC12A3* mutations and healthy subjects. In the clinical validation, recurrent mutations were recognized in 87.5% of allelic mutations of 12 newly-diagnosed GS patients within 4 hours and all confirmed by direct sequencing.

Conclusions: Recurrent *SLC12A3* mutations are very common in Taiwanese GS patients. This novel hotspots-based detection plate may be time, cost, and labor saving to rapidly identify the recurrent hotspots and provide an early molecular diagnosis of GS in patients with chronic hypokalemia.

PO1623

AVR-RD-01, an Investigational Lentiviral Gene Therapy for Fabry Disease, Reduces Gb3 Substrate in Endothelial Cells of Renal Peritubular Capillaries

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Background: Lysosomal disorders are attractive candidates for *ex vivo* gene therapy based on the potential to transform a patient's own cells into a drug product to deliver sustained functional protein/enzyme after a single treatment. Fabry disease (FD) is caused by mutations in the *GLA* gene that result in functional deficiency of the lysosomal enzyme, alpha-galactosidase A (AGA), which leads to pathological accumulation of substrates and metabolites, including globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3). Significant morbidity and early mortality result from damage to kidneys, heart, and brain.

Methods: AVR-RD-01 is an investigational *ex vivo* gene therapy that involves transplantation of autologous stem cells genetically modified with a lentiviral vector which inserts into the human genome a complementary deoxyribonucleic acid (cDNA) sequence that encodes for functional human AGA.

Results: In a Phase 1 trial of AVR-RD-01, 5 patients, previously on enzyme replacement therapy (ERT), after gene therapy demonstrated increases in plasma and leukocyte AGA activity and decreases in substrate (Gb3) and metabolite (lyso-Gb3) in plasma, now sustained up to 32 months. A Phase 2 clinical trial in 8-12 treatment-naïve males (16-50 years) with classic FD investigates the safety, tolerability, and efficacy of AVR-RD-01, including its effect on substrate accumulation in the kidney after 48 weeks. Kidney biopsy results for the first patient in the Phase 2 clinical trial demonstrated reduction in renal peritubular capillary (PTC) Gb3 inclusions, quantitatively assessed by the BLISS methodology. At 48 weeks, Gb3 inclusions were reduced from an average of 3.55 to 0.47 per PTC corresponding to an 87% reduction versus baseline (BL). Leukocyte and plasma AGA activity increased, associated with declines in plasma and urine Gb3 and lyso-Gb3, including an 87% reduction in plasma lyso-Gb3 at 48 weeks versus BL. Adverse events were as expected with the particular conditioning regimens

(i.e. mild/moderate and quickly resolving), underlying FD and pre-existing conditions, with no serious adverse events related to AVR-RD-01 drug product. Low-titer anti-AGA antibodies were transiently detected at week 24.

Conclusions: The latest results from this ongoing open label Phase 2 study will be shared.

Funding: Commercial Support - AVROBIO

PO1624

ILLUMINATE-B, a Phase 3 Open-Label Study to Evaluate Lumasiran, an RNAi Therapeutic, in Young Children with Primary Hyperoxaluria Type 1 (PH1)

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Background: PH1 is a rare genetic disorder that often presents in young children. It is caused by hepatic oxalate overproduction leading to recurrent kidney stones, nephrocalcinosis, progressive kidney failure, and multiorgan damage from systemic oxalosis. There are no approved pharmacologic therapies for PH1. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic that reduces hepatic oxalate production by targeting glycolate oxidase. In ILLUMINATE-A, a randomized, placebo-controlled Phase 3 study in patients with PH1 ≥6 years, lumasiran demonstrated an acceptable safety profile. The study met its primary efficacy endpoint [percent change from baseline, relative to placebo, in 24hr urinary oxalate (UOx) excretion averaged across months 3 to 6, P<0.001] and all tested secondary endpoints. Here, we present results from ILLUMINATE-B, an ongoing open-label Phase 3 study to evaluate efficacy and safety of lumasiran in young children with PH1.

Methods: Key inclusion criteria: <6 years, confirmed PH1 diagnosis, eGFR >45 mL/min/1.73m^2 if ≥12 months or normal serum creatinine for age if <12 months. Patients received lumasiran 3×monthly, then monthly or quarterly. Primary endpoint: percent change in UOx excretion from baseline to month 6.

Results: Eighteen patients enrolled, including 4 patients <2 years; median age at first dose 4.3 years (range: 0.3-6). The baseline mean spot urinary oxalate:creatinine (UOx:Cr) was 0.63 mmol/mmol (range: 0.17-1.71), equivalent to 5.8×ULN for age. As of March 2020, there were no lumasiran-related serious adverse events; no deaths, severe adverse events, or treatment discontinuations. The most common adverse events related to lumasiran were mild, transient injection site reactions in 3/18 patients. Results from the complete primary analysis period (primary and secondary endpoints) will be presented.

Conclusions: Lumasiran demonstrated an acceptable safety profile in this interim analysis of ILLUMINATE-B. These results are consistent with those observed in ILLUMINATE-A in older children and adults and support the continued development of lumasiran for PH1.

Funding: Commercial Support - Alnylam Pharmaceuticals

PO1625

PHYOX3: A Long-Term, Open-Label Extension Trial of Nedosiran in Patients with Primary Hyperoxaluria Type 1, 2, or 3

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Background: Primary hyperoxaluria (PH) is an ultra-rare, autosomal recessive genetic disorder characterized by overproduction of oxalate in the liver. Clinical manifestations can include nephrocalcinosis, recurrent kidney stones, progressive renal impairment, and systemic oxalosis. Nedosiran (formerly DCR-PHXC) is an investigational RNAi therapy administered monthly by subcutaneous injection. It is designed to reduce hepatic LDHA protein thereby inhibiting the final step responsible for overproduction of oxalate in PH1, PH2, and PH3.

Methods: This is an interim analysis of multidose data from the ongoing open-label, rollover extension PHYOX3 trial (NCT04042402) to evaluate long-term safety and efficacy of nedosiran in patients with genetically confirmed PH1, PH2 or PH3. Patients aged 6 years or more who have completed a previous nedosiran trial and their siblings with genetically confirmed PH are eligible.

Results: As of May 2020, 16 participants were enrolled (13 PH1, 3 PH2) in this study. Total exposure (based on 15 participants) to monthly dosing of nedosiran has exceeded 3 years based on the cumulative duration of patient participation in the trial. Seven participants have had exposure to at least 3 monthly doses of nedosiran. Treatment-emergent adverse events (AEs) were observed in 11 participants. Seven participants experienced 33 AEs considered related to study drug: administration-site events (18), blood chemistry findings (6), pain (2), dysuria (1), nasal congestion (1), edema (1), and erectile dysfunction (1). Three AEs were uncoded at this time. None of the participants experienced injection-site reactions (defined as occurring 4 hr or more after injection). All drug-related AEs were mild. There were no drug-related serious AEs. Six out of the 7 participants who have had exposure to at least 3 monthly doses of nedosiran showed normalization or near-normalization of urinary oxalate excretion (defined as < 0.46 mmol/24 hr/1.73 m^2 and ≥ 0.46-0.60 mmol/24 hr/1.73 m^2, respectively) on at least 2 visits after the first dose.

Conclusions: Nedosiran has shown an acceptable safety profile in the interim analysis. This and the sustained reduction of urinary oxalate excretion are encouraging signs of potential long-term safety and clinical benefit of a multidose regimen of nedosiran.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc.

PO1626

A Case of De Novo X-Linked Alport Syndrome Treated by Kidney Transplantation from the Patient's Healthy Mother

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Introduction: X-linked Alport syndrome is a hereditary nephritis that leads to end-stage kidney failure by 40 years of age in most affected males. Although kidney transplantation is well tolerated in X-linked Alport syndrome, donors should be carefully selected since the proband's mother is usually the gene carrier.

Case Description: The patient was a 38-year-old man. Microhematuria had been pointed out during his early childhood and had been diagnosed with Alport syndrome based on the results of a kidney biopsy at five years of age. He developed bilateral sensory deafness at 20 years of age and started hemodialysis due to end-stage kidney failure at 28 years of age. Although an X-linked mode of inheritance was suspected, none of the patient's relatives, including his mother, had kidney disease. Since his mother had normal urinalysis results, living kidney transplantation from his mother was performed when he was 34 years of age. A genetic diagnosis at a later date revealed a splicing variant at c.3107-2A>G in COL4A5 of the patient. However, there was no apparent genetic mutation in COL4A5 of his mother, suggesting that the patient had a *de novo*mutation. The kidney function of both the patient and his mother was stable at 4 years after kidney transplantation.

Discussion: For transplantation in cases of hereditary nephritis, it is preferable to avoid transplantation from an affected individual or the gene carrier. The kidney prognosis of female X-linked gene carriers is reported to be worse than expected. Although there was no genetic mutation in the donor in the present family case, if an X-linked form is suspected, a genetic diagnosis of the donor candidate should be performed before kidney transplantation is considered.

PO1627

Clinical and Economic Impact of Primary Hyperoxaluria: A Retrospective Claims Analysis

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Background: Primary hyperoxalurias (PH; types 1, 2, and 3) are rare genetic disorders resulting in the overproduction of oxalate in the liver and that manifest in renal complications. This study sought to quantify the healthcare resource utilization (HCRU), costs, and clinical characteristics of PH patients.

Methods: This retrospective study analyzed claims from IQVIA PharMetrics® Plus (1/2014-12/2019). PH cohort inclusion was an ICD-10 code for PH (E72.53) and no evidence of secondary hyperoxaluria (SH). A random 5% sample from the same database of patients without PH or SH served as a control cohort (non-PH). Clinical outcomes, including kidney stones, costs, and HCRU were compared between the cohorts for a 12-month period. The Charlson Comorbidity Index (CCI) was used to characterize comorbidities.

Results: The annualized median and mean costs per patient for the PH cohort (n=325; median $10,385; mean $21,541) were significantly higher (p<0.001) than the non-PH cohort (n=2,579,352; median $1,079; mean $5,041). Costs were significantly higher for PH patients across age groups (see table) and care settings, including inpatient/outpatient settings (p<0.001). The majority of PH patient cost (62%) was associated with outpatient visits. The PH cohort saw significantly higher use of specialists compared to non-PH patients (p<0.001), including nephrologists (19% vs 1%) and urologists (66% vs 3%). Over one year, 80% of the PH cohort had at least one kidney stone. The CCI scores for the PH and non-PH cohorts were 0.79 and 0.22, respectively.

Conclusions: The median cost of care for the PH cohort was 10 times higher than the non-PH cohort over all age groups annually, and the PH cohort showed substantially greater HCRU compared to the non-PH cohort. Additional research is required to better understand these costs in an effort to enable more efficient healthcare utilization and improve care delivery to these at-risk patients.

Funding: Commercial Support - Dicerna Pharmaceuticals

	<18 years			18-35 years			36-55 years			55+ years		
	PH	non-PH		PH	non-PH		PH	non-PH		PH	non-PH	
Sample Size	20	651,473		41	725,871		138	791,338		126	410,670	
Average	$27,100	$2,981	*	$21,902	$3,673	*	$17,602	$5,793	*	$24,856	$9,280	*
Median	$7,730	$698	*	$8,951	$810	*	$9,311	$1,350	*	$13,413	$2,496	*

*Indicates p<0.001

PO1628

Identification of Genetic Drivers of Age-Related Renal Histopathology

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Background: Studies to understand age-related changes in the human kidney have been performed by measuring kidney function and damage markers in the urine. These studies have provided valuable information, including clear genetic components underlying kidney disease. However, due to the highly invasive nature of kidney biopsies, it is not possible to identify early causal changes in humans by histological analyses that are hypothesized to precede changes in function and renal damage. However, mouse models provide access to kidneys at specific time points enabling us to conduct histological analyses across lifespan. We established the Aged Mouse Kidney Resource, which consists of kidneys from 600 genetically diverse mice (males and females) at three ages (6, 12, and 18 months). Scanned PAS slides for all mice are publically available at korstanjelab.jax.org, as well as gene expression, protein expression, and DNA methylation data for a subset of kidneys

Methods: Renal histology has been mostly a qualitative or semi-quantitative discipline. We leverage new approaches in image analysis and machine learning and demonstrate the feasibility of quantification on entire sections of mouse kidneys (pathomics) from a large number of animals. We have developed a pipeline that uses machine learning on scanned slides, which allows us to automatically segment glomeruli and quantify mesangial matrix expansion (MME) in a high-throughput fashion.

Results: Applying our pipeline on the 12-month kidneys from our Resource shows an estimated heritability (h^2) of 0.76 for MME and genetic analysis identifies three significant loci with *Abca13* and *Cfl2* as strong candidate genes for two of these loci. On the other hand, we find that the heritability drops to 0.61 and no significant loci were found in the 18-month old kidneys. We hypothesize that this is caused by the increasing effect of environmental variation with age and death before 18 months of animals with fast age-related renal functional decline that reduces the genetic variability and mapping power in the population.

Conclusions: Our results demonstrate the importance of genetic factors contributing to histological phenotypes and the power of combining pathomics and genetics to identify genes involved in age-related histological changes.

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PO1629

Epigenome-wide Association Study of Kidney Function

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Background: DNA methylation regulates gene regulation and may influence estimated glomerular filtration rate (eGFR).

Methods: The study included over 13,000 participants from multi-ethnic studies for discovery and replication. We tested the associations between whole blood DNA methylation and eGFR using normalized beta values from Illumina 450K or EPIC arrays. Analyses were performed in study- and race-stratified samples using linear mixed models and adjusting for age, sex, and study-specific and technical variables. Study-specific results were meta-analyzed, and findings were assessed using integrative epigenomics methods and pathway analyses.

Results: The study identified 93 DMPs genome-wide significantly associated with eGFR, of which 35 replicated in independent samples. We also replicated 6 previously published DMPs including the *ZNF20-ZNF788* locus. Identified DMPs showed significant overlap enrichment with DNase I hypersensitive sites in kidney tissue, sites associated with the expression of genes in *cis*, and transcription factor motifs, in addition to pathways associated with kidney development. Among main findings, we identified a DMP at the *KANK1* gene, which has been previously associated with podocyte dysfunction and nephrotic syndrome.

Conclusions: We identified DMPs associated with eGFR and uncovered associations with genomic regions related to regulatory function in kidney tissue. These findings shed light on epigenetic mechanisms associated with kidney function, bridging the gap between eGFR-associated DNA methylation and tissue-specific chromatin context.

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PO1630

Generation of Monogenic Candidate Genes of Human Nephrotic Syndrome via Three Independent Approaches

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a frequent cause of chronic kidney disease in childhood. The finding of >60 single-gene causes of SRNS, mainly through whole-exome sequencing (WES), has contributed to the understanding of its disease mechanisms. Whereas in ~12-30% of cases with onset <25yo, a monogenic cause is detected, most cases remain molecularly unsolved. This indicates that additional monogenic causes of SRNS may exist.

Methods: We generated 3 independent lists of candidate genes: **1)** 63 published monogenic mouse models of nephrotic syndrome (NS) or proteinuria, obtained from stringent review of published databases and literature; **2)** 64 genes, whose podocytic expression is regulated by WT1 (Lefebvre *Kidney Int* 88:321, 2015); and **3)** a discovery set of 120 candidate genes that we generated by WES analysis of 1,382 NS families over 12 years. We first validated candidate lists **1)** and **2)** for overlap with 63 known human SRNS genes. We then overlapped candidate lists **1)** (mouse models) and **2)** (WT1-regulated genes) with our 120 WES-derived candidate genes **(3)**, in order to identify potential novel genes that may cause monogenic NS.

Results: Twelve of the 63 NS mouse models **(1)** and 5 of the 64 WT1-regulated genes **(2)** overlapped with the control set of 63 known human SRNS genes, indicating relevance of the 2 candidate gene lists. When we evaluated for overlap with our 120 WES-derived candidate genes, 6 overlapped with the mouse candidate list **(1)**, and 4 with the WT1-regulated candidate list **(2)**. Of note, 3 genes (*SYNPO*, *SEMA3G*, *ITGB8*) were shared by all 3 lists. We found a homozygous *SYNPO* mutation (c.2540C>T, p.P847L) in a 4yo patient with NS. We show that loss-of-function of *SYNPO* decreases CDC42 activity and reduces podocyte migration rate, both rescued by overexpression of wild type cDNA, but not by cDNA representing the patient mutation.

Conclusions: By overlapping 2 candidate gene sets with a set of 120 genes resulting from WES analysis in 1,382 families with NS, we identified *SYNPO* as a potential novel monogenic cause of NS.

Funding: NIDDK Support

PO1631

An International Cohort Study of Mutations in RENIN Causing Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: There have been few clinical reports of Autosomal Dominant Tubulo-interstitial Kidney Disease due to *REN* Mutations (ADTKD-*REN*), limiting clinical characterization.

Methods: We formed an international collaboration that identified and characterized 111 individuals from 30 families with heterozygous *REN* mutations.

Results: Sixty-nine (62%) individuals had a *REN* mutation in the signal peptide region (signal group), 27 (24%) in the prosegment (prosegment group), and 15 (14%) in the mature renin peptide (mature group). Laboratory investigations revealed that *REN* signal peptide mutations prevented recognition and translocation of preprorenin into the endoplasmic reticulum (ER), prosegment mutations led to abnormal deposition of prorenin and renin in the ER Golgi intermediate compartment (ERGIC), and mutations in mature renin led to deposition of prorenin and renin in the ER. Signal and prosegment patients were most severely affected, often presenting at <10 years (see Table 1) with anemia, hyperkalemia, and acute and chronic kidney disease. While eGFR was approximately 50 ml/min in children < 10 years, eGFR remained stable until age 20, with mean age of end-stage kidney disease (ESKD) >50 in this cohort. The mean hemoglobin level in children <10 y not receiving erythropoietin was 9.6±1.04 g/dL (7.4-13.8 g/dl), which improved with erythropoietin administration. The serum potassium values decreased and

bicarbonate values increased in 9 patients taking fludrocortisone (4.77±0.55 mEq/L vs. 4.37±0.54 mEq/L, p< 0.01 and 23.7±3.5 mEq/L vs. 25.9±2.3 mEq/L, p=0.003). Patients with mutations in mature renin presented ⟩20y with gout and chronic kidney disease.

Conclusions: There are 3 subtypes of heterozygous *REN* mutations that are pathophysiologically and clinically distinct.

Funding: Private Foundation Support

Patient Characteristics

Characteristics	Signal	Prosegment	Mature	p value
n	69 (62%)	27(24%)	15(14%)	
Age presentation <10 y	23(39%)	11(61%)	0	0.003
Age at presentation (mean±s.d.)	19.7±15.7	22.4±20.2	37.0±12.4	<0.01
Anemia as child	39/43(91%)	11/16(69%)	0	<0.001
Gout	14/55(25%)	13/20(65%)	9/14(64%)	0.74
Age ESKD (mean±s.d.)	53.1±10.6	50.8±17.6	63.6±7.6	<0.01

PO1632

Clinical Manifestations and Mutation Analysis of Idiopathic Renal Hypouricemia

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Background: Idiopathic renal hypouricemia (RHUC), was thougt an autosomal recessive inheritancea disorder, characterized by impaired uric acid (UA) reabsorption in the proximal tubule and subsequent profound hypouricemia, caused by mutations in *SLC22A12* or *SLC2A9*. Most cases of RHUC were reported in Japan, only a few have been detected in China. A retrospective analysis was performed in this study to report the clinical manifestations and genetic mutation profiles of RHUC patients in China.

Methods: The medical history, clinical manifestations, biochemical and genetic data, clinical outcomes of Chinese patients with RHUC were collected in this study.

Results: Seven male and two female patients were diagnosed with idiopathic RHUC according to the criteria: serum uric acid(S_{UA}) level of ≤120μmol/L, fractional excretion of uric acid (FE_{UA}) and exclusion of other diseases that present hypouricemia as a symptom. The median age of onset were 30 (11~48) years old. The median levels of S_{UA} was 83(5~95)μmol/L, the median FE_{UA} was 29%(26.6%~346.83%). Homozygous *SLC2A9* mutations were identified in two male patients, homozygous mutations in *SLC22A12* in two patients, compound heterozygous mutations in *SLC22A12* in one patient, heterozygous mutations in *SLC22A12* in four patients. Exercise-induced acute kidney injury(EIAKI) developed in six patients, including the two patients with mutations in *SLC2A9*, the patient with compound heterozygous mutations in *SLC22A12*, one patient with homozygous mutations in *SLC22A12*, two patients with heterozygous mutations in *SLC22A12*. The two female patients were asymptomatic and the patients with EIAKI were all male. Two patients with heterozygous mutations in *SLC22A12* had nephrolithiasis. Two patients had recurrent EIAKI whereas the renal function of all patients with EIAKI returned to normal. Strenuous exercise was strictly prohibited. Over the median 40 (7~233) months follow-up, no patient developed EIAKI again.

Conclusions: *SLC22A12* mutations were more common than *SLC2A9* mutations in Chinese patients with RHUC, EIAKI only developed in male patients. Heterozygous mutations in *SLC22A12* also resulted in hypouricemia, EIAKI and nephrolithiasis. The prognosis of RHUC was favorable.

Funding: Government Support - Non-U.S.

PO1633

RhoA-Rac1-CDC42 Regulators as Candidates for Monogenic Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) frequently causes chronic kidney disease in children. 58 monogenic SRNS genes are known to cause 11%-29.5% of SRNS in children. These genes map to 12 distinct pathogenic pathways, including RhoA-Rac1-CDC42 regulators (RRCR). Genetic data indicate that many additional monogenic SRNS genes exist.

Methods: To search for additional monogenic SRNS genes, we generated two lists of independent functional candidate genes: i) 123 genes involved in the RRCR pathway, which has been implicated in the pathogenesis of nephrotic syndrome (*Nat Commun* 9:1960, 2018), and ii) 30 genes from a single-cell RNA sequencing (scRNA-seq) dataset (*JASN* 29:2060, 2018).

Results: First, we validated the candidate status of both candidate lists by overlapping them with the 58 known SRNS genes. 12 of the 123 RRCR candidates from list i) (9.7%) overlapped with the 58 known SRNS gene lists (20.6%). Likewise, of the 30 genes from list ii) that were most strongly expressed in podocytes (scRNA-seq), 9 overlapped (30%) with the 58 known SRNS genes (15.5%), thereby validating both functional candidate lists as relevant for SRNS pathogenesis. We then evaluated for overlap of both candidate gene lists [list i) RRCR and list ii) scRNA-seq] with 114 candidate genes that we identified by whole exome sequencing (WES) in 1,382 families. We found that 10 RRCR candidates (8.1%) overlapped with the 114 WES candidates (8.7%). Interestingly, 2 genes (*ARHGEF17* and *MYO9A*) overlapped with all three candidate gene lists, i.e. the 123 RRCR candidates, the 30 scRNA-seq candidates, and the 114 WES candidates. Within the 8 (of 10) remaining candidates the strongest mutation was detected in the *NEK3* gene (*NIMA Related Kinase 3*). By WES we had identified a homozygous truncating mutation, p.N209Kfs*21, in a family of two siblings. We present data on the cell biological role of *NEK3* in podocytes.

Conclusions: Utilizing two independent non-overlapping candidate lists, we established 10 potential novel candidate genes for human SRNS.

PO1634

Generating Monogenic CAKUT Candidate Genes from Existing Single-Cell Transcriptomics Data of Human Fetal Kidney

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most frequent birth defect and the most frequent cause of chronic kidney disease in the first 3 decades of life. Discovery of >34 monogenic causes of human CAKUT has helped mapping pathogenic pathways of CAKUT in humans (*JASN* 29:36, 2018). We hypothesized that genes specific to pathogenic pathways of CAKUT may show a temporo-spatial single-cell mRNA expression pattern in human fetal kidney tissue, and that highly expressed genes may represent novel CAKUT candidate genes.

Methods: First, we evaluated 34 monogenic human genes involved in CAKUT pathways for clustering in a temporo-spatial mRNA expression pattern by using the single-cell mRNA sequencing derived dataset of human fetal kidney at developmental week 17 (Hochane, *PLoS Biol* 21:17, 2019) and week 16 (Lindstrom, *Dev Cell* 45:651, 2018). 86 novel CAKUT candidate genes were generated by Whole Exome Sequencing (WES).

Results: The evaluation of the 34 known CAKUT pathway genes showed that genes involved in the FRAS/FREM, RA signaling and BMP signaling pathways did not cluster in either mRNA dataset. However, genes involved in the pathogenesis of branchiootorenal (BOR) syndrome (*EYA1, SIX1, SIX2*, SIX5) clustered in nephron progenitor cells (NPCs) in both datasets. We therefore concluded that NPCs are relevant for CAKUT pathogenesis. Based on the outcome of this first step, to prioritize potential novel CAKUT genes, we then generated and overlapped two lists of independent candidate genes: i) 86 novel single CAKUT candidate genes derived from WES in 1,380 patients and ii) the 100 highest expressed genes in each NPC type a, b, c and d according to Hochane (*PLoS Biol* 21:17, 2019). This overlap of lists i) and ii) resulted in one gene KIF19 (*Kinesin Family Member 19*), which is therefore considered as a novel candidate gene for human CAKUT.

Conclusions: Genes of the BOR pathway are co-expressed in a temporo-spatial way and expressed in a time-specific and cell-type-specific manner throughout human renal development. Single-cell mRNA expression data from human fetal kidney can be used to prioritize WES-derived CAKUT candidate genes.

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PO1635

CHRM5 Mutations as a Potential Cause of Neurogenic Bladder

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Background: Neurogenic bladder is caused by disruption of neuronal pathways that regulate bladder relaxation and contraction. In severe cases, neurogenic bladder can lead to vesicoureteral reflux, recurrent urinary tract infections, and even chronic kidney disease and renal failure. These symptoms overlap with the manifestations of congenital anomalies of the kidneys and urinary tract (CAKUT). Animal models of bladder dysfunction suggest that neurogenic bladder can be caused by single gene mutations (*PNAS* 96:5746, 1999).

Methods: To identify novel monogenic causes of neurogenic bladder we applied whole exome sequencing (WES) to our worldwide cohort of families with CAKUT.

Results: By WES, we discovered a homozygous missense variant (p.Gln184Arg) in the gene *CHRM5 (cholinergic receptor, muscarinic, 5)* in a patient from a non-consanguineous family with CKD stage 4 secondary to neurogenic bladder with small trabeculated bladder, severe right-sided vesicoureteral reflux (VUR) and bilateral hydronephrosis. Evaluation of WES data of 703 additional patients with CAKUT did not identify further families with mutations in *CHRM5*. *CHRM5* codes for a seven transmembrane-spanning G-protein coupled muscarinic acetylcholine receptor. Crystal structure modeling shows the mutation p.Gln184Arg affecting the second extra-cellular loop between the transmembrane spanning alpha helices 4 and 5. The receptor *CHRM5* is shown to be expressed in murine and human bladder wall. We propose *CHRM5* to be involved in bladder tone regulation and that the molecular defect of our patient causes neurogenic bladder with secondary symptoms as CAKUT. This is similar to *CHRNA3*, which we published as the first gene to cause neurogenic bladder (*AJHG* 105:186, 2019). Deckmann et al (*FASIB* J. 32:2903, 2018) demonstrate that *Chrm5* knockout mice show symptoms of bladder overactivity. Functional studies testing the effect of the variant p.Gln184Arg on *CHRM5*'s receptor function are pending.

Conclusions: We identified a recessive mutation in *CHRM5* as a potential cause of neurogenic bladder in humans.

Funding: Other NIH Support - R01 - DK088767

PO1636

Whole-Exome Sequencing Reveals a Monogenic Cause of Disease in 23.1% of 276 Families with Steroid-Resistant Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (SRNS) overwhelmingly progresses to end-stage renal disease. To date, more than 59 monogenic genes have been identified to cause SRNS. We previously detected causative mutations in 25% using whole exome sequencing (Warejko *CJASN* 13:53, 2018) and in 29.5% of patients with SRNS using targeted panel sequencing (Sadowski *JASN* 26:1279, 2015). However, whole exome sequencing (WES) has become more accessible, with the advantage of detecting not only known monogenic causes of SRNS, but also novel candidate NS-causing genes.

Methods: We employed whole exome sequencing (WES) to detect monogenic causes of SRNS in a large international cohort of 276 families with nephrotic syndrome (NS).

Results: Samples were recruited from April, 1998 to December, 2018 (21 years). WES was performed at the Yale Center of Mendelian Genomics. First, we examined the WES data for mutations in 59 genes known to cause SRNS. In 64/276 families (23.1%), we identified mutations in 22 of the known genes. There were also 7 genes that were identified as phenocopies of SRNS, e.g. *COL4A3*. In 42 families (15.2%), we have identified mutations in a potential novel candidate gene for SRNS. We found a 39.5% solve rate in consanguineous individuals and 10.8% solve rate in non-consanguineous individuals, recapitulating similar solve fractions to what has been previously published (Sadowski 2015; Warejko 2017).

Conclusions: This study confirms that in ~23% of families in our cohort, NS is due to monogenic causes. WES is a viable way to diagnose the underlying cause of NS in children and young adults, and to suggest novel monogenic candidate genes of NS.

Funding: Other NIH Support - 5R01DK76683-14.

PO1637

Recovery from Dialysis in Responsive Primary Hyperoxaluria Type 1 (PH1) Patients After Initiation of Pyridoxine

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Introduction: PH1 is a genetic disorder characterized by hepatic overproduction of oxalate and eventual end-stage kidney disease (ESKD). The only established treatment to reduce hepatic oxalate production is the use of pharmacologic doses of pyridoxine in responsive patients including those with G170R mutations, though emerging therapies to block specific hepatic enzymes are under clinical trial and appear promising. However, whether reducing oxalate production can result in recovery of kidney in a subset of patients with advanced chronic kidney disease (CKD) is unknown. Here we report a series of three G170R homozygous patients with ESKD who experienced recovery of kidney function that allowed dialysis discontinuation following treatment with pyridoxine.

Case Description: Data from the Rare Kidney Stone Consortium PH Registry was reviewed. Among the 41 G170R homozygous patients, 23 progressed to ESKD, including those who are the subject of this report. Median age at initiation or resumption of pyridoxine treatment following ESKD among these three patients was 37 years (range 20-53), and pyridoxine dose was 8.8 mg/kg/d (range 6.8-14.0 mg/kg/d). Median duration of dialysis prior to renal recovery was 10 months (range 5-19). Plasma oxalate (POx) improved after recovery of renal function even while still on dialysis. At a median of 3 months (range 2-46) following discontinuation of dialysis, estimated glomerular filtration rate was 34 ml/min/1.73 m^2 (range 23-52), POx was 8.8 µmol/L (4.6-11.3), and UOx was 0.93 mmol/24 hours (0.47-1.03). Kidney function was maintained during a median of 3.2 yrs (range 1.3-3.8) of follow-up.

Discussion: Our findings challenge the conventional wisdom that ESKD in PH1 is always irreversible. Rather, in selected PH cases advanced CKD could potentially be reversed if hepatic oxalate production is reduced promptly after dialysis initiation. Thus new or emerging treatments may prevent the need for kidney transplantation in a subset of PH1 patients, even after ESKD ensues.

Baseline characteristics of G170R homozygous PH1 patients who recovered renal function after treatment with pyridoxine

Patient	Age at PH1 symptom1 onset (years)	Age at dialysis initiation (years)	Pyridoxine initiation or resumption	Initial POx (µmol/L)	UOx before pyridoxine (mmol/24 hrs)
1	25	37	3 months after dialysis initiation	47.2 on dialysis, prior to pyridoxine initiation	0.95
2	2.5	20	At time of dialysis initiation	26.6 on dialysis, 6 weeks after pyridoxine initiation	2.34
3	33	53	Within 1 week after dialysis initiation	67.9 on dialysis, 6 weeks after pyridoxine resumption	1.87

PO1638

The Distribution of APOL1 Risk Variants and Their Association with CKD in Rural East Africa: The SEARCH-CKD Study

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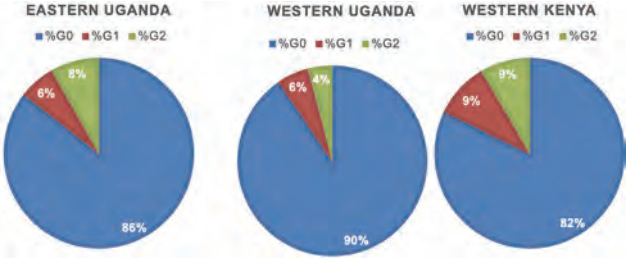
Background: Apolipoprotein L1 (APOL1) high-risk genotypes (G1/G1, G1/G2 or G2/G2) are well-known CKD risk factors that arose in sub-Saharan Africa. The G1 and G2 allele frequencies may be as high as 45% and 24%, respectively in some West African countries, but few studies have examined the association of high-risk genotypes and CKD in Eastern Africa.

Methods: We conducted a study of CKD prevalence among a population-based sample of 3,686 participants (PMC7055898) nested within an HIV trial in rural Uganda and Kenya. We collected dried blood spots (DBS) on filter cards for subsequent genetic studies. After DNA extraction, we genotyped *APOL1* risk variants and used multivariable logistic regression models to assess the association of *APOL1* high-risk genotypes with prevalent CKD defined as a serum creatinine-based eGFR <60 mL/min/1.73m^2 or proteinuria (urine dipstick ≥1+).

Results: We successfully obtained DBS from 90% of all individuals approached for the study. We have extracted DNA and genotyped 492 (~10%) samples (convenient selection). Un-weighted CKD prevalence among these individuals was 7.7% (95% CI: 5.2-11%). The overall allele frequencies for *APOL1* G1 and G2 variants were 6.1% and 5.8%, respectively and varied by region (**Figure 1**). Only 2.2% of individuals had *APOL1* high-risk genotypes. The adjusted odd ratio for association of *APOL1* high-risk genotypes with CKD was 1.5 (95% CI 0.15-15) in this limited sample.

Conclusions: Our study is one of the largest studies to define the prevalence of *APOL1* risk variant frequencies and evaluate the association of *APOL1* high risk genotype with CKD in rural East Africa. Our preliminary results show a relatively low prevalence of APOL1 risk variants—supporting the distinctive west-east Africa cline in APOL1 distribution previously reported. Further genotyping will permit more precise estimation of the association of APOL1 and CKD.

Funding: NIDDK Support



APOL1 risk variant frequencies by study region

PO1639

APOL1 Cytoxicity Is Variant and Dose Dependent

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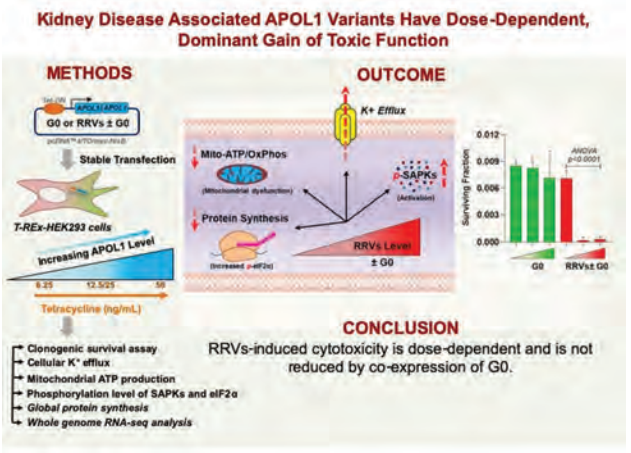
Background: Two coding renal risk variants (RRVs) of *APOL1* gene (G1 and G2), are associated with large increases in chronic kidney disease (CKD) rates among populations of recent African descent, but the underlying molecular mechanisms are unknown. *In vitro* mammalian cell cultures models are widely used to study cytotoxicity of RRVs, but results have been contradictory. It remains unclear whether cytotoxicity is RRVs-dependent or driven solely by variant-independent overexpression. It is also unknown whether the reference APOL1 allele, G0 could prevent cytotoxicity of RRVs.

Methods: We generated tetracycline-inducible APOL1 expression in HEK293 cells and examined the effects of increased expression of APOL1 (G0,G1,G2,G0G0,G0G1,or G0G2) on known cytotoxicity phenotypes including reduced cell viability, increased cell swelling, cellular potassium loss, aberrant protein phosphorylation, and dysregulated energy metabolism. Furthermore, whole genome transcriptome analysis was performed to discover deregulated canonical pathways.

Results: At moderate expression, RRVs but not G0 caused cytotoxicity. RRVs-induced cytotoxicity is dose-dependent and is not reduced by co-expression of G0. RRVs also have dominant effects on canonical pathways relevant for cellular stress response.

Conclusions: In HEK293 cells, RRVs have dominant gain-of-toxic function that worsens with increasing expression. These observations suggest that high steady state levels of RRVs may underlie cellular injury in APOL1 nephropathy, and that interventions that reduce RRVs expression in kidney compartments may be effective for mitigating APOL1 nephropathy.

Funding: Other NIH Support - Common Fund (NIH Director's New Innovator Award), Private Foundation Support



PO1640

Mapping the Genetic Susceptibility of HIV-Associated Nephropathy in a Mouse Model

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Background: We studied the genetic determinants of nephropathy in HIV-1 transgenic (Tg) mice, a model that displays all the clinical and molecular signatures of collapsing FSGS. On the FVB/NJ background over 80% of the Tg-FVB mice develop significant glomerulosclerosis, however F1 hybrids with other inbred strains of mice demonstrate variable penetrance from completely resistant to highly sensitive.

Methods: Tg-FVB mice were crossed with 20 different inbred strains of mice to generate F1 hybrids. At 8 weeks of age, we evaluated the severity of nephropathy by histology, BUN, and proteinuria, hematuria and NGAL was analyzed in the urine. To map loci predisposing to HIVAN, we performed a GWAS using a mixed linear model method.

Results: Six strains (A/J, C3H/HeJ, DBA/1J, KK/HlJ, WSB/EiJ, and LP/J) were highly sensitive to the Tg resulting in severe glomerulosclerosis, 9 strains (129S1/SvImJ, Balb/CJ, C57BL/6J, C57BL/6NJ, C57BL/10J, C57L/J, C58/J, CAST/EiJ and NZB/BINJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 5 strains were (CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HlLtJ and FVB/NJ) had intermediate glomerulosclerosis. The glomerulosclerosis score correlated with the presence of casts, interstitial fibrosis and tubular atrophy, interstitial inflammation, proteinuria, elevated plasma BUN, and the detection of urine NGAL. A GWAS searching for haplotype distribution patterns that matched the high/low strain susceptibility pattern identified a genome-wide signal on Chr 13 within a previously known QTL for HIVAN. The interval contains *Ssbp2*, encoding a DNA binding protein that stabilizes transcriptional complexes by prevent proteasomal degradation. *Ssbp2* is highly expressed in podocytes.

Conclusions: Our data demonstrates differences in the susceptibility of inbred strains to the HIV-1 transgene and suggest *Ssbp2* as culprit in producing susceptibility to HIVAN in the mouse. Future studies will evaluate the role of *Ssbp2 in vitro* and in *Ssbp2* null mice.

Funding: Other U.S. Government Support

PO1641

One Disease Cannot Exclude the Other: The Coexistence of IgA Nephropathy and Alport Syndrome

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Introduction: Alport syndrome and IgA nephropathy (IgAN) have shared clinical characteristics such as persistent hematuria, proteinuria, and progressive renal failure. We describe a case that histologically was diagnosed as IgAN, genetic testing and segregation analysis confirmed the coexistence of Alport. The additional diagnosis came to light when the daughter, a kidney donor candidate presented with persistent microscopic hematuria (MH).

Case Description: A 61-year-old female with diabetes, hypertension and ESRD presented for evaluation of transplant candidacy. The patient was diagnosed with IgAN after a biopsy at age 50. A second biopsy at the age of 61 years, showed granular mesangial and para-mesangial IgA staining, foot process effacement and irregular thickening of the glomerular basement membrane (GBM). Her daughter presented for evaluation as a live kidney donor and reported MH. She had normal renal function and imaging. Cystoscopy and urine cytology were negative. To evaluate the hematuria further, her mother was first screened with a renal genetic panel, KidneySeq™ which demonstrated a likely pathogenic variant in the COL4A3 gene, c.361 G>A, p. Gly121Ser. The donor underwent focused screening and was positive for this familial variant. Subsequently obtained FH revealed that a maternal aunt had early onset deafness, and another had CKD. The donor's daughter was found to have MH. The results suggested that both the transplant candidate and her daughter had a genetic diagnosis consistent with Alport type nephropathy.

Discussion: Pathogenic or likely pathogenic variants in COL4A3 and COL4A4 cause FSGS and AR and AD Alport syndrome. Up to 50% of causal variants are a substitution of glycine in the Gly-X-Y repeat sequence disrupting the triple helical structure of the collagen fiber and causing anomalies in the GBM. Heterozygous carriers of these variants may also manifest with thin basement membrane disease. In this transplant candidate with IgAN and GBM abnormalities, the relative contribution of the COL4A3 variant to her CKD cannot be ascertained. Consequently, the daughter's long-term renal outcome cannot be predicted. The co-existence of both IgAN and Alport syndrome is rarely described in the literature and the importance of the consideration of genetic renal disease is emphasized here in the context of living donor safety.

PO1642

Discovery of Genetic Modifiers in Thin Basement Membrane Nephropathy (TBMN) Using Pedigree-Based Whole-Exome Sequencing

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Background: TBMN is caused by heterozygosity in COL4A3 or COL4A4, and is the carrier state of autosomal recessive Alport syndrome (ARAS). TBMN is less severe than ARAS, but its phenotype can range from asymptomatic microscopic hematuria and/or low-grade proteinuria, focal segmental glomerulosclerosis, to end-stage renal disease (13-25% in patients >60 years). The cause of phenotypic heterogeneity in TBMN is unknown. Previously, we found an autosomal dominant pattern of transmission of isolated microscopic hematuria and low-grade proteinuria in two large pedigrees in Utah with ARAS, which led us to hypothesize that genetic modifiers may affect the severity of TBMN.

Methods: Based on pedigree analysis, 64 participants from two large families with characterized COL4A3 mutation were recruited for WES. In order to identify candidate disease-modifying genes, we used Pedigree-VAAST (pVAAST), a probabilistic algorithm for disease gene prioritization that uses pedigree information to perform linkage analysis. Candidate modifying genes were analyzed using Phevor, an algorithm that performs reprioritization based on information about phenotype, gene function, and disease.

Results: We found 17 candidate modifier genes that co-segregated with hematuria, proteinuria and renal dysfunction (Figure). Of note, GRIP1 co-segregated with the Alport allele, hematuria, proteinuria, renal dysfunction (P=9.4E-04), and had a high biologic correlation score (Phevor score=4.1).

Conclusions: GRIP1 is involved in cell adhesion to extracellular matrix proteins, crucial for kidney morphogenesis, and compound heterozygosity in GRIP1 causes renal agenesis and Fraser syndrome. Whole-exome sequencing in large pedigrees reveal 17 candidate disease-modifying genes in TBMN. Validation studies will be needed to ascertain their role in TBMN.

Funding: Private Foundation Support

Gene	p-value	Score	LOD	Variants	Consequence	IMPACT	AA change	Phevor Score	Phevor Prior	Gnomad AF
NIBAN1	0.000205	19.1	1.5	chr1:184818744	missense_variant	MODERATE	G>V	1.464574637	0.005940594	0.000007966
TPTE2	0.000293	18.56	1.5	chr13:19492871	missense_variant	MODERATE	L>R	8.062057046	0.252674639	
ZC3H11B	0.000431	17.05	1.5	chr1:219610033	missense_variant	MODERATE	P>L	2.162899535	0.059038572	
AXDND1	0.00118	16.94	1.5	chr1:179468524	missense_variant	MODERATE	T>M	0.70402276	0.005940594	0.001295
TMCO4	0.000205	15.65	1.5	chr1:19737453	missense_variant	MODERATE	R>G	1.519466957	0.006735576	
OTUD3	0.000293	15.65	1.5	chr1:19882622	missense_variant	MODERATE	R>G	3.153024378	0.294227852	0.00102
HELB	0.000823	15.57	1.5	chr12:66315374	missense_variant	MODERATE	N>S	3.14023908	0.532189586	0.00001738
UBR4	0.00129	14.44	1.5	chr1:19186624	missense_variant	MODERATE	M>V	2.990807711	0.558196538	0.00001393
PPIC	0.000381	14.368	1.5	chr5:123025822	missense_variant	MODERATE	G>S	2.844809312	0.210499933	0.003629
GRIP1	0.000941	12.69	1.5	chr12:66444626	missense_variant	MODERATE	I>V	4.119624405	0.925405122	0.001499
TBC1D23	0.000264	16.98	1.33	chr17:18636515	missense_variant	MODERATE	L>M	2.817631127	0.147862893	0.000004007
FILIP1L	0.000903	16.23	1.33	chr3:99930971	missense_variant	MODERATE	P>L	2.696359333	0.130916681	0.0002485
CCND1	0.000411	14.82	1.33	chr11:69643844	missense_variant	MODERATE	L>F	5.059937885	0.979253872	0.000001999
FOCAD	0.0011	14.38	1.33	chr9:20789379	missense_variant	MODERATE	T>N	1.688244602	0.050981204	0.0004895
ABCC3	0.00127	14.33	1.33	chr17:50672974	missense_variant	MODERATE	I>N	2.721553509	0.419446203	0.00003198
CYP3A7	0.000371	14.07	1.33	chr7:99731130	missense_variant	MODERATE	L>V	3.323362142	0.438657256	0.0002826

17 candidate disease-modifying genes in TBMN.The higher the Phevor score and the lower the p-value, the more likely the candidate gene is a disease-modifying gene.

PO1643

In the Presence of Genetic Heterogeneity of CAKUT, Whole-Exome Sequencing Establishes a Molecular Genetic Diagnosis in 14% of Cases

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children and young adults. More than 44 monogenic causes of CAKUT have been discovered so far (*NDT* 35:390, 2020). The high number of unsolved consanguineous families with CAKUT strongly suggests the existence of additional monogenic causes of CAKUT.

Methods: We conducted whole exome sequencing (WES) and homozygosity mapping in an international cohort of patients with CAKUT from 211 unrelated families. We evaluated WES data for mutations in the 44 known genes that cause isolated CAKUT in humans and the 179 genes that cause syndromic CAKUT in humans. We then evaluated unsolved cases for potential novel genetic causes of CAKUT using our established criteria for variant identification (*JASN* 29:2348, 2018).

Results: In 30 of 211 (14%) families, we detected mutations in one of the 44 genes for isolated CAKUT or in one of the 179 syndromic CAKUT genes. In particular syndromic cases, reverse phenotyping was helpful to increase certainty of the deleteriousness of a genetic variant. In the remainder, we performed a targeted analysis for novel candidate genes. In 40 families of this subset, we identified likely deleterious mutations in 36 genes not previously reported to cause CAKUT.

Conclusions: In a large, international cohort we detected causative mutations in 14% of families with a diagnosis of CAKUT. We show that when combined with homozygosity mapping and segregation analysis, WES is useful in identifying potential candidate genes in consanguineous families or families with multiple affecteds.

PO1644

Extremely Rare Variants in Four Complement Genes Contribute to Genetic Susceptibility to Atypical Hemolytic and Uremic Syndrome

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Background: The study of complement genetics has dramatically changed the landscape of atypical hemolytic uremic syndrome (aHUS) and has paved the way for highly tailored therapy. However, the assessment of the contribution of each identified variant to aHUS pathogenesis still remains a challenge. In this study we aimed to analyze the enrichment of rare variants in 6 aHUS-associated genes, including *C3, CFH, CFI, CD46/MCP, CFB* and *THBD*, in comparison with a reference population.

Methods: We analyzed the distribution of rare variants in 433 adult patients with a clinical diagnosis of aHUS, without coexisting disease. As a control group, we used European individuals from the 1000 Genomes project (N=503), focusing on the 6 genes of interest. We analyzed the enrichment of genetic variants in the aHUS cohort compared to the reference population.

Results: A total of 168 variants in complement genes, with a minor allele frequency (MAF) <1%, involving 247 alleles, were identified in 224 patients (51.7%). 115 of the identified variants were not reported in the population database gnomAD, including 75 variants detected in *CFH* gene (65%). Variants with a MAF of <0.01% in the *C3 and MCP* genes and variants with a MAF <0.1% in the CFH and CFI genes were enriched in the aHUS population as compared to controls. In contrast, rare variants in *CFB* and *THBD* genes were not significantly enriched in the aHUS population. We identified 18 variants overrepresented in patients, including the CFH/CFHR1 hybrid genes. Among these variants resulting with functional deficiency in the encoded protein the C3 variant p.Lys155Gln associated with risk of advanced age-related macular degeneration was not significantly increased in the aHUS population. Finally, multiple rare variants in a single individual were more frequently present in aHUS patients compared to controls.

Conclusions: We showed the enrichment of extremely rare variants limited to *CFH, CFI, CD46/MCP* and *C3*, genes. The study confirms that a variant with a MAF>0.1% should not be considered at risk for developing aHUS. Our study indicates that targeting the MAF provide reasonable diagnostic tools as a guide to variant classification.

PO1645

Whole-Exome Sequencing Identifies Likely Causative Variants in Four Candidate Genes in 16 Families with Spina Bifida

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Background: Spina bifida (SB) is the most common central nervous system malformation compatible with life and the second leading cause of birth defects. The following lines of evidence support the hypothesis that SB may be caused by multiple monogenic genes: i) congenital nature, ii) familial occurrence, and iii) existence of monogenic mouse models. However, only few monogenic genes have been described so far and the majority of the candidate genes derived from mouse models have not been studied in human SB.

Methods: We evaluated the literature and generated a list of 95 candidate genes from four categories: i) 7 known genes from human isolated SB, ii) 11 genes from human syndromic SB, iii) 35 genes considered risk factors for human SB, and iv) 42 genes from monogenic mouse models for SB. We evaluated whole exome sequencing (WES) data obtained from 16 individuals with SB who were enrolled at Boston Children's Hospital from 06/2019 to 11/2019.

Results: In 4 of 16 families (25%), we identified 4 likely deleterious heterozygous (het) mutations in each one potential SB candidate gene. All variants are very rare with a frequency of less than 0.01% in a control database of 125,000 healthy control individuals (gnomAD). Specifically, in family B4103 with myelomeningocele, we identified a CELSR1 het missense mutation (c.2296G>A; p.Asp766Asn). In family B4197 with myelomeningocele, we identified a TBXT het missense mutation (c.301C>T; p.Arg101Cys). In family B4125 with meningocele, we found a het missense mutation in the human risk SB gene PCYT1A (c.194A>G; p.Glu65Gly). Finally, in the family B4197 with SB, we identified a het missense mutation in the mouse SB gene TULP3 (c.703C>T; p.Asp766Asn). TULP3 variants have not been reported yet in human SB patients.

Conclusions: Through whole exome sequencing, we detected likely deleterious mutations in 4 of 16 cases with a diagnosis of SB. We show that composing a list of 95 candidate genes based on established mouse models and genes known to be related to SB in human facilitates the detection of monogenic causes for SB. We are expanding this study to a larger cohort.

PO1646

APOL1 by Second-Gene Interaction on eGFR Among African Americans Without Diabetes: The Million Veteran Program

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Background: Two high-risk variants in the Apolipoprotein L1 (*APOL1*) gene are associated with eGFR and a substantial increase in risk of end-stage renal disease (ESRD) among African Americans without diabetes. Not all individuals with high-risk variants develop kidney disease, suggesting that unidentified genetic factors may modify the effects of *APOL1*.

Methods: We tested interactions between the *APOL1* haplotype and single nucleotide polymorphisms (SNPs) from 22 independent loci associated with eGFR among 55,004 African Americans without diabetes in the Million Veteran Program. We used linear regression to investigate multiplicative *APOL1**SNP interactions on eGFR at enrollment, adjusting for age, sex, body mass index and the first 5 principal components of ancestry, with Bonferroni-correction for multiple testing (alpha=0.05/22=0.002).

Results: We detected significant interactions between *APOL1* high-risk variants and SNPs at two loci (*GATM/SPATA5L1* (rs62025168, p-interaction= 0.0012) and *UBE2Q2* (rs74024005, p-interaction = 0.0014) (**Table**). *SPATA5L1* is a protein-coding gene with elevated expression in the kidney and previous associations with familial juvenile hyperuricemic nephropathy. *UBE2Q2* is also a protein-coding gene with gene expression in the distal kidney tubule of a murine model.

Conclusions: Our results identify two novel *APOL1*-gene interactions, highlighting that secondary genes may modify the effect of *APOL1* on kidney function, which may uncover underlying biological mechanisms and be useful for prevention.

Funding: NIDDK Support, Veterans Affairs Support

Number of APOL1 high-risk variants	N	eGFR at enrollment, median (IQR)						
		Overall	rs62025168 genotype			rs74024005 genotype		
			AA	AG	GG	AA	AC	CC
0-1	48,002	89 (75,105)	99 (77,118)	91 (77,106)	89 (75, 105)	91 (76, 105)	90 (76, 105)	89 (75, 104)
2	7,002	87 (72, 103)	88 (82, 95)	91 (77,106)	89 (75, 104)	85 (72, 101)	87 (73, 104)	87 (72, 103)
Any	55,004		102 (78, 118)	92 (77,106)	91 (76, 105)	91 (76, 105)	90 (75, 105)	89 (74, 104)
p-interaction			0.0012			0.0014		

PO1647

Results from the Ongoing Phase 2 Open-Label Extension Study of Lumasiran, an Investigational RNAi Therapeutic, in Patients with Primary Hyperoxaluria Type 1 (PH1)

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Background: PH1 is a rare genetic disorder characterized by hepatic overproduction of oxalate, leading to recurrent kidney stones, nephrocalcinosis, progressive renal failure, and multiorgan damage from systemic oxalosis. There are no approved pharmacologic therapies for PH1. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic that decreases hepatic oxalate production by targeting glycolate oxidase. We present long-term safety and efficacy data of up to 22 months exposure from the ongoing Phase 2 open-label extension (OLE) study of lumasiran.

Methods: Phase 2 OLE includes patients with PH1, ≥6 years old, urinary oxalate (UOx) ≥0.7mmol/1.73m^2/day, and eGFR >45mL/min/1.73m^2 who completed the Phase 1/2 study. Patients initially received lumasiran 1mg/kg monthly, 3mg/kg monthly or 3mg/kg quarterly, and all transitioned to 3mg/kg quarterly. Endpoints include safety and change in 24h UOx excretion.

Results: This trial enrolled all 20 patients from the Phase 1/2 study. At baseline of the parent study, patients had a mean age 14.9 years (range: 6-43), mean baseline UOx

2.24 mmol/1.73m^2/day (range: 0.94, 5.18). As of January 2020, patients were dosed in OLE for a median of 15 months (range: 11–22). Adverse events were reported in 19/20 (95%) patients; all were mild or moderate and the majority were assessed as unrelated to study drug. There were no discontinuations or drug-related serious adverse events. The mean max reduction in 24h UOx relative to Phase 1/2 baseline was 74.5% (N=17) and 17/18 patients achieved normal or near normal levels of UOx. Plasma oxalate levels also decreased (mean max reduction 55.2%, N=19). Plasma and urinary glycolate increased and later stabilized, consistent with the effect of lumasiran on glycolate oxidase.

Conclusions: Lumasiran had an acceptable safety profile. Continued therapy with lumasiran maintained reduction of UOx to levels near or below the upper limit of normal, consistent with the Phase 1/2 study. These data further enable ongoing Phase 3 studies to evaluate lumasiran in patients with PH1 of all ages and at all stages of renal impairment.

Funding: Commercial Support - Alnylam Pharmaceuticals

PO1648

Genome-wide Association Study of Lupus Nephritis in Chinese Han Population

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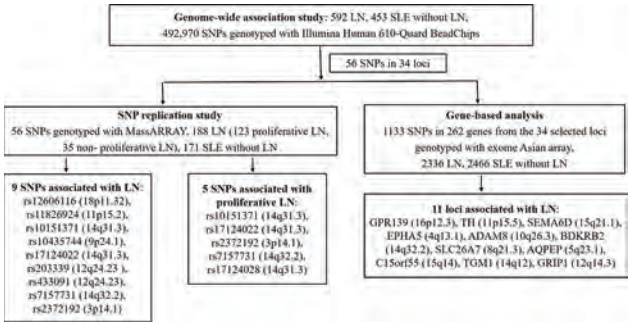
Background: Lupus nephritis (LN) is one of the most common and serious complications of systemic lupus erythematosus (SLE). The genetic factors play a vital role in the pathogenesis of LN. The purpose of this study was to screen for susceptible variants of LN in Chinese Han populations in whole genome.

Methods: A genome-wide association study (GWAS) was performed in 592 LN patients and 453 SLE patients without LN. Fifty-six single nucleotide polymorphisms (SNPs) in 34 loci were selected for replication in independent cohort of 188 LN and 171 SLE without LN patients. Besides, gene-based analysis of selected loci was performed in the enlarged population (2336 LN and 2466 SLE without LN patients) based on exome Asian array data.

Results: We identified 9 SNPs suggesting a correlation with LN ($P<10^{-4}$). The most significant SNP was rs12606116 (18p11.32) with $P=6.75\times10^{-6}$. The rest SNPs were rs11826924 (11p15.2, INSC), rs10151371 and rs17124022 (14q31.3, GPR65), rs10435744 (9p24.1, CD274), rs203339 and rs433091 (12q24.23, CIT), rs7157731 (14q32.2, WDR25), rs2372192 (3p14.1, MAGI1). Gene-based analysis results showed 11 suggestive LN related genes in 11 loci ($P<0.05$): GPR139 (16p12.3), TH (11p15.5), SEMA6D (15q21.1), EPHA5 (4q13.1), ADAM8 (10q26.3), BDKRB2 (14q32.2), SLC26A7 (8q21.3), AQPEP (5q23.1), C15orf55 (15q14), TGM1 (14q12), GRIP1 (12q14.3). The relation of 14q32.2 and LN was showed in both replication stages.

Conclusions: Association Analysis of LN was performed in Chinese Han SLE patients for the first time. Multiple susceptible genes were identified moderately associated with LN which may advance our understanding of the genetic basis of LN.

Funding: Government Support - Non-U.S.



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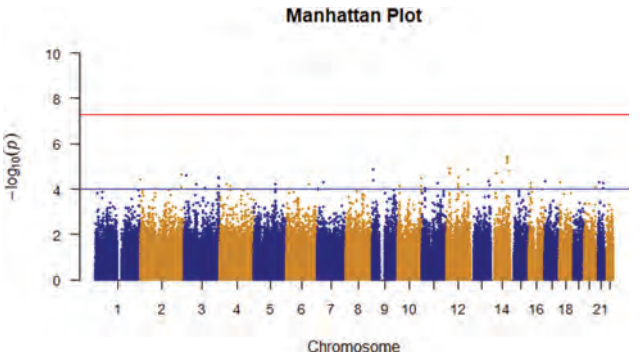

Manhattan plot of genome-wide association analysis of LN.

PO1649

Copy Number Variation Analysis Increases Diagnostic Yield of Exome Sequencing and Facilitates the Identification of Genetic Causation for Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT)

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children and adults under the age of 30 years. In a previous study, we detected by whole exome sequencing (WES) a causative mutation in a known gene for isolated or syndromic CAKUT in 13% of 232 families with CAKUT (JASN 29:2348, 2018). However, WES will not detect the presence of causative copy number variations (CNV), and CNVs have been detected in up to 16% of CAKUT (AJHG 9:987, 2012).

Methods: We performed a genome-wide single nucleotide polymorphism (SNP)-based CNV analysis on the same cohort of 232 families with CAKUT in which we previously conducted WES analysis (JASN 29:2348, 2018). We evaluated the CNVs with the published predefined criteria (Nat Genet 51:957, 2019).

Results: In a subcohort of 170 families of the 232 family CAKUT cohort (JASN 29:2348, 2018) in whom sufficient DNA was available, we detected in 9 families (5.29%) a pathogenic CNV known to cause CAKUT. There was no competing variant by genome-wide CNV analysis, and there was no conflicting variant by WES analysis. In addition, we identified likely pathogenic CNVs in 1.76% of cases, potentially increasing the CNV diagnostic rate to 7.05%.

Conclusions: CNV analysis in this subcohort of 170 CAKUT families increased the diagnosis rate for genetic causes of CAKUT from 13% to 18% - 20%. We also identified three candidate loci that may cause CAKUT.

PO1650

Genotyping of Renal Transplant Patients

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Background: There is an increasing recognition that though individual inherited kidney diseases are rare, when considered as a single cohort inherited forms of kidney disease may account for up to 10% of CKD. This can have implications for potential living kidney donors who are often related to the recipient and at higher lifetime risk of kidney failure. We sequenced patients undergoing renal transplantation to assess what proportion of kidney failure was caused by monogenic kidney disease.

Methods: We identified adult patients undergoing living or deceased renal transplantation. We excluded those with pauci-immune vasculitis, systemic lupus erythematosus, drug-induced causes and those with renovascular kidney disease over the age of 50. Patients underwent targeted next generation sequencing using a custom panel of 127 genes known to cause renal disease. All suspected disease-causing variants were classified by American College of Medical Genetics guidelines and discussed by a multidisciplinary team[KB1].

Results: We sequenced 99 patients who presented for renal transplantation. We were able to detect an ACMG-classified pathogenic/ likely pathogenic variant in 27 (26%) patients. The most common disease-causing variant identified was in *PKD1*, which was identified in 14 patients (14%), accounting for 52% of all individuals with a disease-causing gene identified. Four others (16%) had pathogenic variants in *COL4A4* or *COL4A5* genes. No other disease-causing variant was present in more than one individual.

Conclusions: It is possible to identify monogenic causes of kidney disease in a carefully selected population with ESRD, and this may be useful in stratifying risk in potential living renal donors.

PO1651

21%-51% of a Single-Center, 15-Year Cohort of All Patients with ESKD Prior to the Age of 50 Have Monogenic Kidney Disease

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Background: Often only CKD patients with high likelihood of genetic disease are offered genetic testing. Early genetic testing could obviate the need for kidney biopsies, allowing for adequate prognostication and treatment. To test the viability of a 'genetics first' approach for CKD, we performed genetic testing in a group of renal transplant recipients <50 years, irrespective of cause of transplant.

Methods: From a cohort of 273 transplant patients, we selected 110 that were in care in the UMC Utrecht, had DNA available and were without clear-cut non-genetic disease. Forty patients had been diagnosed with a genetic disease prior to enrollment, in 70 patients we performed a whole exome sequencing based 379 gene panel analysis.

Results: Genetic analysis yielded a diagnosis in 51%. Extrapolated to the 273 patient cohort, who did not all fit the inclusion criteria, the diagnostic yield was still 21%. Retrospectively, in 43% of biopsied patients the kidney biopsy would not have had added diagnostic value if genetic testing had been performed as a first tier diagnostic.

Conclusions: The burden of monogenic disease in transplant patients with ESKD of any cause prior to the age of 50 is 21-51%. Early genetic testing can provide a non-invasive diagnostic, impacting prognostication and treatment and obviating the need for an invasive biopsy. We conclude that in patients who one expects to develop ESKD prior to the age of 50, genetic testing should be considered as first mode of diagnostics.

PO1652

Genome-Wide Analyses Provide Insights into the Genetic Architecture of Kidney Function and CKD Among Hispanics in the Million Veteran Program

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Background: Hispanics (HAs) have a higher risk of progressing to end-stage renal disease (ESRD) than non-Hispanic European Americans. Genetic variants influencing kidney function have been identified through genome-wide association studies (GWAS) of CKD and ESRD, as well as estimated glomerular filtration rate (eGFR), however, small sample sizes have stalled discovery in the Hispanic population.

Methods: We performed a GWAS of eGFR in 32,821 Hispanics from the Million Veteran Program (MVP); eGFR was estimated using the CKD EPI equation with IDMS calibrated creatinine. Patients on dialysis, transplant recipients, or with BMI <18 kg/m^2 were excluded. eGFR was regressed on to common genetic variants (minor allele frequency > 1%) imputed to the 1000 Genomes reference panel adjusted for age, sex, BMI, and the top ten principal components. Analyses were performed by strata of diabetes, estimates from which were aggregated with fixed-effects meta-analysis.

Results: A total of 397 SNPs representing 8 loci exceeded genome-wide significance. The most significant association was at a previously known locus, *SPATA5L/GATM* on chromosome 15 (p-value =3.78Ex10 $^{-21}$). Two novel loci were detected. One in *SLC30A4* (rs2643718 p-value= 4.51x10^{-15}) a protein-coding gene for zinc transmembrane transporter, and another one on *LNC00972* (rs62489732 p-value= 2.64x10-8). Other previously reported signals in the European American population for kidney phenotypes were also found with genome-wide significance : *UMOD/PDILT* (rs71149135 p-value =1.18 x $^{-9}$), *PRKAG2* (rs10224210 p-value 1.99= x10 $^{-12}$), *UNCX* (rs12702509 p-value =2.22 x10 $^{-9}$), *SLC34A1* (rs3812036 p-value = 1.29x10^{-9}) and *ALMS1P1* (rs12713788 p-value =4.14 10^{-8}). Several additional important CKD loci were associated with kidney function at p-values below the genome-wide threshold including: APOL1 (rs6029573 p=2.98 10^{-6}), *TPRKB* (rs35805651 5.49 10^{-7}), *SHROOM3* (rs60529470 p=1.36 10^{-6}). Five of the variants that reached genome-wide significance were exonic variants.

Conclusions: Our study results emphasize the transethnic nature of genetic variation contributing to kidney function. Overall, this is the largest GWAS of eGFR in Hispanics to date, which replicates previously identified loci in tranethnic analysis and detects two novel loci in Hispanics.

Funding: Veterans Affairs Support

PO1653

Assessing Alport Syndrome and Thin Basement Membrane Nephropathy (TBMN) by Optical Coherence Tomography (OCT)

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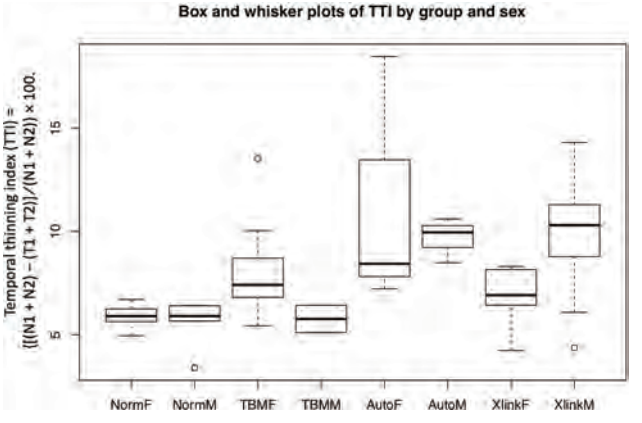
Background: Using OCT to identify temporal macular thinning has diagnostic importance in patients with X-linked Alport syndrome (XLAS) but little prior research has been done to evaluate temporal macular thinning in COL4A3 and COL4A4 compound heterozygotes (ARAS) and simple heterozygotes. (TBMN) Individuals with heterozygous COL4A3 or COL4A4 mutations usually have TBMN, which is considered the carrier state of autosomal recessive Alport syndrome (ARAS). The aim of this study is to assess ophthalmologic findings in simple and compound heterozygotes and to compare them to normal control and XLAS.

Methods: Genotyping was done to detect COL4A3 and Col4A4 mutations and to classify family members as ARAS, TBMN or normal. Temporal thinning index (TTI) was calculated from OCT measurements of the more severely affected eye by comparing the ratio of the retinal thickness of the temporal (T) to the nasal (N) subfields with a published normative database. (Figure, y axis) Student's T-test and ANOVA were used to identify binary and multiple groups' differences. In addition, multivariate linear regression was also performed controlling for age, gender and interaction terms between different variables.

Results: We report results from 12 normal controls, 16 COL4A3 or COL4A4 simple heterozygotes, 7 compound heterozygotes and 18 hemizygous males with XLAS. Mean TTI was 5.75, 7.4, 9.45 and 9.37 in these four groups, respectively. TTI in each group (simple heterozygotes, compound heterozygous, and XLAS) was significantly greater than normal controls (P < 0.01). TTI was not significantly different between simple and compound COL4A3/4 heterozygotes (P= 0.13). Age, gender, and GFR were not associated with significant differences in the regression analysis.

Conclusions: This is the largest study that systematically assessed ophthalmologic findings in XLAS, ARAS and TBMN. OCT may guide our evaluation of family members who are potential donors.

Funding: Private Foundation Support



PO1654

LAMA5 Gene Mutations in Japanese Cases with Infantile Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) have high risks to progress to end stage renal disease. Mutations in genes encoding podocyte-associated proteins have been implicated in about 30% of SRNS cases in children. Recently, *LAMA5* gene mutation have been identified in patients with nephrotic syndrome. The *LAMA5* gene encodes laminin α5, an essential component of the glomerular basement membrane. Here, we report the three cases with *LAMA5* gene mutations.

Methods: We conducted comprehensive gene screening of Japanese patients with severe proteinuria. Using targeted next-generation sequencing, 60 podocyte-related genes were screened in 326 unrelated patients with proteinuria.

Results: *LAMA5* gene variants were detected in two families. The patient 1 and 2 were siblings. They presented with proteinuria at ages three months and four months, respectively. They were subsequently found to have compound heterozygous mutation for *LAMA5* gene (NM_005560). One was nonsense mutation (c.9232C>T, p.Arg3078Ter), and the other was splice site mutation (c.1282+1G>A). The patient 3 presented with proteinuria at 6 months old. She had congenital cataract and hypoplastic kidney. Her renal pathology showed remarkable irregular form of glomerular basement membrane. She was subsequently found to have compound heterozygous mutation for *LAMA5* gene: c.8185C>T (p.Arg2720Ter), c.1282+1G>A. We performed immunofluorescence analysis of laminin α5 and her renal pathology showed completely negative staining pattern.

Conclusions: Our cases show clinical and pathological findings in a very rare disease of *LAMA5* related nephropathy. Patient 3 showed more severe phenotype compare to patient 1 and 2. We speculate the reason for this difference is the position of the variants, i.e. Patient 3 lacks laminin G-like domains that is the major cell-adhesive sites of laminin. *LAMA5* gene mutation screening should be performed in congenital/infantile nephrotic syndrome cases. Further investigation for this disease entity should be notified to all pediatricians.

PO1655

Variation in Phenotype in Utah Families with Autosomal Recessive Alport Syndrome

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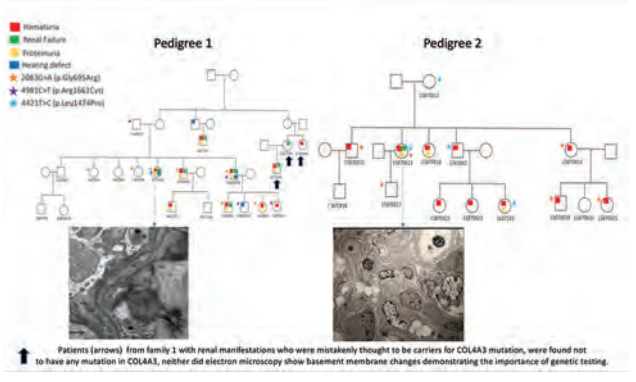
Background: Individuals with heterozygous COL4A3 or COL4A4 mutations usually have thin basement membrane nephropathy (TBMN), which is often considered the carrier state of autosomal recessive Alport syndrome (ARAS). Patients with ARAS usually progress to end-stage renal disease (ESRD) by the fourth decade of life. While ocular abnormalities, hearing loss and renal impairment are classically absent with TBMN, a subset of patients develop focal segmental glomerulosclerosis (FSGS) and 13-25% of patients progress to ESRD. It is unclear why some individuals with heterozygous COL4A3 mutations follow a mild course with isolated microscopic hematuria or low-grade proteinuria while others with the same mutations develop progressive renal dysfunction. It is also unclear why some family members show hematuria while others with the same mutation do not.

Methods: This study was designed to address these clinical questions using unbiased Whole Exome Sequencing (WES) in a population of patients harboring a limited number of pathogenic heterozygous COL4A3 mutations. Our work has focused on detailed examinations of patients carrying the same mutation to assess carefully the inter and intrafamilial variability and assess the impact of mutation on pathology.

Results: Two Utah families (figure) with a unique combination of two pathogenic mutations were identified. These pathogenic mutations have been reported before. However, the compound heterozygous status in each family is unique and has not been reported before. The probands are compound heterozygotes sharing one mutation (c.2083G>A, p.Gly695Arg) but differ in the second mutation (c.4981C>G, p.Arg1661Cys vs c.4421T>C, p.Leu1474Pro).

Conclusions: This study expanded the phenotypic spectrum of COL4A3 mutation carriers. Our findings showed the significant overlap between phenotypes induced by COL4A3 variants and the considerable intra and inter-familial variability and renal disease progression in patients with COL4A3 mutations.

Funding: Private Foundation Support



Family pedigrees.Arrows : Absence of *COL4A3 mutation*

PO1656

Whole-Exome Sequencing as a Predictive Tool for Severe CAKUT

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Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) represent about 1% of births, with about 20% secondary to genetic causes. The Cincinnati Fetal Center is one of the few centers worldwide offering fetal interventions including amnioinfusion and for infants with oligo/anhydramnios. As these infants are phenotypically severe, we predict they will be genetically enriched. We hypothesize that identifying novel genetic variants in infants with CAKUT will aid in determination of clinical course and improve parental counseling.

Methods: We collected blood from infants whose mothers underwent fetal interventions for oligo/anhydramnios for the purpose of Whole Exome Sequencing as well as blood samples from parents for trios testing.

Results: We completed variant calling for 2 singletons and 1 maternal sample. Both patients' mothers underwent multiple amnioinfusions, and the patients required initiation of RRT within week 1 of life. In both patients, we identified a nonsynonymous SNV of HSPG2 on chromosome 1. HSPG2 encodes for perlecan, which has a role in renal embryogenesis, specifically the maturation of the epithelial and mesenchymal tissues of the kidney. We identified a rare heterozygous variant found in 0.28% of the population in 1 patient. In the other patient, we identified 2 variants, which form a state of compound heterozygosity. We found a rare heterozygous nonsynonymous SNV mutation in T-Box Transcription Factor-18 (TBX18) in 1 sample. TBX18 is imperative for the development of ureteric mesenchyme and is expressed in the renal capsule and glomerular mesangial cells. This patient had bilateral VUR and dysplastic kidneys. The other patient had a rare heterozygous nonsynonymous SNV in the transcriptional repressor GLI3 which is implicated in renal morphogenesis. Variants in GLI3 have been described in renal dysplasia and aplasia. This patient was born with bilateral multicystic dysplastic kidneys.

Conclusions: In our pilot data of WES of 2 singletons and 1 maternal sample, we report 3 candidate genes, HSPG2, TBX18, and GLI3, all of which are necessary for renal and urinary tract development, specifically glomerular and ureteric development and transcriptional regulation. In a small cohort, we demonstrate that WES of a severely affected population provides insight into the molecular mechanisms underlying CAKUT, which can aid in prognosis and parental counseling in the future.

Funding: Other NIH Support - T-32 Training Grant

PO1657

Perceived Clinical Utility and Barriers to Genetic Testing in the Adult CKD Population: A Survey of General Nephrologists

Trudy McKanna, Philippe M. Gauthier, Christine Seto, Christin Chong, Monica L. Johnson. *Natera, Inc, San Carlos, CA.*

Background: Genetic testing for chronic kidney disease (CKD) can lead to personalized medicine, family planning opportunities, and living kidney donor screening.[1] Comprehensive genetic testing in CKD patients with a suspected genetic cause or predisposition is important for accurate diagnosis.[2] However, the uptake of genetic testing in the general nephrology setting lags behind other specialties.[3] There exists a lack of information on barriers perceived by nephrologists on genetic testing. This survey aims to understand the current barriers and perceptions to performing genetic testing for kidney disease in a general nephrology setting. We describe here in brief the survey design and preliminary results

Methods: An online, multiple choice survey was sent to 400 general nephrologists in clinical practice to elicit feedback on the use of genetic testing in clinical nephrology care. The questions focused on perceived clinical utility and potential barriers to ordering genetic testing.

Results: Early findings suggest that while clinical utility is acknowledged in many situations, there are opportunities to provide physician education regarding test results and insurance coverage that may increase test adoption. The perceived lack of genetic counseling resources and ethical concerns may inhibit the ordering of genetic testing in patients with CKD. We will present results from the complete dataset of responses to this survey of practicing general nephrologists and provide insights into their concerns about ordering genetic testing.

Conclusions: The survey results will assess current opinions on the utility of genetic testing in an adult CKD population, and identify barriers to ordering this test. Second, survey results will aid in development of targeted strategies to increase utilization of genetic testing. 1. Groopman, EE al., *N Engl J Med.* 2019;380(2):142–51. doi:10.1056/NEJMoa18068912019 2. Wilson PC et al., Kidney360 May 2020, 10.34067/KID.0001342020; DOI: 10.34067/KID.00013420203. 3. Saez-Rodriguez, J et al., *Kidney Int.* 2019 Jun;95(6):1326–37. doi: 10.1016/j.kint.2018.11.048. Epub 2019 Mar 5.

Funding: Commercial Support - Natera, Inc

PO1658

Is There a Contribution of Genes Involved in Hereditary Nephropathies to AKI?

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Background: The diagnosis of hereditary kidney disease has been improving with the use of novel diagnostic tools in the last decades. More than 600 genes have been detected using techniques such as whole exome sequencing. However, it is not clear if those genes causing hereditary nephropaties have any independent contribution in the pathogenesis of acquired nephropaties.

Methods: We analyzed the kidney transcriptomic after 24 hours of acute kidney injury (AKI) induced by folic acid in a murine model. In this database we evaluated if 625 genes described as responsible for hereditary nephropathies were expressed significantly. Later, using transcriptomic databeses of human nephropathies (Nephroseq), we evaluated the correlation between those differentially expressed genes and glomerular filtration. Using the software Gorilla, a functional enrichment analysis was done. Some of those were validated in our laboratory using RT-PCR.

Results: Among 25051 genes, 7443 (29.7%) were found to have a significant modification in their expression in AKI ($p<0.05$). When analyzing 625 responsible for familiar nephropaties, we identified 615 in our database. 260 (41,6%) of those genes were differentially expressed in our model. An association between 241 of those 260 differentially expressed genes and glomerular filtration rate in human nephropaties was identified. The most enriched GO process were "complement activation", "protein activation cascade", "activation of immune response" and "RNA processing". 7 of the 241 mentioned genes, showed changes greater than twofold. On the other hand, 18 of the 241 showed more than a half-fold change. We have validated the expression of 2 of the genes in acute kidney injury (SLC34A3, FN1), which supports the relevance of the transcriptomic results.

Conclusions: Several genes responsible for familiar nephropathies are differentially expressed in acquired nephropathies, suggesting that they could play a role in its

pathogenesis, through complement activation, protein activation of immune response and the regulation of the RNA processing. The identification of those genes showing a more significant change will allow us to select candidates for further studies and new possible therapeutic targets in kidney damage.

Funding: Clinical Revenue Support

Downregulated genes	Upregulated genes
BSND, CASR, CLCNKA, EGF, EHHADH, G6PC, HGD, HSD3B2, KCNJ1, KL, LPIN1, SLC12A1, SLC34A3, SLC37A4, SLC4A1, SLC6A19, TTR, UPB1.	C3, CFI, FGA, FLNA, FN1, SERPINH1, SOX9.

PO1659

Features of Hereditary Nephropathy with COQ8B Mutation

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Background: Mutations in the genes related to biosynthesis of Coenzyme Q 10 (CoQ_{10}, ubiquinone) cause primary CoQ_{10} deficiency resulting in various clinical phenotypes. *COQ8B* (also known as *ADCK4*) has been first reported in association with nephropathy in 2013, and previously a Korean cohort has reported six patients, notably accompanied by medullary nephrocalcinosis in all the six cases. Because these patients can benefit from CoQ_{10} replacement, early differential diagnosis is essential. This study systematically reviewed clinical features and genotypes of patients with *COQ8B*-associated nephropathy.

Methods: Electronic databases were searched using related terms (till March 30, 2020). This report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: From 126 articles searched, there were 11 eligible studies with 49 patients with *COQ8B*-associated nephropathy. Of them, 26 patients were Caucasian and 21 were Asian (the rest had no data regarding ethnicity). Female to male ratio was 2:1. Median age at diagnosis was 14.6 years. Proteinuria was reported in 100% of the patients with median serum albumin level of 3.7 g/dL and creatinine level of 1.45 mg/dL. Twenty two patients (43%) had chronic kidney disease and twelve patients had end-stage renal disease (25%)/ Transplantation was performed in 6 cases out of which 5 had no recurrence. Of 33 patients available for pathology reports, most (32/33, 97%) patients showed histology compatible with focal segmental glomerulosclerosis (FSGS) and seven (14%) patients had abnormal mitochondrial aggregation in the podocyte cytoplasm visualized by electon microscopy. Seven (14%) patients presented with medullary nephrocalcinosis who were notably all Koreans. Outcomes related to CoQ_{10} replacement was reported in 14 cases and half of them reported partial or complement remission. Effect of calcineurin inhibitors were reported in 7 cases which showed partial remission in 4 cases.

Conclusions: *COQ8B*-associated FSGS is a rare hereditary nephropathy which can greatly benefit from early diagnosis and CoQ_{10} supplement. Aberrant mitochondrial accumulation in the cytoplasm of the podocytes and increased medullary echogenicity may add to diagnostic suspicion. So far, all patients with *COQ8B* mutation reported in South Korea had medullary nephrocalcinosis.

PO1660

CKD in Patients with Primary Hyperoxaluria Type 3: A Meta-Analysis from Literature

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Background: Primary hyperoxaluria type 3 (PH3) is considered the most benign phenotype of all forms of primary hyperoxaluria. Being it typical that patients with PH type 1 and 2 develop chronic kidney disease (CKD) or end-stage renal disease (ESRD), it appears to be more or less uncommon that patients with PH3 are on risk of CKD and even do not develop ESRD. We now aimed to determine the number of PH3 patients reported to have any kind of CKD.

Methods: We performed a literature meta-analysis, searching in PubMed and Embase with the following keywords: primary hyperoxaluria, PH, primary hyperoxaluria type III, PH III or PH3.

Results: We found 151 patients in 18 relevant papers published between 2010-2019. Age of diagnosis/disease onset ranged from 1 month to 48 years of life. Most of the patients suffered recurrent urolithiasis, most often during the first years of life, but recurrent kidney stone episodes were also found later in life. The most common mutations found were the c.700+5G>T splice site mutation (37%) and the p.E315del mutation (22%). In 77 patients any information was provided with regard to renal function, in 22 of those kidney function was said to be normal, but no eGFR or CKD stage was mentioned. In 25 patients kidney function was found to be normal based on eGFR levels. CKD stage 1 was reported in 21 patients, CKD stage 2 in 5 patients, CKD-3 in 2 patients and 1 patient each had CKD stage 4 or ESRD, respectively. In 10 patients, follow-up measures were available, as their data were included in two papers (5 years apart from each other). Here, in 1 patient eGFR significantly declined from 134 to 68.1 ml/min/1.73 m^2, while 2 patients remained in CKD-1 and in 5 kidney function remained normal over time. In 1 patient kidney function ameliorated under standard treatment of care from CKD 1 to normal.

Conclusions: There is a massive bias in the data published, as data on kidney function is mostly not completely reported. Kidney function was normal only in 22 of the 54 patients (41%) with complete information. CKD-2 or worse was observed in 16.7% of PH3 patients, and even one patient with ESRD was described. Also, one PH3 patient had died at age 4 months because of respiratory failure and not because of PH. Thus, as true long-term follow-up data is still missing, we nevertheless suspect PH3 not being as benign as currently being reported.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc.

PO1661

Segmental Expression of Nephrin in the Slit Diaphragm of a Patient with a Nonsense Mutation in NPHS1

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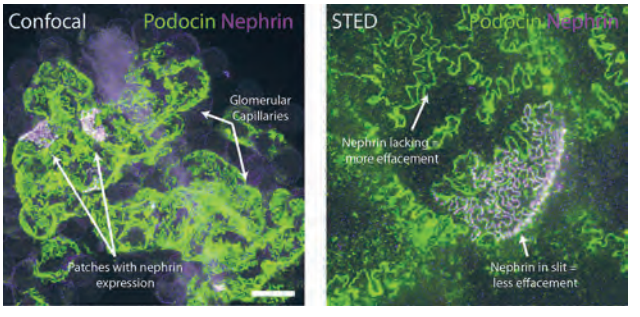
Background: Nephrotic syndrome due to nonsense mutations in the *NPHS1* gene typically presents with a severe congenital proteinuria. However, patients harboring nonsense mutations close to the carboxyl terminus of the *NPHS1* encoded nephrin protein can present with a milder phenotype. In this study, we use high-resolution microscopy to investigate the expression pattern of nephrin p.1160X in a patient with such a mutation.

Methods: We used confocal and stimulated emission depletion (STED) microscopy to visualize the distribution of nephrin p.1160X at the glomerular filtration barrier and to study the correlation between nephrin expression and foot process morphology.

Results: Confocal microscopy revealed a highly heterogeneous expression pattern of nephrin p.1160X. While most glomerular capillaries showed absence of nephrin, there were sharply defined patches with almost normal levels (see figure). To clarify whether this unexpected pattern was due to sporadic re-expression of a wild-type nephrin, we used antibodies raised against the carboxyl terminus of nephrin which is lacking in the mutant protein. These data confirmed expression of nephrin p.1160X. Moreover, qPCR and cell culture experiments indicated normal levels of nephrin mRNA, but a decreased stability of p.1160X nephrin which could partly be rescued by inhibition of proteasomes.

Conclusions: We here show, that mutations in *NPHS1* may result in heterogeneous expression patterns of the truncated protein. We also found a directly observable link between insertion of nephrin in the slit diaphragm and normal foot process morphology. Taken together, these data suggest potential therapeutic interventions targeting proteasomal degradation of nephrin as a novel treatment strategy in selected patients with congenital nephrotic syndrome.

Funding: Government Support - Non-U.S.



Micrographs showing patches of nephrin p.1160X in glomerular capillaries. Severe foot process effacement is only present outside of these patches.

PO1662

A Delayed Diagnosis of Gordon Syndrome: Better Late Than Never!

Meenakshi Sambharia, Christie P. Thomas, Lama A. Noureddine. *University of Iowa, Iowa City, IA.*

Introduction: Gordon syndrome, also known as Pseudohypoaldosteronism Type II (PHA-II) or Familial Hyperkalemic Hypertension (FHH), is a rare Mendelian syndrome causing hypertension(HTN), hyperkalemia and non-anion gap metabolic acidosis. Genes responsible are the with- no-lysine kinase 1 and 4 (WNK1/WNK4), kelch-like 3 (KLHL3) and cullin 3 (CUL3). WNK1/WNK4 are expressed in the DCT, connecting tubule and collecting duct. WNK4 reduces cell surface expression of the thiazide sensitive Na-Cl co-transporter (NCCT) and the potassium channel, ROMK. WNK1 prevents WNK4 from interacting with NCCT. KLHL3 and CUL3 are part of a ubiquitin ligase complex that targets WNK4 for degradation. While FHH from WNK1, WNK4 and CUL3 have an autosomal dominant (AD) mode of inheritance, disease from KLHL3 can be autosomal recessive (AR) or AD. AR disease presents at an earlier age with severe hypertension and hyperkalemia.

Case Description: A 56-year-old Caucasian male with history of recurrent atrial fibrillation with multiple cardioversions was referred to renal clinic for evaluation of chronic hyperkalemia. Upon presentation, he had been on furosemide 40mg and sodium polystyrene sulfonate (SPS) 30mg daily for the last 6 years for K^+ values as high as 7 mEq/L

with normal renal function. Initially the hyperkalemia was attributed to Type IV RTA from heavy NSAID use. Renin and aldosterone levels were low at 0.1ng/ml/hr and 6.1ng/dl respectively. He was suspected to have Gordon syndrome and was referred for genetic counseling and testing. He had a family history of HTN in his mother, father and multiple brothers. His daughter, in her 30s, also had a history of long-standing hyperkalemia. Genetic testing identified a heterozygous likely pathogenic missense variant in KLHL3: ***NM_001257194:c.1487G>A,p.Arg496His.*** Based on prior reports and within this clinical context, this variant confirmed a diagnosis of AD FHH. Furosemide was switched to low hydrochlorothiazide, SPS was discontinued and hyperkalemia resolved.

Discussion: Hypertension with hyperkalemia should prompt evaluation for Gordon syndrome. Thiazides are the treatment of choice. When suspected, genetic testing confirms diagnosis, prompting disease-guided therapy and preventing life-threatening consequences.

PO1663

Burden of Alport Syndrome in the United States: A Retrospective Observational Cohort Study Using Optum Humedica Data

Amanda Wilson, Ali Hariri, Pronabesh Dasmahapatra. *Sanofi Genzyme, Cambridge, MA.*

Background: To understand patient characteristics, treatment patterns and natural history of patients diagnosed with Alport syndrome (AS) in the US.

Methods: The study was a retrospective, observational cohort study of electronic health records (EHRs) in the Optum Humedica database. Patients were identified from January 1, 2008 to March 31, 2018, with 1+ inpatient or 2+ outpatient encounters (at least 30 days apart) by ICD-10 code, or by ICD-9 code with at least 2 non-negative mentions of AS in the physician notes within 90 days of diagnosis. Controls were matched to cases on age, sex, and Elixhauser Comorbidity Index (excluding kidney-related comorbidities). All patients had 12 months of activity prior to the AS diagnosis.

Results: A total of 628 patients met the AS criteria; 624 were matched with 2,496 non-AS controls. Median age was 38 years (47.6% were 40 years or older) and 43% were female. At baseline, 27.4% of the AS cohort recieved ACE inhibitors and 11.7% with ARBs, as compared with 15.8% and 6.8% of the controls, respectively ($p<0.0001$ for both); 25 (4%) of the AS cohort and 2 (0.1%) of the matched non-AS cohort had a kidney transplant ($p<0.001$). Baseline eGFR was significantly lower in the AS cohort (mean [sd] 54.4 [42.5] mL/min/1,73 m^2) compared with the matched non-AS cohort (mean [sd] 96.7 [32.8] mL/min/1,73 m2; $p<0.001$). Median time to ESRD was 504 days, to kidney transplant 786.5 days, and to death 807 days.

Conclusions: Alport syndrome has a significant unmet medical need due to the burden of kidney disease and short time to onset ESRD.

Funding: Commercial Support - Sanofi Genzyme

	Matched AS-cohort (n=624)	Matched non-AS cohort (n=2496)	p-value
Age, years, median (Q1, Q3)	38 (23, 54)	38 (23, 54)	1
0–15, n (%)	76 (12.2)	304 (12.2)	
16–39, n (%)	251 (40.2)	1004 (40.2)	
≥40, n (%)	297 (47.6)	1188 (47.6)	
Female, n (%)	268 (43.0)	1072 (43.0)	1
Baseline Treatment, n (%)			
ACE inhibitors	171 (27.4)	395 (15.8)	<0.001
ARB	73 (11.7)	170 (6.8)	<0.001
Kidney transplant	25 (4.0)	2 (0.1)	<0.001
Baseline eGFR, mL/min/1,73 m^2, mean (sd)	54.4 (42.5)	96.7 (32.8)	<0.001
<15, n (%)	140 (22.9)	41 (1.6)	
15-29, n (%)	52 (8.3)	35 (1.4)	
30-44, n (%)	35 (5.6)	58 (2.3)	
45-59, n (%)	42 (6.7)	61 (2.4)	
60-89, n (%)	85 (13.3)	302 (12.1)	
≥90, n (%)	115 (18.3)	967 (38.7)	
Unknown/missing, n (%)	155 (24.7)	1032 (41.3)	
Time to Event, n (median days)			
ESRD	235 (504)		
Kidney transplant	36 (786.5)		
All-cause mortality	49 (807)		

PO1664

A Case with Somatic and Germline Mosaicism in *COL4A5* Detected by Multiplex Ligation-Dependent Probe Amplification in X-Linked Alport Syndrome

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Introduction: X-linked Alport syndrome (XLAS) is a progressive hereditary kidney disease caused by mutations in *COL4A5* gene encoding the type IV collagen α5 chain. To date, 11 cases with somatic mosaicism in *COL4A5* have been reported; however, all of them involved single-nucleotide variations (SNVs). Copy number variations (CNVs) in *COL4A5* have also been reported, and pathogenic CNVs are relatively rare. Here, we report a female XLAS patient with somatic mosaicism identified by CNVs in *COL4A5*.

Case Description: The case was a 35-year-old female, the mother of the proband, whose only clinical symptom was hematuria. The proband was the son of this patient. His hematuria was detected at 3 months of age, and gross hematuria was occasionally exhibited. At the age of 2, proteinuria was persisted, so kidney biopsy was performed. The pathological findings showed diffuse thin basement membrane and partial basket-weave change. Then he was conducted a gene test at the age of 4. He exhibited moderate proteinuria (0.68 g/g creatinine) and hematuria, and his serum albumin was slightly low (3.5 g/dl). He had bilateral hyperopia but no deafness or kidney dysfunction. There was no familial history of ESRD. He diagnosed with XLAS by gene testing, which showed a large hemizygous deletion from exon 3 to 51 in *COL4A5* detected by *next-generation sequencing* and then confirmed by *multiplex ligation-dependent probe amplification* (MLPA). Then, MLPA analysis revealed that the female patient had the same deletion with only a 20% copy number reduction compared with a normal female control; she was thus diagnosed with XLAS with somatic mosaicism.

Discussion: Previous XLAS cases with somatic mosaicism in *COL4A5* had SNVs, and these changes could be detected by sequencing analysis. In contrast, our case had somatic mosaicism of CNVs in *COL4A5*. CNVs in *COL4A5* are relatively rare (5%) and, CNVs were usually detected by the absence of PCR products or MLPA. This case clearly featured a germline variant because the patient's son exhibited XLAS. In conclusion, this is the first case report with somatic and germline mosaicism caused by CNVs in an XLAS patient detected by MLPA. This information was important for the genetic counseling of this affected family.

PO1665

Phenotype Characteristics of Patients with Novel and Described COL4A5 Mutations Causing X-Linked Alport Syndrome in Croatian Population

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Background: Alport syndrome (AS) is an inherited renal disorder caused by mutations in collagen IV genes. The most common type is X-linked AS caused by COL4A5 mutations which presents as a progressive nephritis with hematuria, ultrastructural changes of glomerular basement membrane, sensorineural hearing loss and ocular lesions. Males are usually more severely affected.

Methods: We are presenting genotype-phenotype correlation for Croatian patients with X-linked AS. Next generation sequencing for COL4A3, COL4A4 and COL4A5 was performed as part of the nationwide project "Genotype-phenotype correlation in Alport syndrome and thin basement membrane nephropathy (TBMN)". There were 24 male and 26 female patients from 36 unrelated families. Probands were selected based on the kidney biopsy findings.

Results: We have identified 23 mutations, 13 being novel and 10 previously reported. In two patients additional COL4A4 mutations were found. Male patients, median age 27 years, presented with hematuria (96%), proteinuria (54%), sensorineural hearing loss (27%) and ocular changes (4.5%). Most patients (62%) had normal, 17% mildly and 21% moderately reduced kidney function. No one had severe renal insufficiency or ESRD. Kidney biopsy was performed in 18 male patients and AS was the most common diagnosis (67%) followed by TBMN with FSGS (17%) and isolated TBMN (11%). In one patient (5%) the diagnosis was inconclusive for AS or TBMN. Female patients, median age 16 years, presented with hematuria (89%) and proteinuria (19 %). There were no ocular abnormalities and the hearing loss was present in 5% of patients. Most females (73%) had normal kidney function while 8% had mild, 12% moderate, 3.5% severe reduction of renal function and 3.5% had ESRD. The kidney biopsy was performed in 14 female patients. The most common diagnosis was AS (65%) followed by isolated TBMN (21%) and TBMN with FSGS (7%). Only 1 specimen (7%) was signed out as inconclusive for AS or TBMN.

Conclusions: We have presented characteristics of 50 Croatian patients with X-linked AS. In our cohort 56% of mutations were novel. While renal biopsy provides information about degree and the type of renal parenchyma damage, genetic analysis is crucial for diagnosis.

Funding: Government Support - Non-U.S.

PO1666

Clinomics Implementation in the Mayo Clinic Nephrology Practice

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Background: Next generation sequencing has been increasingly used to diagnose monogenic kidney diseases. In 2018, we launched the Nephrology Genetics Clinic (NGC) with a primary focus to identify the etiology of unexplained nephrotic syndrome, chronic kidney disease, or stone disease/nephrocalcinosis. An essential component of the NGC is the Genomic Odyssey Board (GOB) which consists of nephrologists, geneticists, genetic counselors, pathologists, translational 'omics scientists, and trainees who meet at least monthly to interpret the genetic findings in the context of the patient's clinical data. Clinical and research follow-up recommendations are made after this careful multidisciplinary review and discussion.

Methods: In 2018 and 2019, the GOB reviewed 118 cases (9 cystic, 79 glomerular, 4 CAKUT, 10 stones, 7 tubulo-interstitial (TI), and 9 other; **Table 1**). Genetic testing was performed with a targeted analysis of 344 kidney disease-related genes (with *MUC1* variant analysis in subset of TI cases).

Results: A definite genetic diagnosis was achieved for 34 families (29%). After a multidisciplinary evaluation of variants of uncertain significance (VUS), another 16 (13.6%) were deemed to have variants likely related to the phenotype. The highest diagnostic yield was achieved in individuals with TI diseases (50%), followed by cysts (33.3%), glomerular (28.7%), CAKUT (25%), stones (20%), and others (11%). Of the unresolved/partially resolved cases, the GOB decided to pursue research activities such as trio whole exome sequencing or transcriptome sequencing for 22 (31%) families.

Conclusions: Implementation of genomic testing and analysis by a multidisciplinary team in a nephrology cohort with clinically suspected monogenic disease has provided a firm diagnosis in 29% of families, often resulting in changes in management/treatment. Ongoing research screening is likely to increase this yield.

Funding: Private Foundation Support

	N= 118	Solved/Likely solved	Unsolved with candidate VUS	Unsolved	Ongoing Analysis*
Cystic	9	3	1	5	1
Glomerular	79	23	13	43	19
Stone	10	2	0	8	1
TI disease	7	4	0	3	2
CAKUT	4	1	0	3	2
Other	9	1	2	6	1

*Research, local exome analysis, other.

Table 1: Results of Genetic Analysis by Disease Group

PO1667

CD11b Activation Suppresses Pro-Inflammatory suPAR in Myeloid Cells and Reduces Lupus Nephritis in Mice

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Background: Lupus nephritis (LN) is a debilitating glomerular disease and a comorbidity of systemic lupus erythematosus (SLE). CD11b, the alpha-chain of integrin CD11b/CD18, plays a critical role in cell signaling. Several mutations in the gene ITGAM, encoding CD11b, are associated with SLE and LN, these mutations are reported to reduce integrin function. suPAR is produced by myeloid cells upon pro-inflammatory activation and is a circulating risk factor for glomerular diseases. suPAR is downstream of Toll-like receptor signaling, where TLR-activation increases suPAR levels. We previously showed that activation of CD11b suppresses TLR-dependent pro-inflammatory signaling. Here, we investigate if this mechanism includes control of suPAR levels, which may provide novel therapeutic options for LN.

Methods: To investigate TLR-dependent signaling affected by CD11b activation, we utilized in vitro assays using primary macrophages and genetically engineered K562 cells expressing CD11b and CD18. K562 cells were developed to express either wild type CD11b or CD11b carrying mutations commonly found in LN patients. These cells were treated with TLR agonists or LN patient sera and level of suPAR in cell supernatants was assessed by ELISA. For complementary in vivo studies, we utilized our newly generated mouse model, where we incorporated a constitutively active CD11b point mutation (I332G) globally in mice to generate a model for CD11b activation – CD11b knock-in model. C57BL/6 wild type mice, the CD11b knock-out and the CD11b knock-in mice were used in models of SLE and LN to determine the effect of CD11b activation on circulating suPAR levels and course of the disease.

Results: TLR-stimulation increased suPAR levels in vitro and in vivo. Importantly, CD11b activation resulted in significantly reduced suPAR levels in both systems, suggesting a novel mechanism for controlling glomerular diseases. Additional mechanistic studies are on-going to define the exact molecular mechanism of action.

Conclusions: Using these models, we have identified a possible link between CD11b activation and suPAR levels in myeloid cells. These studies will provide understanding of the influence CD11b has on signaling pathways and inflammation associated with LN.

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PO1668

Drug-Induced Thrombotic Microangiopathy as a "Second-Hit" Phenomenon

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Introduction: Thrombotic Microangiopathy (TMA) syndrome is a diverse group of inherited or acquired diseases characterized by microvascular thrombosis and endothelial damage. Etiologies include drugs, thrombotic thrombocytopenic purpura, shiga toxin mediated hemolytic uremic syndrome (HUS), and complement mediated HUS. Environmental triggers are proposed as a second hit precipitating the disease process in some cases of atypical HUS (aHUS). We hereby present a case of drug induced TMA in a patient with an underlying pathogenic mutation for aHUS.

Case Description: 41-year-old male with presented to an outside hospital with AKI requiring dialysis and uncontrolled hypertension. He had a positive urine toxicology and admitted to marijuana, amphetamines (crystal meth), and heroin use. Labs revealed severe anemia and thrombocytopenia along with low haptoglobin, elevated LDH, and schistocytes on blood smear. Shiga toxin assay was negative with normal ADAMS-TS 13 and coagulation profile. C3 was notably low at 63 mg/dL. As such, he was diagnosed with presumed aHUS and treated with steroids, eculizumab, and plasmapheresis. He was then transferred to our facility where a kidney biopsy confirmed TMA. The etiology was presumed to be drug induced, however genetic evaluation showed heterozygosity for a pathogenic variant in the Complement Factor H (CFH) gene region. Notably, his sister also carried the diagnosis of aHUS. The patient was restarted on eculizumab and remained dialysis dependent on discharge. Unfortunately, he was then lost to follow up.

Discussion: Atypical HUS is associated with a myriad of genetic mutations involving the alternate complement pathway. Pathogenic variants of CFH gene have been implicated in autosomal dominant and recessive forms of the disease. While drug use might have triggered the TMA in our patient, it is likely that his underlying mutation was the first hit creating a disease predisposition. It remains unclear how frequently a culprit mutation is present in patients with presumed drug induced TMA. However, in patients with persistent TMA and a suggestive family history, clinical suspicion for aHUS should be maintained. This distinction is important as drug discontinuation alone would be ineffective for aHUS whereas complement-blocking therapies could be potentially curative.

PO1669

In Silico Prediction Performance for Type IV Collagen Variants

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Background: Advances in genomics technology and knowledge has led to increased sequencing for diagnosis, including in kidney disease. However, sequencing can reveal rare missense variants for which the relationship to disease is unclear. To address this need, *in silico* programs have been developed to assign variant categorization. Recently, pathogenic variants in *COL4A3/A4/A5* have been reported to account for a significant minority of chronic kidney disease. Here we evaluate the performance of *in silico* programs for type IV collagen variants.

Methods: Rare *COL4A3/A4/A5* missense variants were identified in an FSGS cohort, unscreened controls (gnomAD) and disease databases (ClinVAR, ARUP, LOVD). Comparisons between *in silico* predictions, disease database classifications and functional characterization were performed.

Results: *In silico* predictions and functional characterization classified all 9 definitely pathogenic *COL4A3/A4/A5* variants in the FSGS cohort correctly. *In silico* predictions correctly classified the majority (93-97%) of definitely pathogenic *COL4A3/A4/A5* variants in ClinVAR, ARUP and LOVD. However, a significant proportion of benign variants were predicted as pathogenic. Thirty-five percent of *COL4A3/A4/A5* missense variants obtained from gnomAD were also predicted deleterious. *In silico* predictions tended to overestimate the effects of *COL4A* variants of uncertain significance (VUS) when compared to functional characterization.

Conclusions: Our results demonstrate that *in silico* programs are sensitive but not specific to assign *COL4A3/A4/A5* variant pathogenicity, with misclassification of benign variants. Limitations of our computational work include overestimation of *in silico* program sensitivity given that they have likely been used in the categorization of variants labelled as pathogenic in disease databases; and the lack of clinical data to correlate rare variants in gnomAD controls.

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PO1670

Genetic Studies of the Etiology and Complications of Nephrotic Syndrome by Large-Scale Exome Sequencing

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Background: Idiopathic nephrotic syndrome (NS) is a major cause of renal failure. NS and its complications, including venous thrombosis, hypercholesterolemia and cancer display strong genetic predisposition. We hypothesize that the utility of exome sequencing (ES) will optimize precision medicine for clinical management of NS and its risk factors.

Methods: ES was performed in 2007 NS patients with variable onset age and steroid responsiveness. ACMG guidelines for clinical variant interpretation were used to classify monogenic causes and risk predisposition for a) NS in curated gene lists (glomerulopathies, N=127; expanded nephropathies, N=679); b) Incidental variants in 59 ACMG actionable-genes; c) Genetic risk for NS complications (Coagulation, N=100; lipid metabolism/cardiovascular risk, N=35); d) Germline cancer predisposition (N=77).

Results: We identified a monogenic cause for NS in 13% of cases, with *COL4A3* (2.2%), *COL4A5* (1.8%) and *WT1* (1.3%) representing the lead causes. Monogenic causes were enriched in FSGS and steroid resistant nephrotic syndrome cases. Analysis of the expanded nephropathy gene panel revealed an additional diagnostic rate of ~1%, representing coincidental diagnoses or phenocopies. *APOL1* associated FSGS risk genotypes were identified in 5% of cases. Variants of actionable potential were noted in 2.9% of patients, led by *BRCA2* (3.9%), *MYBPC3* (3.5%) and *LDLR* (0.25%). Variants predisposing to coagulation defects, lipid metabolism and cancer risk were found in ~11% of cases. Overall, we identified a monogenic cause or predisposing risk factor to NS or its complications in 27%, corresponding to 1 per 4 cases.

Conclusions: Our results reveal the importance of ES in the diagnosis of NS and its complications, with implications in risk stratification and clinical management. We showed that one every 4 cases carried a genetic variant that has potential to help clinicians optimize precision medicine approaches at the single-patient level. Our results enable designing cost-effective panels to maximize yield in routine clinical practice.

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PO1671

Additional Mutations in NRIP1 in Families with Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT)

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first three decades of life. In a previous study, we identified a dominant mutation in nuclear receptor interacting protein 1 (*NRIP1*) as causing urinary tract malformations via dysregulation of retinoic acid signaling (*JASN* 28:2364, 2017), which remains the only family with *NRIP1* mutation reported so far.

Methods: To identify additional families with *NRIP1* mutations, we performed whole exome sequencing (WES) in 232 families with CAKUT. We also screened for mutations in *NRIP1* in a cohort of 59 affected individuals with small kidneys and a suspected diagnosis of nephronophthisis (NPHP).

Results: By WES analyses, we discovered three heterozygous mutations (one frameshift and two missense) in three unrelated CAKUT families. In particular, individual B3864 with bilateral hydroureteronephrosis and right grade 5 vesicoureteral reflux (VUR) carried a heterozygous frameshift variant (c.2028_2031del; p.Asn676Lysfs*27). Individual A3460 with left renal agenesis harbored a heterozygous missense variant (c.970C>T; p.His324Tyr). In individual A782 with right renal agenesis, we identified a heterozygous missense variant (c.1343G>A; p.Arg448Gln). Family B3977 with an NPHP diagnosis, showing bilaterally increased echogenicity and corticomedullary cysts, carried a heterozygous missense variant (c.2252T>G; p.Leu751Arg). The four variants occurred 2, 0, 2, and 17 times, respectively as heterozygous in the gnomAD database of 125,000 healthy control individuals. All affected individuals exhibited an isolated CAKUT phenotype.

Conclusions: This study confirms that germline mutations in the transcription co-factor *NRIP1* gene are a novel genetic cause of human autosomal dominant CAKUT and strengthens the association between retinoic acid and renal malformations.

PO1672

Recessive Mutations in SEMA3G as a Potential Novel Cause of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. The identification of monogenic causes of SRNS has revealed ~60 single-gene etiologies. While in 12-30% of patients with SRNS a causative mutation may be detected, many remain without a molecular diagnosis (Sadowski *JASN* 26:1279, 2015). These genes are predominantly expressed in glomerular podocytes and the encoded proteins merge onto molecular complexes and pathways that are essential to podocyte development or homeostasis.

Methods: To identify novel monogenic causes of NS, we performed whole exome sequencing (WES) in an international cohort of 1,382 NS patients.

Results: We identified homozygous mutations in *SEMA3G* in 3 unrelated children with nephrotic syndrome, 1 nonsense mutation (c.1078C>T, p.Arg360*), 1 essential splice site mutation (c.460-2A>G, predicted to lead to skipping of exon 5 and thus causing a frame-shift and truncation of the protein) and 1 missense mutation (c.2225G>A, p.Arg742Gln). SEMA3G is a secreted protein that has been implicated in cell migration and axon guidance, and shown to protect podocytes from inflammatory kidney disease in a mouse model (Ishibashi *Sci Rep* 6:25955, 2016). We evaluated publicly available kidney single-cell RNA sequencing datasets and found *SEMA3G* to be predominantly expressed in podocytes (Karaiskos *JASN* 29:2060, 2018). We then performed co-immunofluorescence staining in adult rat kidney sections for Sema3g and established markers of podocytes (nephrin), endothelial cells (CD31), and mesangial cells (αSMA). The Sema3g signal was strongest in podocyte foot processes as indicated by partial overlap with nephrin but lack of overlap with CD31, or αSMA signal.

Conclusions: We, here, identified recessive mutations in *SEMA3G* as a potential novel cause of nephrotic syndrome in children.

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PO1673

Using Clustering to Facilitate Gene-Based Rare-Variant Collapsing for a Diverse Cohort of FSGS Patients

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Background: Several focal segmental glomerulosclerosis (FSGS) genes have been discovered through family studies. Rare-variant case-control studies, however, have been largely underpowered and/or restricted to a single ancestry.

Methods: We performed exome sequencing of 1,989 cases with FSGS and compared them to 18,835 controls. Using gene-based collapsing, we looked for genes with an excess of rare qualifying variants (QVs) in cases or controls. Standard collapsing was complicated by the diverse ancestry of our cases that not only included African, Asian, and Hispanic samples, but also Caucasian subpopulations not well represented in public databases or our controls. Therefore, we extended our collapsing workflow by a clustering step based on principal components reflecting ancestry. We performed coverage harmonization and frequency filtering within the clusters to capture population-specific differences. We used the Cochran-Mantel-Haenszel test to test for an association between disease status and QV status while controlling for cluster membership.

Results: Collapsing analyses were conducted on all cases together and on pediatric, adult, steroid-resistant, and steroid-sensitive subgroups. We detected a significant enrichment of QVs in known FSGS genes *WT1*, *INF2*, and *NPHS2*; additional signals in other FSGS genes (e.g. *PAX2*, *COL4A3*, *COL4A5*, *CD2AP*); and two novel ones that did not reach study-wide significance due to the limited sample size and phenotype heterogeneity. In several models and subgroups, the majority of the top 10 genes was formed by known FSGS genes, confirming the robustness of our novel approach.

Conclusions: We show that our new collapsing approach decreases inflation when samples with different ancestries are analyzed together, while preserving the underlying disease signals. We are currently more than doubling our case cohort, which should increase the power to detect significant signals in known FSGS genes, clarify the suggestive signal in two new genes, and allow well-powered sub-phenotype analyses.

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PO1674

eNOS/NO Signaling Attenuates Progression of Age-Related Kidney Diseases via Suppression of Inflammasome

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Background: Ageing affects the function of the immune system and leads to immunosenescence, which is characterized by defective immune responses and increased systemic inflammation (also termed inflammageing). Inflammageing is maladaptive and results from multiple mechanisms, including aberrant inflammasome activation. The ASC is an essential component of inflammasome. Endothelial dysfunction is also a common pathophysiologic mechanism of age-related organ damage. Nitric oxide (NO) produced by endothelial nitric oxide synthase (eNOS) is an important mediator in the maintenance of vascular homeostasis. We've reported that the eNOS-NO pathway attenuates the progression of kidney injury via suppression of inflammasomes. However, the relationship between the eNOS-NO pathway and inflammageing in the kidney remains unclear. To determine if the eNOS-NO pathway attenuates kidney damage via the regulation of inflammasome in ageing kidney, we used eNOS-deficient mice (eNOSKO) and eNOS-ASC double-knockout mice (eNOS-ASC-DKO).

Methods: Wild-type mice (WT) and eNOSKO were used to determine the role of the eNOS-NO pathway in ageing kidneys. WT and eNOSKO were sacrificed at 18 months of age to harvest kidney tissue. The localization of inflammasome activation in the kidney was evaluated with immunohistochemical analyses. To determine the role of inflammasomes in ageing kidneys, we generated eNOS-ASC-DKO. The mRNA expression of inflammasome components were determined in isolated glomeruli.

Results: The glomerular injury was more exacerbated in eNOSKO-18M than in WT-18M. In the immunohistochemical, the expression of ASC coexisted with the macrophages detected by F4/80 staining in eNOSKO-18M. These data suggested that the inflammasome activation was located in the macrophages. In the isolated glomeruli, mRNA of inflammasome components were higher in eNOSKO-18M than in WT-18M. The glomerular damage were ameliorated in eNOS-ASC-DKO-18M compared to eNOSKO-18M. In summary, in eNOSKO, inflammasomes were activated in macrophages, and interstitial fibrosis was exacerbated. However, in eNOS-ASC-DKO-18M mice, the tubulointerstitial damage was attenuated.

Conclusions: Endothelial NOS/NO signaling ameliorates kidney damage in the aging process via the modulation of inflammageing associated with inflammasome-activation.

PO1675

Alpha Lipoic Acid Supplementation Prevents the Age-Related Decrease in Nuclear Reduced Glutathione Levels in Kidneys from Old Female Lewis Rats

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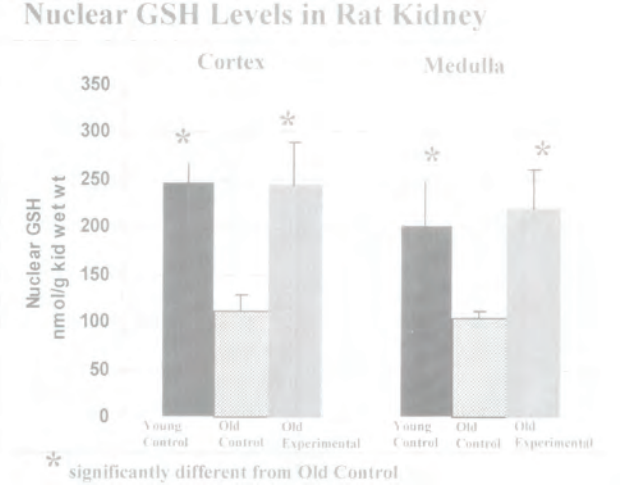
Background: The purpose of the present study was to investigate whether supplementation with alpha lipoic acid reverses the decrease in nuclear reduced glutathione (GSH) levels in kidneys from old rats. GSH is the major antioxidant inside cells, and a decrease in GSH levels is associated with increased oxidative damage caused by free radicals.

Methods: There were three groups of female Lewis rats used in the study. The Young Control rats (n=4) were 3 months of age, the Old Control rats (n= 4) were 22 months of age, and the Old Experimental rats (n=4) were 22 months of age. Only the Old Experimental rats received alpha lipoic acid (100 mg/Kg body wt) by i.p. injection for one week. The kidneys were harvested from anesthetized rats, and the cortex and medulla were separated and homogenized. The nuclear fractions were isolated using differential centrifugation. The GSH levels were measured with a spectrophotometric assay. Comparisons between groups were done using ANOVA followed by the Fisher's LSD post hoc test. All data are shown as X ± SEM. Statistical significance was determined at $p \leq 0.05$.

Results: Supplementation with alpha lipoic acid reversed the age-related decrease in nuclear GSH levels in the kidney cortex and medulla from old rats. The GSH levels were not different from the levels observed in young rats.

Conclusions: The findings suggest that dietary supplementation is beneficial to cell nuclei in rat kidney by preventing the decrease in GSH levels observed with age.



PO1676

SIRT3 Confers Protection and Mediates Sex Differences in Aging-Related Kidney Injury

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Background: Fibrosis and mitochondrial dysfunction are hallmarks of most progressive CKD. Studies suggest women have slower progression of CKD and lower ESKD incidence before menopause vs. men. SIRT3, a major mitochondrial acetyltransferase, is critical in maintaining mitochondrial homeostasis and anti-oxidative defense. We observe higher kidney mitochondrial SIRT3 (mtSIRT3) in females vs. males; mtSIRT3 declines with age but sex differences persist. We hypothesize that SIRT3 protects from and mediates sex differences in aging-related kidney injury and fibrosis.

Methods: Male and female WT, SIRT3 transgenic (Tg), inducible kidney tubule-specific SIRT3 knockout (iKO) or global SIRT3 KO mice were aged under physiologic conditions. Kidney fibrosis was detected by trichrome staining and expression of fibrosis markers (α-SMA; fibronectin). 6-month (mo) old male or female WT mice were treated with S.C. implantation of a 200 mg, 21-day-release testosterone pellet for 3 wks.

Results: In male mice, we observed that lower kidney mtSIRT3 expression vs. age-matched females is associated with higher baseline ROS generation, and development of tubular cytoplasmic vacuoles by 6-mo and fibrosis by 14-mo. Aging-related changes are attenuated in SIRT3 Tg males. Conversely, 6-mo iKO male mice display higher ROS, tubular injury and fibrosis vs. age-matched control males. In contrast to male mice, WT females display minimal tubular vacuolization or fibrosis at 14-mo. SIRT3 knockdown aggravates tubular injury and fibrosis in aged 14-mo iKO females; outcomes similar to WT males. Furthermore, young (2-3 mo) male and female global SIRT3 KO mice display baseline kidney injury characterized by: increased urinary albumin excretion, ROS and tubular injury vs. WT. Mechanistic studies show that testosterone (T) administration to WT males increased serum T ~4-fold, decreased kidney mtSIRT3, and caused kidney injury (decreased CrCl and increased tubular vacuolization). T increased kidney mtSIRT3 and caused no measurable kidney injury in WT females, possibly due to an associated increase in serum estradiol.

Conclusions: 1) SIRT3 is critical for kidney tubular epithelial cell survival under physiologic conditions, and inhibits development of tubular injury and fibrosis in aged kidneys; 2) sex-dependent differences in kidney SIRT3 expression may mediate sexual dimorphism in CKD outcomes.

Funding: Veterans Affairs Support, Private Foundation Support

PO1677

Percutaneous Renal Biopsy in Frail and High-Risk Patients

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Background: Many patients (pts) with End Stage Kidney Disease (ESKD) do not undergo percutaneous kidney biopsy (KB) and do lack a definite diagnosis. Whether KB is beneficial in the extreme patients' categories, remains controversial. Aim: To analyse the benefit/risk balance in terms of therapeutic options and general outcome of KB procedure in these borderline categories.

Methods: Files for all biopsies performed in our Centre between 2013 and 2019 (# 903 inpatients' native kidney) were retrospectively analysed with special focus on histological diagnosis, biopsy complications, and post-biopsy patient's outcome. Two groups of high risk patients were identified 1. >75 years old patients, and 2. patients requiring dialysis at the first clinical evaluation. A rigorous protocol of screening of the bleeding risks was adopted.

Results: Of the 903 biopsies, 217 cases had group 1, and 92 group 2 criteria. Group 1: mean age 80 years, main histological diagnoses: ANCA associated vasculitis (AAV); membranous nephropathy (MN), diabetic nephropathy, IgA glomerulonephritis (IgAGN), cast nephropathy, renal amyloidosis, focal segmental glomerulosclerosis (FSGS). Group 2: mean age 60 years, most frequent histological diagnosis: AAV; cast nephropathy, nephroangiosclerosis, IgAGN, diabetic nephropathy, renal amyloidosis; FSGS. Five major complications (2,3%), including AV fistula with spontaneous resolution in 4 pts and 1 case of severe bleeding requiring arterial embolization, and 14 minor complications (6,5%), including post biopsy haematomas <2cm in 12 pts and haematuria in 2 pts were observed in group 1. Only 1 major complication (AV fistula) and 4 minor complications, including post biopsy <2cm haematomas in group 2 were identified in group 2. Histological diagnosis conditioned or changed treatment strategy in 71% of elderly pts (group 1), and 63% of pts in dialysis (group 2). Dialysis discontinuation was achieved in 30 out of 92 pts (36,6%) with a sparing of over 1 million euro/year.

Conclusions: Given its high diagnostic value (especially in patients who are willing to be transplanted), the prognostic significance, and the potential impact on the treatment policy, indications to percutaneous KB in elderly and dialysis pts should be probably revised.

PO1678

CKD Is an Independent Risk Factor for Mortality in Elderly Patients Affected by COVID-19

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Background: COVID-19 infection, an acute respiratory syndrome caused by coronavirus, has recently emerged as a lethal pandemic. Many elderly patients have chronic kidney disease and several other comorbidities that are associated with worse outcomes. We hypothesized chronic kidney disease (CKD) in elderly patients is an independent risk of mortality and more severe COVID-19, even after adjustment for comorbidities.

Methods: This is a retrospective study, which enrolled 120 patients attended in a tertiary academic hospital divided into 2 groups, CKD (N=58) and non-CKD (N=62), according to eGFG < or ≥ 45ml/min/1.73m^2. Charlson Comorbidity Index was used to evaluate comorbidities.

Results: Patients with CKD have a significantly (all p values <0.05) higher leucocytes count, C-reactive protein, troponin, and lactate dehydrogenase; they also presented lower albumin. There was no difference in body mass index (BMI), lymphocytes, hemoglobin, age, gender, Charlson Comorbidity Index, or duration of symptoms between groups. Patients with CKD presented more severe COVID-19, as evidenced by a higher inspiratory oxygen fraction (p=0.001), major radiological findings in computed tomography, ground-glass opacity (25% non-CKD and 53.1% CKD group presented lesion in >75% lung, p=0.042), and higher mortality (40.3% non-CKD vs. 75.9% CKD, p=0.0001). Logistic linear regression has revealed that CKD (RR 5.4, p=0.0001) was independent associated with mortality after adjustment for Charlson comorbidity Index (RR 1.2, p=0.034), age (p=0.551), gender (p=0.820) and BMI (p=0.941).

Conclusions: Elderly patients with CKD have a higher and independent risk for mortality after COVID-19. These patients should be closely monitored during this pandemic situation in order to avoid further damage.

PO1679

Efficient Follow-Up and Its Effects on Questionnaire Responses in the EQUAL Study in the United Kingdom

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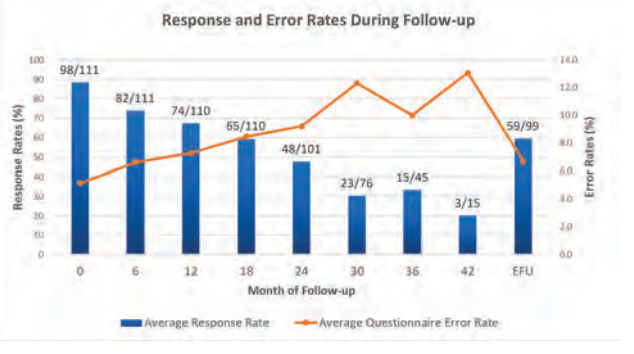
Background: Minimising patient contact is more important amidst the COVID-19 pandemic; yet altering follow-up data collection methods may introduce unintentional bias. We describe our findings from the European Quality (EQUAL) study in which UK patients switched from 'traditional' clinic follow-up (TFU) to 'efficient' postal follow-up (EFU).

Methods: EQUAL is a prospective study on treatment in people aged ≥65 with advanced chronic kidney disease (eGFR ≤20mL/min/1.73m^2). UK patients were recruited to EQUAL from 2013-2017. During TFU, patients were invited to complete a questionnaire (SF-36, Dialysis Symptom Index and Renal Treatment Satisfaction Questionnaire) at research clinics every 3-6 months. In 2018, all alive patients were invited to switch to EFU, which used an abbreviated questionnaire administered centrally by post. Questionnaire response and error rates for six-monthly TFU and the first EFU are presented for UK patients who consented to EFU.

Results: In total, 506 UK patients were recruited. In 2018, 236 of these patients were alive and almost half (n=111) consented to the change in follow-up. Of those consenting to EFU, response rates fell from 88.2% (98/111) to 59.0% (65/110) for patients who completed 1.5 years of TFU. Of those who were recruited earlier and had completed 3.5 years of TFU, response rates fell again to 20% (3/15). The response rate for the first EFU questionnaire was 59.6% (59/99) of those alive. Errors almost trebled throughout TFU, before falling to baseline at the first EFU.

Conclusions: In this prospective study of older people with advanced CKD, response rates fell and error rates rose during TFU. On introducing a shorter postal questionnaire, response and error rates improved to levels resembling early TFU. This suggests that even in older people with advanced CKD, returning questionnaires by post is acceptable and may provide more complete data than costly TFU. This is acutely relevant in this period of limited contact in the COVID-19 pandemic.



Response and error rates across follow-up, from those consenting to EFU.

PO1680

CKD in the Very Elderly: When Is It Only Aging?

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Background: Chronic kidney disease (CKD) diagnosis is increasingly common in the elderly and is associated with increased morbidity and mortality. As life expectancy increases, so does the prevalence of risk factors for CKD such as hypertension and diabetes. On the other hand, it is known that after 30 years, glomerular filtration rates decrease progressively, in a process called renal senescence. This study aims to identify risk factors for progressive CKD *versus* renal senescence in patients over 80 years.

Methods: We developed a single center retrospective study with 101 patients over 80 years followed by a nephrologist with CKD (estimated glomerular filtration rate (GFR) < 60 mL/min/ 1.73 m²) diagnosed for at least for 5 years. Progressive disease was defined as GFR decline greater than 5 mL/min/1.73 m²/year.

Results: Of 101 patients, 55.4% (n = 56) were male. Thirty eight percent presented CKD of undetermined etiology. Average GFR progression rate was 2.0 ± 4.4 ml/min/1.73m² /year and in about 66% GFR decline rate was less than 5 ml / min / 1.73m². Regarding CKD complications, 37.6% had anemia and 18.7% needed erythropoiesis-stimulating agents. No patient was under phosphate binders and 4% needed vitamin D analogues. About 20.9% presented metabolic acidosis requiring supplementation. In the progressive CKD group, there was a higher prevalence of obesity (OR 4.1, p = 0.04) and metabolic acidosis (OR 6.1, p = 0.01). Nephrologist follow-up time was also statistically different between the groups (6.1 years in progressive CKD vs 4.1 years in non-progressive CKD, p = 0.04). In the multivariate analysis, only the presence of metabolic acidosis (1.07, 95% CI [1.1-7.5]) was associated with the development of progressive CKD.

Conclusions: In patients over 80 years, average rate of progression of CKD was 2.0 mL / min / 1.73 m2 / year, which, associated with the reduced life expectancy of patients in this age group, allows us to state that the vast majority will not reach CKD stage 5. According to this resuts, only patients with metabolic acidosis are at risk of developing progressive CKD. Nephrology consultation does not seem to have an impact on CKD progression, since the group with progressive disease had the longest follow-up.

PO1681

Using the Difference in Estimated Glomerular Filtration Rate by Cystatin C vs. by Serum Creatinine (eGFRDiff) to Assess Muscle Mass and Frailty in Older Adults

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Background: Preliminary work has shown that the difference in estimated glomerular filtration rate by cystatin C vs by creatinine (eGFRDiff) is associated with frailty and mortality. As creatinine is influenced by muscle mass, more so than cystatin, we aim to determine whether muscle mass explains the relationship between eGFRDiff and frailty.

Methods: In the Health Aging Body Composition study, 2980 (97% of HABC) had baseline serum creatinine, cystatin C, and muscle mass measures on imaging. eGFRs were calculated using CKD-EPI equations (cystatin-based [$eGFR_{Cys}$] and creatinine-based [$eGFR_{Cr}$] respectively), and eGFRDiff was $eGFR_{Cys} - eGFR_{Cr}$. Total thigh muscle area was evaluated on computed tomography. Frailty was scored on a continuous scale including standing and walking tasks; the lowest quartile of scores were defined as frail.

Results: Mean age was 74 (±3) years, $eGFR_{Cys}$ was 72 (±19), $eGFR_{Cr}$ was 68 (±15), and eGFRDiff was 4 (±14) mL/min/1.73m². Compared to participants with minimal difference in eGFR (within 10 mL/min/1.73m²), those in the positive eGFRDiff group (>10 mL/min/1.73m²) were less likely to have fallen in the past year (19% vs. 21%), had stronger grip strength (31 vs. 30kg) and walked faster (1.22 vs. 1.17m/s). Higher eGFRDiff was significantly associated with larger thigh muscle area. In cross-sectional analyses, each 1 SD increment in eGFRDiff was associated with 30% lower odds of frailty in models adjusted for demographics, cardiovascular risk factors, and chronic kidney disease category (**Table**). This relationship was attenuated when adjusting for measures of muscle mass and strength but remained statistically significant.

Conclusions: The difference $eGFR_{Cys}$ - $eGFR_{Cr}$ provides information on older adults' functional status which is only partially explained by muscle quantity and quality.

Cross-sectional association of eGFRDiff with frailty in HABC participants

Outcome: Frail	eGFRDiff (per SD =14 increase)	
n=2980	OR (95%CI)	p value
unadjusted	0.69 (0.63; 0.76)	<0.0001
Model 1*	0.70 (0.64; 0.78)	<0.0001
Model 2**	0.79 (0.71; 0.89)	<0.0001

*adjusted for age gender race education BMI serum albumin CRP

smoking HTN, antiHTN meds, diabetes CKD category by eGFRCr

**further adjusted for total thigh muscle area & grip strength

PO1682

The Difference in eGFR by Cystatin C vs. Creatinine Is Strongly Associated with Mortality Independent of Measured GFR

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Background: In preliminary work, we have shown that the difference in glomerular filtration rate (eGFR) estimated by cystatin C [$eGFR_{Cys}$] and creatinine [$eGFR_{Cr}$], was associated with risk of frailty, hospitalization, cardiovascular events and mortality. Prior studies lacked directly measured GFR so it remained uncertain if associations were influenced by kidney function.

Methods: 567 participants of the Berlin Initiative Study (BIS) had baseline GFR measured by iohexol clearance (mGFR), as well as serum creatinine and cystatin C levels. $eGFR_{Cr}$ and $eGFR_{Cys}$ were calculated using CKD-EPI equations, and eGFRDiff was defined as $eGFR_{Cys}$ - $eGFR_{Cr}$. Mortality was recorded during up to 8 years follow-up. The association between eGFRDiff and mortality was assessed using Cox regression.

Results: Average (SD) age was 79 (±6) years, $eGFR_{Cys}$ 63 (±21), and $eGFR_{Cr}$ 69 (±17) for an eGFRDiff of -6 (±12) mL/min/1.73m². Compared to participants with minimal differences in eGFR, those with a substantially positive difference eGFRDiff (≥10 mL/min/1.73m²) were younger (76 vs. 78 years), less were diabetic (17% vs. 24%) and fewer took antihypertensives (59% vs 76%). Those with a substantially negative eGFRDiff (≤ -10 mL/min/1.73m²) were at much higher death risk which was minimally influenced with or without adjustment for measured GFR, age, sex, and urine albumin/ creatinine ratio (**Table**).

Conclusions: In BIS, an $eGFR_{Cys}$ estimate that was substantially less than an $eGFR_{Cr}$ estimate was associated with significantly higher risk of death. This association remained after adjusting for mGFR. Important clinical information beyond kidney function is embedded in eGFRDiff.

Funding: Private Foundation Support

Table. Association of eGFRDiff with Mortality in Older Adults in the Berlin Initiative Study

All cause mortality	eGFRDiff= eGFRCys-eGFRCr	eGFRDiffGroups		
		Negative (eGFRCys-eGFRCr ≤ -10)	Reference (-10< eGFRCys-eGFRCr ≤+10)	Positive (eGFRCys-eGFRCr > +10)
	n=567 # events=154	n = 200 # events =74	n = 308 # events=73	n = 59 # events=7
Age mean (SD), years	79 (6)	79 (6)	78 (6)	76 (5)
Female N (%)	243 (43)	76 (38)	140 (45)	27 (46)
mGFR mean (SD) mL/min/1.73m2	60 (16)	57 (14)	60 (17)	72 (14)
	Hazard Ratio (95% CI) Per 1SD=12 point increment	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Unadjusted	0.64 (0.55; 0.76)	1.73 (1.25; 2.39)	1 (ref)	0.51 (0.23; 1.10)
adjusted for mGFR	0.68 (0.57; 0.82)	1.75 (1.26; 2.42)	1 (ref)	0.94 (0.42; 2.07)
adjusted for age, sex, mGFR and urine alb/crea ratio	0.71 (0.60; 0.85)	1.71 (1.23; 2.37)	1 (ref)	1.01 (0.46; 2.25)

PO1683

Outcomes of Haemodialysis in Incident Elderly Haemodialysis Patients: Single-Centre Experience

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Background: In the UK, elderly patients represent the most rapidly expanding group of the dialysis population. However, there remains little evidence to suggest improved quality of life or increased life expectancy, particularly in those over 80 years old.

Methods: We retrospectively reviewed patients who were initiated on haemodialysis (HD) between January and October 2019 in a tertiary renal centre in the United Kingdom. Data were collected using an electronic database. Baseline characteristics, 3 and 12-month mortality were recorded. Data were presented as counts with percentages and mean +/- SD.

Results: There were 263 patients initiated on HD, of which 120 (45.6%) were over 70 years; 67 were aged 70-79 years (group A) and 53 were aged 80-90 years (group B). Mean age was 78.1 ± 5.3 years and 74% were of white ethnicity. Baseline characteristics are summarized in table 1. Sixty patients remained on HD, 14 recovered, 6 moved to other modalities and 40 died. The 90-day mortality was 21% (18% in group A, 25% in group B); 6-month mortality was 27% in group A and 34% in group B; 1-year mortality was in 36% in group A and 35% in group B. In those established on HD (>90 days), 1-year mortality was 12% (17% in group A, 4% in group B).

Conclusions: We report a high 1-year mortality of 35% in the elderly population. However, the majority occurred during the 1st 90 days. For those established on HD, mortality is 12%; this is substantially lower than the UK renal registry data for over 75s which was 23% in 2017. Mortality was comparable between age groups, although we were limited by small sample size. A key question is whether there is a difference in quality of life and life expectancy in this cohort.

	70-79 years (n=67)	80 + years (n=53)
Male gender	40 (60%)	35 (66%)
Female gender	27 (40%)	18 (34%)
White ethnicity	51 (76%)	38 (72%)
Black ethnicity	1 (2%)	3 (6%)
Other ethnicity	15 (22%)	12 (23%)
90-day mortality	18%	25%
12-month mortality	36%	35%
>90 days on HD, 12-month mortality	17%	4%

Baseline characteristics and mortality in elderly incident haemodialysis patients.

PO1684

Cost Effectiveness Study of Hyperkalemia Management

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Background: Patiromer (PAT) is a sodium-free, non-absorbed potassium (K^+) binder approved for the treatment of hyperkalemia (HK). There is limited real-world evidence on the cost implications associated with PAT treatment of HK. The objective of this study was to assess the cost-effectiveness of treating HK with PAT vs. no K^+ binder in a Medicare Advantage population.

Methods: This retrospective, matched cohort study was conducted using the de-identified Optum Clinformatics® Data Mart Database from 1/1/16–12/31/18. Two HK cohorts were identified: PAT exposed and unexposed (NoPAT). Patient inclusion criteria included pre-index serum K^+ ≥5.0 mEq/L and HK diagnosis (ICD-10 code) and ≥6 months insurance enrollment post-index. Propensity score matching and coarsened exact matching with baseline variables were used to identify the complete set of matching unexposed and exposed HK episodes. Follow-up began on index date and ended at the first censoring event (insurance disenrollment, death, 12/31/18, sodium polystyrene sulfonate or sodium zirconium cyclosilicate initiation, PAT discontinuation [exposed only], PAT initiation [unexposed only]). Cost outcomes measured at 6 months post-index: total, inpatient, emergency department (ED), outpatient services and outpatient pharmacy (mean US$ [CI 95%]).

Results: The study population was 2004 patients (1002 matched pairs). Overall, mean age was 74 years and 60% were male. Patients had a mean of 5 comorbidities. Comorbidities included: DM (73%), CHF (35%), and ESRD (10%). At 6 months post-index, 300 (150 matched pairs) PAT and NoPAT patients remained uncensored. Total PAT mean cost difference (savings) of $7220 ($2211,$9584) was observed at 6 months post-index ($P<0.01$). This cost difference included a pharmacy increase of $3094 ($3964,$2224) and a decrease in medical costs, specifically, inpatient $4718 ($2222,$7215), outpatient $4781 ($2274,$7288), and ED $815 ($488,$1142).

Conclusions: At 6 months post-index, PAT cohort observed a 27% reduction in cost compared with the unexposed cohort for HK management. Further study is warranted to replicate these findings in a large cohort.

PO1685

Effects of Veverimer on Serum Bicarbonate and Physical Function in Elderly Patients with Metabolic Acidosis in CKD

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Background: Use of $NaHCO_3$ to treat acidotic pts with CKD increases daily Na load which may be particularly detrimental to elderly pts who may have hypertension and congestive heart failure. Veverimer is a non-absorbed polymer that treats metabolic acidosis (MA) by binding and removing HCl from the GI tract. It is not an exchange resin and does not introduce unwanted cations such as Na or K. In Phase 3 randomized, blinded, placebo-controlled trials, veverimer significantly increased serum bicarbonate and improved subjective and objective measures of physical function in pts with MA in CKD (Wesson et al. *Lancet*, 2019). Here we report data from pts aged ≥65 yrs from these studies.

Methods: Patients were treated for up to 1 yr with veverimer or placebo with frequent determinations of blood bicarbonate. Physical function was assessed at Baseline and Weeks 12, 40, and 52 using the KDQOL-PFD which quantifies limitations on daily activities and by performance on the repeated chair stand (RCS) test.

Results: Of the 217 pts randomized, 113 (52%) were ≥65 yrs (mean 72 yrs). Select comorbidities included HTN (98%), diabetes (70%), and CHF (40%). At Baseline, the mean eGFR was 30.7 mL/min/1.73m² and the mean serum bicarbonate was 17.2 mEq/L. In this elderly cohort, more pts receiving veverimer met the primary study endpoint, had a significant increase in serum bicarbonate, and improved both KDQOL-PFD scores and RCS time (**Table**) compared with placebo. These effects of veverimer exceeded the minimal clinically important difference for both the KDQOL-PFD (+3 to +5 points) and RCS (-1.7 seconds). Safety was similar in both treatment groups.

Conclusions: In older adults with CKD, treatment with veverimer significantly increased serum bicarbonate levels and improved how pts felt and functioned. The safety of veverimer was not different from placebo.

Funding: Commercial Support - Tricida, Inc.

Efficacy Endpoints	Placebo (N = 48)	Veverimer (N = 65)
Primary Endpoint: proportion increasing serum bicarbonate by > 4 mEq/L or achieving normalization at Week 12	25%	76% P<0.0001
Change from baseline in Serum Bicarbonate (LS mean, mEq/L) at Week 12	+2.1	+5.4 P< 0.0001
Patient-Reported Physical Function (Change from baseline in mean [SD] KDQOL-PFD total score at Week 52)*	-0.13 (20.84)	+10.95 (21.57) P = 0.003
Objective Measurement of Physical Function	-2.46	-2.59 (7.55)

P-values are vs. placebo; An ANCOVA rank-based method was used for physical function endpoints

*Based on evaluable patients enrolled in controlled extension study (placebo, n=38; veverimer, n=58)

PO1686

Design of a Consensus-Based Geriatric Assessment Tailored for Older Patients Approaching ESKD

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Background: Routine geriatric evaluation in older patients approaching end stage kidney disease (ESKD), benefits disclosure of highly prevalent unidentified functional and cognitive impairments. Although recommended in guidelines, a suitable standardized geriatric test set is lacking. We aim to propose a consensus-based test set for geriatric assessment useful in both routine care and research in older (≥ 65 year) patients approaching ESKD.

Methods: A multidisciplinary expert panel of physicians, nurses and supportive disciplines with clinical and/or scientific experience in geriatric nephrology was assembled. Preconditions and selection-criteria for the selection of potential measures resulted from general geriatric principles, critical appraisal of literature, inventory of conventional instruments, and focus group meetings with patients, carers and health professionals. Older patients (aged ≥65 years) approaching end-stage kidney disease (eGFR < 20 ml/min/1.73M2) were selected as the target population. An expert panel meeting and subsequent round of comments by email led to agreement on the best suitable test set.

Results: The final consensus set contains instruments in functional, cognitive, phycological, and somatic domains, and patient preferences, nutritional status and fall risk. The set comprises a patient questionnaire (six instruments) and a professional-administered test set (including ten instruments). Estimated time for administration in pilot testing was 20 and 40 minutes respectively.

Conclusions: We propose a consensus-based nephrology-tailored geriatric assessment, to benefit clinical care for older (pre-)ESKD patients and enhance research comparability. Future research should investigate effectiveness, feasibility of implementation, patients satisfaction and the value for treatment decision making and outcome improvement.

Funding: Private Foundation Support

PO1687

Correlation Between Patient-Reported Physical Limitation and Objective Physical Performance on the Repeated Chair Stand Test Among Patients with Non-Dialysis Dependent CKD and Metabolic Acidosis

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Background: CKD accelerates the loss of physical function, in part due to the development of sarcopenia caused by metabolic acidosis (MA). Decline in the ability to rise from a seated position is consequential as it can lead to loss of independence. However, physical performance is not routinely measured in CKD clinical practice.

Methods: We evaluated the correlation between patient-reported limitation on daily activities on the Kidney Disease and Quality of Life Physical Function Domain (KDQOL-PFD, a 10-item survey in which possible responses are "not limited at all", "limited a little", and "limited a lot") and the standardized 5-times repeat chair stand time (RCS) using data from a 1 year randomized trial of pts (N = 196) with MA in CKD (Wesson et al. *The Lancet*, 2019). These measures showed an ability to detect change - pts in the veverimer group improved significantly on both.

Results: There was a significant, direct correlation between improvement (i.e., higher score) over 1 yr on the KDQOL-PFD total score and improvement on the RCS (i.e., faster time), (Pearson's product-moment correlation, 0.33, $P < 0.001$). Additionally, 5 of the 10 individual KDQOL-PFD activity limitations correlated significantly with RCS time: "lifting or carrying groceries"; "bending, kneeling, or stooping"; "walking one block", "walking several blocks", and "bathing or dressing yourself" (P-value < 0.05 for

the correlation for all questions). Using a linear model, we found that each category of decline in the KDQOL-PFD for these individual questions was associated with significant deterioration of RCS time in the range of 3.29 to 3.80 seconds, exceeding the minimally clinically important difference of 1.7 seconds (Jones et al. *Thorax*, 2013).

Conclusions: Our findings suggest that asking pts if they are limited in their ability to do daily activities such as walking 1 block or lifting or carrying groceries may be a practical way to screen for significant physical performance declines known to have important health, social, and economic consequences. Routine identification of pts with physical functional decline might allow for earlier implementation of interventions to forestall further impairment.

Funding: Commercial Support - Tricida, Inc.

PO1688

Mobility in Older Hemodialysis Patients: A Mixed Methods Study

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Background: Mobility, or the ability to move reliably and safely, impacts quality of life and predicts future disability and mortality. This is especially relevant for older adults, who comprise a large part of the hemodialysis (HD) population. For older hemodialysis patients, factors that limit mobility and which specific components of mobility are involved are not well-defined. Using a mixed methods approach, we investigated these factors and components in older HD patients.

Methods: Eligibility criteria were age ≥60 years and receipt of maintenance HD. Participants had a single in-person assessment that occurred in their home when feasible. We administered the Short Physical Performance Battery (SPPB) to assess balance, walking speed, and lower leg strength (range 0-12 for full SPPB, range 0-4 for individual domains). We conducted semi-structured key informant interviews, using an interview guide based on the literature. Interview transcripts were descriptively coded and major themes were extracted using both deductive and inductive approaches.

Results: A total of 31 persons enrolled, with a mean age of 72.5±8.1(S.D.) years and mean vintage of 4.6±3.5 years; 42% were female and 68% African-American. Mean overall SPPB was 4.4±2.3 points; mean scores for balance, walking and lower leg strength were 2.3±1.1, 1.8±1, and 1.3±0.7 points, respectively. Mean gait speed was 0.46±0.22 meters/second. Coding inter-rater reliability > 0.8. Three major themes emerged: 1) losses in balance and walking are the most debilitating, 2) fluctuations in mobility are frequent, and 3) post-HD procedure fatigue and the presence of amputations limit mobility (Table).

Conclusions: In a diverse sample of older HD patients, mobility is significantly limited with multiple domains affected. Patients identified balance and walking as the most problematic, and cope with frequent changes in mobility. Future studies should focus on improving balance and walking, and include strategies to mitigate fluctuations in mobility.

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Key themes regarding mobility in older hemodialys patients

Theme	Quote
Specific domains of mobility that are limited: balance and walking	"Oh, give me more balance so my back don't hurt when I try to walk around." -Female, age in 70s
Frequent changes in mobility	"I get off the machine, crawl around the corner to the car. 'Cause I have my good days and my bad days on dialysis… It seems like it's miles and miles and miles down the road when it's only right around the corner." -Male, age in 60s
Impact of post-HD procedure fatigue on mobility	"'Cause you're on dialysis three days a week for hours, and then you're tired when you come home…After I came on, my walking got considerably worse. That's why I had to go to the walker. I'm hoping that's where it ends at." -Female, age in 70s

PO1689

Rehabilitation in CKD

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Background: Older patients with impaired renal function (renal patients: RP) often show the criteria of a geriatric patient with increasing stages of CKD. Geriatric phenomena such as frailty are considered a predictor of poor outcomes particularly during acute illness in these patients. These consequences can be alleviated in patients without renal insufficiency (HP) by rehabilitative measures both in acute geriatrics units (AG) and in inpatient geriatric rehabilitation facilities (RG). So far it is largely unknown whether RP benefit from this type of rehabilitation to the same extent as HP. We have now examined this question by evaluating a large geriatric database.

Methods: The Geriatrics in Bavaria-Database (GiB-DAT) was established with the support of the Ministry of Health as a quality assurance project. It comprises the vast majority of anonymized records of cases treated in Bavarian AG and RG. In this study all data records for the years 2012-2019 from AG and RG were evaluated. The following parameters were examined: At admission: age, gender, cognition (Minimal Status Examination: MMSE), emotion (Geriatric Depression Scale: GDS), degree of care (DC); at discharge: number of diagnoses and medication; at admission and discharge: self-help ability (Barthel Score: BS), mobility (Timed Up and Go-Test: TUG) and place of residence.

Results: Both in AG and RG, HP (AG/RG n=116513/248831) and RP (AG/RG n=27294/45984) did not relevantly differ in age, gender, MMSE, GDS and DC. The number of diagnoses (AG: 10.7 vs. 9.3; RG 10.3 vs. 8.3) and drugs (AG 10.1 vs. 9.3; RG 9.9 vs. 9.0) was slightly higher in RP compared to HP. No major differences between RP and HP were observed at the beginning of the rehabilitation in BS, TUG and place of residence. In RP/HP, BS improved during rehabilitation by +14.4/14.5 (AG) and +21.1/21.9 (RG) points and the number of patients "able to walk" in the TUG by +22.1/20.6% (AG) and +14.3/14.5% (RG) respectively. Domestic living could be maintained in 66.0/68.9% (AG) and 81.6/81.5% (RG). Subgroup analysis of CKD-stages 3-5 showed no relevant difference for any of the examined parameters both in AG and RG.

Conclusions: RP benefit to a similar extent as HP from rehabilitative measures both in AG and RG with respect to improvement of self-help ability, mobility as well as the preservation of private residency. This was observed regardless of the stage of renal insufficiency.

PO1690

Predictors of Functional Status Change in Patients with CKD Between Two Hip Fracture Events: A 6-Year Prospective Study

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Background: Patients with chronic kidney disease (CKD) are susceptible to recurrent hip fractures (Hip#). Functional status decline after Hip# is transient, exacerbated by frailty, sarcopenia and co-morbidities. We studied the prognostic value of clinical and laboratory parameters for functional status change in CKD after recurrent Hip#.

Methods: Patients with CKD G3b-5 admitted with 2 separate Hip# events between June 2013 and Dec 2019 in a North West UK tertiary care hospital were included. Difference in Karnovsky Performance Status (KPS) Scale between 1st and 2nd Hip# admission determined functional status change. KPS is a linear scale between 0 (dead) and 100 (normally active). Parameters assessed include Clinical Frailty Scale (CFS), Hopkins Frailty Score (HFS), CKD FI-LAB, Sernbo Score, Charlson's Co-morbidity Index, Nottingham Hip Fracture Score, ASA Score and Abbreviated Mental Test Score. Differences in each parameter score between 1st and 2nd Hip# admission were recorded. ROC curve analyses was performed to assess discriminative ability between individual scoring tools.

Results: 37 patients met inclusion criteria (F:M 1.8:1; mean age 84.5±10.2 yrs). 10 were receiving long-term dialysis, whilst non-dialysis CKD patients had a mean eGFR 33±15 mL/min/1.73m^2. Mean age difference between Hip# is 1.4 yrs (p=0.032). Mean KPS difference between Hip# is -10.6 (p=0.028). AUC values from ROC analyses are shown in Table 1.

Conclusions: There was a significant decline in functional status between Hip#. Frailty assessment tools (CFS, HFS and CKD FI-LAB) had the best predictive performance for functional status change. Frailty measures may be utilized as risk prediction tools of functional status change from first Hip# admission. Further Research is needed on post-Hip# interventions that aim to maintain functional status and reduce subsequent fracture risk.

Funding: Government Support - Non-U.S.

Table 1

Predictors	AUC Value (95%CI)
Clinical Frailty Scale	0.96 (0.90-1.00)
Hopkins Frailty Score	0.95 (0.89-1.00)
CKD FI-LAB	0.91 (0.83-0.99)
Sernbo Score	0.85 (0.77-0.93)
Charlson's Co-morbidity Index	0.78 (0.69-0.88)
Nottingham Hip Fracture Score	0.74 (0.66-0.82)
ASA Score	0.67 (0.59-0.75)
Abbreviated Mental Test Score	0.56 (0.51-0.61)

PO1691

Which Parameters Best Predict Mortality After Hip Fracture for Patients with CKD? Insights from a 6-Year Prospective Analysis

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Background: Hip fracture is more prevalent in patients with CKD and has associated worse clinical outcomes than those without CKD. Uncertainties remain on which clinical or laboratory parameters best predict mortality outcomes following hip fracture for patients with CKD.

Methods: Patients with CKD G3b-5 admitted to a tertiary hospital in North West UK with hip fracture between June 2013 and Dec 2019 were included. Mortality outcomes

at 1st year, 3rd year and 6th year after hip fracture were assessed. Parameters assessed on hospital admission included Clinical Frailty Scale (CFS), Hopkins Frailty Score (HFS), CKD FI-LAB, Sernbo Score, Charlson's Co-morbidity Index, Nottingham Hip Fracture Score, ASA Score and Abbreviated Mental Test Score. ROC curve analyses were performed to evaluate ability of individual scoring tools to predict mortality outcomes after hip fracture.

Results: A total of 397 patients met study inclusion criteria of which 42 were receiving long-term dialysis. Mean age was 83.5±9.2 yrs. Non-dialysis patient mean eGFR was 37.4±14.9 mL/min/1.73m^2. Mortality at 1, 3 and 6 years were 38% (n=151), 60% (n=239) and 77% (n=305) respectively. AUC values from ROC curve analyses are presented in Table 1.

Conclusions: Frailty assessment tools (CFS, HFS and CKD FI-LAB) had the best predictive value for short- and long-term mortality after hip fracture for patients living with CKD. A comprehensive frailty assessment should be performed on patients with CKD admitted after a hip fracture to identify those at greatest risk of adverse outcomes. Further research is needed to evaluate interventions that aim to reduce mortality risk after hip fracture for patients living with CKD.

Funding: Government Support - Non-U.S.

Table 1: AUC values of tools used to predict mortality following hip fracture

Predictor	AUC Value (1 year mortality)	95%CI	AUC Value (3 year mortality)	95%CI	AUC Value (6 year mortality)	95%CI
Clinical Frailty Scale	0.95	0.89-1.00	0.93	0.87-0.99	0.95	0.89-1.00
Hopkins Frailty Score	0.91	0.84-0.98	0.91	0.83-0.99	0.93	0.86-1.00
CKD FI-LAB	0.86	0.78-0.93	0.87	0.80-0.94	0.90	0.83-0.97
Sernbo Score	0.85	0.78-0.92	0.86	0.79-0.93	0.83	0.76-0.90
Charlson's Co-morbidity Index	0.88	0.81-0.94	0.86	0.79-0.93	0.89	0.82-0.96
Nottingham Hip Fracture Score	0.85	0.77-0.92	0.83	0.76-0.90	0.80	0.73-0.87
ASA Score	0.74	0.66-0.81	0.75	0.67-0.82	0.78	0.70-0.87

PO1692

Mortality Outcomes of Dialysis Patients Who Sustained Neck of Femur Fractures in a Tertiary London Renal Centre

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Background: Patients with end stage renal disease have an increased risk of fractures, including neck of femur (NOF) fractures, partly due to bone mineral disorders. Studies show higher post-operative mortality rates in this group, attributed to abnormal vitamin D metabolism, challenges with fluid status, and dialysis sessions impeding physical therapy rehabilitation. St Helier hospital has an onsite tertiary renal centre and the Hip Fracture Unit has been ranked as one of the best performing in the country. We sought to establish if this on-site standardised local practice translated to reduced mortality outcomes in dialysis patients who sustained NOF fractures.

Methods: We performed a retrospective analysis of the 30 day mortality of dialysis patients sustaining NOF fractures between April 2011 and July 2018. Patients with NOF fractures were identified from the National Hip Fracture Database and dialysis patients from the renal unit database. We reviewed demographics, pre and post-surgical parameters and 30-day unadjusted mortality.

Results: We identified 3164 NOF patients and 46 of these patients were on dialysis (n=46). 43 were on haemodialysis and 3 were on peritoneal dialysis. The dialysis cohort included 20 females and 26 males and average age was 77 years (53-95). ASA grades were 3 in 23 patients, 4 in 22 patients, and 5 in 1 patient. 29 operations were conducted under general anaesthesia, 16 under spinal anaesthesia and 1 patient had non-operative management of a subcapital fracture. All patients had a pre-operative review by an orthogeriatrician and remained under joint care of the orthopaedic, orthogeriatric and renal teams. 30-day unadjusted mortality for the dialysis cohort was 8.70% (4 deaths), compared to 7.60% for the general cohort (RR 1.144, CI 0.445-2.942, P = 0.7801). Average length of stay for the dialysis cohort was 26 days (5-87). Average length of survival for the dialysis cohort was 801 days following admission.

Conclusions: Previous studies have demonstrated 2 to 4 fold increased mortality in dialysis patients with NOF fractures. Our data shows that patients on renal replacement therapy did not have higher 30-day mortality compared to the general cohort. A multidisciplinary service with close collaboration between specialities can lead to good outcomes in this high risk population.

PO1693

Intensive Blood Pressure Control and Fall Injuries in Older Adults: A Systematic Review and Meta-Analysis

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Background: Hypertension is the leading preventable risk factor for cardiovascular disease (CVD), and its prevalence increases with age. While prior studies suggested that intensive blood pressure (BP) control achieved a reduction in CVD, antihypertensive treatments can cause adverse events such as falls. Falls are one of the leading causes of hip fractures and traumatic brain injuries. However, it remains unclear if intensive BP control could lead to an increased risk of falls.

Methods: We performed a systematic literature search up to April 2020. We selected randomized control trials (RCTs) and cohort studies which compared the risk of falls in the intensive BP control group with that in the less intensive control group the elderly. Risk ratios (RRs) with corresponding 95% confidence interval (CI) were synthesized.

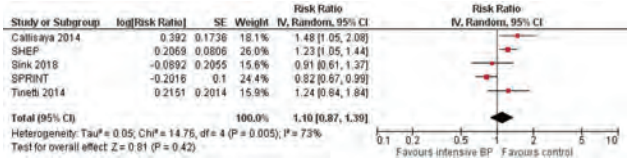
Results: Five studies (three RCTs and two cohort studies) were included, with 11,245 patients. The characteristics were shown in Table. Intensive BP control was no associated with significantly increased risk of falls, but the results showed high heterogeneity. (RR [95% CI]; 1.10 [0.87-1.39], I2= 73%)

Conclusions: In older patients, intensive BP control was not associated with an increased risk of falls, but with high heterogeneity. The proportion of frail patients might be a source of heterogeneity. Further studies that stratify patients with risk of frail are needed.

Characteristics of the studies included in the Meta-analysis

Study	Design	Definition of intensive BP control	Age (years)	Follow up (years)	Total number of patients	Male (%)	Smoker (%)	Obesity (%)	Diabetes Mellitus (%)	Myocardial infarction (%)	Heart failure (%)	Cognitive impairment (%)	Prior falls (%)
Callisaya 2014	Prospective cohort	0 or >3 medications	>60	1.0	237	57.4	53.6	N/A	11.8	11.0	N/A	N/A	18.1
SHEP	RCT	active treatment or placebo	>60	4.5	4736	43.2	49.8	N/A	10.1	4.9	N/A	1.7	N/A
Sink 2018	RCT	sBP target <140 or <120	>75	3.3	2242	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SPRINT	RCT	sBP target <140 or <120	>75	3.3	2636	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tinetti 2014	PS matched cohort	0 to <0.2 DDD or >2.5 DDD	>70	3.0	1394	41.6	7.2	16.2	32.5	1.6	23.0	16.0	8.5

BP: Blood pressure; RCT: Randomized controlled trial



Forrest plot

PO1694

Potentially Inappropriate Antihypertensive Medications and Mortality in Older Adults on Hemodialysis

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Background: Older patients on hemodialysis often have difficult to control hypertension, but also suffer from orthostatic or post-dialysis hypotension. Some orthostasis-causing antihypertensives (i.e., central alpha agonists (CAA) and alpha blockers (AB)), are considered potentially inappropriate medications (PIMs) for older adults because they carry more risk than benefit. We sought to determine if these PIMs are associated with mortality risk among older adults on hemodialysis.

Methods: Using USRDS analytic files, we studied adults aged ≥66 years initiating in-center hemodialysis (ICHD) from 2013-2014 with a Medicare Part D prescription for CAA or AB at initiation. All had Medicare Parts A, B, and D ≥1 year prior to initiation, no hospice care within prior 6 months, and continued ICHD for ≥120 days. We classified patients as continuing or discontinuing CAA/AB at 120 days and examined risk of death over 2 years using Cox models adjusted for demographics, dual Medicare and Medicaid eligibility, comorbidity index, diabetes, ESRD cause, hospitalization count in prior 12 months, pre-dialysis nephrology care, facility for-profit status/region, nursing home residence, and functional limitation (CMS form 2728). We tested interaction between CAA/AB continuation and functional limitation. We censored models for discontinued dialysis, hospice, loss to follow up, modality change, and transplant.

Results: Of 5,981 patients, mean age 75.6±6.5, 51.4% women, and 24.6% black. Most [65.5% (n=3,920)] continued CAA/AB prescription at 120 days. Compared to those who discontinued, those who continued were more likely to be black (26.3 vs. 21.3%), dual eligible (31.5 vs. 27.3%), and have no functional limitations (84.1 vs. 79.8%). With a smaller proportion of deaths compared to discontinuers (17.3 vs. 20.9%), continuation of CAA/AB was associated with a lower hazard of death (unadjusted HR 0.78, 95% CI: 0.68-0.90). After adjustment, this was attenuated and not significant (aHR 0.88, 95% CI: 0.76-1.01). The association was not modified by functional limitations (p=0.54).

Conclusions: We did not find increased mortality among older adults on ICHD who continue CAA or AB prescriptions after 120 days, providing some reassurance on their use in all older adults on ICHD.

Funding: Other NIH Support - NIA, Private Foundation Support

PO1695

Tailoring the Beers Criteria for Mortality Risk Stratification Among Older Adults Initiating Hemodialysis

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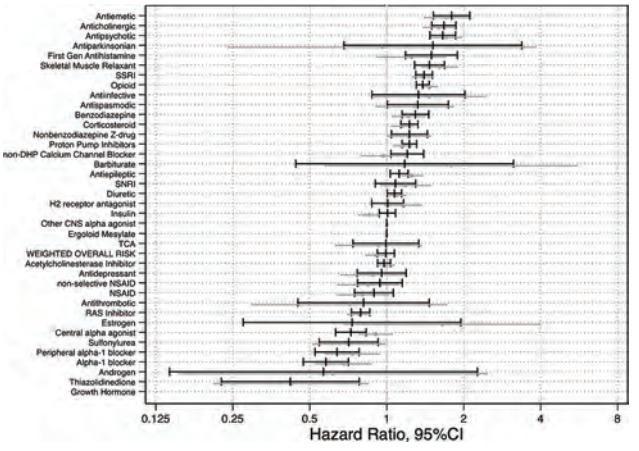
Background: American Geriatrics Society's Beers Criteria lists potentially inappropriate medications (PIMs) that carry more risk of harm than benefit in older adults, but PIM risks may differ in kidney failure. To tailor the Beers Criteria, we developed a novel mortality risk score for older patients initiating hemodialysis.

Methods: We assembled a USRDS cohort of 39,098 adults aged ≥65 initiating hemodialysis (2013-2014) and enrolled in Medicare Part D by 90 days post-initiation. We used Part D claims days' supply to quantify prescription length of Beers Criteria PIMs. In a training cohort (60% sample), we identified which of 38 PIM classes were associated with mortality using Cox modeling; censoring for loss of Medicare coverage, modality change, or 9/1/2015. Models were adjusted for demographics, initiation year, comorbidities, drug dependence, smoking status, inability to ambulate, and institutionalization. PIMs classes that were associated with mortality were summed to create a PIM count risk score. We used Cox models to estimate the association of PIM count risk score (time-varying) with mortality in training and validation cohorts.

Results: The training cohort (n=23,521) had mean age 75 years, 43% women, 21% black, and 75% (n=17,706) had ≥2 PIM fills/month. We identified 15 PIMs (HR >1) to include in the risk score (Figure). Patients with ≥2 fills/month (vs. no fills) were more likely institutionalized (13.8 vs. 10.1%), non-ambulatory (20.8 vs. 17.2%), and have cardiovascular disease (62.4 vs. 50.7%). Compared to those with no fills, there was increased mortality risk among those with 1 fill (aHR=1.32;1.25-1.39) and ≥2 fills (aHR=1.66;1.56-1.75).

Conclusions: We identified 15 of 38 PIM classes associated with mortality to yield a novel PIM count risk score. This score facilitates tailoring the Beers Criteria to promote age-appropriate prescribing in older adults initiating hemodialysis.

Funding: NIDDK Support, Other NIH Support - NIA, Private Foundation Support



PIM Classes and Mortality Risk

PO1696

Symptoms and Suffering at the End of Life in ICU Patients Receiving Dialysis

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Background: Patients with end-stage kidney disease (ESKD) on dialysis suffer from a significant burden of physical symptoms. Little is known, however, about the symptoms that intensive care unit (ICU) patients receiving dialysis experience at the end of life.

Methods: This is a cohort study conducted at NewYork-Presbyterian Hospital / Weill Cornell Medical Center and Brigham and Women's Hospital from September 2015 to March 2017. Nurses who cared for deceased ICU patients were interviewed within 3 weeks of the deaths about patients' physical and psychological symptoms in their last week of life. On a 1-10 scale, nurses rated 16 different symptoms on how much they contributed to a patient's suffering and rated the patient's overall suffering in the last week of life. Study staff abstracted demographic and clinical data from patient charts.

Results: One-hundred nurses completed interviews on 200 deceased patients, 67 of whom underwent dialysis in the last week of life (for ESKD or acute kidney injury). Mean dialysis patient age was 63 years; 39% were female; 32% were non-white; 12% were Hispanic. The nurses rated patients who underwent dialysis in the last week of life as having significantly more suffering from painful, broken skin than non-dialysis patients (mean 4.6 vs. 3.5 out of 10, P=0.045) but significantly less suffering from hunger (mean 2.4 vs. 3.6 out of 10, P=0.012) or thirst (mean 3.2 vs. 4.8 out of 10, P=0.005). There was also a trend towards more suffering from swelling in the dialysis patients (mean 6.2 vs. 5.3 out of 10, P=0.083). An unadjusted linear regression model revealed that receipt of dialysis in the last week of life was significantly associated with perceived overall suffering (β=1.35, P=0.006); however, after adjustment for painful, broken skin (β=0.19, P=0.013) and swelling (β=0.20, P=0.007) in the model, the relationship between dialysis and overall suffering was attenuated (β=0.84, P=0.074).

Conclusions: Nurses rated ICU patients who received dialysis in the last week of life as suffering from more painful, broken skin but less hunger or thirst than non-dialysis patients. The relationship between dialysis and perceived overall suffering was attenuated by painful, broken skin and swelling, suggesting that attention to these problems might reduce suffering at the end of life in ICU dialysis patients.

Funding: Other NIH Support - National Cancer Institute CA197730 to HGP

PO1697

Want to Reduce Regret with Dialysis Initiation? Implement Shared Decision-Making

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Background: The American Society of Nephrology's "Choosing Wisely Campaign" recommends that nephrologists should not initiate chronic dialysis without implementing a shared decision-making (SDM) process. The current literature lacks details on the relationship of SDM with outcomes such as quality of life and decisional regret.

Methods: We surveyed 223/380 (response rate 59%) hospitalized patients receiving maintenance dialysis in the Upstate, NY, and asked them about their experience with dialysis decision-making using the SDM-9 Questionnaire. Quality of life and decisional regret were assessed by KDQ0L-36 and Decisional Regret Scale, respectively. Candidate predictors in the final linear regression model included age, sex, time on dialysis, race, marital status, income level, education level, quality of life, fear of death, and decisional regret.

Results: Nearly 41% of patients were <65 years old, 47% were women, and 41% were White. The mean scores for SDM were 25.9 ± 12.2. In the bivariate analyses, patients who were married or in a relationship had greater mean SDM scores ($p<0.01$) than those who were single. Patients with higher scores on SDM had less anxiety over death and less decisional regret. (R = -0.17 and -0.29, respectively). The candidate predictors in the final model together explained 21.4% of the variance in SDM ($p = 0.02$). SDM decreased for every 0.15 unit increase in decisional regret score (CI: -0.25, -0.07) when controlling for all other predictors in the model.

Conclusions: We found that patients with higher scores on the SDM-9 Questionnaire had less decisional regret regarding their decision to initiate dialysis. Future interventions to implement SDM in clinical settings are a top research priority.

Funding: Private Foundation Support

PO1698

Attitudes Towards Physician-Assisted Death in Patients Receiving Maintenance Dialysis

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Background: During recent years, the debate about the legalization of physician-assisted death (PAD) has intensified at both public and policy levels. Surveys and polls on this issue have included seriously ill patients such as those with cancer; however, voices of patients receiving maintenance dialysis are not represented in the current literature.

Methods: We surveyed 223/380 (response rate 59%) hospitalized patients receiving chronic dialysis in Upstate, NY. We asked patients about their views on PAD using the following two questions: (1) Which of the following best describes your views about whether a physician should ever be allowed to take the final action in response to a patient's request for assisted death? (2) In case you had a great degree of pain and suffering and if physician-assisted death were legally available, do you think you might request it for yourself? Response options for the first and second questions included: (a) support/yes (b) oppose/no (c) uncertain. Candidate predictors in the final logistic regression model included age, time on dialysis, race, marital status, income level, education level, spirituality, social support, symptom burden, sense of burdensomeness, fear of death, and fear of the dying process.

Results: Nearly 41% of patients were <65 years old, 47% were women, and 41% were White. Fifty-five percent supported PAD, 20% expressed uncertainty, and 22% opposed it with missing data on 3% of patients. In response to the question, if patients would choose PAD for themselves, in case of pain and suffering, and if PAD was legally available: 37% said yes, 44% no, and 17% chose the unsure option. In the bivariate analyses, those who supported PAD had lower mean spirituality, higher anxiety about the dying process, and had spent more time on dialysis compared to those who opposed or were uncertain ($p<0.05$) about it. In the final model, none of the candidate predictors were significant for support or opposition/uncertainty about PAD.

Conclusions: More than half of hospitalized dialysis patients supported PAD, while fewer would actually use this option in case of pain and suffering. In the absence of the legalization of PAD in the NY state, the promotion of palliative care and hospice services and high-quality end-of-life care for dialysis patients are high priority policy issues.

Funding: Private Foundation Support

PO1699

Perspectives on Conservative Management of Advanced Kidney Disease: A Qualitative Study of US Patients and Family Members

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Background: Growing recognition of the limits of maintenance dialysis for some groups of patients has led to the emergence of conservative care models for advanced kidney disease in several countries outside the US. There is strong interest in replicating similar models in the US, however little is known about how these models are perceived by US patients and family members.

Methods: We conducted a qualitative study using cognitive interviews with 14 patients aged ≥75 years with advanced kidney disease and 6 of their family members about their perception of conservative care approaches in other countries as described in available patient decision aids on treatment of advanced kidney disease. We performed an inductive thematic analysis of interviews to identify themes reflecting participants' understanding and receptivity to conservative care.

Results: Subjects were mostly white (n=15) and had at least some college education (n=16). 4 prominent themes emerged from analysis of interviews: 1) *Core elements of conservative care*: aspects of conservative care that were appealing to participants included a whole-person, multidisciplinary approach to care that focused on symptom management, maintaining current lifestyle and managing health setbacks; 2) *Importance of how conservative care is framed*: participants were more receptive to conservative care when this was framed as an active rather than passive treatment approach and were accepting of uncertainty in disease prognosis; 3) *An explicit approach to shared decision-making*: participants believed decisions about conservative care or dialysis address considerations about risk and benefits of treatment options, family and clinician perspectives and personal goals, values and preferences; and, 4) *Relationship between conservative care and dialysis*: although conservative care models outside the US are generally intended to serve as an alternative to dialysis, participants' comments implied that they did not view conservative care and dialysis as mutually exclusive

Conclusions: Although participants in this study found many aspects of conservative care models developed in other countries to be appealing, models will likely require adaptation to meet the needs and preferences of US patients and their families.

Funding: Private Foundation Support

PO1700

Feasibility and Acceptability of Telepalliative Care in Rural Dialysis Units

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Background: Limited access to palliative care is a key barrier to its integration in routine dialysis care. We evaluated the feasibility and acceptability of telepalliative care while patients received dialysis in rural units.

Methods: The target population included any patients with end-stage kidney disease receiving dialysis. Palliative care physicians and APPs conducted consultations as per their usual practice and used a large wall mounted screen with centrally positioned camera. Patients used an iPad attached to an IV pole positioned next to the dialysis chair. Patients were provided the option of having family present, receiving the consult on dialysis or off dialysis in a private room. Feasibility was measured by 1-month completion rate. Acceptability was measured using an adapted telemedicine questionnaire.

Results: We recruited 40 patients to undergo a telepalliative care consultation while receiving dialysis. Four specialty palliative care clinicians (3 physicians and 1 nurse practitioner) conducted the visits. The recruitment rate was 35% (40/113), scheduling rate was 97.5% (39/40) and completion rate was 85% (33/39). Thirty-six patient participants (15 women, 21 men) completed the baseline survey. One patient requested family to be present during the conversation. No patients requested to have the conversation off dialysis in a private room. Audiovisual aspects of the conversation were rated highly. More than 3/4 reported the visit being at least as good as an in-person visit and 40% felt the televisit was better. Patients felt the appointment was relevant to them, but they were less certain that they learned new things about their condition, and they were mixed about whether the appointment changed the way they think about dialysis.

Conclusions: Telepalliative care is acceptable to patients receiving dialysis and is a feasible approach to integrating palliative care in rural dialysis units.

Funding: Private Foundation Support

Acceptability of Telepalliative care in dialysis

Acceptability score, (Likert score 1-5, 1=strongly agree/very helpful)	1.75	
Telepalliative was better than in-person visit	41%	
Telepalliative was no better or worse than in-person	38%	
Telepalliative was worse than in-person visit	21%	
Requested to meet again with palliative care	Yes	56%
	Maybe	34%
	No	9%

PO1701

Abstract Withdrawn

PO1702

Modestly Low eGFR Is Not Associated with Cognitive Decline in the Elderly

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Background: Kidney disease is associated with cognitive impairment. Whether mild to moderate CKD is associated with cognitive decline in older adults is not clear. We evaluated changes in cognition in relation to baseline eGFR in the elderly Alzheimer's Disease Neuroimaging Initiative (ADNI) participants.

Methods: ADNI is an NIH funded, multicenter study, which includes participants with normal and impaired cognition who were administered a comprehensive battery of neuropsychological tests every six months. We related the CKD-epi eGFR with previously validated composite scores for memory (ADNI-Mem) and executive function (ADNI-EF) in multivariable linear regression analysis.

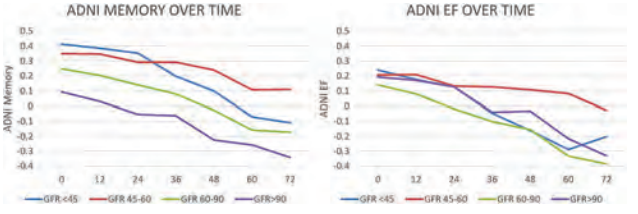
Results: 1127 participants with a mean age of 73.8±7.1 years, 57% men, 97% Caucasian, and mean follow up for 6±2.6 years were included. Mean baseline eGFR was 76.4±19 ml/min/1.73 m^2. ADNI-Mem and ADNI-EF scores declined across all eGFR categories (figure). Older age and lower education were associated with declines in both ADNI-Mem and ADNI-EF scores. Baseline eGFR was not associated with declines in either ADNI-Mem or ADNI-EF scores (table).

Conclusions: There is no association between baseline eGFR and cognitive decline in elderly persons with mild-moderate impairment in kidney function.

Funding: Other NIH Support - K23-AG055666

Multivariable linear regression model for ADNI-Mem score and ADNI-EF score

	Beta estimate for decline in ADNI-Mem score	95% CI	*p* value	Beta estimate for decline in ADNI-EF score	95% CI	*p* value
Age (+10)	-0.12	-0.20, -0.03	0.006	-0.28	-0.37, -0.19	<0.0001
Female sex	0.31	0.18, 0.44	<0.0001	0.14	-0.01, 0.28	0.07
Caucasian race	-0.12	-0.36, 0.11	0.29	0.15	-0.10, 0.4	0.24
Years of education (+1)	0.08	0.06, 0.10	<0.0001	0.10	0.08, 0.12	<0.0001
eGFR (+10)	-0.03	-0.06, 0.01	0.11	0.004	-0.03, 0.04	0.84



Change in ADNI-Mem and ANDI-EF scores by eGFR categories.

PO1703

Post-Operative Delirium and Cognitive Decline in Kidney Transplantation

Nadia M. Chu, Xiaomeng Chen, Dorry L. Segev, Mara McAdams-DeMarco. *Johns Hopkins University, Baltimore, MD.*

Background: Post-operative delirium may be a marker for greater cognitive vulnerability to stressors. As such, those with post-operative delirium may experience steeper decline in cognitive performance following stressors of surgery post-KT.

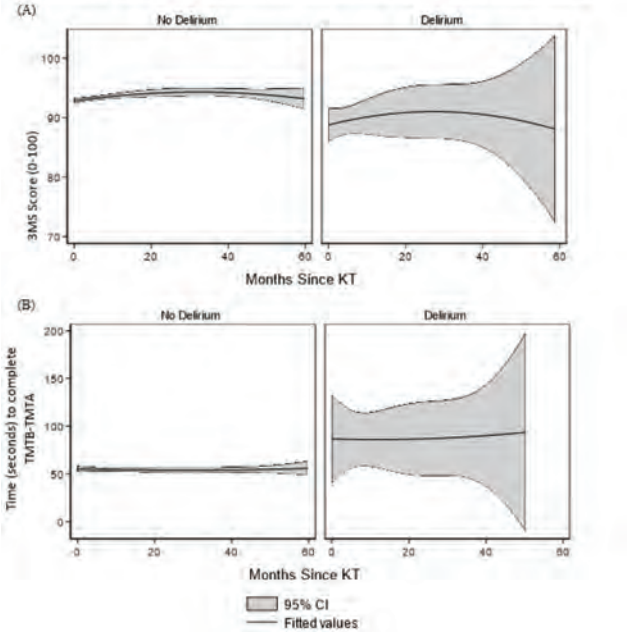
Methods: We used a single center cohort of 912 adult KT recipients with delirium assessments abstracted from medical records and global (3MS) and domain-specific (executive function: time to complete TMT-B minus TMT-A) cognitive performance measured at KT, 1-month, 3-months, 6-months, 1-year, and annually thereafter post-KT. We used mixed effects models to describe repeated measures of cognitive performance and compare trajectories by post-operative delirium.

Results: Among 912 KT recipients, 44 (4.8%) had post-operative delirium. Delirium was associated with higher levels of cognitive impairment at KT (18.2% vs 8.0%), and was associated with lower 3MS component scores including memory, identification/association, and orientation. After adjustment, those with delirium had 3MS scores that were on average 3.6 points lower than those without delirium (95%CI: -6.9, 0.3) at time of KT; delirium was not associated with differing global cognitive trajectories post-KT (difference=0.04 points/month, 95%CI:-0.1, 0.2) (Figure1A). However, delirium was associated with lower executive function at KT (difference=44.0s, 95%CI: 17.4, 70.6) and steeper decline in executive function post-KT (difference=-1.1s/month, 95%CI:-2.1,-0.05) (Figure1B).

Conclusions: KT recipients with delirium experience greater decline in executive function, indicating greater cognitive vulnerability with potential vascular etiologies. Nephrologists and transplant centers should be aware of cognitive risks associated with post-KT delirium and implement available preventative interventions to reduce risk of delirium.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging (NIA)

Figure1. Unadjusted cognitive trajectories by post-operation delirium status among kidney transplant (KT) recipients (n=912). (A) Global cognitive function: 3MS Scores ranging from 0-100, where lower scores equate to poorer cognitive function, and (B) Executive function: time to complete Trail Making Test Part B (TMTB) minus time to complete Trail Making Test Part A (TMTA), where longer time equates to poorer executive function.



PO1704

A Comparison of Frailty Measures Among Patients Referred for Kidney Transplantation

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Background: Frailty is highly prevalent in patients referred for kidney transplantation. While the Fried Frailty Phenotype (FP) is widely used, less is known about other frailty assessment tools. We assessed and compared the prevalence of frailty using three tools in kidney transplant waitlist candidates.

Methods: Kidney transplant waitlist candidates were prospectively enrolled from five centers from June 2016-Feb 2020. Frailty was primarily defined using the FP as three or more of slowness (using walk time), weakness (using grip strength), weight loss, low activity or exhaustion (the latter three using questionnaires). Secondary tools included a Frailty Index (FI) consisting of 37 variables across the domains of social function/cognition, function, mobility and comorbidity, and the Clinical Frailty Scale (CFS), a frailty screen based on clinician gestalt that ranges from 1 (very fit) to 8 (very severely frail). We used adjusted logistic regression to identify factors associated with frailty measured by the FP. Area under the receiver-operator characteristics (ROC) curves were calculated to compare the FP to the FI and CFS.

Results: Of 542 enrolled patients, 64% were male, 80% were white, and the mean age was 54±14. The prevalence of frailty by the FP was 16%; it was 27% for those >65 years old. Of the FP components, low grip strength (41%), and exhaustion (36%) were the most prevalent. Using an established cut point of 0.25 yielded a prevalence of 38% by the FI (46% for those >65). Using a cut-off of 5 on the CFS (mildly frail), frailty prevalence was 4% (7% for those >65). The mean FI score was 0.23±0.14 (max 0.70) and median CFS score was 3 (IQR 2,3) or "managing well". Diabetes (adjusted odds ratio; aOR 2.0, 95% CI 1.0, 3.8), and cerebrovascular disease (aOR 3.3 95% CI 1.3, 8.5) were associated with frailty defined by the FP. Area under the ROC curve for the FP and FI/CFS were 0.86 (good) and 0.69 (poor) respectively.

Conclusions: The prevalence of frailty varies using different measurement tools and there are differences in perceived (CFS) versus measured (FP/FI) frailty among patients referred for transplantation. Determining which tool is most associated with outcomes for waitlisted patients is a future objective of this study.

PO1705

DNA Double-Strand Breaks of Human Glomerular Endothelial Cell-Induced Collagen Type VI Excretion and Nodular Lesions in Various Kidney Diseases

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Background: Collagen deposition is the common histological end-point of progressive chronic kidney diseases (CKDs). We focused on collagen type VI (COL6) which is known as components of nodular lesions. This study was performed to test the hypothesis that glomerular endothelial cells with DNA double-strand breaks (DSBs) induce the accumulation of COL6 in various kidney disease and evaluated the mechanism of COL6 accumulation after DSBs.

Methods: We examined various kidney diseases (n:180) in which DSBs and glomerular fibrosis were detected by phospho-histone H2AX (γ-H2AX) expression and COL6 accumulation. In *vitro* study, we investigated the relationship between DSBs and COL6 excretion and the intracellular signal pathways in human glomerular endothelial cells (HRGECs) using mitomycin C (MMc)-induced DNA damage, and other two agents; Neocarzinostatin (NCS) and camptothecin (CPT). We examined the effect of DSBs response signal pathways, i.e. ATM, ATR and DNA-PK using their specific kinase inhibitors (KU55933, VE-821, Nu7441).

Results: COL6 and γ-H2AX were detected in glomeruli in which the γ-H2AX-positive area was identified as the independent factor for the % COL6-positive area (β: 0.553, t = 2.842, p = 0.009). Furthermore, COL6 was a component of the nodular lesions found in various kidney diseases. In *vitro* study of MMc-induced DNA damage, COL6 excretion detected by the decrease of COL6 positive cells was suppressed in the ATR-inhibited group (p <0.01 for 2 h, p <0.001 for 24 h). Moreover, CPT treated cells induced the COL6 excretion as well as MMc treated cells (p <0.001 for MMc, p=0.002 for CPT).

Conclusions: This study showed that DNA damage-sensing kinase of ATR was activated in response to DSBs and induced COL6 secretion of human glomerular endothelial cells. Furthermore, DNA damage may induce the nodular glomerulosclerosis in various kidney diseases.

Funding: Government Support - Non-U.S.

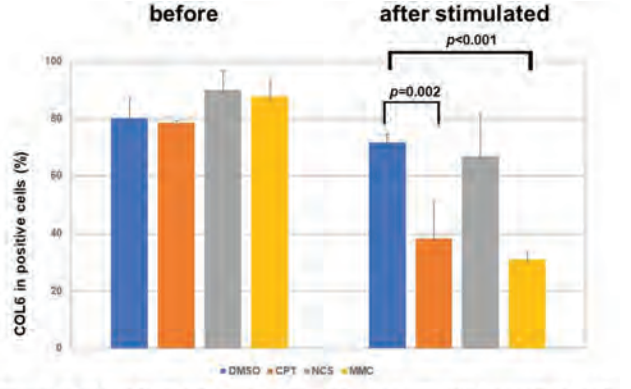

Figure. ATM and Rad3-related (ATR) is associated with COL6 secretion (n=3).

PO1706

Clinical Course of a Patient with FSGS and a Basement Membrane Defect

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Introduction: We present a case of a patient with a familial basement membrane abnormality who developed nephrotic syndrome and worsening CKD due to FSGS and outline her response to immunosuppressive therapy over 15 months. Our case suggests that immunosuppressive therapy may benefit such patients and delay progression to ESRD.

Case Description: A 38-year-old woman with microscopic hematuria was found to have a urine Pr/Cr ratio of 2.4 during pregnancy. Her s.Cr was 1.4-1.6 mg/dL and she had over 13g of proteinuria during pregnancy. After delivery, the serum creatinine stabilized between 1.1-1.3 mg/dL and her urine Pr/Cr ratio was 8.0 with an unrevealing serologic workup. She has no family history of renal insufficiency, but her father and 14-year-old daughter have microscopic hematuria. A renal biopsy revealed FSGS with ultrastructural GBM alterations including thinning and lamellation as well as nearly complete foot process effacement. Collagen IV staining demonstrated a normal IF pattern for α2 and α5 chains. She was started on prednisone, however, her glycemic control deteriorated and therapy was stopped after 1 week. She was then treated with Losartan and Cyclosporine and her Pr/Cr ratio improved to 1.3-1.5 mg/dL but her serum creatinine gradually rose to 2.0 mg/dL. Losartan was changed to Diltiazem and CsA was changed to MMF. Her s.Cr has trended down to 1.4 mg/dL with a urine Pr/Cr of 1.9 fifteen months after diagnosis. She was referred for genetic testing and was found to be heterozygous for a mutation of COL4A4 (Exon 39, c.3679G>A, p.Gly1227Arg).

Discussion: Prior case series have demonstrated the coexistence of familial FSGS and hereditary GBM abnormalities. However, it has not been fully elucidated whether FSGS occurs as a primary process or secondary to the GBM abnormalities nor is it known whether such patients benefit from immunosuppression. Our case details the course of a patient with nephrotic syndrome due to FSGS and thin basement membrane changes with normal collagen IV staining found to have a genetic COL4A mutation which is not known to be a pathogenic variant. She demonstrated a partial response to immunosuppression with greater than 75% improvement in proteinuria and stabilization of the serum creatinine with treatment with MMF suggesting that immunosuppressive therapy may alter the course of disease in patients with a dual diagnosis of FSGS and thin basement membrane abnormalities.

PO1707

VEGFA-Angpt-Tie2 Participates in the Interaction Between Mesangial Cells and Glomerular Endothelial Cells in Rat Anti-Thy-1 Nephritis

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Background: Mesangial cells and glomerular endothelial cells, as the renal intrinsic cells,are involved in the occurrence and development of various kidney diseases. In mesangial proliferative glomerulonephritis, the endothelial cells are affected by the signals from mesangial cells and show pathological changes such as diffuse capillary proliferation. But the specific signaling pathway mechanism is still unclear.

Methods: By establishing the rat model of anti-Thy-1 nephritis,and co-culturing mesangial cells and endothelial cells in the transwell system.

Results: By establishing the rat model of anti-Thy-1 nephritis, we found that the damage of mesangial cells in the glomeruli was accompanied by the proliferation of diffuse endothelial cells on the 7th day. Furthermore, we found that activated mesangial cells can promote endothelial cell proliferation and migration through co-culturing mesangial cells and endothelial cells in the transwell system, and vice versa. VEGFA expression was increased in activated mesangial cells, which promoted the expression of Angpt2 in endothelial cells. Angpt2 binds to Tie2, the endothelial cell surface receptor, and inhibits the phosphorylation of Tie2, thereby causing endothelial cell proliferation. When VEGFA neutralizing antibody was added into the co-culture system, the expression level of Angpt2 in endothelial cells decreased, the phosphorylation level of Tie2 increased, and cell proliferation was inhibited. If Angpt1 was added into the co-culture system and combined with Tie2, the effect of Angpt2 could be competitively inhibited, and the endothelial cell proliferation could be alleviated. In addition, after we injected Angpt1 into rats of anti-Thy-1 nephritis, the expression of Angpt2 in glomeruli decreased, the phosphorylation level of Tie2 increased, and the proliferation of endothelial cells decreased significantly.

Conclusions: The above results suggest that VEGFA-Angpt-Tie2 signaling pathway is involved in the interaction between mesangial cells and endothelial cells in mesangial proliferative glomerulonephritis. Angpt1 can be used as a new method to treat mesangial proliferative glomerulonephritis.

PO1708

GBM Deposition of Collagen 3α1 in Alport Glomeruli by Mesangial Filopodia Injure Podocytes via Aberrant Signaling Through DDR1 and Integrin α2β1

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Background: We have previously shown in In Alport mice that ET_AR activation in mesangial cells results in sub-endothelial invasion of glomerular capillaries by mesangial filopodia. The filopodia deposit mesangial matrix in the GBM, including laminin 211 which activates NF-kB, resulting in induction of inflammatory cytokines culminating in tubulointerstitial fibrosis. Here we show that collagen 3α1 is also deposited in the GBM, where it contributes to podocyte injury through activation of DDR1 and integrin α2β1 receptor signaling.

Methods: Wild type and Alport kidneys from mice were dual immunostained with anti- collagen 3α1 and anti-laminin 211 antibodies and analyzed by confocal microscopy. Dual staining with anti-DDR1 and anti-collagen 3α1 was analyzed by super resolution microscopy (SR-SIM). Cultured murine Alport podocytes were overlaid with recombinant collagen 3α1 or not for 24 hours and RNA analyzed by RNA-seq. These same cells were subjected to Si-RNA knockdown for integrin α2 or DDR1 and the RNA analyzed by RNA-seq. Results from this study were compared with RNAseq from RNA isolated from 7-week-old wild type and Alport mouse glomeruli.

Results: Collagen 3α1 localized to the mesangium in wild type mice and was found in both the mesangium and in the GBM in Alport mice where it co-localized with laminin 211. SR-SIM showed that collagen 3α1 staining was juxtaposed to DDR1 staining on podocytes and thus available for binding podocyte receptors. Numerous genes associated with podocyte injury are up-regulated in both Alport glomeruli and GECs treated with collagen 3α1, including osteopontin, TGF-β1/2, and collagen 1α1 among many others. Knockdown of α2β1 integrin or DDR1 ameliorated induction of selective profibrotic genes in GECs treated with collagen 3α1.

Conclusions: Collagen 3α1 is deposited in the GBM by mesangial filopodia where it activates DDR1 and α2β1 receptors resulting in podocyte injury and likely contributing significantly to glomerular damage. This may explain why deletion of either DDR1 or α2β1 integrin in Alport mice ameliorates renal pathology.

Funding: Other NIH Support - NIDCD

PO1709

Protection of the Remnant Rat Glomeruli from Mechanical Stress Through Structural Adaptation and Pharmacological Intervention After 5/6-Nephrectomy: A Modeling Study

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Background: 5/6-nephrectomy leads to increased blood flow and pressure in the remaining glomeruli, ultimately resulting in sclerosis. It is hypothesized that these hemodynamic alterations increase mechanical stresses, including shear stress on the glomerular endothelial cells and circumferential hoop stress on podocytes, however these mechanical stresses have not been rigorously quantified. In renoprival conditions glomerular capillary diameters increase, and it is unclear how these structural adaptations affect the mechanical stress magnitudes.

Methods: A mathematical microvascular hemodynamic model was developed to simulate blood flow and plasma filtration on each capillary segment of an anatomically-accurate rat glomerular capillary network. Model parameters were adjusted to match glomerular hemodynamic data for control and 5/6-nephrectomized conditions with and without the presence of the ACE inhibitor, enalapril (Meyer TW et al. *Kidney Int.* 1987;31(3):752-759). Glomerular capillary diameters were increased according to experimental imaging data (Ferrell, Nicholas, et al. *AJP-Renal* 308.6 (2015): F588-F593) to simulate glomerular structural adaptations post-5/6-nephrectomy.

Results: Post-5/6-nephrectomy, glomerular capillary structural adaptations reduced mean network shear stress from 156.5 to 92.8 dynes/cm^2. Without structural adaptations enalapril reduced mean shear stress to 136.1 dynes/cm^2. The increase in glomerular capillary diameter reduced shear stress while the increased diameters combined with glomerular hypertension increased mean hoop stress from 90.9 to 104.3 kPa. The combination of enalapril and structural adaptations resulted in a mean network shear stress of 81.1 dynes/cm^2 and hoop stress of 69.7 kPa.

Conclusions: Our results indicate that glomerular structural adaptations protect the glomerular endothelial cells from increased levels of shear stress, thus preserving kidney function. However, these structural adaptations in turn lead to increased hoop stresses. The combination of enalapril with structural adaptations reduces mechanical stress, providing protection and maintaining function for longer periods.

Funding: NIDDK Support

PO1710

Major Vault Protein Contributes to Increased Interstitial Fibrosis in a Murine Model of CKD

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Background: Chronic kidney disease (CKD) is a global health issue characterized by interstitial fibrosis and tubular atrophy, and progressive CKD results in kidney failure. There is currently no effective intervention for interstitial fibrosis. We previously showed that major vault protein (MVP), a key component of the vault complex, contributed to increased matrix protein deposition in murine unilateral ureteral obstruction (UUO) animal model. We extended our investigations to a murine model of CKD.

Methods: CKD was induced in MVP wild-type (WT) and knockout (KO) mice by feeding with standard chow containing 0.2% adenine for 8 weeks, after which time mice were sacrificed and kidneys were harvested and examined. Spot urine albumin-to-creatinine ratio was also measured. MVP WT and KO mice fed with standard chow served as controls.

Results: MVP WT mice with CKD showed increased MVP expression, predominantly in proximal tubular epithelial cells, compared to MVP WT control mice, and this was accompanied by development of proteinuria, tubular atrophy, tubulo-interstitial macrophage infiltration, and increased interstitial α-smooth muscle actin, fibronectin and collagen III expression. MVP KO mice with CKD showed less proteinuria ($P<0.05$) and less severe kidney histopathological features with reduced immune cell infiltration, and also reduced expression of fibrosis mediators compared to WT CKD mice. Exogenous TNF-α, IL-6, or MCP-1 increased MVP expression in cultured renal proximal tubular epithelial cells.

Conclusions: The data suggest that progressive CKD in this murine model is accompanied by increased renal tubular epithelial MVP expression, and MVP may contribute to the pathogenesis of tubulo-interstitial injury and damage.

Funding: Government Support - Non-U.S.

PO1711

Signaling at the Mesangial Cell (MC) Membrane in Light Chain Deposition Disease (LCDD) and AL-Amyloidosis (AL-Am) Involves Sortilin-Related Receptor (SORL1), Caveolins, and C-Fos

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Background: AL-Am and LCDD are two diametrically opposed glomerulopathies in terms of mesangial alterations produced by glomerulopathic light chains (GLCs). Their pathogenesis involves surface MC interactions resulting in cytoskeletal changes, c-fos translocation, phenotypic transformations, lysosomal activation (AL-Am), rough endoplasmic reticulum expansion (LCDD), and ultimately, mesangial matrix alterations. The present study addressed signaling pathways involved.

Methods: Human (H) MCs (both caveolin 1- wild type / knock-out) were incubated with monoclonal LCs purified from the urine of renal biopsy-proven AL-Am, LCDD, myeloma cast nephropathy (MCN) patients or albumin for up to 96 hours at different time frames. The samples were analyzed using light, immunofluorescence and electron microscopy, including immunolabeling for c-fos, kappa / lambda light LCs, caveolin-1 and SORL1.

Results: Co-localizations in cup-shaped MC membrane indentations (caveolae) of GLCs with caveolin-1, and SORL1 were documented using double immunofluorescence and immunogold labeling ultrastructural techniques. Upon interactions with GLC (but not MCNLCs or albumin) caveolae on the surface of MCs increased dramatically, SORL1 was activated and c-fos translocated from cytoplasm to nuclei.

Conclusions: SORL1 is a key component of GLCs signal transduction in MCs. Co-localization supported the notion that Interactions of GLCs with MCs occurred in caveolae activating SORL1. Caveolin-1 knock out HMCs abolished c-fos translocation from cytoplasm to nuclei and the downstream mesangial alterations (i.e. mesangial expansion / increased protein production) in LCDD group. In ALLC group, c-fos translocation and amyloid production were decreased but not totally abolished, suggesting that other mechanism may be involved in amyloidogenesis. C-fos plays a crucial role following SORL1 activation to promote mesangial cell phenotypic transformation essential for amyloidogenesis and extracellular matrix over production, in AL-amyloidosis and LCDD, respectively.

Funding: Private Foundation Support

PO1712

Compartmental Differences Within the COL3A1 Network in Proteinuric Kidney Disease: Informing Drug Activity Using the Jaccard-Tanimoto Index

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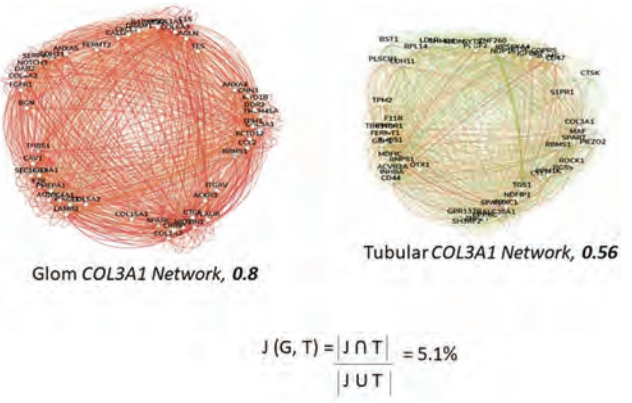
Background: In proteinuric kidney disease, type III collagen (COL III) participates in mesangial expansion, crescent organization, and glomerulosclerosis. Matrix deposition within the tubulointerstitium is associated with worse prognosis. A semi-quantitative analysis was conducted to understand compartmental differences within the *COL3A1* transcriptomic network, and to inform therapeutic potential of drugs that mitigate COL III deposition.

Methods: Proteinuria and renal *COL3A1* (day 21) mRNA were measured in adult male Wistar rats administered PAN (~100 mg/kg, intraperitoneal). HumanBase was used to build glomerular (G) and tubular (T) *COL3A1* transcriptomic networks. Network analysis was restricted to 51 elements each, inclusive of *COL3A1*, with a minimum interaction confidence of 0.01. The Jaccard-Tanimoto similarity index was used to calculate common elements within the two compartments.

Results: The rat PAN model was associated with increased proteinuria (*, $p<0.01$ vs. sham) which correlated directly and significantly with renal *COL3A1* mRNA expression level. Network analysis revealed a relative strong glomerular *COL3A1* interactome with an average strength of 0.8±0.08 and a relatively weaker tubular *COL3A1* interactome with an average strength of 0.56±0.01. The Jaccard-Tannimoto similarity index between the glomerular and tubular COL3A1 signaling elements was 5.1%.

Conclusions: Glomerulosclerosis in proteinuric kidney disease may result from a relatively strong *COL3A1* transcriptomic network within that compartment. Tubulointerstitial matrix deposition is rare in proteinuric kidney disease, possibly due to a weaker *COL3A1* transcriptomic network in that compartment. Drugs designed to specifically mitigate COL III deposition might be most effective against glomerulosclerosis.

Funding: Other U.S. Government Support



PO1713

The Correlation Between Urinary MicroRNA-21 and Renal Parameters in Patients with IgA Nephropathy

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Background: The expression of microRNA-21 (miR-21) in renal tissue is reported to be related to tubulointerstitial fibrosis and renal outcome in IgA nephropathy. In this study, we examined whether the urinary concentration of miR-21 is related to clinicopathological parameters and short-term changes in renal function in patients with IgA nephropathy.

Methods: We extracted and quantified microRNAs in morning spot urine in 88 patients with IgA nephropathy at biopsy and five control subjects, and examined the relationship between clinical and histological parameters, one-year changes in eGFR and urinary miR-21. The concentrations of microRNAs and proteins were corrected to the concentration of urinary creatinine and were log-transformed for simple correlation analysis.

Results: The urinary excretion of miR-21 was detected in all subjects, and the urinary concentration of miR-21 in patients with IgA nephropathy was significantly higher than those in controls. Among 88 patients with IgA nephropathy, urinary miR-21 levels showed a significantly positive correlation with the urinary concentration of total microRNA (r=0.65), total protein (r=0.40), beta2-microglobulin (r=0.62), and N-acetyl-beta-D-glucosaminidase (NAG) (r=0.37), but not with baseline GFR, and urinary red blood cells. In contrast, the urinary miR-21 levels did not show a significant correlation with histological changes, including glomerular proliferation/sclerosis and tubulointerstitial fibrosis. The one-year changes in eGFR after biopsy showed a significant inverse correlation with the urinary concentration of miR-21 (r=-0.31) and total protein (r=-0.37), but not total microRNA, beta2-microglobulin, and NAG. The correlation between urinary miR-21 and one-year eGFR change was similar in the subjects with and without steroid treatment.

Conclusions: In this study, the urinary excretion of miR-21 was associated with clinical parameters and one-year changes in renal function in patients with IgA nephropathy, suggesting that urinary miR-21 might be used as a biomarker of IgA nephropathy.

Funding: Government Support - Non-U.S.

PO1714

Diagnostic Delay and the Clinical Prodrome in US Adults with Systemic Light Chain (AL) Amyloidosis with Renal Involvement

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Background: Early therapy for AL can reverse renal impairment, but AL diagnosis (dx) is often delayed. We report the first population-level study of the diagnostic delay and prodrome in systemic AL patients (pts) with prior signs/symptoms (S/Sx) of renal impairment.

Methods: Pts with renal S/Sx at AL dx were identified in the US Optum Clinformatics® claims data since June 2001. AL was defined as ≥1 inpatient or ≥2 outpatient AL codes, followed by ≥1 anti-plasma cell therapy in 2 yrs. Renal S/Sx were defined as ≥1 prior dx code for stage 1-3 chronic kidney disease (CKD), renal failure/ESRD, nephrotic syndrome, acute kidney injury, or proteinuria. We described prevalence and overlap of S/Sx and time from first S/Sx to AL dx in renal AL pts. Kaplan-Meier estimates and log-rank tests compared time to AL diagnosis by prior monoclonal gammopathy (MG).

Results: Of 870 renal AL pts (67% of AL pts), 70% had CKD, 46% had renal failure, 58% had acute renal failure, 29% had nephrotic syndrome, and 61% had proteinuria by AL dx. Median time since first renal S/Sx and AL dx was 196 days, with a median of 205 days since CKD dx and 23 days from first nephrotic syndrome dx (**Figure**). Among renal AL pts, 89% had cardiac S/Sx, 67% had neurologic S/Sx, and 57% had ≥3 systems involved. Median time from first nephrology visit for renal S/Sx and AL dx was 67 days (6 visits). AL dx was earlier for pts with prior MG than without (median 83 vs 210 days, *P*=0.002).

Conclusions: The median time to AL dx after the first renal S/Sx was 196 days and 67 days after the first nephrology visit. The presence of a prior MG shortened the time to AL dx.

Funding: Commercial Support - Janssen Research & Development LLC

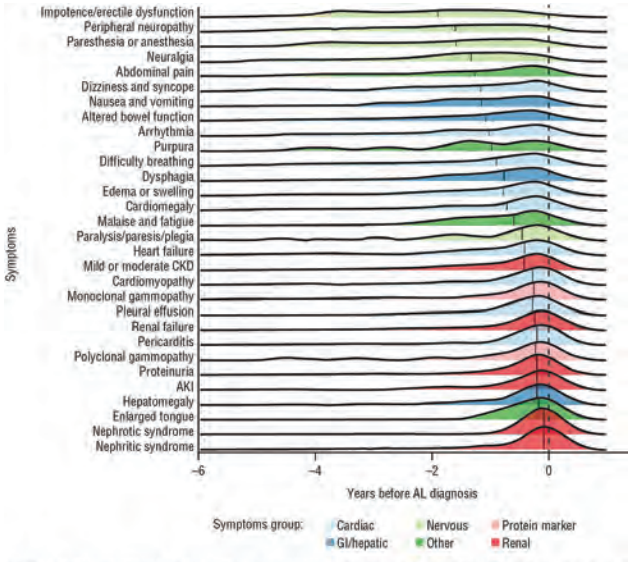

Figure. Estimated probability distribution of first diagnosis of signs and symptoms before AL diagnosis in renal AL pts (n=870) ordered by median days to AL diagnosis (black line).

PO1715

Case of Leukocyte Cell-Derived Chemotaxin 2-Associated Renal Amyloidosis

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Introduction: Amyloidosis is a disorder characterized by the abnormal deposition of insoluble protein fibrils in tissues. The most recently described form of amyloidosis is derived from leukocyte cell-derived chemotaxin 2 (LECT2).

Case Description: 60 yo with history of HTN and COPD referred for evlauation of CKD. Creatinine of 1.29 (6/2017) and 1.65 (09/2017). urinalysis no protein and 1 RBC. 24 hour urine protein showed 190 mg of protein. Renal Ultrasound was normal and all other serolgic labs were normal. She had a Renal Biopsy that showed Cango red positive amyloid deposits and Mass Spectromety based proteomic analysis showed peptide profile consistent with ALECT-2 type Amyloid deposition.

Discussion: Ever since the first case of ALECT2 was discovered in 2008, several cases have been reported. ALECT2 affects patients mainly of Hispanic origin, especially Mexican Americans. It is less common in African Americans and Caucasians. The pathogenesis of this disease is related to accumulation of a protein called LECT2 which was first isolated in 1998. LECT2 protein is a multifunctional factor involved in chemotaxis, inflammation, immunomodulation, and the damage/repair proces. Most patients with ALECT2 present with minimal proteinuria, bland urine sediment and impaired renal function, and the diagnosis of ALECT2 is usually incidental following biopsies for unrelated conditions or uncertain diagnoses. ALECT2 is a slowly progressive disease likely due to the selective involvement of the interstitium. A full nephrotic syndrome is uncommon in renal ALECT2. Neither the renal function nor the proteinuria correlates with the amyloid load in the renal biopsy. There is no specific therapy for ALECT2. Transplantation remains the only effective treatment. But there is a high risk of recurrence in view of ongoing synthesis of the abnormal protein by the liver. In addition to the renal biopsy findings, confirmation of ALECT2 diagnosis requires immunohistochemistry or chemical analysis by tandem mass spectrometry.

PO1716

Idiopathic Fibrillary Glomerulonephritis: A Report of Two Cases

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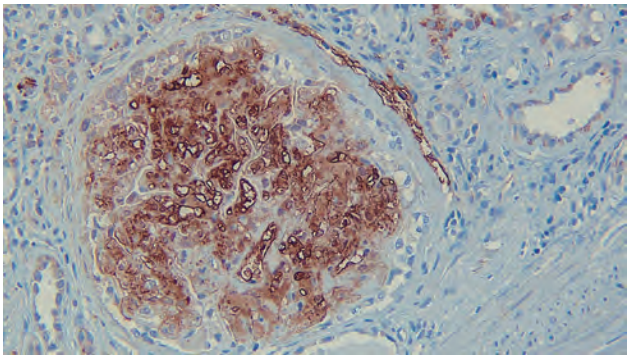
Introduction: Fibrillary glomerulonephritis(FGN) is a rare glomerular disease characterized by the presence of fibrillar deposits in glomeruli and is associated with poor prognosis, often leading to end stage renal disease(ESRD). Previously considered to be idiopathic, new data suggests there is a secondary association in 30-50% of cases with underlying hepatitis C infection, malignancy, dysproteinemia and autoimmune disease. Immunohistochemical staining for DNA-J heat shock protein B9(DNAJB9) is emerging as a marker for rapid diagnosis of FGN.

Case Description: We report two patients with FGN who initially presented with monoclonal gammopathy(MG), but varied clinical courses. First patient, 60 year-old female presented with MG(IgG4 subclass), acanthocyturia and nephrotic syndrome. Renal biopsy showed PAS positive deposits in capillary loops and mesangium; Immunofluorescence microscopy showed IgG, C3, κ and λ light chains. Electron microscopy showed 20nm non-branching randomly arranged fibrils. Five years later, she is still in remission after treatment with bortezomib, cyclophosphamide and dexamethasone. Another 63 years old female presented with renal failure, positive pANCA and MG. Biopsy showed DNAJB9-positive sclerosing and proliferative FGN with 10% cellular crescents and severe interstitial fibrosis and tubular atrophy. She was treated with corticosteroids and rituximab for idiopathic FGN mimicking type III RPGN. However, she became dialysis dependent.

Discussion: FGN has broad presentation and course despite aggressive therapy. A study determined the strongest predictor of outcome to be initial serum creatinine. Other predictors were age, degree of glomerulosclerosis and proteinuria. Knowledge of pathogenesis along with renal pathology can help differentiate this from other fibril deposition diseases like amyloidosis and immunotactoid glomerulopathy. It is imperative to promptly identify FGN as it often progresses to ESRD and has limited data on optimal therapy.



Immunohistochemistry stain for DNAJB9. Glomerulus show diffuse extracellular smudgy staining. mag x200.

PO1717

A Case of Secondary Focal Segmental Glomerulosclerosis and Thrombotic Microangiopathy in a Heart Transplant Patient

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Introduction: A few case reports have shown that focal segmental glomerulosclerosis (FSGS) can lead to thrombotic microangiopathy (TMA) in chronic kidney disease patients with severe hypertension. One case report presented the development of FSGS and TMA in liver transplant patient on Tyrosine kinase inhibitor. We present a case of FSGS without vascular injury despite clinically diagnosed TMA in heart transplant patient.

Case Description: A 42-year old female with history of postpartum cardiomyopathy with implantable cardioverter defibrillator since 2005 was admitted for heart transplant evaluation. Patient developed rapid progressive worsening of renal failure requiring hemodialysis after the heart transplant. Urinalysis showed proteinuria, hematuria; blood work showed hemolytic anemia, thrombocytopenia and schistocytes. TMA was diagnosed and eculizumab was started while continuing with hemodialysis. Heart biopsy showed no rejection, but kidney biopsy revealed the pathological diagnosis of secondary FSGS of not otherwise specified type without vasculitis under both light and electron microscopy. No significant glomerular staining seen on immunofluorescence microscopy as well. Patient was maintained on immunosuppressive regime with mycophenolate, tacrolimus and prednisone, receiving eculizumab weekly for 3 months, and subsequently recovered from hemodialysis.

Discussion: It is very rare to have FSGS without microangiopathy in hematologically confirmed TMA. Calcineurin induced inhibitors (CIN) are known to cause various forms of acute kidney injury including FSGS. In our case, presumed calcinuerin induced nephrotoxicity presented as secondary FSGS without angiopathy. This case reflects the unpredictability of the etiology of kidney disease based solely on clinical features and blood tests. No improvement in kidney function necessitated the renal biopsy. It also raises the challenging points in treatment regime in transplant patient populations.

PO1718

D-Penicillamine-Induced ANA(+)ANCA(+) Crescentic Glomerulonephritis in Wilson Disease

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Introduction: Wilson's disease is an inherited autosomal recessive disorder caused by loss of function of a copper exchanger adenosinetriposphate encoded by ATP7B, which results in impaired biliary copper excretion and accumulation of copper in plasma and tissues. In the kidney, copper accumulation may affect tubular cells, but was never associated with glomelular lesions. Some patients have been reported as crescentic glomerulonephritis with Wilson's disease treated with D-penicillamine[1)2)].

Case Description: A 45 years old female was consulted to adult nephrology clinic on worsening chronic kidney disease. She had prescribed 800mg metalcaptase for 3

years on compound heterogenous Wilson's disease diagnosed by liver biopsy, Western blotting and gene sequence on ATP7B[3]. Serum creatinine(Cr) was around 4.5 mg/dl, antimyeloperoxidase(MPO)-ANCA 350 U/ml, antinuclear factors titer 1/640. Both anti-proteinase(PR3) antibody and anti-glomelular basement membrane(GBM) antibody were negative. Renal biopsy specimen show pauci-immune crescentic glomerulonephritis with 7/9 fibrous or fibrocellular crescents, and 2/9 global collaptic sclerosis. Also, mild diffuse interstitial fibrosis was found with lymphoid and other chronic inflammatory cells. No pathological finding was detected on vasculitis. Diagnosed as ANCA-associated glomerulonephritis, methyl-prednisolone(PSL) pulse therapy was given and preceded to oral PSL[4]. PSL was gradually reduced and terminated after seven years, along with getting MPO-ANCA<3.5 U/ml.Cr was improved to 1.5mg/dl in spite of presence of mild diffuse interstitial fibrosis. Hereafter 15 years, no medication except metalcaptase was given, but regretfully Cr has been deteriorated to 4.5mg/dl,MPO-ANCA~15-25 U/ml. Other paraproteinemia or malignant diseases including multiple myeloma was excluded. Taken together for these 25 years, D-penicillamine-associated interstitial nephritis[1)2)] has suspected. Oral zinc acetate was once truncated due to gastroenterological side effect, then planned to change to trientene.

Discussion: The pathogenesis of drug-induced ANCA-associated vasculitis has not been proven. There is a hypothesis that MPO binds to drug metabolites and alters the MPO antigenic property[2]. Treatment of AAV is usually with mPSL pulse, cyclophosphamide, and/or rituximab. **References**:1)Am J Kidney Dis 2007;**50**:821.2) Clin Nephrol 2016;**85**:296.3)Kanzo-Hepatology(Tokyo)1996;**37Suppl2**:116.4)Japan J Nephrol 1998;**40**:518.

PO1719

In Silico Prediction of Potential New Biomarkers of IgA Nephropathy Interstitial Lesion

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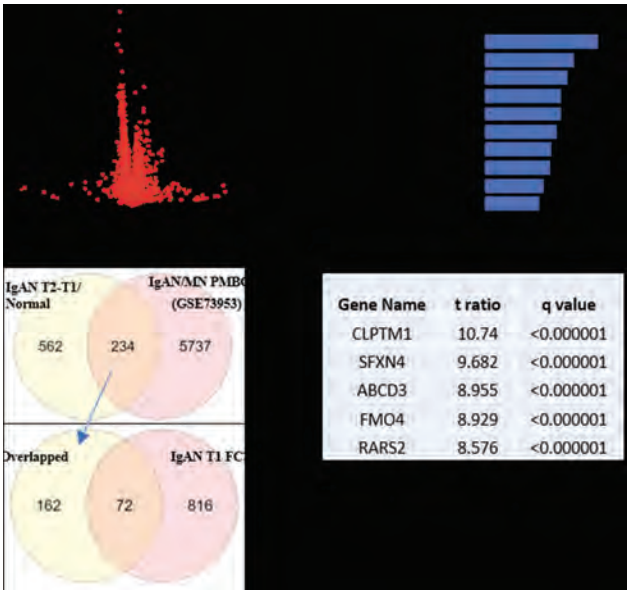
Background: IgA nephropathy remains one of the major causes of end stage renal diseases globally. Interstitial lesion in IgA nephropathy is correlated with unfavorable prognosis. This study aims to find new potential biomarkers in IgA nephropathy patients with interstitial lesion based on an *in silico* method.

Methods: Proteomics matrix data from IgA nephropathy patients are obtained from a local renal biopsy patient cohort. Discovery is determined using the Two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli, with Q = 1%. Transcriptomic data from peripheral mononuclear blood cell of IgA nephropathy patients are obtained from GEO (GSE73953). Detection of transcriptomic difference genes are made with limma method in GEO2R.

Results: Multiple t test indicates 887 differentially expressed genes between IgA nephropathy interstitial lesion (T1 or T2) and control renal tissues. KEGG pathway annotation reveals that cytochrome p450 related drug metabolism pathway and oxidative phosphorylation pathway are significantly clustered in IgA nephropathy patients with interstitial lesion. No herbal medicine or drug use (apart from ACEI or ARB) were recorded. Differential gene analysis reveals a total of 250 genes with positive discoveries in peripheral mononuclear blood cells of IgA nephropathy compared with membranous nephropathy (GSE73953). Further screening of overlapping genes demonstrates that ABCD3, CLPTM1, FMO4, RARS2, SFXN2 are the most significantly enriched proteins in IgA patients with interstitial lesion.

Conclusions: Preliminary results from this *in silico* study of proteomics and transcriptomics data in IgA nephropathy patients using a T score specific and overlapping screening approach provide a new possibility of noninvasive detection of interstitial lesion in IgA nephropathy patients.



PO1720

Pacemaker Macula Densa Cells Form a Nephron-Level Autonomous Somatosensory Neuronal Network

Georgina Gyarmati, Anne Riquier-brison, Urvi Nikhil Shroff, Janos Peti-Peterdi. *University of Southern California, Los Angeles, CA.*

Background: The autonomous nervous system in several organs performs local control of organ functions. Macula densa (MD) cells that are specialized renal epithelial cells capable of sensing the local tissue environment and releasing various chemical messengers to control nearby cells have well-known neuronal features. This study addressed the hypothesis that MD cells perform neuron-like functions that play important roles in maintaining key organ functions.

Methods: MD-GT mice with MD-specific inducible expression of the Ca^{2+} sensitive fluorescence reporter GCaMP5 and the calcium insensitive tdTomato were developed to visualize the Ca^{2+} homeostasis of MD cells with multiphoton microscopy (MPM). Whole transcriptome RNA seq was performed to establish the gene profile of MD cells providing molecular detail of their function.

Results: MD cell imaging in vivo revealed regularly oscillating, propagating Ca^{2+}-firing pacemaker activity with peaks showing ~4-fold elevations and average frequency of 0.03/s. This phenomenon was preserved in freshly isolated MD-GT cells in vitro indicating autonomous pacemaker function. Several divergent stimuli altered steady-state Ca^{2+} and/or firing frequency, including mechanical (tubule flow), altered tubular fluid composition (low salt diet), local autacoids (angiotensin II), systemic hormones (AVP, CaSR mimetic), and metabolic states (diabetic hyperglycemia). Bolus injection of the β-agonist Isoproterenol caused the most robust changes in firing frequency as compared to control (frequency fold change 3.4±0.6 and 0.9±0.1, respectively). Diabetic hyperglycemia was associated with the greatest increase in steady-state MD cell Ca^{2+} level compared to control (2.4±0.2 and 1.1±0.1, respectively). RNA seq analysis revealed enrichment of numerous genes involved in membrane depolarization and pacemaker activity, such as voltage-dependent sodium, potassium, and calcium channels (Scn4b, Scn2b, Kcnd3, Kcnc2, Cacna1d), in afterhyperpolarization (Kcnn2), in the initiation of pacemaker activity (Itpr1), and in synapse formation and transmission (Nsg2, Tmem158, Syt5-13, Sv2a).

Conclusions: This study uncovered new neuron-like functional and molecular features of MD cells and established them as chief sensory neuroepithelial cells that form a nephron-level autonomous neuronal network to control key organ and somatosensory functions.

Funding: NIDDK Support

PO1721

A New View of Macula Densa Cell Protein Synthesis

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Background: Macula densa (MD) cells, a chief regulatory cell type in the kidney, have prominent protein synthetic organelles. mRNA translation and protein synthesis are tightly regulated processes and the mTOR and Wnt signaling pathways play a central role in regulating this activity. The present study aimed to examine the role of Wnt/mTOR in regulating MD protein synthesis.

Methods: Changes in bulk protein synthesis activity were quantitatively visualized using an OPP-incorporation based fluorescence assay in a new mouse MD cell line (mMD^{Geo}) treated with low salt medium or the GSK3b inhibitor lithium to activate MD cells. For studies *in vivo*, MD-Wnt^{gof} and MD-$mTOR^{gof}$ mice were developed using a nNOS-Cre inducible system with Wnt and mTOR gain-of-function, respectively, to

upregulate signaling specifically in MD cells. MD gene profiling validated by data from Human Protein Atlas (HPA) was used to confirm the expression of various pathways and regulators of protein synthesis and vesicular exocytosis.

Results: OPP experiments in mMD^{Geo} cells *in vitro* showed that low salt (5.98 ± 1.15) and lithium (5.67 ± 0.24) treated cells had significantly higher protein synthetic activity as compared to control (3.13 ± 0.15). Similarly, MD cells *in vivo* in wildtype mice on a low salt (2.59 ± 0.26) or lithium diet (2.00 ± 0.26) had significantly higher OPP fluorescence as compared to control diet (1.16 ± 0.18). Upregulation of MD-Wnt signaling in MD-Wnt^{gof} mice (1.36 ± 0.04) also resulted in a significant increase in MD protein synthesis as compared to control (1.16 ± 0.06). The expression of MD-enriched secreted proteins (Ccn1, Pappa2, Nov, Cxcl14) was enhanced in activated MD cells. Finally, results from MD gene profile analysis with HPA validation showed high and MD-specific expression of several pathways involved in mRNA translation (p70S6K, eIF3C, eEF2), chaperones (HSP90AB1) along with certain elements of regulated vesicular exocytosis.

Conclusions: In summary, the unique MD microanatomy and cell-specific protein synthetic machinery support the robust synthesis and secretion of a diverse array of tissue remodeling and angiogenic proteins which are regulated by mTOR and Wnt signaling in these cells. The regulatory pathways MD protein synthesis and secretome may be targeted to enhance endogenous glomerular and vascular tissue remodeling and repair.

Funding: NIDDK Support, Private Foundation Support

PO1722

Kidney Transcriptome-Wide Association Study Analysis Identifies Dach1 as a Kidney Disease Risk Gene

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Background: Genome-wide association studies (GWAS) has identified more than 300 loci where genetic variants are associated with kidney function, however, the causal variants, genes, cell types and the disease mechanism remain mostly unknown. Transcriptome-wide association studies (TWAS) is a method to prioritize GWAS-identified variants by linking gene expression data to phenotypic and genetic variation.

Methods: We obtained genotype and gene expression data for 121 microdissected human kidney tubule and glomerular samples. We applied a variety of TWAS models, such as Mendelian Randomization, TWAS Fusion, Metaxcan. Bulk kidney epigenome maps and single cell ATAC-Seq data were used for fine-mapping. We generated tubule specific Dach1 knock-out (KspCre/Dach1flox/flox) and transgenic (Pax8-TREDach1) mice to define the functional role of Dach1 in kidney disease development. Murine cultured tubule cells and single cell RNA sequencing were used for functional studies.

Results: Integration of the 3 TWAS methods with CKD GWAS datasets highlighted only 5 genes those levels were consistently influenced by the GWAS variants. Expression of DACH1; a transcription factor, was lower in tubules of patients with CKD risk variant. Immunofluorescence analysis indicated that DACH1 was mainly expressed in podocytes and in distal convoluted tubule (DCT) in the kidney. Bulk and single cell ATAC denoted that disease risk variants localized to a regulatory region in the DCT. Mice with tubule specific Dach1 deletion developed more severe renal fibrosis when challenged with folic acid (FA) compared to controls. Mice with tubule specific Dach1 overexpression were protected from FAN-induced kidney fibrosis. Single cell RNA sequencing and cultured primary renal tubule cells indicated that Dach1 plays role in controlling cell proliferation and inflammatory gene expression contributing to fibrosis development.

Conclusions: Integration of GWAS, TWAS, single cell expression, epigenome analysis, mouse models and cultured cell systems identified Dach1 as a causal gene for CKD.

Funding: NIDDK Support

PO1723

Role of Plin5 Deficiency in Podocyte Lipotoxicity and the Progression of Alport Syndrome

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Background: Alport Syndrome (AS) is a hereditary disease caused by mutations in collagen type IV. We and others have demonstrated pathogenic renal lipid accumulation in experimental AS (Col4a3KO mice). Excess lipids stored in lipid droplets (LD) as cholesterol ester and triglyceride (TG) are known to cause lipotoxicity. Excessive FFA catabolism resulting from excessive lipolysis of TG is a major contributor to cell lipotoxicity in obesity and diabetes. Perilipin 5 (PLIN5) is a LD-related protein that plays a critical role in the regulation of triglyceride lipase activity and in the interactions between LD and mitochondria, where it protects mitochondria from excessive exposure to FFA. Here we test the hypothesis that PLIN5 is express in podocytes and that excessive TG breakdown occur in AS podocytes as a consequence of PLIN5 deficiency.

Methods: Immortalized AS podocytes (AS podocyte) and WT podocytes were established and characterized in our laboratory by breeding the Col4a3KO mice (Jackson Laboratory) to Immorto mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in podocytes from Col4a3KO mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. Mitochondrial function was determined by utilizing Seahorse XF cell mito stress kit. To determine ATP linked respiration and proton leak, 1.5uM Oligomycin was injected to cells and analyzed by Seahorse XF96 Analyzer (Agilent).

Results: We demonstrate that PLIN5 is expressed in podocytes and the expression of PLIN5 is significantly decreased in AS podocytes when compared to WT podocytes ($p<0.01$). AS podocytes also showed significantly increased rates of TG lipolysis ($p<0.05$), intracellular free fatty acids ($p<0.05$) and apoptosis ($p<0.01$) when compared to WT podocytes. AS podocytes had increased proton leak, implying that the FFA may uncouple the mitochondria, leading to mitochondrial dysfunction and apoptosis. Moreover, ezetimibe, which *in vivo* improved kidney function, was found to *in vitro* restorePLIN5 expression in a dose-dependent manner.

Conclusions: Our study suggests that podocyte PLIN5 deficiency may cause podocyte injury in AS through excessive TG lipolysis and mitochondrial dysfunction.

PO1724

The Mesenchymal Stem Cell Marker Meflin Defines a Novel Subset of Renal Fibroblasts and Counteracts the Action of TGF-β

Shun Minatoguchi, Shoji Saito, Shoichi Maruyama. *Nagoya university graduate school of Medicine, Department of Nepgrology, Nagoya, Japan.*

Background: Fibroblasts proliferation is the hallmark of renal fibrosis and is important for the progression of CKD. Recently developed single-cell sequencing technology has revealed the substantial heterogeneity of cells that constitute the kidney in health and disease. The heterogeneity of renal fibroblasts, however, has not been completely understood. We recently reported that a fibroblast subset marked by Meflin, a marker of undifferentiated mesenchymal stem cells, has a role to suppress fibrosis in cardiac disease conditions and pancreatic cancer. In the present study, we examined the role of Meflin and the distribution of Meflin-positive fibroblasts in kidney by using cultured fibroblasts and mouse models.

Methods: We evaluated the expression of Meflin in normal and fibrotic kidney by in situ hybridization(ISH). To assess the expression of Meflin at a cellular level, we used the rat renal fibroblast cell line NRK49f.

Results: ISH revealed that Meflin was expressed by some rare stromal cells found in the interstitial and peri-glomerular areas in the normal kidney. Meflin-positive cells were also detected in the wall of middle-sized vessels in the medulla of the kidney. Induction of renal fibrosis by obstructive nephropathy(UUO model) led to a significant proliferation of Meflin-positive cells, which seemed to be distinct from αSMA positive myofibroblasts. Consistent with this, the analysis of single-cell transcriptomic databases showed Meflin and αSMA are expressed in distinct subsets of fibroblasts in the kidney. The expression pattern of Meflin was also confirmed by lineage tracing assay. In the UUO model, some of Meflin-lineage cells were positive for αSMA, suggesting that they give rise to myofibroblasts in the progression of fibrosis. Finally, we assessed the function of Meflin using NRK49f. Meflin expression was significantly downregulated by TGFβ stimulation, and exogenous Meflin overexpression led to the suppression of TGFβ induced αSMA and vimentin expression.

Conclusions: Our present study identified a new subset of renal fibroblasts, which is positive for Meflin but negative or weakly positive for α-SMA. Consistent with our previous studies, Meflin has a role to counteract the action of TGF-β, implying that Meflin-positive fibroblasts have a role to suppress or alleviate renal fibrosis.

Funding: Private Foundation Support

PO1725

CD14 Contributes to Increased Inflammation and Fibrogenesis in Lupus Nephritis

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Background: CD14 is a GPI-anchored membrane protein that serves as a pattern recognition receptor in the clinical setting of sepsis. CD14 transfers lipopolysaccharide (LPS) from the acute phase protein LPS-binding protein (LBP) to TLR-4/MD-2 complex, to initiate signal transduction and cytokines release. Serum CD14 level is increased in SLE patients, but little is known about its clinical significance or pathogenic role in lupus nephritis (LN).

Methods: Serum LPS and CD14 levels were determined in LN patients and healthy subjects using commercially available assays. CD14 expression in LN kidney biopsies was examined with cytochemical staining. CD14-overexpressing HK-2 cells were generated and the role of CD14 in inflammatory and fibrotic processes investigated.

Results: Serum LPS and CD14 levels were significantly higher in LN patients compared to healthy subjects ($P<0.05$, for both). Kidney biopsies from active LN patients showed increased CD14 expression, predominantly in proximal tubular epithelial cells, compared with normal kidney tissue. CD14 overexpression did not affect cell proliferation in HK-2 cells, but was associated with increased IL-6 secretion and fibronectin expression, by 26.73±4.63 fold and 3.19±2.28 fold respectively. Upon stimulation with either LPS or endotoxin-free TGF-β1, CD14-overexpressing HK-2 cells showed further augmentation of IL-6 secretion and fibronectin expression ($P<0.05$, for all). In contrast, HK-2 cells deficient in CD14 showed attenuated fibronectin expression upon LPS or TGF-β1 stimulation.

Conclusions: Our data show that active LN is accompanied by increased serum and renal tubular epithelial CD14 expression, and CD14 may contribute to LPS- or cytokine-dependent inflammatory and fibrotic processes in the setting of LN.

Funding: Government Support - Non-U.S.

PO1726

CircZNF609 Participates in the Pathogenesis of Focal Segmental Glomerulosclerosis by Sponging miR-615-5p

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common cause of adult nephrotic syndrome, but its mechanism remains unclear. We recently identified and validated that circZNF609 increased in renal biopsies of lupus nephritis patients. We aim to verify whether circZNF609 participates in the pathogenesis of FSGS and the underlying mechanisms.

Methods: FSGS was induced by adramycin (ADR) injection to mice. Proteinuria and serum albumin were examined six weeks after ADR administration. Glomerulosclerosis and tubulointerstitial fibrosis were verified on PAS and Masson staining. Podocyte injury indicated with Wilms tumor 1(WT1) and Podocin, pro-fibrotic proteins including collagen 1 (COL1) and transforming growth factor-beta1 (TGF-β1) were analized by western blotting. Further, renal circZNF609 and miR-615 were measured by qPCR and fluorescence in situ hybridization (FISH). The correlation between renal circZNF609 and above indices were analyzed. In vitro study, circZNF609 in bovine serum albumin (BSA) stimulated HK2 cells for 24 h, which mimic the toxicity of proteinuria from FSGS to tubules. CircZNF609, miR-615, COL1 and TGF-β1 were analyzed by qPCR. Lastly, The renal localization of circZNF609 in FSGS patients was stained by FISH.

Results: In vivo study, proteinuria and hypoalbuminemia were found six weeks after FSGS onset by ADR injection. Glomerulosclerosis and tubulointerstitial fibrosis showed on PAS and Masson staining. CircZNF609 was upregulated while miR-615-5p was downregulated in FSGS mice analyzed by qPCR and FISH. Podocyte proteins WT1 and Podocin were decreased; pro-fibrotic proteins COL-1 and TGF-β1 were increased on western blotting. Renal circZNF609 positively correlated and miR-615-5p negatively correlated with podocyte injury and renal fibrosis. Importantly, circZNF609 and miR-615-5p co-localized on glomeruli and tubules on FISH. Perfect match seeds were found between circZNF609 and miR-615-5p and COL-1. In vitro study, circZNF609 increased and miR-615-5p decreased after BSA stimulation and negatively correlated between each other. COL-1 and TGF-β1 were upregulated and negatively correlated with miR-615-5p. Lastly, circZNF609 was confirmed to increase in glomeruli and tubules in renal biopsies from FSGS patients.

Conclusions: We conclude that circZNF609 may play an important role in FSGS by sponging miR-615-5p and may be a novel therapeutic target.

Funding: Government Support - Non-U.S.

PO1727

The Role of Proteoglycans in Glomerular Physiology and Pathophysiology

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Background: Diabetic kidney disease (DKD) is the leading cause of renal failure in the world. Diabetes is associated with damage to the endothelial glycocalyx (eGCX), the layer of negatively charge molecules, such as proteoglycans (PGs) that cover the cells. The negatively charge restrain the flow of charged molecules, as albumin, over the filtration barrier. Loss of the glomerular eGCX leads to proteinuria without other visible damage to the barrier, but the composition of this structure is still largely unknown. The aim of this study was to gain new knowledge about the composition and role of the eGCX in health and DKD.

Methods: The negatively charged PGs in the eGCX was eluted from rats using 1 M NaCl solution (high salt, HS). 1 M mannitol was used as osmotic control (HO) and 0.15 M NaCl as physiological salt (NS). Solutions were introduced intra-arterially to rat kidneys under anesthesia *in vivo*. Venous effluent was analyzed using mass spectrometry. Fractional clearance of albumin and GFR was measured. Electron microscopy (EM) was used to investigate morphology. Expression of PGs and PG related genes in glomeruli from patients with DKD was investigated using deep sequencing data from the Swedish DKD cohort (DKD n=19, controls n=20).

Results: We identified 17 PGs in the eluates from rats. PGs were found in in the highest yields in the HS samples. EM demonstrated that the eGCX thickness was significantly reduced in the HS rats compared to NS. Rats perfused with HS had significantly increased fractional clearance of albumin and reduced GFR, compared to NS and HO, 10 minutes after perfusion. In glomeruli from patients with DKD 12 PGs were found to be significantly regulated, and 4 of these PGs were also identified in the eGCX eluates from rats. There was an overall decrease in expression of enzymes responsible for PG side chain synthesis and an increase in proteins involved in PG degradation.

Conclusions: In our study, we identified several PGs novel to the glomerular eGCX. We show that loss of eGCX leads to proteinuria and reduced GFR, strongly suggesting that the eGCX is important for preventing proteinuria. In glomeruli from patients with DKD we found significant changes in the gene expression of PGs, indicating a changed composition of the matrixes in the glomeruli. Further investigation is needed to clarify how these changes are involved in development of DKD, and especially the eGCX.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1728

Low- vs. Standard-Dose Rituximab for Induction and Maintenance Treatment of ANCA-Associated Vasculitis in Elderly Patients: A Single-Centre Observational Study

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Background: ANCA associated vasculitis (AAV) affects more than 20 per million population per year, with a peak age of 65-74 years. Elderly patients (Age > 65 years) with AAV tend to have higher rates of mortality and treatment-related adverse events. However, outcomes are better for those treated with immunosuppressive regimens. Rituximab is now widely used in the treatment of AAV based on the results of randomized controlled trials. Elderly patients were relatively under-represented in these trials. We aimed to examine the outcome of elderly patients who received either low dose Rituximab (LDR) or standard-dose (SDR) for remission induction and maintenance.

Methods: We investigated the outcome of three treatment strategies in the elderly patients who presented with AAV to our Vasculitis clinic from July 1, 2007 to July 9, 2017. These strategies included: LDR (17 patients), SDR (14 patients) and Cyclophosphamide/ Azathioprine (Cyc/A) 26 patients. LDR patients received two doses of 500mg Rituximab fortnightly followed by six monthly 500mg doses for 2 years. SDR patients received 1g Rituximab fortnightly followed by six monthly 1g doses for 2 years. Cyc/A patients received 1.5mg/kg oral Cyclophosphamide for 3 months followed by 18 months of Azathioprine.

Results: Among 57 AAV patients, 17 received LDR, 14 received SDR and 26 were treated with Cyc/A. 56% were females, mean age of 79.6 +/- 4 (LDR), 72.4 +/- 7.2 (SDR), and 71.1 +/- 5 (Cyc/A) (p=0.001). The distribution of MPA and GPA was 11:6 in LDR, 7:7 in SDR and 18:8 in Cyc/A, respectively. Relapsing AAV was significantly higher in SDR 12 of 14 compared to LDR 3 of 17, and Cyc/A none (p=0.0001). There were no significant differences in serum creatinine, BVAS scores or CRP between groups. Patients survival at 24 months was 88% (LDR), 92% (SDR), and 77% (Cyc), p=0.3. The mean corticosteroids dose at 3 months from onset of treatment was significantly lower in the LDR (7.6 +/- 1.7) and SDR (8.6 +/- 3.1) compared with Cyc/A (12.5 +/- 3.6), p=0.001. One patient relapsed in the SDR group and 4 in the Cyc/A group. Hospitalization for infections were significantly lower in the LDR (3 episodes) compared to Cyc/A (17 episodes), p=0.004.

Conclusions: Low dose Rituximab for remission induction and maintenance was associated with similar patient outcome compared to SDR.

PO1729

Efficacy of Rituximab and Plasma Exchange in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Severe Renal Disease

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Background: Treatment of patients with ANCA-associated vasculitis (AAV) and severe renal involvement is not established. We describe outcomes in response to rituximab (RTX) versus cyclophosphamide (CYC) and plasma exchange (PLEX).

Methods: A retrospective cohort study on MPO- or PR3-ANCA positive patients with AAV (MPA and GPA) and severe renal disease (eGFR<30mL/min/1.73m^2). Remission, relapse, end-stage renal disease (ESRD) and death after remission-induction with CYC or RTX, with or without the use of PLEX were compared.

Results: Of 467 patients with active renal involvement, 251 had severe renal disease. Patients received CYC (n=161) or RTX (n=64) for remission-induction, and 51 were also treated with PLEX. Predictors for ESRD and/or death at 18 months were eGFR<15mL/min/1.73m^2 at diagnosis (HR 3.092, [95%CI 1.493-6.401], p=0.002), renal recovery (HR 0.274, [95%CI 0.118-0.637],p=0.003) and renal remission at 6 months (HR 0.402, [95%CI 0.179-0.902],p=0.027). RTX was comparable to CYC in remission-induction (BVAS/WG=0) at 6 months (HR 1.374, [95%CI 0.909-2.076];p=0.132). Addition of PLEX showed no benefit on remission-induction at 6 months (HR 0.732, [95%CI 0.440-1.219],p=0.230), in the rate of ESRD and/or death at 18 months (HR 1.052,[95%CI 0.508-2.180], p=0.891), in progression to ESRD (HR 1.056, [95%CI 0.496–2.247], p=0.887), or survival at 24 months (HR 0.542, [95%CI 0.159–1.853], p=0.330).

Conclusions: The apparent benefits and risks of using CYC or RTX for the treatment of patients with AAV and severe renal disease are balanced. The addition of PLEX to standard remission-induction therapy showed no benefit in our cohort.

PO1730

Time to CD20 B-Cell Return After Rituximab in Patients with Antineutrophil Cytoplasmic Antibody Vasculitis

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Background: Rituximab (RTX) has been shown to be an effective maintenance treatment for ANCA vasculitis. However, the optimal dosing regimen is not well-defined. We analyzed data from the MAINTANCAVAS trial (NCT02749292) to determine time to CD20 B cell return in patients who were treated with ≥ 2 years of continuous B cell depletion and subsequently randomized into the trial and dosed for B cell return or a rising ANCA titer.

Methods: All patients in the MAINTANCAVAS trial were included. Patients were enrolled after ≥ 2 years of continuous B cell depletion. B cells were measured at 3-month intervals with a ± 2 week window. Days to B cell return were calculated as the time from the last rituximab dose (1000 mg) to date of first detectable CD20 B cells by flow cytometry. Kaplan Meier curves were produced for each round of B cell depletion.

Results: We analyzed data from 109 patients. Median (IQR) duration of B cell depletion was 280.0 (272.0 – 363.0) days until first episode of recovery (Table 1). >80% of subjects had B cell return by 1 year and <10% had B cell return prior to 6 months (Figure 1). Median (IQR) duration of B cell depletion was 265.0 (247.0 – 354.5) days for patients who received a second round of rituximab (Table 1).

Conclusions: This data suggests that after 2 years, maintenance RTX dosing can be extended beyond 6 months for many patients. Further analysis is needed to determine optimal dosing based on B cell return vs ANCA titer and the associated adverse event profiles and RTX utilization.

Table 1. Demographics and B cell depletion duration (median (IQR)).

# of subjects	109
Male Female	57 52
Hispanic or Latino Not Hispanic or Latino Black or African American Asian	1 103 2 3
MPO PR3	59 50
<3 years on Rituxan >3 years on Rituxan	52 57
Initial B cell depletion duration Second episode duration	280.0 (272.0 - 363.0) 265.0 (247.0 - 354.5)

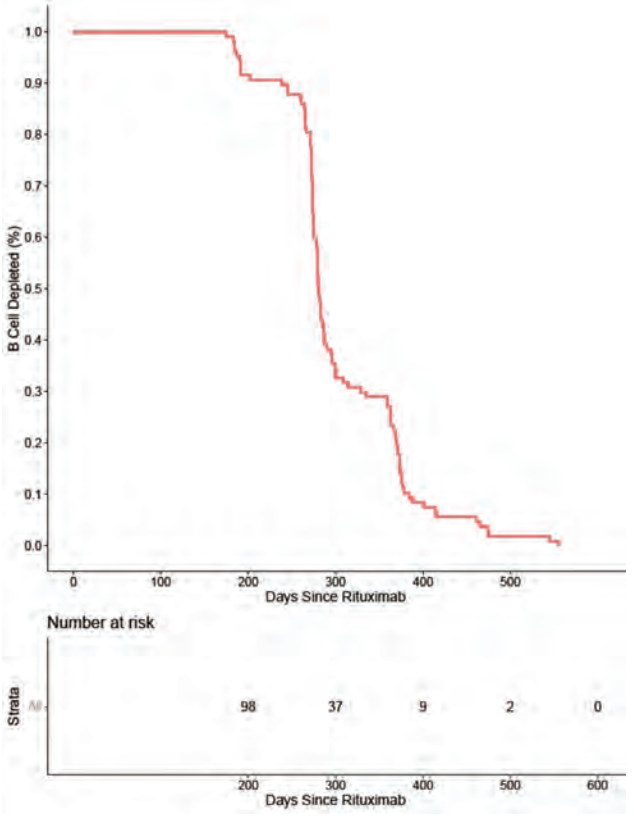

Figure 1. Kaplan-Meier for B cell depletion.

PO1731

Predictive Significance of Urinary CD11b and CD163 for the Renal Outcomes in ANCA-Associated Glomerulonephritis

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Background: We hypothesized that the detection of leukocyte-derived CD11b (α subunit of integrin Mac-1) and CD163 (scavenger receptor) in urine may reflect renal inflammation and predict the renal outcomes in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-GN). The aim of this study was to evaluate the clinical significance of urinary CD11b (U-CD11b) and CD163 (U-CD163) as alternative noninvasive tests for ANCA-GN.

Methods: U-CD11b and U-CD163 levels were examined using ELISA in ANCA-GN urine samples from institutional cohort (n = 88) and a nationwide cohort (n = 138), and their association with renal histology were analyzed. Logistic regression analyses were performed on a nationwide ANCA cohort to determine the associations of the two urinary molecules with renal remission failure at 6 months or with yearly eGFR slope over a 24-month observation period.

Results: The significant elevations of U-CD11b and U-CD163 were observed in ANCA-GN patients histologically classified to the crescentic category. Histological analyses focusing on the distributions of $CD11b^+$ or $CD163^+$ leukocyte subsets in diseased glomeruli demonstrated dominant distribution of $CD11b^+$ cells in undisrupted area than in glomerular crescent as contrasted with global distribution of $CD163^+$ cells in diseased glomerulus. In addition, levels of U-CD11b and U-CD163 significantly correlated with crescent formation rate, respectively with $CD11b^+$ cell and $CD163^+$ cell number in glomerular crescents. Association analyses of both urinary molecules with post-treatment renal outcomes at 6 months after the treatment demonstrated that U-CD163 levels were significantly reduced and those at the time of diagnosis were already increased in patients who failed to remission or progressed renal insuficiency. Although these associations were not found in U-CD11b, analyses to determine the associations of the two urinary molecules and other clinical parameters with yearly impairment of renal function over a 24-month observation period demonstrated U-CD11b, but not U-CD163, at diagnosis as an independent factor predicting renal recovery.

Conclusions: Although both U-CD11b and U-CD163 reflect renal leukocyte accumulation, U-CD11b at diagnosis predicts the recovery rate after the treatment of ANCA-GN.

Funding: Government Support - Non-U.S.

PO1732

Urinary Biomarkers as a Tool for Monitoring Remissions and Predicting Relapses in Autoimmune Glomerulonephritis

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Background: Complement-mediated injury, inflammation and fibrosis play central roles in the pathogenesis of autoimmune glomerulonephritis. The use of urinary biomarkers as a surrogate of these pathways of injury could assist clinicians during the clinical follow-up. We investigated the value of urinary biomarkers of complement activation, inflammation and fibrosis during periods of sustained remission among patients with autoimmune glomerulonephritis.

Methods: We prospectively examined 100 patients with ANCA-associated vasculitis, focal segmental glomerulosclerosis, IgA nephropathy, lupus nephritis, membranoproliferative glomerulonephritis and membranous nephropathy. Proteinuria, urinary sC5b-9, monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor-β1 (TGF-β1), expressed as creatinine ratios, were measured at presentation and during follow-up visits. We used standard definitions of remission and relapse for each type of glomerulonephritis. Wilcoxon signed-rank test was used to compare changes in urinary biomarkers during remissions and relapses.

Results: We identified 95 periods of active disease and 82 episodes of sustained remission. Inactive periods lasted a median of 22 (11-32) months. Eighty percent (n=66) of these were not followed by a relapse. During these episodes of remission, urinary biomarkers continued to steadily decrease, achieving a reduction of 40% for proteinuria, 40% for urinary sC5b-9, 38% for MCP-1 and 40% for TGF-β1 (all $p < 0.05$). Twenty percent (n=16) of inactive periods reflected remissions with subsequent relapses. Biomarker levels during the inactive period preceding relapses did not significantly change for proteinuria (+8%), urinary sC5b-9 (+15%) and MCP-1 (4%), while they decreased for TGF-β1 (-30%, p=0.02). During relapses, we observed a 3.2-fold (1.9-8.3) increase in proteinuria and a significantly greater 8.5-fold (4.2-56.9) increase in urinary sC5b-9 (p=0.001). By contrast, urinary MCP-1 and TGF-β1 increased significantly less than proteinuria.

Conclusions: Failure to achieve a sustained reduction in urinary biomarkers during remission was associated with a subsequent risk of relapse of autoimmune glomerulonephritis. Urinary sC5b-9 appears to be a more discerning marker of immunological relapse.

Funding: Private Foundation Support

PO1733

Clinical Impact of PRTN3 Polymorphism in Antineutrophil Cytoplasmic Antibody (ANCA) and Similar Vasculitides

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Background: Genetic variants associated with ANCA vasculitis include a single-nucleotide polymorphism (SNP) at the proteinase 3 (*PRTN3*) locus, however the impact of this risk variant on demographics and disease characteristics has not been fully described.

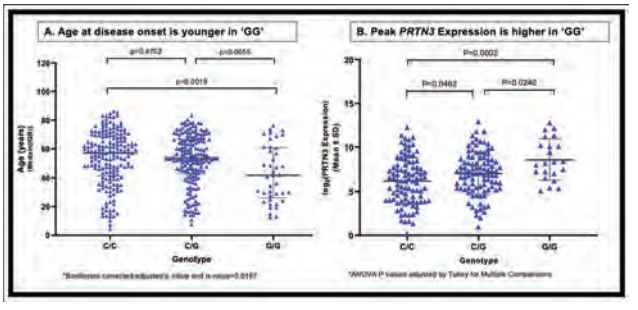
Methods: 401 patients with ANCA and similar vasculitidies from the Glomerular Disease Collaborative Network were genotyped for the *PRTN3* SNP (rs62132293): myeloperoxidase (MPO) (n= 197), proteinase3 (PR3) (n = 170), dual positive (n=9), and seronegative (n=25). SNP homozygous ("GG") were compared to heterozygotes ("CG") and homozygous ("CC"). *PRTN3* expression was measured by quantitative polymerase

chain reaction amplification of cDNA from patient peripheral blood polymorphonuclear leukocytes during active disease. Comparisons were done using Fisher exact and Wilcoxon tests or ANOVA. Bonferroni correction and Tukey test used for multiple comparisons Cox regression was used for multivariable time to relapse and end stage kidney disease (ESKD), with hazards ratios (HR), 95% confidence intervals (CI) reported.

Results: 179 CC, 181 CG and 41 GG patients with median follow-up of 4.8 years were studied. GG patients were significantly younger at disease-onset than others (FIGURE, A). There were no statistical differences in race/sex categories, ANCA seropositivity, organ involvement, or estimated glomerular filtration rate between groups. In a subset of the cohort (n=298) GG had significantly higher peak expression of *PRTN3* (FIGURE, B). In the entire group, renal disease was predominant (CC 78%, CG 83%, GG 76%, p = 0.34) and the majority of the treated patients reached remission (91% CC, 88% CG and 90% GG, p=0.79). Upon remission there was no difference in time to first relapse in GG vs. others (HR 1.02, CI 0.62,1.68, p=0.94) and time to ESKD (HR 0.62, CI 0.15, 2.67, p=0.52) adjusted for age and seropositivity.

Conclusions: Disease starts at an earlier age among GG patients, with no clear impact on outcomes. Higher *PRTN3*expression may explain earlier disease onset.

Funding: NIDDK Support



PO1734

The Compositional and Functional Changes of Gut Microbiota in Crescentic Glomerulonephritis

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Background: Crescent glomerulonephritis(CreGN) is the most dangerous glomerulonephritis, but the specific mechanism remains unclear. Recent evidences suggested that gut microbiota was associated with kidney injury. This study aimed to observe the role of gut microbiota in CreGN.

Methods: A comparative analysis of the gut microbiota was performed in 10 CreGN patients and 10 matched healthy controls by 16S rDNA amplicon sequencing, and half of each group were also analyzed by metagenomics for further function analysis.

Results: The mean age of the 10 CreGN patients was 54.8±17.1 years, with 70.0% were female. The median eGFR was 5.4(interquartile range:3.6-9.5)ml/min/1.73m2. Compared to controls, CreGNs showed a significant lower richness(683.2±113.4 vs.800.1±73.5, *P*= 0.015) despite a similar level of Shannon index(diversity)(5.4±0.6 vs.5.6±0.5,*P*=0.579). PCoA showed a different pattern of clustering in CreGN(*P*=0.036, Fig.1a). There were 66 differentially enriched bacteria genera, with a significant($q<0.05$) lower relative abundance of *Agathobacter, Prevotellaceae, Faecalibacterium, Dialister, Megamonas,* and *Alloprevotella* genera, and a higher relative abundance of *Faecalitalea, Anaerostipes, Paraprevotella,* and *Streptococcus* genera(top 10)in CreGN. All the genera above showed significant correlations with renal injury indicators. For example, *Agathobacter* was significantly correlated with creatinine(r =−0.77),24h urine protein(r =−0.86), and eGFR(r=0.73)(Fig.1b). Besides, *Agathobacter, Prevotellaceae, Faecalibacterium,* and *Dialister* were also confirmed as significant biomarkers by LEfSe(Fig.1c). Metagenomics showed 21 significant differentially enriched functional categories, with a decreased proportion of genes involved in"digestive system"(q=0.022) and an increased risk of"infectious diseases: bacterial"(q= 0.011) in CreGN.

Conclusions: Gut microbiota in CreGN differed at compositional and functional levels compared with healthy controls, and correlated well with renal injuries.

Funding: Government Support - Non-U.S.

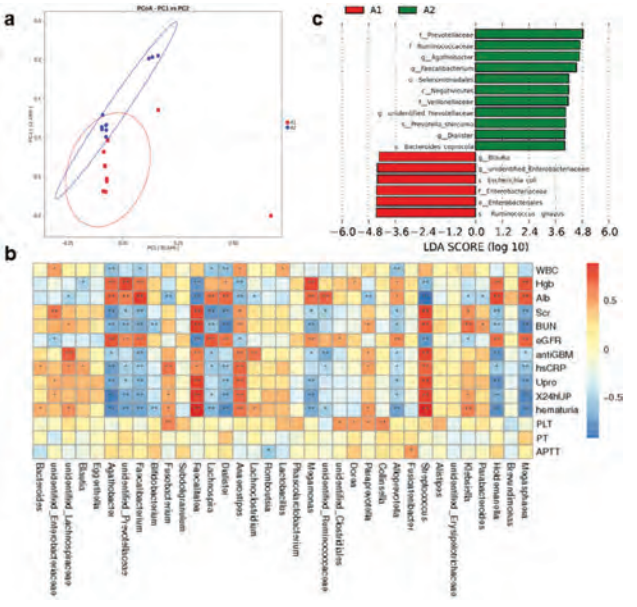

Figure 1. Altered gut microbiota in CreGN. a)PCoA. b)LEfSe. c)Spearman correlation. A1:CreGN, A2:Control.

PO1735

Role of Repeated Renal Biopsy in ANCA Vasculitis

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Background: Pauci-immune necrotizing crescentic glomerulonephritis is a severe renal complication of AAV. Despite immunosuppressive therapy, relapses are frequent during the course of the disease. Kidney biopsy is routinely used to diagnose AAV at initial presentation. Although the activity of renal AAV is not easily evaluated by plasma or urine biomarkers, kidney biopsy is rarely performed when relapse is suspected. We herein analyze the clinical, laboratory and renal pathology data from patients who underwent repeated kidney biopsies during the course of AAV.

Methods: We retrospectively reviewed data from 37 patients who underwent at least 2 kidney biopsies in our centre, between 2002 and 2018. The first renal biopsy (B1) was constantly performed at diagnosis. A follow-up biopsy (B2) was performed for purpose, either for suspicion of refractory disease or confirmation of renal relapse. Modifications of renal pathology between B1 and B2 were studied, by comparing presence of active and chronic lesions.

Results: The median delay between B1 and B2 was 3,3 [0,9-5,8] years. B2 was done for suspicion of refractory disease (n=8) or of renal relapse (n=29). Causes of B2 were : persistence or reappearance of haematuria in 78% of cases, increase of creatinine in 43%, increase of ANCA titer in 67%. Systemic AAV activity was more important at B1 vs B2 (median BVAS 18 vs 9), as well as renal dysfunction (median sCreat 200 vs 156 µmol/l). Active glomerulonephritis was constantly found at B1 but was present in only 35% of B2. Presence of cellular crescents decreased from 71,4 to 29,7% (p = 0,002), whereas fibrinoid necrosis decreased from 80,6 to 35,1% (p = 0.0003). Five factors were significantly associated with the presence of active lesions : presence of at least one extra-renal AAV manifestation (p = 0.0006), increase of ANCA titer (p = 0.0022), CRP>30mg/l (p = 0.001), absence of IF/TA (p=0,02) and high percentage of normal glomeruli (p=0,014) at B1. Interestingly, level of proteinuria and persistence of hematuria were not associated with histological activity at B2 (p =0,64 and 0,22 respectively). In contrast, chronic lesions were more severe at B2 compared to B1 (p <0,0001 and 0,014 respectively).

Conclusions: Despite several clinical and laboratory signs suggesting active renal AAV, B2 revealed no relapse in 2/3 of cases, allowing avoidance of a new immunosuppressive induction treatment.

PO1736

Single-Center Experience of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in a Region of Central Appalachia

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Background: Antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) is a rare disease with significant morbidity and mortality. Suspicions that our caseload of AAV might exceed the estimated 3 in 100,000 incidence estimates prompted us to investigate the characteristics of our patients with AAV.

Methods: A retrospective study of all patients diagnosed with AAV at our center prior to December 31, 2019 was performed. Patients were identified based on ICD10 (349),

ICD 9 (1846) codes or diagnosis of a positive ANCA lab test (589). Charts were reviewed for demographic and clinical information. Incidence was estimated for the 10-year period being January 1, 2009 using population estimate.

Results: A total of 225 patients had a confirmed diagnosis of AAV of whom 114 were males (50.6%) and 111 females (49.4%). 94.7% were Caucasian, 2.2% African American and 2.2% Hispanics, reflective of our population. Most were older (50.2% >60 years). The kidneys(67.6%), lungs (42.7%) and ENT organs(30.2%) were most commonly involved. The predominant ANCA subtype was p-ANCA(52.3%), followed by c-ANCA (43%) and ANCA-negative (4.7%). p-ANCA was most common in patients with renal involvement (58.8%) and c-ANCA was most common in patients with ENT involvement (60%); p <0.01. Of those with renal involvement, 51 needed dialysis (33.6%), 47 of whom became dialysis-dependent (30.9%). Mortality was high in patients with kidney (32.2%) and lung involvement (30.2%) compared to those with ENT involvement (16.2%); p=0.04. Preliminary estimates suggest a regional incidence that may exceed that of other states.

Conclusions: In our population, p-ANCA was the predominant subtype and incidence estimates did not mirror those of other areas. These findings suggest that AAV may differ in subtype predominance and incidence by geographic setting.

Organ Involvement

Organ involved (N of patients)	c-ANCA N (%)	p-ANCA N (%)	Neg ANCA N (%)
Renal (152)	59 (39.9%)	87 (58.8%)	2 (1.4%)
Lung (96)	44 (46.8%)	47 (50%)	3 (3.2%)
Eyes (15)	9 (60%)	5 (33.3%)	1 (9.1%)
ENT (68)	45 (68.2%)	15 (22.7%)	6 (9.1%)
Skin (21)	8 (38.1%)	9 (42.9%)	4 (19%)
Brain (19)	10 (52.6%)	7 (36.8%)	2 (10.5%)
Heart (3)	2 (66.7%)	1 (33.3%)	0 (0%)
GI (2)	0 (0%)	2 (100%)	0 (0%)

PO1737

Exploring the Role of Type I Interferons in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) is a group of autoimmune diseases characterised by inflammation of small blood vessels. Type I interferons (IFNs) are cytokine mediators of the innate immune response, most known for their anti-viral properties. Dysregulation of type I IFNs is a major factor in the development of several autoimmune diseases, now termed type I interferonopathies, and thought to be the pathogenic link with chronic inflammation in these conditions. Despite evidence of type I IFNs driving autoimmunity, they have not been comprehensively studied in AAV. We hypothesised that type I IFN responses are systemically dysregulated in AAV, indicative of a type I interferonopathy.

Methods: Matched whole blood and serum samples collected from healthy individuals (n=67), disease control patients (n=32) and AAV patients (n=71) were obtained from the Rare Kidney Disease Biobank of Ireland. qPCR was used to measure gene expression in blood of seven type I IFN stimulated genes (ISGs) characteristic of type I interferonopathies: *IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1* and *STAT1*. Serum type I IFN regulated proteins (CXCL10, MCP-1 and CCL19) were assessed by ELISA.

Results: No significant difference in ISG gene expression was observed between control samples and AAV patients for any ISG analysed, irrespective of treatment received, age or sex. No significant differences in MCP-1, CCL19 and CXCL10 expression were observed between each cohort. CXCL10 levels were significantly lower in AAV patients on immunosuppressive treatment. Markers of Type I IFN responses did not correlate with clinical measurements of disease severity in AAV patients.

Conclusions: Systemic type I IFN responses are not dysregulated in AAV and are unlikely to contribute towards AAV pathogenesis; therefore AAV should not be considered as a type I interferonopathy

Funding: Private Foundation Support

PO1738

Angiotensin Converting Enzyme-Overexpressing Neutrophils Suppress Glomerular Injury in Crescentic Glomerulonephritis

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Background: Angiotensin Converting Enzyme (ACE) is well known as the responsible enzyme to regulate blood pressure by producing angiotensin II in renin-angiotensin system, while recent studies have revealed that ACE has a novel function in immune cells. We previously found that ACE overexpressed myeloid lineage cells promoted an inflammatory response resulting in increasing resistance to bacterial infection and tumor growth. These results prompt us to investigate the effect of overexpressed ACE in myeloid lineage cells on immune complex (IC)-mediated crescentic glomerulonephritis (GN).

Methods: We induced the nephrotoxic serum nephritis (NTN) in C57Bl/6 (WT), and NeuACE mice that overexpressing ACE in neutrophils. In addition, IC uptake and IC-mediated responses were investigated in both WT and NeuACE neutrophils by *ex vivo* experiments.

Results: Seven days after induction of NTN, NeuACE mice showed less severe proteinuria, histological glomerular injury, and less number of macrophages infiltration into the glomeruli than those in WT mice. While production and serum level of autologous antibody titer were comparable, IC deposits in glomeruli were reduced in NeuACE mice compared to WT mice. In *ex vivo* experiments, IC uptaking was significantly promoted in NeuACE neutrophils as compared to WT cells. As an underlying mechanism of the promoted IC uptaking in neutrophils, we found that serum level of complement C3b and expression of complement receptor CR1/2 on neutrophils were significantly elevated in NeuACE mice. Furthermore, we confirmed that anti-CR1/2 blocking antibody abolished the uptaking of IC in neutrophils and the NeuACE serum enhanced IC uptake in both normal and ACE overexpressing neutrophils. These results suggest that ACE in neutrophils directly or indirectly pre-activate C3, and that both the elevated CR1/2 expression and the increased serum C3b play the pivotal role in IC uptake by neutrophils. Despite the increase in IC uptaking, neutrophils from NeuACE mice showed better cell survival after IC stimulation compared to those from WT mice.

Conclusions: Overexpressed ACE in neutrophils contributes to the effective elimination and suppression of IC deposits in glomeruli via C3b-CR1/2 axis, ameliorating glomerular injury in crescentic GN. These results indicate a novel immunological aspect of ACE in GN.

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PO1739

Recurrence of Anti-GBM Disease: An Epiphenomenon?

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Introduction: The simultaneous presentation of anti-GBM antibodies with ANCA-associated glomerulonephritis occurs in about 40% of individuals with anti-GBM disease. However, recurrence of anti-GBM disease is rare. We report a case of relapsing disease where the recurrent anti-GBM may have been caused by the ANCA-induced glomerular injury.

Case Description: A 62-year-old woman presented with generalized weakness and arthralgia. Creatinine was elevated to 1.7 mg/dL from 0.8 mg/dL, urinalysis showed 3+ blood and 1+ protein with dysmorphic RBCs. Her serologies showed an elevated anti-MPO and a moderately high anti-GBM titre. Her renal biopsy revealed crescentic glomerulonephritis with segmental linear IgG staining of the glomerular basement membrane on immunofluorescence. In 2015, at the time of her presentation, she was treated with plasmapheresis, cyclophosphamide and maintained on tapering doses of azathioprine and prednisone. In 2017, as her immunosuppression was tapered, her Pcr rose, her urine showed RBCs and her anti-GBM titer, which had been undetectable each month, again became positive. She was retreated with a similar regimen. In 2019, she had another relapse with a higher ANCA titer, a mild rise in creatinine and hematuria. Her anti-GBM, by comparison, remained negative. Her repeat renal biopsy was consistent with vasculitis, but the immunofluorescence at this time was negative. She was treated with an escalated steroid dose and with rituximab. She appears to be in clinical and laboratory remission at this time with a persistently negative anti-GBM, but with continued anti-MPO positivity. A re-review of her initial biopsy showed that there was linear staining, but it was discontinuous and segmental.

Discussion: On initial presentation, this patient appeared to have anti-GBM disease with concomitant ANCA positivity, a not uncommon combination. Both titers rose with her first relapse. However, during her second recurrence she was noted to have an elevated ANCA with necrotizing vasculitis and was promptly treated. At that time, her anti-GBM remained negative. We suggest that this patient has an ANCA-positive vasculitis and that the anti-GBM may have been a secondary or epiphenomenon due to release of GBM antigens as a result of glomerular damage by anti-MPO antibodies [1]. We believe that this might explain the unusual recurrence of anti-GBM serology in this patient.

PO1740

Activation of the cGAS-STING Signaling Pathway Is Associated with Glomerular Diseases

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Background: Podocytes express elements of the innate immune system which may be involved in the local immune response and contribute to chronic inflammation and glomerular damage. The cGAS-STING pathway is activated as part of the innate immune response to pathogens or host cytosolic DNA and has been shown to regulate inflammation and energy homeostasis under obesity conditions, kidney fibrosis and acute kidney injury. Whether cGAS-STING pathway contributes to development and progression of glomerular diseases remains largely unknown. This study aimed at filling this gap.

Methods: Immortalized human podocytes were cultured in RPMI medium and differentiated for 14 days. c-diAMP treatment (10 μM) was performed for 24h. Real-time PCR and Western blot analysis were used to evaluate mRNA and protein expression. Male and female, 8-week-old C57BL/6J mice were randomly divided into two groups: control (n=7) and I.P. injected with a single dose of c-diAMP, 25 mg/kg (n=9). The animals were sacrificed 72 h after injection, blood and kidneys were harvested and processed for in-depth phenotypical analysis, including urinary albumin-to-creatinine ratio, histological analysis, transmission electron microscopy analysis (foot process effacement quantification), immunohistochemistry, glomeruli isolation and serum analysis.

Results: *In vitro*, podocytes showed expression all of the cGAS-STING components at the mRNA and protein level under physiological conditions and treatment with c-diAMP, an antagonist of STING, lead to activation of the cGAS-STING pathway. *In vivo*, treatment of mice with c-diAMP resulted in an increased expression of all components along the cGAS-STING pathway at both the mRNA and protein levels. Histology data show that c-diAMP-treated mice have a lower number of podocytes per glomerulus and a lower podocyte density, showing an increase in foot process effacement. This is further confirmed by increase in blood urine nitrogen and serum creatinine levels and in the urine albumin-to-creatinine ratio.

Conclusions: Genes of the cGAS-STING pathway are expressed in human podocytes and the pathway can be activated both *in vitro* and *in vivo*. Activation of the cGAS-STING pathway in mouse models *in vivo* is associated with increased podocyte injury and contributes to the glomerular diseases.

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PO1741

C5a Enhanced the Recruitment of CD16^{+} Monocytes by CX3CL1-CX3CR1 Axis in ANCA-Associated Vasculitis

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Background: Monocytes play a major role in ANCA-associated glomerulonephritis. The mechanism is not well understood. Additionally, it is a consensus that C5a participates ANCA-associated vasculitis (AVV) pathogenesis. The relevance of C5a in terms of monocytes recruitment, as well as the nature and function of monocytes has not been well studied in AAV.

Methods: Monocytes in blood was counted and its phenotypic characteristics were analyzed by Flow cytometry. C5a and monocyte - related cytokines and chemokines was detected in AAV. The phenotype of monocytes in Kidney tissues from MPO-AVV patients was studied by immunohistochemistry and immunofluorescence. The chemoattractant activity of chemokines produced by human renal glomerular endothelial cells(HRGEC) for monocytes was observed.

Results: Monocytes were higher in activated MPO-AAV patients. The proportion of CD16+ monocytes in the peripheral blood of the patients was significantly reduced and CX3CR1 was highly expressed in CD16+ monocytes. C5a, IL-6, TNF-α, and chemokine CX3CL1 were significantly increased in serum of activated MPO-AAV patients. CD16+ monocytes were clearly seen in the glomeruli of MPO- AVV patients. Chemokine CX3CL1 was expressed in glomerular endothelial cells. Consistently, we demonstrated C5a enhance recruitment of CD16+ monocyte via CX3CL1 produced by TNF-αinduced HRGEC in vitro.

Conclusions: We report an altered distribution of monocyte subsets in MPO-AAV patients; CD16+ monocytes may be recruited to kidney through CX3CL1-CX3CR1 axis to aggravate ANCA-associated GN.

PO1742

Melanocortin 5 Receptor (MC5R) Deficiency Aggravates Glomerular Injury and Proteinuria in the Autologous Phase of Nephrotoxic Serum (NTS) Nephritis

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Background: The successful use of corticotropin in steroid-resistant nephrotic glomerulopathies suggests a unique proteinuria-reducing activity of adrenocorticotropic hormone that is steroidogenic-independent and may be attributable to its melanocortinergic activity. It remains uncertain which melanocortin receptor conveys this beneficial effect. Emerging evidence implicates MC5R signaling in the regulation of immune response. However, the role of MC5R in glomerular disease is unknown.

Methods: NTS nephritis was induced in MC5R knockout (MC5R$^{-/-}$) and wild-type (WT) mice. Kidney function, proteinuria and renal pathology were evaluated in the autologous phase.

Results: On 14 days after NTS injection in the autologous phase, MC5R$^{-/-}$ as compared with WT mice exhibited an exacerbated kidney dysfunction and injury, as evidenced by higher serum creatinine levels, heavier proteinuria and aggravated renal pathology, featured by crescent formation, glomerular hypercellularity, mesangial expansion, protein casts in renal tubules, inflammatory infiltration in both glomeruli and tubulointerstitium and renal fibrosis. Consistent with the worsened proteinuria, MC5R$^{-/-}$ mice displayed more severe podocyte injury and loss, as evidenced by diminished WT-1 staining and loss of homeostatic podocyte markers, like synaptopodin and podocin, as determined by immunohistochemistry staining and immunoblot analysis of isolated glomeruli. Mechanistically, although glomerular basement membrane-reactive rabbit IgG was found to deposit in glomeruli in both MC5R$^{-/-}$ and WT mice to a comparable magnitude, MC5R$^{-/-}$ mice demonstrated much more glomerular deposition of autologous anti-rabbit IgG together with enhanced fixation of the terminal complement complex C5b-9 along glomerular capillary loops in the autologous phase, suggesting that a potentiated humoral immune response to NTS antigen resulting from MC5R deficiency may contribute to the aggravated NTS nephritis.

Conclusions: MC5R signaling is essential for protection against glomerular injury and proteinuria in murine NTS nephritis via, at least in part, a regulatory effect on humoral immunity.

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PO1743

Glomerular Complement Proteins in Thrombotic Microangiopathy

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Background: Thrombotic Microangiopathy (TMA) is a clinicopathological entity resulting from complement abnormalities (atypical hemolytic uremic syndrome, aHUS) and a number of secondary causes including malignant hypertension, autoimmune diseases and drugs. Distinguishing aHUS from secondary TMA is a challenge. A comprehensive evaluation of complement burden in TMA has not been done.

Methods: Glomeruli were laser microdissected and mass spectrometry (MS) was performed. The glomerular complement protein profile was analyzed in aHUS (n=12) and secondary TMA (n=12). The spectral counts obtained from MS are semiquantitative with regards to abundance of the protein.

Results: C3 was the most the abundant complement protein in all cases (Figure). The remaining complement proteins were grouped into classical (C1/C4A/C4B), terminal pathway (C5/6/7/8A/8B/9), and complement regulatory proteins (CRP=CFH/CFHR1-2-3-5/CFB/CFD). MS studies show accumulation of C3, and complement proteins of classical and terminal pathways in all cases. Overall, there was greater accumulation of complement proteins in secondary TMA compared to aHUS (248.3 vs. 192.5). Importantly, even though C3 was higher in aHUS, both classical pathway and terminal pathway protein accumulation were higher in secondary TMA compared to aHUS. Among the secondary TMA, drug-induced TMA showed the highest accumulation of complement proteins compared to autoimmune and hypertension-induced TMA (306.9 vs. 217 vs. 219.9, respectively). Finally, CRP were present in all TMA, of which CFH was the most abundant protein.

Conclusions: Complement proteins of all pathways were identified in TMA. C3 followed by C4A/C4B and C9 were most abundant proteins. Higher counts of C3 in aHUS versus higher counts of C4A/C4B in secondary TMA, suggests a greater role of alternative pathway in aHUS and a greater role of classical pathway in secondary TMA.

Protein category	Proteins	aHUS (n=12)	Secondary TMA (n=12)
C3	C3	63.75	53
Terminal	C5/6/7/8A/8B/9	32.9	50.1
CRP	CFH/CFHR1-2-3-5/CFB/CFD	32.9	48.25
Classical	C1QB/C1QC/C1R/C1S/CR1/C4A/C4B	63	97
Total		192.55	248.35

Protein category	Hypertension (n=5)	Autoimmune (n=3)	Drug (n=4)
C3	42.6	52	67
Terminal	56	46	46
CRP	36.1	47.6	63.75
Classical	85.2	72.3	130.2
Total	219.9	217	306.9

MS: Total spectral counts in TMA.

PO1744

Complement 3 Glomerulonephritis in a Patient with Microscopic Polyangiitis

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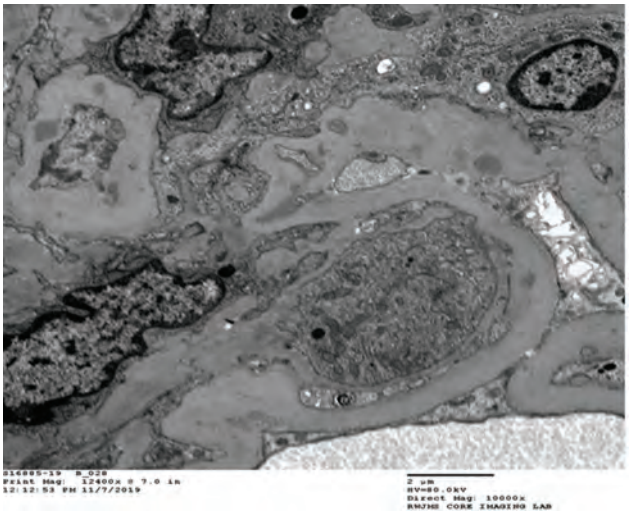
Introduction: C3GN is a rare disorder of excess alternative complement pathway activation, with renal biopsy characteristic of glomerular C3 deposits. We present a unique case, where patient has H/O MPA, admitted for AKI and hematuria, found to have C3GN on renal biopsy.

Case Description: 69 yo M with H/O CKD stage 4 due to microscopic polyangitis (baseline Cr 2.6 - 2.9), spinal stenosis, HTN and BPH presented with complaint of painless hematuria, epistaxis, decrease UOP and weight gain x 4 days. He was diagnosed with MPA in 2005 after a renal biopsy, recieved treatment with steroids, Cyclophosphamide for 18 months, switched to MMF for 2 years and then to Azathioprine which was discontinued due to intolerance (off all immunosuppressant's since 2012.). On admission labs; BUN/Cr 90/6.5, K 5.6, ESR 39, C-RP 1.24, P-ANCA and MPO positive. UA +3 protein, +3 blood, > 182 RBCs and 16 WBCs. Random urine protein > 600 mg per dl. C3 was low (44.1), C4 normal. AH50 was low (36.1%). Hepatitis panel, C-ANCA, PR-3 and anti-GBM were negative. Pt was admitted with preliminary diagnosis of AKI on CKD 2/2 MPA flare and was started on pulse dose of steroid. He was also started on HD and plasmapheresis. Renal biopsy showed active crescents with strong C3 global glomerular staining in the mesangium and the capillary wall and trace to no staining of IgG, IgA, IgM, C1q, kappa, lambda. S. EM showed measnagial and sub endothelial deposit suggestive of active crescentic C3 GN.

Discussion: C3 GN is rare in clinical practice. Incidence is estimated to be 2–3 cases per 1,000,000 in the United States. MPA, like other ANCA-associated vasculitis, is typically associated with a pauci-immune GN. We presented a case with signs, symptoms, labs and histopathology consistent with both C3GN and MPA. It is unclear whether this patient truly had both diseases, which are typically caused by different immunologic pathways. Depressed C3 levels and normal C4 levels, diffuse glomerular C3 deposits on immunohistochemistry, and subendothelial deposits on electron microscopy strongly supports the diagnosis of C3GN in our patient with MPA.



PO1745

Eculizumab Use in Scleroderma Renal Crisis with Thrombotic Microangiopathy

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Introduction: Scleroderma renal crisis is a life-threatening condition with increased mortality and morbidity leading to end-stage renal disease in about 25% of cases. Here we report a case of newly diagnosed scleroderma renal crisis with thrombotic microangiopathy (TMA) successfully treated with eculizumab.

Case Description: A 44-year-old African American female with no significant past medical history, presented with acute pulmonary edema in the setting of malignant hypertension and severe accelerated acute kidney injury (AKI) with rapidly declining GFR and clinical features of systemic sclerosis sine scleroderma. Patient was commenced on renin-angiotensin system blockade (ACEI). Despite good blood pressure control on ACEI, her creatinine continued to rise with persistent hemolysis. The kidney biopsy revealed severe features of scleroderma renal crisis with active thrombotic microangiopathy (TMA), and the decision was made to treat the patient with Eculizumab in addition to ACEI. Kidney function rapidely improved on treatment from a peak creatinine of 9.5mg/dl to 2.5mg/dl over few weeks without requiring dialysis, combined to resolution of all TMA features. Eculizumab was stopped after 3 months, without sign of relapse 2 months after discontinuation.

Discussion: TMA is a common feature of SRC, reported in about 50% of cases. The positive C4d staining on the kidney biopsy in our patient supports complement activation through the classical or mannan-binding lectin (MBL) pathway. Several studies identified the presence of auto-antibodies directed against endothelial cells that could lead to complement activation. Presence of autoantibodies against vascular receptor (against angiotensin II type 1 receptor and endothelin-1 type A receptor) have been associated with pulmonary hypertension, pulmonary fibrosis and digital ulcers but no association with SRC and TMA has been reported yet. On the other hand, hemodynamic shear stress itself has been shown to activate the classical pathway, and trigger secondary TMA. In addition, an increased FBb/FB ratio has been reported in a SRC with TMA, suggestive of subsequent recruitment of the alternative pathway through the C3b feedback cycle leading to further endothelial injury. These data support the potential role of complement blockade for the treatment of SRC with TMA.

PO1746

Thrombotic Microangiopathy and AKI Induced After Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitors

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Introduction: Vascular Endothelial Growth Factor (VEGF) inhibition can cause worsening hypertension, proteinuria, acute and chronic kidney injury, as well as glomerular disease from Thrombotic Microangiopathy (TMA) and other nephrotic disorders when given systemically. These same agents are given intravitreally for age related macular degeneration (AMD) and Diabetic Retinopathy (DR) among other ophthalmologic conditions, albeit at lower doses than those given for systemic indications. Systemic absorption of anti-VEGF agents when given intravitreally has been shown consistently along with evidence of significant intravascular VEGF suppression. While worsening hypertension has only been seen in some large-scale studies, case reports show worsening proteinuria and diverse glomerular diseases. These include TMA-associated lesions like Focal and Segmental Glomerulosclerosis with Collapsing Features (cFSGS).

Case Description: In this paper, we report 3 cases of TMA likely associated with use of intravitreal anti VEGF therapy. These patients developed the signature lesion of VEGF blockade in a 6 month – 11-month time frame after starting intravitreal VEGF inhibitors.

Discussion: The literature is reviewed showing similar cases. Intravitreal VEGF blockade may cause these adverse events in a hitherto unidentified subgroup of patients. Further studies are needed to determine the event rate and identify which patients are at increased risk for hypertension, proteinuria worsening, renal injury, and glomerular diseases from intravitreal VEGF blockade.

Table 1 TMA and CFSGS observed with Intravitreal VEGF blockade

Reference	N	Age	Gender	Agent	Pathology on biopsy
Nobakht (4)	1	96	F	Luc→Bev→Aflib	CFSGS
Chenugpasitporn (32)	1	67	M	Bev	TMA
Pelle (39)	1	77	F	Ran	TMA
Touzani (43)	1	72	M	Bev	TMA
Yen (44)	1	56	M	Bev	Endotheliosis/ possible TMA
Shye et.al. (46)	1	58	M	Bev	CFSGS
CC (Hanna et.al.)	3	56,43,77	M, F, F	Bev x 2, Aflib x 1	Chronic TMA x 2, FSGS, Endotheliosis/Chronic TMA

Afl, aflibercept; Bev, bevacizumab; CC, current case; CFSGS, collapsing focal and segmental sclerosis; Aflib, aflibercept; F, female; FSGS, focal and segmental sclerosis; M, male; N, number; Ran, ranibizumab; TMA, thrombotic microangiopathy

PO1747

Bintrafusp α-Associated Thrombotic Microangiopathy

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Introduction: Immune check point inhibitors (ICPIs) have been reported to cause acute kidney injury. Acute tubulointerstitial nephritis is the most common finding on renal biopsy. This has resulted in recommendations to forgo renal biopsy in some patients and therapy with empiric steroids. Here we present a different renal pathology related to use of Bintrafusp-α, a novel therapy targeting TGF-beta and PD-L1.

Case Description: A 41 year old man with metastatic cholangiocarcinoma was admitted for hypertension urgency and acute kidney injury following 2 cycles of Bintrafusp-α in 6 weeks. Exam was remarkable for BP 204/101 mmHg, pulse 62/min, muscle wasting and anasarca. His labs revealed hemoglobin 8.9 g/dL, platelets 109 × 10^9/L, occasional schistocytes, lactate dehydrogenase 626 U/L(112–222 U/L), undetectable haptoglobin, serum creatinine 2.8 mg/dL, microscopic hematuria and protein creatinine ratio 2.79g/g. ADAMTS13 activity 72% (≥70%), antiphospholipid antibody was negative, complement levels normal. The renal biopsy demonstrated acute and subacute thrombotic microangiopathy(TMA). The patient received a dose of Soliris empirically, pending workup for atypical HUS. Further doses of Soliris were held as TMA was attributed to immunotherapy and atypical HUS genetic testing panel returned negative.

Discussion: TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia. The most studied secondary cause of TMA is drugs. The pathogenesis of drug-mediated TMA is either the generation of an immunologic reaction or its direct dose- and time-dependent toxicity. ICPI monotherapy has a nephrotoxicity incidence of 2-5%. In the largest retrospective study of 1016 patients treated with ICPI therapy, 17% developed AKI, 2% experienced stage 3 AKI and 0.4% required dialysis. TMA was documented in 1 patient receiving Ipilimumab and was HD-dependent. The National Comprehensive Cancer Network guidelines recommend empirically treating AKI in some

patients with steroids. We believe renal biopsy is essential, if safe, to rule out causes of AKI that are not remediable with steroids. Renal biopsy would expand our knowledge on the pathology of AKI post-ICPI treatment. We report the first case of TMA associated with the new bifunctional immunotherapy for solid cancers.

PO1748

Atypical Hemolytic Uremic Syndrome Attributed to Complement Dysregulation in Setting of Metastatic Prostate Cancer Patient

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Introduction: Thrombotic microangiopathy (TMA) is a collection of syndromes, with the most frequent types encountered being hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and atypical HUS. Atypical HUS (aHUS) may be attributed to inherited or acquired complement abnormalities, or secondary causes such as pregnancy, malignancy, transplantation, drugs. Malignancy-associated aHUS is caused by a two-hit event with complement activation playing minor role while in primary aHUS, the primary hit is complement dysregulation. We describe an unusual case of aHUS in a metastatic cancer patient attributed primarily to complement dysregulation.

Case Description: A 64-year old male with history of metastatic prostate adenocarcinoma with spinal involvement presented with a chief complaint of new onset hypertension. He reported dark "coke-colored" urine for one day with intermittent episodes of hematuria. Patient last received chemotherapy with cabazitaxel five months prior. Rest of history and physical exam was unremarkable. Laboratory findings were significant for thrombocytopenia, anemia, and peripheral smear demonstrating schistocytes. Cr peaked at 6.58 mg/dL, ADAMTS13 activity was 100%, and stool PCR was negative for shigella. Complements C3 and C4 were within normal limits. Patient became oliguric with worsening acidosis and was initiated on renal replacement therapy. He underwent a bone marrow biopsy showing no evidence of infiltration of malignancy into the bone marrow. He then had a renal biopsy with pathology showing acute TMA with fibrin thrombi in approximately 50% of the glomeruli. sC5b9 levels were elevated. He was initiated on Eculizumab 900mg once weekly and began to show signs of renal recovery. Within two weeks, he was transitioned off renal replacement therapy.

Discussion: Primary aHUS as a result of complement dysregulation can occur in patients with malignancy. This patient had elevated sC5b9 complex levels with increased alternative pathway activation. He responded to eculuzimab, monoclonal antibody inhibiting activation of C5, with full recovery of his renal function. In cases of aHUS presenting in patients with malignancy, physicians should be aware that aHUS may still occur secondary to the primary hit of complement dysregulation and should consider treatments targeting this complement pathway.

PO1749

An Unusual Case of Complement-Mediated Thrombotic Microangiopathy

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Introduction: Thrombotic microangiopathy is a specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis. Diagnosis is made by tissue biopsy Complement mediated TMA is hereditary deficiency of regulatory proteins that restrict activation of alternative pathway or hereditary abnormality of proteins that accelerate activation of this pathway. Deficiency of complement factor H or I can also be acquired

Case Description: 19-year-old female with ulcerative colitis presented with bloody diarrhea and decreased oral intake for one week. She endorsed not taking mesalamine and use of naproxen daily for two weeks. Laboratory data, leukocytosis 22k with 84% neutrophils, 5% bands and schistocytosis, hemoglobin 6.1g/dL, thrombocytopenia, BUN 77 mg/dL, creatinine 7.16 mg/dL, Lactate dehydrogenase 1042IU/L and haptoglobin undetectable. Coomb's test negative The patient was admitted for presumed Colitis flare given methylprednisolone. Renal biopsy obtained for acute kidney injury showed glomerular basement membrane duplication, multi layering and arterioles showed focal obliterative changes and onion skinning. 5% global sclerosis and 18% of glomeruli showed segmental sclerosis. Electron microscopy showed active endothelial injury, including subendothelial expansion. Microangiopathic anemia, thrombocytopenia and acute kidney injury raised concern for TMA. Shiga toxin negative and ADAMTS13 activity ~ 71%. Complement factors and autoantibodies to H, I, and B and membrane cofactor were sent out Patient started treatment for TTP, presumably aHUS. She received solumedrol 500mg/day IV x 3 and then prednisone 60mg/day. Plasma exchange was initiated. She was noted to have persistent high LDH and undetectable haptoglobin indicating ongoing MAHA. After 2 weeks of meningococcal vaccine, she was started on Eculizumab. Prednisone, Eculizumab and PEX were continued. In the interim, labs showed CFH level~ 105 mcg/mL (normal range 160-142). A genetic renal panel, which tested for CFH, CFI, CFI, MCP, and several other genes, confirmed she had a heterozygous deletion of a CFH related gene, CFHR1/CFHR3, as well as autoantibodies to CFH

Discussion: In our case, aHUS was likely predisposed by her heterozygous deletion of CFHR1/CFHR3 genes. What makes this case unusual is she did not have a homozygous deletion, but developed autoantibodies to CFH, to our knowledge has not been previously reported.

PO1750

A Case of "Immunofluorescence-Negative" Lambda Light Chain Deposition Disease

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Introduction: Light chain deposition disease (LCDD) is the most common form of monoclonal immunoglobulin deposition disease (MIDD). Pathologically, glomeruli develop nodular expansion of mesangial regions and deposits of monoclonal light chain (LC) positive, electron dense deposits within glomerular and tubular Basement menbrane. (1,2) The majority of monoclonal LC in LCDD are of kappa type. (3) We report a case of lambda LCDD with negative immunofluorescence microscopy (IF), but with characteristic granular, basement membrane, electron dense deposits on ultrastructural examination.

Case Description: A 42-year-old Caucasian female with no PMHx, no NSAID, Chinese herbal or PPI use presented with fatigue, malaise and dark urine for 2 weeks. She had a normal BP and no edema. Labs: Scr was 2.4 mg/dL with unknown baseline levels, BUN 26 mg/dL, Hb level 9.0 gm/dL with MCV of 90 fl, with a negative autoimmune panel. Urine microscopy showed 10 RBC/HPF and 24-hour protein excretion was 460 mg. SPEP and immunofixation detected a Lambda LC monoclonal paraprotein. Serum free Lamba LC level was 1044 mg/L with free kappa/lambda LC levels ratio of 0.03. A kidney biopsy revealed nodular expansion of glomerular mesangial regions, modest amount of IFTA. RBCs and red cell casts were present in tubules. Direct IF microscopy with FITC-conj. anti-human IgG, IgM and IgA heavy chains and Kappa/lambda light chains was negative with testing performed in duplicate. Ultrastructural examination revealed powdery, granular electron dense deposits diffusely along tubular and glomerular basement membranes with focal areas of podocyte foot process effacement. Bone marrow biopsy revealed plasma cell neoplasm.

Discussion: Our patient underwent autologous SCT after pretreatment with Melphalan. Renal function has been stable at stage III CKD. She never developed HTN or significant proteinuria, which usually are some of the presenting features of LCDD. She had lambda LC paraproteinemia, which is a more common feature of heavy chain deposition disease than LCDD. Direct IF microscopy was negative, which could be due to abnormal LCs being truncated in the tissue deposits, and commercially available, FITC-conj., anti-human Abs might not have been able to detect them. (4) This case emphasizes the fact that negative staining by routine, direct IF microscopy methods does not exclude the presence of MIDD.

PO1751

Hydralazine-Induced Vasculitis and Pulmonary-Renal Syndrome

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Introduction: Hydralazine, an arterial vasodilator, is a commonly used medication for the management of hypertension, heart failure with reduced ejection fraction (HFrEF), and hypertensive emergency in pregnancy. Hydralazine-induced antinuclear cytoplasmic antibody (ANCA) vasculitis leading to pulmonary-renal syndrome (PRS) is a very rare and fatal condition. A high degree of clinical suspicion, thorough history, early diagnosis, and prompt treatment is associated with a good clinical outcome.

Case Description: A 79-year-old woman with past medical history of type 2 diabetes mellitus, hypertension, lung mass, coronary artery, cerebrovascular accident, and chronic anemia presented with lethargy. Her home medications included aspirin, hydralazine, metoprolol tartrate, amlodipine, atorvastatin, and baclofen. On admission, serum creatinine was 2.5 mg/dl and erythrocyte sediment rate was more than 140 ml/min. Urinalysis showed positive urine RBC and leukocyte esterase. Chest radiograph and CT chest without contrast showed bilateral posterior opacities. Bronchoscopy showed thick mucus secretion and inflamed erythematous mucosa on left lung. Bronchoalveolar lavage showed positive bronchial fluid RBCs. Serology work-up was positive for antinuclear, antineutrophil cytoplasmic, anti-histone, anti-myeloperoxidase, and anti-proteinase 3 antibodies. Complement C3 level was low. Hydralazine was empirically held early at admission and the patient was started on intravenous corticosteroids. Consequently, patient's supplemental oxygen requirement decreased. However, serum creatinine up trended to 3.9 mg/dl requiring a need for renal replacement therapy. Patient decided not to undergo hemodialysis and opted for hospice care.

Discussion: Pathogenesis of hydralazine induced vasculitis is not well understood. It has multifactorial involvement with dose dependent relationship. A higher incidence is seen in females, patients with HLA DR4 genotype, slow hepatic acetylators, and those with a history of thyroid disease. Diagnosis is mainly based on constitutional and system-specific symptoms, thorough medication history, serology workup, and a strong clinical suspicion. In the setting of prolonged hydralazine use, clinicians should consider this rare condition which requires prompt diagnosis, early discontinuation of offending drug, and treatment with immunosuppressive therapy.

PO1752

A Case of Granulomatosis with Polyangiitis Complicated by Renal Mass-Like Lesion

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Introduction: Granulomatosis with polyangiitis (GPA) is a multiorgan systemic disease. Some cases of GPA may mimic IgG4-related disease (IgG4-RD) on histologic examination. Here we report a case of GPA complicated by renal mass-like lesion with infiltration of IgG4-positive plasma cells.

Case Description: A 76-year-old woman was diagnosed with otitis media with effusion 6 years before admission, and scleritis 3 years before admission. She developed nasal leaks and nasal bleeding a year before admission, and high fever and general malaise a month before admission. She visited nearby hospital and was detected a mass-like lesion in the right nasal cavity. Contrast-enhanced computed tomography (CT) of the head revealed an enhanced soft-tissue from the right middle meatus to the nasal septum and cervical lymphadenopathy. Serum proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) was positive (271.7 U/mL) with high C-reactive protein (CRP) level (29.7 mg/dL). Urinalysis findings showed minor proteinuria (0.1 g/gCr), but elevated tubular injury markers such as urinary beta 2-microglobulin. So, she admitted to our department. Contrast-enhanced CT of the abdomen revealed a 47-mm large mass-like lesion in the right kidney, and CT-guided renal biopsy was performed. Cellular to fibro-cellular crescent and fibrinoid necrosis were observed in the glomerulus. In the interstitium, granulomas with multinucleated giant cells and infiltration of IgG4-positive (IgG4+) plasma cells were observed. In addition, cell infiltration into the arteriolar wall and the rupture of lamina elastica were observed. From these findings with small vessel vasculitis, we diagnosed her as GPA with infiltration of IgG4+ plasma cells. After two courses of methylprednisolone pulse therapy, we added two courses of cyclophosphamide pulse therapy. With improved symptoms and serum data (PR3-ANCA level reduced from 266.8 to 39.0 U/mL), mass-like lesions in nasal turbinate and right kidney diminished.

Discussion: We experienced a case of GPA complicated by renal mass-like lesion. Renal biopsy revealed a coexistence of microvasculitis and infiltration of IgG4+ plasma cells. Further investigation will be required to clarify the role of IgG4+ cells in the pathogenesis of GPA.

PO1753

Granulomatosis with Polyangiitis and Acute Tubulointerstitial Nephritis in the Absence of Glomerulonephritis

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Introduction: Isolated TIN in the absence of glomerular involvement is uncommon in ANCA-associated vasculitis(AAV).

Case Description: 77 year old female with normal renal function presented with acute kidney injury (AKI) with peak SCr 482 μmol/L and required dialysis. She received antibiotics for sinusitis and pneumonia 2 weeks prior. Urinalysis noted iso-morphic RBCs and proteinuria of 2g/24hours. Anti-proteinase3(PR3) antibody was positive at 114U/ml. Anti-nuclear, anti-dsDNA and anti-GBM antibodies were negative. Bronchoalveolar lavage was negative for alveolar hemorrhage. Kidney biopsy revealed minor glomerular abnormalities and acute TIN with interstitial non-necrotising granuloma and multinucleated giant cells. Ziehl-Neelsen stain was negative. Immunofluorescence, electron microscopy were non-contributory. She was treated for possible drug-induced interstitial nephritis with oral prednisolone 0.6mg/kg and therapy was rapidly tapered due to cytomegalovirus infection. She was on prednisolone 5mg daily by 3 months. SCr improved to 174μmol/L and anti-PR3 was 4.4U/ml. A year later, she presented with episcleritis, fever, weight loss and AKI. SCr was 399μmol/L with glomerular hematuria and proteinuria. Patient refused a repeat biopsy but in view of AKI with concurrent rise in the anti-PR3 antibody at 95.1U/ml, she was diagnosed with PR3-ANCA granulomatosis with polyangiitis (GPA) and treated with cyclophosphamide, prednisolone and dialysis.

Discussion: Our patient had PR3-ANCA GPA that presented with isolated granulomatous TIN without glomerulonephritis. Rapid improvement in renal function after low-dose prednisolone monotherapy was consistent with treatment response for TIN. In AAV, isolated TIN may be caused by vasculitis of the peritubular capillaries. Most cases of AAV with isolated acute TIN improved with no treatment or prednisolone monotherapy. Thus, it is important to recognize that isolated acute TIN is an unusual presentation for AAV.

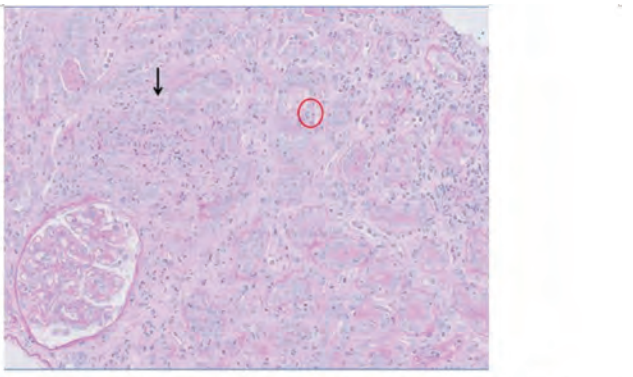

Figure 1.Acute tubulointerstitial nephritis is present, with polymorphs and lymphocytes within oedematous interstitium, including lymphocytes seen within tubular profiles. A vague granuloma is present (black arrow) where epithelioid histiocytes are observed together with other inflammatory cells. Acute tubular damage with a tubular mitosis (red circle) is also noted. A glomerulus with slightly wrinkled capillary walls is seen. (PAS stain)

PO1754

Coexisting Proteinase 3 Antineutrophil Cytoplasmic Antibody-Associated Crescentic Glomerulonephritis, Immunoglobulin A Nephropathy, and Lambda Light Chains

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Introduction: Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome that develops within weeks and is manifested by glomerular disease that is histologically delineated by crescent formation and progressively worsening renal function. The most common causes of RPGN include anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, immune complex-mediated injury, and anti-glomerular basement membrane disease. We report a case of proteinase-3 (PR-3) ANCA associated crescentic glomerulonephritis with concurrent immunoglobulin A (IgA) nephropathy and lambda light chain. The co-existence of ANCA associated crescentic GN, IgA nephropathy and lambda light chain is rare.

Case Description: A previously healthy 53-year-old Caucasian woman with newly diagnosed Granulomatosis with Polyangiitis (PR-3 ANCA positive) presented with tachycardia, cough and congestion over the past 2 months. Physical examination was notable for sinus tachycardia and tenderness to palpation over maxillary sinuses. Urinalysis revealed active sediment with dysmorphic red blood cells. Initial workup was significant for serum creatinine of 1.35 mg/dl (baseline of 0.7 mg/dl), positive C-ANCA 1:160, anti-Proteinase-3 antibody 28.4 (normal <1) and 24-hour urine protein of 576 mg. Preliminary native kidney biopsy light microscopy showed active and organizing crescentic glomerulonephritis involving 15 of 34 (44%) non-globally sclerotic glomeruli. Immunofluorescence and electron microscopy were significant for granular mesangial staining for IgA and lambda light chain and presence of few mesangial electron-dense deposits. The patient was empirically pulsed with intravenous steroids for three days. She was given one dose of Rituximab with a planned second dose two weeks after discharge.

Discussion: Rapidly progressive ANCA associated crescentic GN along with mesangial staining for IgA and lambda light chain is extremely uncommon with limited literature. By presenting this case, we highlight the significance of a renal biopsy as an essential tool for diagnostic purposes and the need to have a low threshold to biopsy in otherwise clinically straight forward cases given unexpected histologic and immunologic findings that could affect therapy and consequently patient's morbidity and mortality.

PO1755

A Case of Microscopic Polyangiitis Accompanied by Refractory Immune Thrombocytopenic Purpura

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Introduction: Microscopic polyangiitis (MPA) is an idiopathic autoimmune disease characterized by systemic vasculitis that predominantly affects the small blood vessels and is mediated by the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Immune thrombocytopenic purpura (ITP) is also an autoimmune disease characterized by autoantibody induced platelet destruction and reduced platelet production, leading to low blood platelet count. Secondary ITP is defined as an ITP induced by other diseases including autoimmune disorders. Here we present a rare case of a patient who developed ITP just after treatment with steroids for MPA with rapidly progressive glomerulonephritis (RPGN).

Case Description: 66-year-old female was hospitalized due to microscopic hematuria, proteinuria, elevated serum creatinine (2.8mg/dL) and high Myeloperoxidase-ANCA (MPO-ANCA) titres (94.1U/ml). We performed a renal biopsy that revealed pauci immune crescentic glomerulonephritis. After the definitive diagnosis of MPA, the patient was treated with intravenous corticosteroids and oral prednisone (0.8mg/kg). Although serum creatinine subsequently improved to 1.6mg/dl, the peripheral platelet count was

rapidly reduced from 20×10^9/L to 2×10^9/L after a week treatment with steroids. She was frequently treated with platelet transfusion. Bone marrow examination revealed normal morphology of all the cell lines, with increased megakaryocytes. Based on the clinical findings, we diagnosed as ITP. Then, the patient received rituximab followed by thrombopoietin-receptor agonists eltrombopag. After a week of treatment with oral eltrombopag at 25mg daily, the platelet count increased from 0.5×10^9/L to 4×10^9/L. After six weeks from initiation of eltrombopag, her platelet count remains $>3\times10^9$/L, and she has not shown any signs of bleeding or hemorrhage. MPO-ANCA titres reduced to 1.3U/ml.

Discussion: It is a novel case of MPA with RPGN accompanied by ITP. It was recently recognized that diversity existed in both pathogenesis and clinical characteristics in patients with ITP. Present case showed the possibility for an association of pathological mediator for both diseases. Although further studies are needed to confirm this idea, present findings provide clues for our understanding of this association for a better management of these diseases.

PO1756

Rituximab Rescue in Anti-GBM Nephritis

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Introduction: Anti-GBM nephritis is a rare, severe autoimmune disease. If left untreated or in patients requiring dialysis at presentation, it has a renal survival of 8% at 1 year. Conventional therapy includes corticosteroid, cyclophosphamide and plasmapheresis. An anti-B cell agent, rituximab is more recently being used in refractory cases (defined as no response after 4 weeks of standard therapy).

Case Description: 59-year-old female with hypertension presented with 1 month of fever, generalized malaise, and cough following recent travel to Iraq. Laboratory evaluation showed serum creatinine 1.3 mg/dL with hematuria and proteinuria (0.8g/day). ANA, ANCA, RF, Hepatitis B/C, HIV, RPR, and streptozyme panel were negative. Renal and pulmonary imaging were unremarkable. With creatinine rising rapidly, renal biopsy was performed revealing acute focal segmental necrotizing and crescentic glomerulonephritis involving 50% of glomeruli. Anti-GBM antibody level was 8U. Plasmapheresis daily, cyclophosphamide and steroids were initiated. She remained non-oliguric, but developed edema requiring intermittent diuresis. On day 15, plasmapheresis was reduced to every 48 hours. Anti-GBM antibody failed to decline, therefore 1 gr of rituximab infusion was initiated 3 weeks later. Standard therapy was continued until the second dose of 1gr of rituximab 2 weeks later. Patient was discharged with creatinine stable at 4 mg/dL, anti-GBM antibody level at 1.4U and on prednisone taper. On follow up day 75, antibody levels were undetectable and on day 147 she remained dialysis free.

Discussion: Our patient presentated with favorable prognostic markers including non-oliguria, low creatinine and anti-GBM antibody levels, negative ANCA, involvement of 50% of glomeruli, and no dialysis requirement. Despite these factors, she did not respond to standard therapy alone. Our patient was initiated on rituximab earlier than reported refractory cases while continuing standard therapy until the 2nd dose of rituximab, with a favorable outcome of remaining dialysis free. We suggest early use of rituximab with overlapping of the standard regimen is safe and effective in older age group.

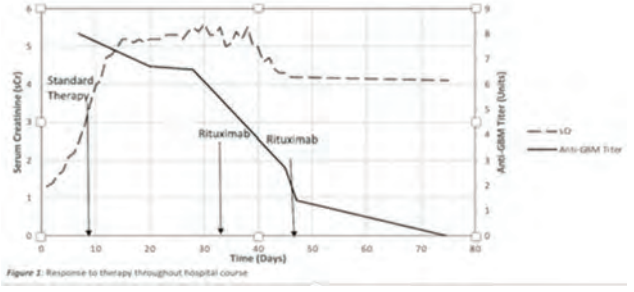

Figure 1: Response to therapy throughout hospital course

PO1757

Rare Case of Myeloperoxidase-ANCA-Positive Polyarteritis Nodosa

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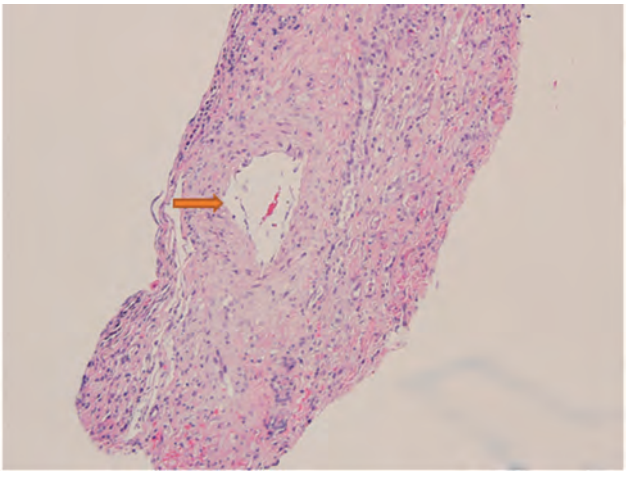
Introduction: Polyarteritis Nodosa (PAN) is systemic necrotizing vasculitis involving medium-size vessels. PAN is typically not associated with positive antineutrophil cytoplasmic antibodies (ANCA) titter. Here, we report a patient who presented with abdominal pain, hematuria, sub-nephrotic range proteinuria, acute kidney injury (AKI) with high MPO ANCA titer who was diagnosed with PAN.

Case Description: 40-year-old male with asthma presented with abdominal pain, generalized weakness and myalgia, weight loss of 25 pounds over the last 2 months. Two weeks prior to presentation, patient was diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) and started on prednisone at the outpatient clinic. Physical exam was significant for hypertension, abdominal tenderness and petechial rash in the lower extremities. Laboratory findings were significant for serum creatinine 1.6 mg/dl, ESR 93 mm/hr, CRP 25 mg/dl, ANCA titer 1:160 with MPO – 46 units. Urinalysis revealed 28 RBC/hpf with urine protein/creatine - 1.4 g/g. Esophagogastroduodenoscopy and skin biopsy of petechial rash were negative for vasculitis. Kidney biopsy reveled focal arterial fibrinoid necrosis with mixed interstitial inflammatory infiltrate consistent with necrotizing arteritis involving predominantly medium size arteries, leading to a diagnosis of PAN (fig 1). Patient was treated with pulse dose methylprednisolone and cyclophosphamide for PAN with maintenance prednisone.

Discussion: PAN is a rare disease involving multiple organ systems, including the kidney, and is typically not associated with a positive ANCA titer observed in small-vessel vasculitis. In the largest database of biopsy-proven PAN (n=348), French Vasculitis Study Group, 253 patients had ANCA titer done at the time of diagnosis with PAN, and all were negative. Kidney biopsy revealed a rare diagnosis of MPO-ANCA+ PAN which was critical to determining the management in this patient.



Arrow Shows necrotizing arteritis of medium size arteries

PO1758

Complement-Mediated Thrombotic Microangiopathy in a Patient with Anti-GBM Disease: A Case Report

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Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a rapidly progressive glomerulonephritis, caused by pathogenic antibodies directed against the α3NC1 epitope of type IV collagen, and accompanied by pulmonary hemorrhage in about 50% of cases. Here we present a case of anti-GBM disease in combination with hemolysis, a rare and poorly understood association.

Case Description: A 22 y/o male with a history of tobacco use was admitted for oliguric acute kidney failure requiring initiation of dialysis. Kidney biopsy showed linear GBM staining for IgG, κ and λ, supporting the diagnosis of anti-GBM nephritis with crescentic involvement of all glomeruli and positive serum anti-GBM antibody. High dose corticosteroids were given but additional immunosuppression was held due to low probability of benefit in the setting of severe renal limited disease. One week after biopsy, the patient developed fever, and his Hb decreased to 6 g/dL due to microangiopathic hemolytic anemia with low haptoglobin, elevated LDH, mild platelet decline, and negative Coombs test. Additional workup was negative for malignancy, cobalamin deficiency, malignant hypertension, or infection including shiga-toxin, showed normal ADAMTS13 activity, C3, C4, factor H, I, B, and no CFH autoantibody, but an elevated sC5b9 level demonstrating terminal complement activity. Repeat kidney biopsy revealed an acute thrombotic microangiopathy (TMA) along with previously diagnosed anti-GBM disease. Treatment with Eculizumab was started, but diffuse alveolar hemorrhage (DAH) developed 19 days after admission and thus plasmapheresis and cyclophosphamide were initiated with reduction of anti-GBM titers and hemolysis and resolution of DAH.

Discussion: Anti-GBM disease and complement-mediated TMA are both exceedingly rare clinical entities. While hemolysis has been reported in the literature, this is the first report of complement-mediated TMA driving hemolysis in the setting of anti-GBM. Dysregulated activation of the alternative pathway in complement-mediated TMA and literature reports supporting a role for both classical and alternative pathways in anti-GBM disease suggests a possible link between the two diseases and a previously unrecognized role for complement dysregulation in cases of hemolysis observed in the setting of anti-GBM.

PO1759

IgG4-Related Kidney Disease Associated with an Unusual Vasculitic Peripheral Neuropathy

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Introduction: IgG4-related disease is a systemic autoimmune fibro-inflammatory disorder showing lymphoplasmacytic infiltrates with predominance of IgG4+ plasma cells and variable amounts of storiform fibrosis in the affected tissues. When kidneys are the only organs involved it is called IgG4-related kidney disease (IgG4-RKD). Neurologic involvement is less common and known to manifest as hypophysitis and pachymeningitis.

Peripheral neuropathy is rare. Our case illustrates an unusual presentation of IgG4-RKD with vasculitic peripheral neuropathy, which has never been reported before

Case Description: A 55-year-old Southeast Asian woman with allergic rhinitis presented to her PCP with burning and tingling from the knees down and difficulty with gait for about 6 months. Neurological examination was notable for weakness of ankle dorsiflexion and plantarflexion and loss of pinprick and vibration sense distal to ankles. This was attributed to iron deficiency anemia and a compressed nerve. However, her symptoms worsened on iron supplements and gabapentin and were accompanied by weight loss. CT scan of abdomen showed heterogeneous masses of the kidneys with few enlarged retroperitoneal lymph nodes. Kidney biopsy was performed and showed storiform fibrosis and plasma cell rich interstitial inflammation (>30 IgG4+ plasma cells/HPF) suggesting IgG4-RKD. Further work up was significant for serum IgE 1309 IU/ml (1.5-165), IgG4 177 mg/dl (2.4-121), ANA >1:1280, positive MPO-ANCA, RF 38 IU/ml (<14), ESR 77 mm/hr. CRP, complement levels and kidney function were normal. Prior to initiating therapy for IgG4 RKD she was referred for sural nerve biopsy for concern of associated vasculitis. Nerve biopsy showed severe myelinated and unmyelinated fiber loss in all fascicles, a recanalized epineural blood vessel, and dense perineural mononuclear cell infiltrates consistent with vasculitic neuropathy. Additionally, immunostaining showed IgG4 plasma cells up to 10/HPF. Her symptoms resolved with steroids, IVIG and rituximab. Serum IgG4 level improved to 26 mg/dl.

Discussion: IgG4-RD can have varied systemic manifestations. Although neurologic disease is less commonly seen in IgG4-RD, we report for the first time an associated vasculitic neuropathy that should be considered and worked up in symptomatic patients

PO1760

Differential Expression of Interferon-Stimulated Genes in ANCA-Associated Vasculitis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multi-systemic, necrotising vasculitis, causing severe morbidity and mortality. It is characterised by the presence of auto-reactive antibodies against neutrophil granule components, myeloperoxidase (MPO) and proteinase 3 (PR3). The disease course remains variable, and patients suffer substantial morbidity and mortality. Therapeutic advances are hampered by a lack of understanding of the mechanisms driving both initial disease susceptibility and long-term clinical outcome. To increase our understanding of disease mechanism and to uncover untargeted pathways for treatment, we studied the transcriptomes and serum proteomes of patients with active AAV.

Methods: The transcriptional profiles and protein expression of patients with AAV (31 PR3-AAV, 15 MPO-AAV, 1 dual ANCA positivity, 4 ANCA-negative) were studied at the time of diagnosis or during an active flare, whilst on minimal immunosuppression, along with healthy controls. AAV patients were profiled longitudinally at 3 and 12months. Separated leucocyte transcriptomes were profiled, using Affymetrix HuGene ST1.1 gene expression microarray. Transcriptional profiles were available on peripheral blood mononuclear cells (PBMCs), neutrophils, monocytes and CD4 and CD8 T cells. Protein expression was assessed on the SOMAscan platform. Analytical techniques included differential gene-expression, weighted gene co-expression network, gene set enrichment and multi-omics factor analyses.

Results: Here we identify, a module of interferon stimulated genes (ISG) that distinguishes the serological subtypes of AAV, MPO- and PR3-ANCA. This module of ISG was upregulated in MPO- compared with PR3-AAV during the time of active disease and at 3 months post treatment. The signature was present in the neutrophil, monocyte and PBMC transcriptome but was absent in T cells. Multi-omic factor analysis revealed a parallel upregulation of interferon like proteins in serum, coinciding with the increase in gene expression.

Conclusions: AAV causes severe morbidity and mortality. The differential expression of ISG in MPO compared with PR3-AAV highlights potential differences in pathogenesis. The presence of an interferon response in MPO-AAV opens new avenues for targeted treatment with agents such as Jak inhibitors and monoclonal anti-IFN-α antibodies.

PO1761

IL233-Induced Remission from Lupus Glomerulonephritis Involves Regulation of Mitochondrial Function and Canonical WNT Signaling

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Background: We recently showed the efficacy of a hybrid cytokine IL233 to protect mice from lupus glomerulonephritis (GN). We have now investigated the status of mitochondrial function, canonical Wnt signaling and metabolic fitness of regulatory T cells (Tregs), risk factors known to be associated with lupus GN to further delineate the mechanisms of protection offered by IL233.

Methods: We made use of the recombinant hybrid cytokine (IL233) bearing activities of IL-2 and IL-33 and tested its efficacy to prevent glomerular nephritis in the adenovirus (Ad)IFNa accelerated lupus GN NZM2328 model. Kidney lysates were screened for transcripts of mitochondrial and Wnt inhibitor genes by real time PCR and Western blotting. Mitochondrial membrane potential and metbolic fitness in IL233 treated mouse glomerular endothelial cells (MGECs) was investigated by flow cytometry and Seahorse assay. Metabolic fitness of Tregs with and without IL233 treatments were investigated by Seahorse assay by employing *ex vivo and in vivo* approaches.

Results: Analysis of transcript levels of mitochondrial function and biogenesis related genes (Pgc1α, Nrf1, Nrf2, Tfam, Drp1 and Mfn1) confirmed that IL233 treated kidneys displayed an elevated status. *In vitro*, changes in Pgc1α and its downstream target Nrf2 were recapitulated in treated MGEC cells. IL233 treated Tregs (*ex vivo and in vivo*) and MGECs (*in vitro*) also exhibited better mitochondrial metabolic fitness and displayed elevated levels of basal respiration, maximal respiration and ATP production investigated by the Seahorse assay. Wnt activators LRP6, Dvl3 and Wnt mediators - Axin1, GSK3a and GSK3b were significantly reduced in IL233 protected kidney. Levels of Axin2 was significantly upregulated with IL233 treatment indicating activation of a negative feedback loop for Wnt inhibition.

Conclusions: We present in depth mechanistic evidence of the observed remission from lupus GN with IL233 treatment. IL233 treated kidneys exhibit better mitochondrial dynamics and function. We show *in vitro, in vivo* and *ex vivo* evidence of IL233 treatment leading to betterment of mitochondrial function and metabolic fitness. Canonical Wnt signaling was attenuated. The data presented confirms the therapeutic efficacy of IL233 as a promising therapeutic agent for lupus nephritis and kidney injury.

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PO1762

Prediction of Histologic Class Using Deep Learning on Renal Biopsies from a Trial of Obinutuzumab for Proliferative Lupus Nephritis

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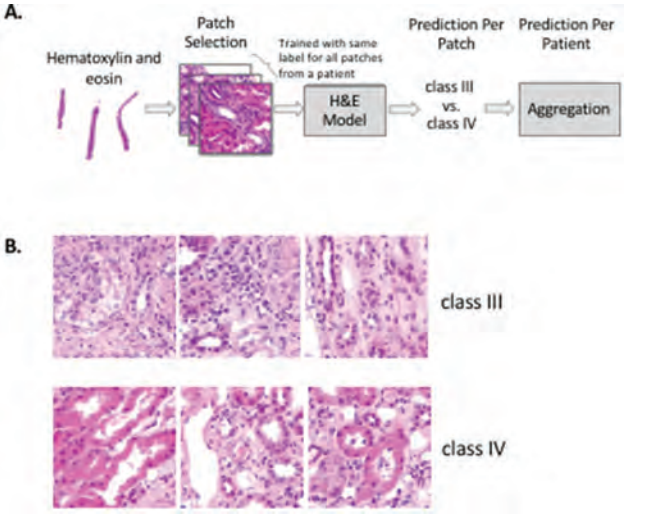
Background: Glomerular lesions in lupus nephritis (LN) are classified according to the International Society of Nephrology and the Renal Pathology Society classification system and significant disagreement between pathologists can occur on histopathologic lesions. The aim of this study was to assess if deep learning on renal biopsy whole-slide images could be used to predict class III vs. IV status among patients enrolled in a randomized trial of obinutuzumab for the treatment of proliferative LN (NCT02550652).

Methods: Baseline biopsies from 84 of the 126 patients randomized were available for analysis. From each hematoxylin and eosin (H&E) slide, patches of 512x512 pixels were extracted resulting in an average of 500 patches per slide. An Inception v3 neural network (NN) with weights pretrained on the ImageNet dataset was used to make a prediction for each patch, which were then combined to make a prediction for the patient (Fig. A). From the initial weights, all slide's layers were further fine-tuned using the cross-entropy loss between the model's prediction and the patient's true class. To evaluate the trained model, 25% of patients were held-out as a test set.

Results: The NN was able to classify the held-out patients with an area under the receiver operating characteristic of 0.82 (95% CI 0.60 - 1.00). Patches associated with class III vs. IV prediction could be extracted from each patient to provide interpretation (Fig. B).

Conclusions: These preliminary results showed that deep learning on renal biopsies can predict LN histologic class. The predictive patches provided additional interpretation. Such objective classification method has potential value to help minimize reading variability between pathologists.



(**A**) Computational pipeline for predicting the lupus nephritis histologic class of a patient from a whole-slide image. Examples of whole-slide image and patches were shown. (**B**) Examples of patches identified by the model as being most indicative of class III or IV.

PO1763

A Prospective Randomized Study on Preemptive Immunosuppressive Therapy in Lupus Nephritis Patients with Asymptomatic Serological Reactivation

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Background: The optimal management for asymptomatic serological reactivation (ASR) in lupus nephritis (LN) patients remains undefined. Our previous retrospective study suggested that pre-emptive moderate increase in immunosuppression may prevent subsequent clinical relapses.

Methods: We prospectively randomized LN patients with ASR (defined as ≥2-fold increase of anti-dsDNA to >100 IU/mL, with or without change in complement level, and absence of clinical lupus exacerbation) to receive pre-emptive treatment or unchanged management ('Control' group). Pre-emptive treatment included increasing prednisolone to 0.5 mg/kg/D, and the dose of mycophenolate to 1g/D or azathioprine to 75 mg/D, then tapered over 12-16 weeks back to the original dosages.

Results: Eighteen patients pre-emptive group and 17 in control group respectively). Pre-emptive group showed lower anti-dsDNA and higher C3 levels after 12 weeks compared with Controls ($p<0.001$, for both) (Figure 1). Pre-emptive group showed significantly lower incidence rates of all clinical relapses and renal relapse during subsequent 9 months follow-up compared with Controls (11.1% vs 41.2%, $p=0.02$; and 0% vs 17.6%, $p=0.03$; respectively). The pre-emptive group showed lower serum miR-148a compared with baseline value and also the Controls ($p<0.001$, for both). There was no clinically significant adverse event.

Conclusions: Our results suggest that pre-emptive moderate increase of immunosuppressive treatment reduces the risk of disease flare in LN patients with ASR and is well tolerated.

Funding: Government Support - Non-U.S.

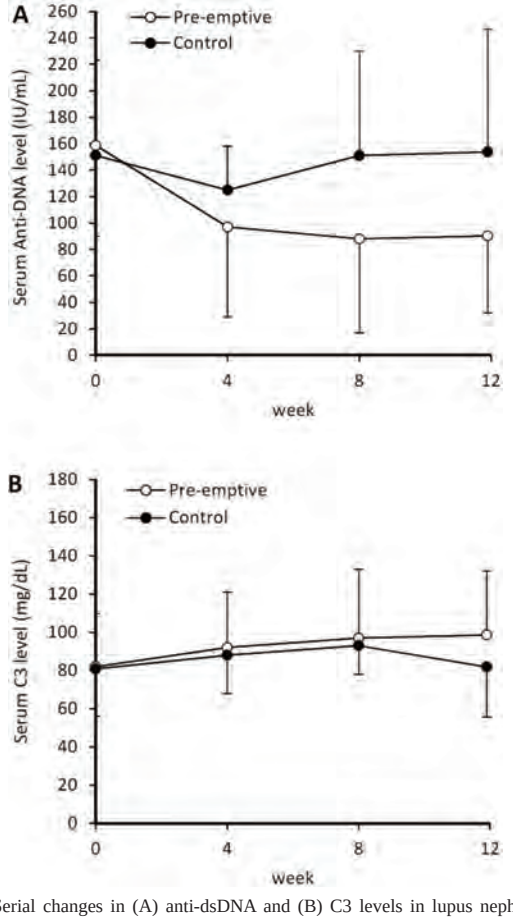

Figure1. Serial changes in (A) anti-dsDNA and (B) C3 levels in lupus nephritis with asymptomatic serological reactivation who have or have not reecieved pre-emptive immunosuppressive treatments.

PO1764

Kidney Thrombotic Microangiopathy Associated to Lupus Nephritis Is Mediated by the Activation of the Alternative Complement Pathway

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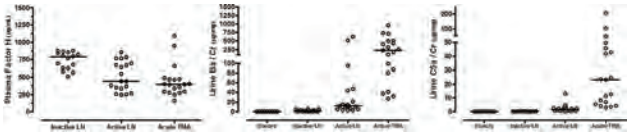
Background: Thrombotic microangiopathy (TMA) in the context of lupus nephritis is a rare disease whose pathogenesis has been linked to complement activation. This study aimed to evaluate complement pathway activation products in plasma and urine from patients with LN associated TMA (LN-TMA) and to compare its levels to patients with active LN (aLN), patients with inactive lupus (iSLE) and kidney donors (KD).

Methods: Plasma and urine samples were obtained from 19 patients with acute LN-TMA and 19 patients with biopsy-proven aLN matched by histologic activity index. Patients with iSLE (n=16) and kidney donors (n=10) were included as controls. Complement activation fragments C3a, C4a, C5a, Ba, C5bC9, and factor H were assessed by ELISA. Kidney C4d deposition was detected by immunohistochemistry. After 12 months, complement activation products were re-assessed after treatment.

Results: Both, the acute LN-TMA and aLN patients had increased plasma Ba and C5bC9 along with decreased plasma C3, C4, C4a, and factor H. Urine C5a, Ba, and C5bC9 were higher in patients with acute LN-TMA than in aLN. The levels of the urine complement fragment correlated with the degree of interstitial inflammation, interstitial fibrosis, and tubular atrophy in the kidney biopsy. After treatment, the levels of circulating C3, C4, and factor H increased, and the levels of urine C5bC9 decreased. In two patients with repeated LN-TMA episodes, factor H and urine C5a levels decreased, while urine Ba and C5bC9 increased after treatment in each episode. There was no difference in C4d fragment deposition in glomerular capillaries, tubular basement membrane, peritubular capillaries, and arterioles, between patients with aLN and those with acute LN-TMA.

Conclusions: The levels of plasma and urine complement activation products suggest that the pathogenesis of acute LN-TMA is mediated through activation of the complement alternative pathway.

Funding: Government Support - Non-U.S.



Levels of plasma factor H (A), urine complement fragment Ba (B) and urine complement fragment C5a (C) in the studied groups.

PO1765

Glycol Chitosan-Based Tacrolimus-Loaded Nanomicelle Therapy Ameliorates Lupus Nephritis

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Background: Hydrophobically modified glycol chitosan (HGC) nanomicelles loaded with tacrolimus (HGC-TAC) enhance the renal delivery of tacrolimus. Here, we determined whether the administration of HGC-TAC nanomicelles decreases kidney injury in a model of lupus nephritis.

Methods: Lupus-prone female MRL/lpr mice were randomly divided into 2 groups and given either intravenous vehicle or HGC-TAC (0.5 mg/kg tacrolimus) weekly for 8 weeks. Age-matched MRL/MpJ mice without *Fas^{lpr}* mutation were treated with a vehicle and used as healthy controls.

Results: Weekly treatment with intravenous HGC-TAC remarkably reduced genetically attributable lupus activity, blood urea nitrogen, and proteinuria in lupus nephritis-positive mice. In addition, HGC-TAC treatment mitigated renal dysfunction and histological injury, including glomerular proliferative lesions and tubulointerstitial infiltration. Furthermore, HGC-TAC treatment reduced renal inflammation and inflammatory gene expression, as well as ameliorated the increased glomerular fibrosis. Moreover, the administration of HGC-TAC appeared to regulate renal injury via the TGF-β1/p38MAPK/NF-κB signaling pathway.

Conclusions: Our study clearly indicates that weekly treatment with HGC-TAC nanomicelles reduces kidney injury resulting from lupus nephritis by preventing inflammation and fibrosis. This advantage of HGC-TAC nanocarriers may improve drug adherence and treatment efficacy in lupus nephritis patients.

Funding: Government Support - Non-U.S.

PO1766

Renal Activity Index for Lupus Nephritis Distinguishes Active Renal Disease Among Lupus Patients

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Background: Conventional tools to identify active nephritis in SLE (LN) fail to supersede invasive kidney biopsy. The renal activity index in lupus (RAIL) was developed using 6 urinary biomarkers to reflect disease activity (Brunner, *et al*. 2016). Our objective was to test RAIL for identifying active LN in childhood-onset SLE.

Methods: Urine samples obtained from cross-sectional sampling of 2 cSLE cohorts, classified as active LN, inactive LN or non-LN SLE. RAIL scores were calculated from ELISA or nephelometry data for six urine markers (NGAL-1, ceruloplasmin, MCP-1, adiponectin, hemopexin, kidney injury molecule-1). Data collected included ISN/RPS histologic classification and extra-renal component of SLE disease activity index (SLEDAI) score.

Results: Among 117 cSLE patients, 37 had active LN; 30, inactive LN; 50, no-LN. RAIL scores of inactive LN and no-LN group largely overlapped, so they were combined (Group 2) and compared to active LN (Group 1, Table). Group 1 had higher RAIL score (0.7 vs. -1.1). After adjusting for age and extra-renal SLEDAI score, RAIL score odds ratio was 2.16 (95%CI 1.4-3.3, p=0.001) for active LN. A receiver operating curve (ROC) for an adjusted RAIL cut-off score of 0.35 produced an AUC=0.9 (sensitivity 86%, specificity 84%) for active LN. Adjustment for urinary protein and creatinine did not influence results.

Conclusions: The RAIL score is highly accurate in distinguishing active from inactive LN and non-LN SLE. Scores >0.35 identify cSLE patients who very likely have active LN.

Clinical characteristics and distribution of RAIL scores among Group 1 (active LN) and Group 2 (inactive LN + active non-LN SLE) patients

	Group 1 Active LN N = 37	Group 2 Inactive LN + Non-LN SLE N = 80	p-value
Age (y), median (IQR)	15 (13-17)	18 (16-21)	< 0.0001
Extra-renal SLEDAI, median (IQR)	9 (6-13)	2 (0-4)	< 0.0001
GFR, median (IQR)	91 (60-129)	108 (98-126)	0.05
Urinary creatinine, median (IQR)	92 (61-191)	134 (73-184)	0.32
Urinary protein, median (IQR)	254 (98-404)	21 (11-50)	< 0.0001
Urinary microalbumin, median (IQR)	254 (189-316)	15 (9-43)	< 0.0001
RAIL Score, median (IQR)	0.7 (-0.1-1.6)	-1.1 (-2.5-0.3)	< 0.0001
NIH-AI, median (IQR)[¥]	9 (4-13)	0 (0-0)	< 0.0001
NIH-CI, median (IQR)[¥]	1 (0-2.75)	0 (0-0)	0.11

[¥] Includes only active (N=24) and inactive LN (N=4) patients with sampling performed within 30 days of kidney biopsy

PO1767

A Novel Inflammatory Dendritic Cell in Lupus Nephritis

Latha Prabha Ganesan,[1] Ana Malvar,[2] John P. Shapiro,[1] James M. Turman,[1] Huijuan Song,[1] Valeria G. Alberton,[2] Bruno J. Lococo,[2] Sethu M. Madhavan,[1] Anjali A. Satoskar,[1] Daniel J. Birmingham,[1] Wael Jarjour,[1] Brad H. Rovin,[1] Samir V. Parikh.[1] OSU Nephrology *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Hospital Fernandez, Buenos Aires, Argentina.*

Background: Progress in Lupus Nephritis (LN) management has been limited and treatment outcomes remain sub-optimal. Knowledge on intra-renal changes during LN flare and the major immune cells that drive local inflammatory damage will lead to improved outcomes in LN.

Methods: We performed transcriptomic analysis on serial kidney biopsies of proliferative LN (n=58). Glomeruli and Tubulointerstitium (TI) were isolated using LCM, and 580 immune transcripts were analyzed using Nanostring human immunology panel. Guided by transcriptomic analysis, multi-color, high-resolution confocal immunofluorescence (IF) analysis using antibodies against various immune cell markers, was performed on LN flare kidney biopsies (n=5) and healthy nephrectomy controls (n=5), to identify the dominant intra-renal immune cell phenotypes present during LN flare.

Results: Transcriptomic analysis identified Fc receptor gamma chain (FcRγ), to be the most significantly overexpressed glomerular immune transcript (Fold change (FC): 3.5, P=1E-10) and also overexpressed in the TI (FC: 1.7, P=0.001) compared to controls. Confocal IF analysis found FcRγ to be abundantly present in the peri-glomerular (PG) region and to a lesser extent in the TI during LN flare. FcRγ was weakly expressed in controls. Further IF analysis identified the phenotype of FcRγ expressing cells to be CD11c+,DC-SIGN+,MHC II+,CD64+,CD14+, CD16+,CD206-,CD68-,CD123-,CD3-,CD11b-. This signature aligns with a dendritic cell (DC) phenotype but distinct from plasmacytoid and conventional DC. It is most consistent with an inflammatory dendritic cell (infDC) phenotype. Importantly, confocal IF identified CD3+ T cells present in close proximity to PG infDC.

Conclusions: In this study, we identified a novel population of InfDC not previously described in LN. During LN flare, InfDC are present in abundance in the PG region. Their presence next to T cells suggests infDC dictate the nature of the T cell response during LN flare. Targeting infDC or their associated T cell phenotype may attenuate renal inflammation and improve outcomes in LN.

Funding: Other NIH Support - NIAMS

PO1768

Burden of Illness of Lupus Nephritis in Patients with Systemic Lupus Erythematosus

Christopher F. Bell,[1] Benjamin Wu,[1] Bin Xie,[2] Shirley Huang,[1] Benjamin Chastek,[2] Bernie Rubin,[3] Joan Von Feldt,[3,4] Gary Bryant.[3] *[1]GlaxoSmithKline, Research Triangle, NC; [2]Optum, Eden Prairie, MN; [3]GlaxoSmithKline, Philadelphia, PA; [4]University of Pennsylvania, Philadelphia, PA.*

Background: Approximately 35% of adults with systemic lupus erythematosus (SLE) develop lupus nephritis (LN). LN is associated with an increased risk of renal failure, cardiovascular disease, and death. Little is known about healthcare resource utilization (HRU) or costs of care for patients with LN versus those without SLE.

Methods: This retrospective cohort study used Optum Research Database administrative claims data (GSK Study 213062). Patients with LN had ≥2 renal diagnosis codes during 08/01/2017–07/31/2018 and ≥1 inpatient or ≥2 outpatient SLE diagnosis codes >30 days apart in the 12 months prior to index; index date was the date of first renal diagnosis code. The control cohort had plan members with no diagnosis codes for SLE or LN during 08/01/2016–7/31/2018. Control patients were matched 1:1 to patients with LN based on baseline demographics. Inclusion criteria: ≥18 years of age at index, and continuous medical and pharmacy coverage in the 12 months pre and post index. HRU in the 12 months post index captured ambulatory visits, emergency department (ED) visits, and hospitalizations. Total healthcare costs in the 12 months post-index were quantified combining health plan– and patient-paid amounts and adjusted using the Consumer Price Index.

Results: Across the LN and control cohorts, 2326 patients met study criteria; 38.5% were 45–64 years of age, 44.1% were ≥65 years of age, 85.6% were female, 58.1% were located in Southern USA states, and 66.3% were covered by Medicare. The LN cohort had a significantly higher mean (standard deviation [SD]) number of ambulatory visits (53.93 [55.34] vs 18.27 [21.61]), ED visits (2.87 [7.91] vs 0.86 [2.31]), and hospitalizations (0.86 [1.48] vs 0.12 [0.51]) versus the control cohort, respectively. Mean (SD) total costs were $50,958 ($86,100) for the LN cohort, which were significantly higher than $10,737 ($21,741) in the control cohort. Differences in cost were largely driven by mean (SD) medical expenses for the LN cohort versus the control cohort ($40,648 [$78,134] vs $6,781 [$14,773] respectively). All p-values were <0.001.

Conclusions: All-cause HRU and costs were higher for patients with LN than patients without SLE. This study quantifies the economic burden associated with LN.

Funding: Commercial Support - GSK

PO1769

Clinico-Pathological Associations with Serum Thrombomodulin Level in Patients with Lupus Nephritis

Tak Mao D. Chan, Kelvin Y. Yu, Desmond Y. Yap, Susan Yung. *The University of Hong Kong, Hong Kong, Hong Kong.*

Background: Conventional serological markers do not always correlate with clinical activity or histolopathology in lupus nephritis (LN). There is evidence of endothelial activation and injury in LN pathogenesis. Thrombomodulin (TM), a component of endothelial glycocalyx, is shed into the circulation in endothelial cell injury. We investigated clinico-pathological associations of circulating TM level.

Methods: TM level was measured by ELISA in sera collected serially every 3-4 months over ≥2 years (n=482) from 31 patients with biopsy-proven Class III/IV LN. Patients with non-renal SLE or non-lupus kidney diseases (CKD) and healthy subjects were included as Controls.

Results: Patients with active LN had the highest serum TM level, compared with LN patients in remission, patients with active non-renal SLE, CKD patients, or healthy subjects (P<0.01, for all). Serum TM level correlated with anti-dsDNA antibody titre, proteinuria, serum creatinine, SLEDAI-2K and renal SLEDAI-2K score; and inversely correlated with eGFR and C3 (P<0.05, for all). 8 patients had blood samples collected before disease flare, and 6 showed increased TM level (3.65±2.16 months before clinical flare). All episodes of LN flare were accompanied by elevated TM level, which decreased after treatment. A temporal relationship was noted between TM level and anti-dsDNA titre and C3 levels, proteinuria, SLEDAI-2K and renal SLEDAI-2K scores. TM level also correlated with renal interstitial inflammation score (r=0.54, P=0.0081). ROC analysis showed that serum TM level distinguished active LN from healthy subjects (sensitivity 100.00%, specificity 100.00%), from LN in remission (sensitivity 89.66%, specificity 68.97%), from active non-renal SLE (sensitivity 90.91%, specificity 100.00%), and from CKD (sensitivity 89.66%, specificity 56.52%) (P<0.001, for all).

Conclusions: Determination of serum TM level may facilitate early diagnosis of active LN, and may be useful in monitoring the response to treatment.

Funding: Government Support - Non-U.S.

PO1770

Enhanced Na-K-ATPase Expression Mediates B-Cell Survival in Lupus Kidneys

Irene Chernova, Joseph Craft. *Yale University School of Medicine, New Haven, CT.*

Background: Systemic lupus erythematosus (SLE, lupus) is a multi-organ autoimmune disease characterized by antibody deposition in target organs, including the kidney. Kidneys of affected patients are characterized by lymphocytic infiltrates that correlate with tissue damage and disease severity. The kidneys are also characterized by a high salt environment not found elsewhere in the body. Thus, infiltrating lymphocytes are presented with the unique challenge of surviving in a high salinity environment which may define their phenotype and function. We now describe the molecular mechanisms utilized by immune cells when faced with this hypertonic microenvironment.

Methods: We utilized lupus-prone (MRL^{lpr}) and wildtype (C57BL/6) mice and renal biopsy samples from lupus nephritis patients for this study. B cells from mice were cultured *in vitro*under standard versus high salt conditions. Kidney immune cell subsets were identified using flow cytometry and immunofluorescence techniques.

Results: B cells from lupus-prone (MRL^{lpr}) mice have enhanced survival when exposed *in vitro* to a high salt environment, compared to cells from control, non-autoimmune mice. The salt transporter Na-K-ATPase, and specifically its gamma subunit Fxyd2, is upregulated in the kidney and is necessary for kidney epithelial (tubular) cell survival under high salt conditions. We hypothesized that infiltrating lymphocytes also utilize Na-K-ATPase upregulation to survive in the hypertonic environment of the kidney. We found high expression of Na-K-ATPase alpha and gamma subunits on kidney-localized B cells of lupus-prone mice and high gamma subunit expression in B cells from human lupus kidney biopsies. Inhibition of Na-K-ATPase activity with a small molecule inhibitor ouabain led to increased cell death when lupus-prone B cells, but not control B cells, were cultured in high salt conditions, suggesting a role for Na-K-ATPase in the enhanced survival of MRL^{lpr} B cells in high salt. *In vivo* treatment of MRL^{lpr} mice with ouabain depleted renal-infiltrating B cells, but not T cells. MRL^{lpr} mice lacking the gamma subunit of Na-K-ATPase appear to phenocopy the ouabain-treated mice in preliminary analyses.

Conclusions: These studies identify a novel role for Na-K-ATPase in B cell survival in the hypertonic renal microenvironment and suggest it is a potential therapeutic target in lupus nephritis.

Funding: Other NIH Support - R21 AI142145-01, R37 AR40072-28

PO1771

TNIP1/ABIN1 Mutation Contributes to Lupus Nephritis via Chemokine IP-10 Induction

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Background: We previously reported TNIP1 gene variants as risks for lupus nephritis (LN). TNIP1 encodes the protein ABIN1, which is a polyubiquitin binding protein that negatively regulates the prominent immune regulatory transcription factor NF-κB. We reported that transgenic mice with impaired ABIN1 ubiquitin binding function (ABIN1[D485N]) spontaneously develop SLE-associated autoimmunity and LN and that ABIN1 determines the severity of LN via activation of kidney and immune cell inflammation. Interferon gamma-inducible protein -10 (IP-10) is a pro-inflammatory chemokine and NF-κB target that has been implicated in the pathogenesis and as a diagnostic marker of LN. The current project tested a hypothesis that LN development is mediated by induction of IP-10 expression due to loss of cellular ABIN1 activity.

Methods: In order to test our hypothesis, we measured urine and serum IP10 in ABIN1[D485N] mice using ELISA and utilyzed IHC techniques to measure kidney IP10 expression. Additionally, we used ELISA to measure urinary IP10 levels in human subjects with LN (with and without TNIP variant rs4958881) and in healthy controls.

Results: We found that serum, urine, and kidney cell IP-10 expression is enhanced in ABIN1[D485N] mice. We also found that urinary IP-10 levels are higher in LN patients with TINIP1/ABIN1 variant rs4958881 when compare to LN patients without the TNIP1 variant and healthy controls. The rs4958881 variant also correlated with disease severity.

Conclusions: Our findings indicate that TNIIP/ABIN1 mutation contributes to the pathogenesis of LN via kidney and immune cell induction of IP-10 secretion and that serum and urinary IP-10 are promising diagnostic markers for LN especially in patients with TNIP1 variants. Further, successful Phase 2 clinical trials with IP-10 mAb for ulcerative colitis indicate its potential for effective LN treatment.

Funding: NIDDK Support

PO1772

Comparative Cross-Tissue and Cross-Species Transcriptome Analyses Predict Lupus Nephritis in Human Systemic Lupus Erythematosus and Guide Therapy in a Tissue-Specific Manner

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Background: Despite advances, morbidity and mortality in systemic lupus erythematosus (SLE) and lupus nephritis (LN) remain increased. Most clinical trials on novel therapies failed to meet their primary end-points, highlighting the need for therapeutic interventions targeting pathways enriched within individual tissues.

Methods: We applied RNA-sequencing to spleen, kidneys and brain from NZB/W-F1 lupus-prone mice at three stages: the pre-puberty, pre-autoimmunity and nephritic stage. Differentially expressed genes (DEGs) were analyzed with DESeq and functionally annotated with gProfiler. ChEA and Genes2Network were used to infer transcription factors and identify proteins that physically interact with them, respectively. KEA was used to link kinases predicted to regulate DEGs. Implications for human disease were explored in our whole-blood RNA-sequencing dataset of 120 SLE patients [55 LN and 65 non-LN SLE patients and 58 healthy individuals (HI)]. The L1000CDS^2 engine was used to identify drugs/small molecules predicted to reverse DEGs. Human orthologs of DEGs were compared to human DEGs. Using machine learning, orthologs from the mouse dataset were used to predict LN in the human dataset, which was split in training and validation sets.

Results: We define lupus-susceptibility and lupus-progression signatures that reveal pathways and gene hubs, and a common cross-tissue signature that depicts transcription factors as putative upstream regulators and kinases as potential targets. Tissue-specific signatures uncovers distinct tissue response and repair mechanisms in end-organ injury and distinct targets. 7 small molecules/drugs are predicted to reverse gene signatures in both murine and human SLE.193 orthologs accurately predict LN patients from HI (accuracy=0.86, sensitivity=0.82, specificity=0.91 in the validation set) and 30 orthologs with age and gender best predict LN from non-LN SLE patients (accuracy=0.71, sensitivity=0.73, specificity=0.69 in the validation set).

Conclusions: A murine cross-tissue transcriptome analysis uncovers gene signatures, pathways and tissue-specific targets. The cross-species transcriptome analysis predicts LN in human SLE and guides therapy in a tissue-specific manner.

PO1773

An Inducible Model of Early Lupus Nephritis

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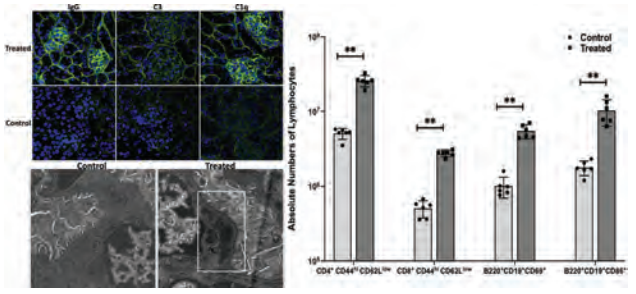
Background: Lupus nephritis (LN) is characterised by polyreactive antibodies targeting 'planted' glomerular autoantigens. But how these deposits recruit inflammatory mediators and the roles of resident and recruited cells is unclear. Distinguishing damaging pathways from protective tissue responses is a major challenge. With disease progression, non-specific signals of fibrosis become dominant and human tissue comparisons are confounded by genetic and environmental heterogeneity. A way to separate these early and late pathological events is to use murine models of nephritis. Topical treatment with toll like receptor-7(TLR7) agonist Imiquimod(IMQ) for 8 weeks has been shown to induce glomerulonephritis(GN), significant weight loss and mortality. Using detailed renal and immune phenotyping we explored the suitability of this model to study the very early, active stages of LN.

Methods: 6-week female BALB/c mice were treated 3 times weekly for 5 weeks with topical IMQ or Vaseline control(n=6/group). Immune profiling of spleen, bone marrow and mesenteric lymph node was by flow cytometry. Kidneys were fixed and processed for Period Acid Schiff, immunofluorescence and TEM. Serum was assayed for creatinine, urea and albumin.

Results: Treated mice had increased numbers of activated splenic CD4 and CD8 T cells($CD44^{hi}CD62L^{low}$,$P<0.001$), Tregs($CD4^+CD25^+FOXP3^+$,$P<0.01$) and activated B cells($B220^+CD19^+CD86^+CD69^+$,$P<0.001$). IMQ did not result in weight loss, mortality or significant changes in serum creatinine or urinary protein creatinine ratio but kidney histology showed mild mesangial hypercellularity with strong glomerular positivity for IgG, C1q and C3. TEM showed early basement membrane duplication, focal subendothelial and mesangial deposits and mild podocyte effacement.

Conclusions: This study characterises the IMQ model of LN revealing $CD44^{hi}$ T cell activation and TEM evidence of immune deposits reminiscent of human class II lupus. Treatment for 5 weeks is well tolerated without overt renal failure and creates a model for studying the early pathways involved in immune complex GN and associated therapeutic targets.



PO1774

Efficacy and Safety of Non-Mitogenic Anti-CD3 in the Treatment of Lupus-Prone Mice

Masashi Morita, Masayuki Mizui, Satoshi Masuyama, Yoshitaka Isaka. *Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Armenian hamster anti-mouse CD3ε monoclonal antibody (145-2C11) is known to suppress T cell function in vivo by reducing T-cell receptor (TCR) expression and inducing T cell depletion. However, it has also mitogenic potentials through the functional Fc portion. Although in vivo administration of Fc-deleted 145-2C11 F(ab')2 was reported to ameliorate lupus in mice, the detailed mechanisms are still unclear. Recently developed Fc-modified 145-2C11 (2C11 silent; 2C11S), which lacks the ability to bind complement or Fc receptor, is expected to be stable and safe in vivo as compared with native 145-2C11 (2C11N). Whether 2C11S has therapeutic potential in lupus remains to be elucidated.

Methods: Twenty micrograms of Armenian hamster anti-CD3ε (hamster 2C11N), mouse anti-CD3ε (mouse 2C11N), mouse anti-CD3ε Fc-silent (2C11S), or isotype control IgG1κ (IC) were injected intraperitoneally to C57BL6 mice. Lymphocyte number, TCR expression and plasma cytokines from peripheral blood were checked in time series. Next, 2C11S, 2C11N, and IC were administered (100 μg / week, 4 times, intraperitoneally) to NZB/W F1 mice at the age of 10 (early phase) and 20 (active phase) weeks, respectively. Renal histology, immune cell infiltration, and gene expression of cytokines/chemokines were evaluated.

Results: As compared with 2C11N, 2C11S reduced TCR expression on T cells in vivo for longer period (more than 96 hours) without inducing cytokine release. In early phase of lupus, the rate of change in anti-dsDNA IgG titers (day28 / day0) were significantly reduced in 2C11S group (IC; 2.9±2.0, 2C11S; 2.1±3.0, 2C11N; 2.0±1.8, IC vs 2C11S; p=0.03), which was associated with the decreased number of both follicular helper-T cells and germinal center B-cells in spleen. In active phase, glomerular hypercellularity was diminished in 2C11S group (glomerular cell number: IC; 53±18, 2C11S; 44±6.1, 2C11N; 47±6.6, IC vs 2C11S; p=0.03) and lymphocyte infiltration into kidney was significantly reduced in 2C11S group. In addition, reduction of inflammation-related genes such as IFNγ and IL-2 in kidney indicated improvement of lupus nephritis by 2C11S.

Conclusions: 2C11S, but not 2C11N, suppressed autoantibody production and ameliorated lupus nephritis, possibly through stable down-regulation of TCR. Targeting CD3 to modulate TCR expression could be a novel therapeutic approach in lupus.

PO1775

Suboptimal Serological and Clinical Remission on Supportive Therapy in Phospholipase A2 Receptor Membranous Nephropathy

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Background: A traditional notion is that one third of patients with primary membranous nephropathy (MN) are expected to achieve spontaneous clinical remission without immunosuppressive therapy (IST). Thus, Kidney Disease Improving Global Outcomes (KDIGO) recommends at least 6 months of supportive therapy (SUPPT) without IST in patients with primary MN with low risk for developing end-stage renal disease. Recently, phospholipase A2 receptor (anti-PLA2R) antibody titers have been added to decision-making algorithms. Our objective was to examine and contrast the rates of serological and clinical remission in patients with PLA2R-MN managed by either SUPPT or IST.

Methods: We retrospectively reviewed records of adult patients diagnosed with PLA2R-MN in native kidneys over the last 5 years at our single medical center. Trajectories of anti-PLA2R titers were extracted. Rates of partial remission (PR) (reduction in urine protein-to-creatinine ratio (UPCR) to 0.5 to 3.0 g/g) and complete remission (CR) (UPCR < 0.5 g/g) were assessed at varying time points within a 24 month interval and compared between patients managed by either SUPPT or IST.

Results: We included 25 patients, median age 59 years, 44% women, 60% black. Positive PLA2R antigen in kidney biopsy was verified in 18/27 (72%). Eight patients were managed by SUPPT and 17 by IST. The median serum creatinine at the time of biopsy was 1.0 mg/dL for both groups (p=0.58), whereas the median UPCR were 5.6 g/g in the SUPPT arm and 10.5 g/g for IST (p=0.004). Median anti-PLA2R titer at baseline were 49 (17-76) and 258 (35 - >1500) RU/mL for the SUPPT and IST arms, respectively, p=0.0058. By the 18-month time mark, 9/17 (53%) in the IST group achieved serologic remission (negative anti-PLA2R titer) vs 0/6 (0%) in the SUPPT arm (p=0.02) (missing follow up anti-PLA2R titer in 2 SUPPT patients). At 24 months, CR and PR was achieved in 1/8 (12.5%) and 3/8 (37.5%) of patients under SUPPT and in 3/17 (17.6%) and 8/17 (47%) of those under IST (p=0.75 and p=0.66, respectively).

Conclusions: Despite baseline characteristics denoting less aggressive disease, patients with PLA2R-MN under SUPPT therapy did not achieve greater rates of clinical remission and exhibited a lower rate of serological remission. Current algorithms dictating choice of SUPPT as initial treatment in low-risk PLA2R-MN should be revisited.

PO1776

Glomerular Proteomics Reveal Shared Pathways Across Several Disease

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Background: Glomerular diseases are caused by a variety of immunologic and metabolic disturbances. While there is considerable disease heterogeneity, morphologic patterns of injury are limited and clinical phenotypes are similar across diseases. This suggests that mechanisms of inflammation and the glomerular response to injury is similar across disease states. Characterizing these mechanisms may provide insights into the common pathways of glomerular injury and lead to new insights in pathogenesis and treatment. As a first step, we used an agnostic proteomics approach to identify common regulated pathways across a variety of glomerular disorders.

Methods: Kidney biopsies from 36 patients across several glomerular diseases and 21 controls (transplant donor biopsies) were used. Glomeruli were isolated using laser-capture microdissection, processed, and submitted for LC-MS/MS. Peptides were analyzed for spectral count quantitation. Spectral counts of each disease were compared to control samples that were analyzed in the same batch. Only peptides with a spectral count coefficient of variation <1 were included in expression ratio calculations. Disease-to-control expression ratios >2 or <0.5 were used for pathway analysis using Reactome. The top 10 pathways were grouped into domains and are depicted in figure 1.

Results: Pathways involved in complement regulation and activation, fibrin clot formation, and platelet aggregation were upregulated in most disease categories. On the other hand, pathways of carbohydrate, protein, amino acid metabolism, and cell cycle pathways were downregulated in most disease categories.

Conclusions: Proteomic analysis of a heterogeneous population of glomerular diseases identified several shared dysregulated pathways that may reflect common final pathways associated with glomerular injury. These pathways reflect important immunologic and metabolic changes that have the potential to be leveraged therapeutically across a variety of glomerular diseases in a manner similar to RAAS blockade.

	n	Complement Regulation	Complement activation	Fibrin clot formation	Platelet Activation	Lipid transport and metabolism	Carbohydrate metabolism	Protein and AA metabolism	Lipid metabolism	Cell Cycle
IgA Nephropathy	3									
IgA Vasculitis	3									
Staph Aureus-associated glomerul	4									
Class IV lupus nephritis	3									
Class V lupus nephritis	2									
APOL-1 FSGS	3									
Primary FSGS	3									
Diabetic Nephropathy	2									
Fibronectin Nephropathy	2									
IgG-1 Membranous Nephropathy	8									
IgG-4 Membranous Nephropathy	3									

Top regulated pathway domains. Red: upregulated, blue:downregulated

PO1777

Glucocorticoid Toxicity in the Ponticelli Regimen

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Background: Idiopathic membranous nephropathy (IMN) is a immune complex mediated renal disease and the leading cause nephrotic syndrome in non-diabetic adults. Long term relapse data for modern drugs like Calcineurin inhibitors and B-cell therapy are lacking. Modified Ponticelli regime offers 70% relapse free survival for 10 years however toxicity of cyclophosphamide and glucocorticoids(GC) remains major concern. Assessment of GC toxicity has not been assessed in this cohort. This study looked at the GC toxicity of patients in the year following treatment completion[1,2]

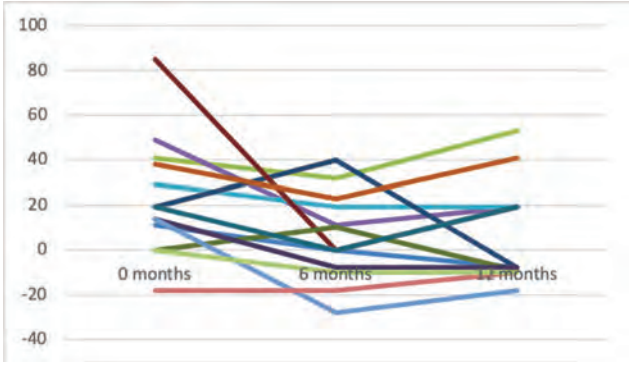
Methods: The glucocorticoid toxicity index (GTI)was calculated for 15 IMN patients treated with modified Ponticelli regime at time of treatment completion(0) and then 6 and 12 months post treatment completion, and compared to a pre-treatment baseline. The total dose of steroids received during treatment was also calculated.

Results: Mean cumulative prednisolone dose was 11.05g. The results at 0,6 and 12 months post completion of the Ponticelli regime for individual patients is shown on the graph. At completion 12/15 patients demonstrated GC toxicity, 7 at 6 months improving to 6/15 at 12 months. Effect on blood pressure (BP) was the most common indicator of GC toxicity at 12 months: 4/15 patients. 6 patients were in negative points at 12 months, due to improvement in weight, BP and lipid levels

Conclusions: Overall apart from BP, only 2/15 patients had evidence of damage due to GC exposure at 12 months in spite of very high cumulative GC doses. This lower level incidence of GC toxicity could be due to less impact on hypothalamo-pitutary axis due to unusual dosing regime of alternating months. Limitations: Relatively small cohort and

retrospective design 1- Ponticelli C, Passerini P. Treatment of the nephrotic syndrome associated with primary glomerulonephritis. *KI.* 1994;46:595–604 2- Bjorneklett R, Vikse BE, Svarstad E, et al. Long-term risk of cancer in membranous nephropathy patients. *Am J Kidney Dis.* 2007;50:3:396-403

male: female	Average Age	Average cumulative glucocorticoid dose	Average GTI 0 months	Average GTI 6 months	Average GTI 12 months
13:2	54.2	11405g	22	7.9	6.4



PO1778

Experimental Membranous Nephropathy in a Novel Transgenic Rat Model of Decay-Accelerating Factor Deficiency Generated by CRISPR-Associated Protein 9 (Cas9) Genome Editing

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Background: Decay accelerating factor (DAF), controls extent of formation of C3 and C5 convertases. Using clustered regularly-interspaced short palindromic repeats, CRISPR/ associated protein 9 (Cas9) genome editing a DAF deficient (*daf*$^{-/-}$) rat model was generated. The present study describes the renal and extrarenal phenotype of this model and responses to podocyte injury in experimental membranous nephropathy (MN).

Methods: daf+/- rats were produced by injecting multiple CRISPRs targeting Cd55 exon 2 into Sprague-Dawley rat embryos. A founder harboring a net 4-bp deletion in exon 2 was backcrossed to the parental strain and litters were genotyped. 1 ml of anti-Fx1A serum was injected in daf+/+ and daf-/- rats to induce MN. Control rats received a single dose (1ml) of normal rabbit serum. DAF protein and mRNA levels were determined by western blotting and Real time PCR Renal function assessment involved measurement of serum urea and creatinine levels and urine albumin/creatinine ratio. C3 deposition was confirmed by immunofluorescence (IF) and western blot (WB) analysis.

Results: daf-/- rats were healthy, viable and able to reproduce normally. DAF was completely absent in renal and extrarenal tissues (lung, heart) at protein and mRNA level. There was no effect on glomerular Crry and CD59 protein expression. There were no glomerular or tubulointerstitial lesions in daf-/- rats compared to daf+/+ and no change in serum urea and creatinine or in urine protein excretion. There was a significant increase in proteinuria 14 days following anti-Fx1A injection in daf-/- rats accompanied by increased glomerular C3 deposition.

Conclusions: In experimental MN, DAF attenuates proteinuria. The daf-/- rat model provides a valuable tool to assess role of DAF in regulating complement activation in glomerular diseases, such as MN, which is best characterized in this species.

PO1779

T-Cell Epitopes of M-Type Transmembrane Phospholipase A2 Receptor in Primary Membranous Nephropathy

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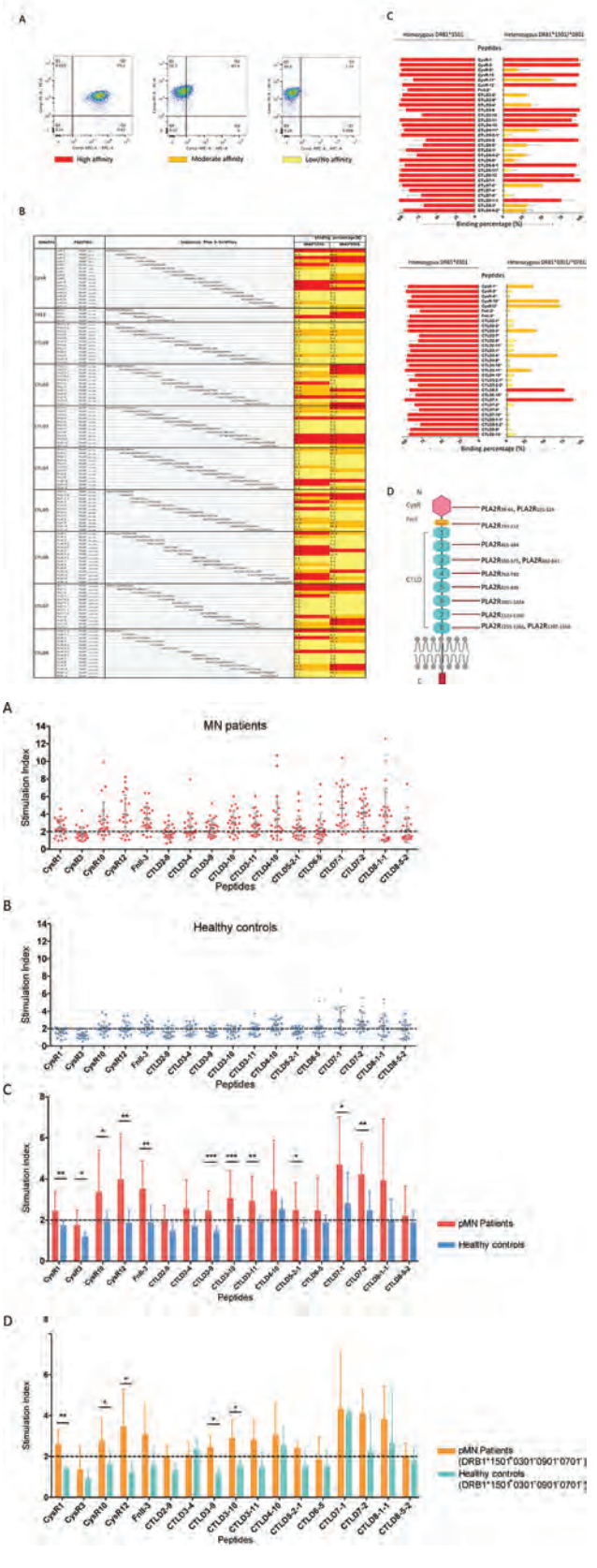
Background: PLA2R is the major autoantigen of pMN. There is no information on T cell epitopes. We previously identified the risk HLA molecules DRB1*1501 and DRB1*0301.

Methods: 123 linear peptides, each consisting of 15-22 amino acids and overlapping by 8-12 amino acids, were synthesized across PLA2R. Their binding capacity to DRB1*1501 and DRB1*0301 were assessed by flow cytometry. Proliferation of CD4$^+$ T cells from patients with anti-PLA2R positive pMN was analyzed after peptide stimulation using CFSE dilution assay. Cytokines produced by activated PBMC were measured by cytometric beads array.

Results: We found 17 peptides that bound to both DRB1*1501 and DRB1*0301 molecules with high capacity. Among them, 11 peptides induced significant proliferations of CD4$^+$ T cells from patients with anti-PLA2R positive pMN: $PLA2R_{38-52}$(CysR1), $PLA2R_{52-66}$(CysR3), $PLA2R_{101-120}$(CysR10), $PLA2R_{113-129}$(CysR12), $PLA2R_{193-212}$(FnII-3), $PLA2R_{602-621}$(CTLD3-9), $PLA2R_{612-631}$(CTLD3-10), $PLA2R_{622-641}$(CTLD3-11), $PLA2R_{829-838}$(CTLD5-2-1), $PLA2R_{1121-1140}$(CTLD7-1) and $PLA2R_{1129-1150}$(CTLD7-2). Upon activation, PBMCs had similar pro-inflammatory cytokine profiles, predominantly IL-6, TNF-α and IL-10, and to a lesser extent IL-4/5/13 and IL-17.

Conclusions: Thus, we identified 11 potential T-cell epitopes on PLA2R.



PO1780

Investigating the Role of Complement in Membranous Nephropathy Using a Novel Ex Vivo Podocyte Model

Sarah M. Moran,[4] Carolina Ortiz,[1] Moin Saleem,[3] Daniel C. Cattran,[2] Christoph Licht.[1] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Toronto General Hospital, Toronto, ON, Canada; [3]Bristol Royal Hospital for Children, Bristol, United Kingdom; [4]Queen's University Faculty of Health Sciences, Kingston, ON, Canada.*

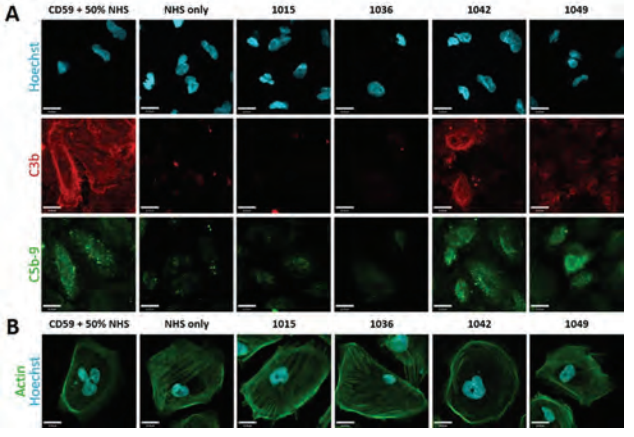
Background: Membranous nephropathy (MN) is an immune-mediated glomerular disease and is the commonest cause of nephrotic syndrome in adults. Progressive loss of kidney function leading to end-stage kidney disease occurs in up to one third of patients. We aimed to explore the potential functional link between antibody positive primary MN and the innate immune complement system using an ex vivo model of human podocytes.

Methods: Using a human podocyte ex vivo model, we evaluated complement activation via immunofluorescence staining for deposition of C3b and C5b-9, and functional alterations (demonstrated by cytoskeletal rearrangement) via IF staining for ActinGreen. Activation of complement via the classical pathway was used as positive control (incubation of podocytes with anti-CD59 and 50% NHS for 30 min), whereas NHS-only treated cells were used as negative control. Four patients with biopsy proven primary membranous nephropathy and detailed clinical phenotype were recruited from the Toronto GN Registry. To determine the role of complement in MN pathogenesis, podocytes were incubated with patient serum for 30 min.

Results: 2/4 patients who were nephrotic, antibody (aPLA2R or THSD7A) positive with no current immunosuppression demonstrated (1) positive C3b and C5b-9 staining confirming complement activation (Fig. 1A), and (2) reduced actin staining confirming impaired cytoskeletal organization (Fig. 1B). The remaining 2 patients with negative findings were Ab positive and treated with rituximab at the time of sample collection.

Conclusions: We successfully applied a new ex vivo model using podocytes to demonstrate complement activation in non-immunosuppressed MN patients. Further studies are needed to elucidate the detailed structural and functional consequences of complement activation in MN.

Figure 1



PO1781

Red Herrings: Delayed Immune Checkpoint Inhibitor-Associated Interstitial Nephritis with Membranous Glomerulonephritis and Myeloperoxidase-ANCA Antibodies

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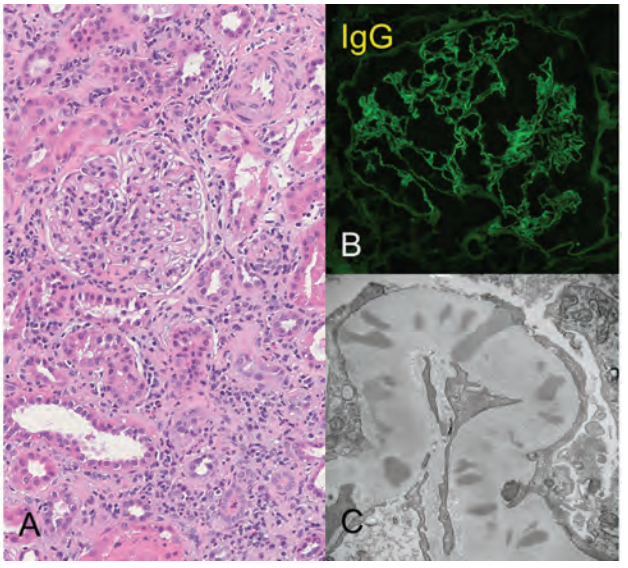
Introduction: Immune checkpoint inhibitor (ICI) indications are expanding. The most common renal pathology is interstitial nephritis. Here, we report a late presentation of ICI-induced interstitial nephritis with concurrent membranous glomerulonephritis (MGN) and MPO-ANCA antibodies.

Case Description: A 52-year-old woman with stage IV small cell lung cancer and prior gastric sleeve surgery on PPI therapy presented with diarrhea and AKI 5 months after discontinuing nivolumab. Her serum creatinine (SCr) was 5.5 mg/dL on presentation, from a baseline of 0.8 mg/dL, along with 0.69 g/g proteinuria and an MPO-ANCA titer of 19 units. Her PPI was discontinued and her AKI rapidly improved with hydration to a SCr of 1.5 mg/dL. Three weeks later, and four days after resuming her PPI, her SCr increased to 7.6 mg/dL. Repeat MPO-ANCA titer was 7 units. Renal biopsy showed diffuse interstitial nephritis and glomerular capillary wall thickening **(Figure 1A)**. Immunofluorescence showed capillary wall and mesangial IgG4-dominant depositions which did not colocalize with PLA2R **(Figure 1B)**. Penetrating subepithelial and intramembranous deposits along with thickened membrane were suggesting a late stage MGN **(Figure 1C)**. The patient was diagnosed with ICI-associated interstitial nephritis, likely provoked by PPI. Following a steroid taper, her SCr improved to 1.2 mg/dL.

Discussion: We reported a late-manifestation of ICI-associated interstitial nephritis (6 months after last exposure) in the setting of PPI use. This case is unique because of its late presentation (>90% of cases present within 3 months from the last dose), and findings of MPO-ANCA antibodies and MGN. Given her mild proteinuria and downtrending ANCA titer, we hypothesized that these were not the cause of AKI, but both were likely ICI-associated nonetheless. Nephrologists should be aware of these rare ICI-associated autoimmune conditions.



PO1782

A Case of Membranous Nephropathy After Nivolumab Administration

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Introduction: Nivolumab is one of the molecularly targeted drugs and is an anti-human PD-1 monoclonal antibody. We report a case of nephrotic syndrome caused by Nivolumab for treatment-resistant gastric cancer.

Case Description: The patient is a 61-year-old man. In June of -4 years before admission, total gastrectomy was performed for gastric cancer, and postoperative chemotherapy was administered as a second-line treatment, but peritoneal dissemination occurred. Nivolumab therapy was started in June of -2 years as a third-line treatment. She developed secondary adrenal insufficiency, which was considered an immune-related adverse event (irAE) with Nivolumab after the first dose, and oral hydrocortisone was initiated. In March of -1 year, mediastinal and hilar lymphadenopathy and skin pruritus, which were considered to be immune-related adverse events, were observed again, so Nivolumab was once discontinued, but it was resumed in April after improvement of the skin symptoms. However, proteinuria with hypoalbuminemia was appeared in June, Nivolumab was stopped again and the patient was finally consulted to our department in July. His serum albumin was 2.8 g/dL and urine protein was 5.9 g/gCr. Since the right kidney was atrophic, the open kidney biopsy was carried out in September. Light microscopy did not reveal thickening of the basement membrane, spike formation or bubbling appearance, however, immunofluorescence staining showed granular staining of IgG, C3, C1q and all of IgG subclasses although PLA2R staining was negative. Electron microscopy revealed electron-dense deposits under the epithelium, suggesting secondary membranous nephropathy. Though the urine protein tended to decrease after the discontinuation of Nivolumab, Prednisolone 40 mg/day was started and resulted in the complete remission in the 19th hospital day.

Discussion: There are several reports of interstitial nephritis by Nivolumab, however, the report of nephrotic syndrome is rare. Particularly, no case of membranous nephropathy by Nivolumab has ever been reported and this case is considered to be valuable.

PO1783

Evolution of Resolving Clinical and Histological Changes in Kidney Grafts from a Donor with Primary Membranous Nephropathy

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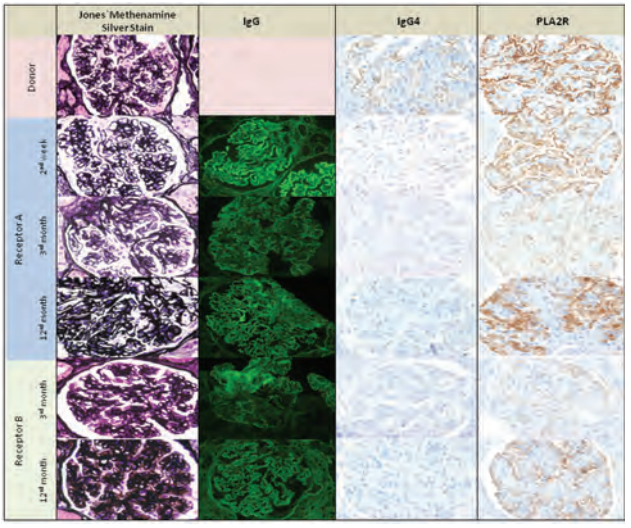
Introduction: Primary membranous nephropathy (PMN) is an autoimmune disease limited to the kidney that is characterized by the presence of circulating PLAR2 antibodies in 70% of the cases and usually positivity for PLA2R and IgG4 by immunohistochemistry (IHC) staining. We report the clinical and histopathological evolution of two recipients from a donor after circulatory death (DCD) with PMN.

Case Description: DCD Maastricht III was a 63-year-old male, died from respiratory failure. His serum creatinine was 0.9 mg/dL, no urinalysis was performed. The Remuzzi-score preimplant-biopsy was 1 point for the right kidney (recipient A) and 2 points for the left kidney (recipient B). Thymoglobulin as induction therapy, with tacrolimus,

mycophenolate mofetil, and prednisone as a maintenance immunosuppressive regimen for both recipients. A kidney biopsy was performed two weeks after in recipient A due to delayed graft function. It was compatible with MN with both PLA2R and IgG4 subepithelial deposits. The donor's kidneys biopsies were reexamined, revealing MN, with high intensity for PLA2R and IgG4 in IHC. Recipient B 3rd-month protocol allograft biopsy revealed histology compatible with MN, without the presence of PLA2R and IgG4 in IHC. At one year follow-up, both recipients maintain graft function and the protocol biopsies showed a negativization of IgG4 but the persistence of PLA2R in IHC, this positivity was attributed to the variability inherent to the technique.

Discussion: Given the reversal of PMN changes in the grafts, it is probably safe to transplant a patient from an asymptomatic donor with PMN as long as he maintains unaltered renal function. Observation of IgG4 immune complexes is more accurate to assess histological remission.



PO1784

Coexistence of Bullous Pemphigoid and Membranous Nephropathy

Brigette Thomas, Dhishna Chaudhary, Anika Bethel, Enoemem M. Okpokpo. *Florida Atlantic University Charles E Schmidt College of Medicine, Boca Raton, FL.*

Introduction: Bullous pemphigoid (BP) is an autoimmune disease with linear deposition of IgG and C3 in the skin basement membrane. BP is rarely associated with renal abnormalities like membranous glomerulonephropathy (MN). We describe a rare case of MN in a patient with BP.

Case Description: 75-year-old male, intermittently treated with prednisone for upper extremity (UE) skin lesions, presents with bilateral UE pruritic bullae, bilateral lower extremity (LE) and scrotal edema. He was previously treated for LE edema. Renal indices confirmed nephrotic range proteinuria. Kidney biopsy showed subepithelial immune deposits consistent with primary MN (immunostain negative for PLA2R). He was treated with furosemide and lisinopril. Skin biopsies of his bullae were inconclusive. His LE edema and UE bullae progressed due to lack of follow up, leading to this hospitalization. Labs revealed eosinophilia, hypoalbuminemia and nephrotic range proteinuria. HIV, hepatitis panel, ANA, SPEP and UPEP were negative. Malignancy was ruled out. Diagnosis of BP was finally confirmed via positive indirect immunofluorescence and ELISA testing. Treatment was limited to ethacrynic acid since ACEi/ARBs and furosemide are known to induce BP. Initiation of prednisone and rituximab resulted in cessation of new bullae and decrease in proteinuria.

Discussion: Both BP and MN are immune complex diseases involving two different basement membranes, so their occurrence together is not coincidence. Although our patient's kidney biopsy had negative immunostaining, the electron microscopy identified only subepithelial deposits, characteristic of primary, not secondary MN. This coincides with few cases in literature identifying BP occurring exclusively with primary MN. Our patient developed BP manifestations prior to MN and received intermittent prednisone without formal diagnosis of BP. Perhaps corticosteroids suppressed his MN symptoms leading to delay in diagnosis. Improper treatment of MN with known BP inducing medications led to persistent bullae formation. As the severity of skin lesions decreased, so did the proteinuria, suggesting that progression of bullae may be a sign of worsening MN. This case highlights the importance of thorough history taking, detail review of medications and appropriate outpatient follow up.

PO1785

Phospholipase A2 Receptor (PLA2R) Positive Membranous Nephropathy (MN) in Celiac Disease

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Introduction: In a 2011 study, PLA2R antibody (Ab) was detected in lupus MN, HBV MN, and solid tumor associated MN, with IgG4 stained glomeruli. PLA2R+ patients did not achieve remission with HBV treatment and tumor resection, suggesting a coincidental occurrence of primary membranous nephropathy (PMN). PLA2R Ab levels in cases of PMN were higher (87.5%) than non-membrane nephropathy (0%) in a 2018 study. PLA2R was positive in 40 cases of secondary membranous nephropathy SMN (25%), including lupus MN, HBV MN, and atypical MN. In 2014, a case of celiac disease (CD) and H. Pylori infection with PLA2R+ MN was reported. Remission was achieved by H Pylori eradication without immunosuppression. In 2002, 2007 and 2009, three cases of renal failure due to MN in CD patients were reported raising the possibility of a link between the two conditions. We report the fourth case on the association of CD and MN to date.

Case Description: 40-year-old male with iron deficiency anemia and small bowel biopsy proven CD presented with pleural effusions, hypoxia, and generalized anasarca. Infectious and rheumatologic work up was negative. Lung biopsy showed hemosiderosis reaching diagnosis of Lane-Hamilton Syndrome (LHS) (idiopathic pulmonary hemosiderosis (IPH), CD, chronic anemia). Three years prior, he was diagnosed with PMN by PLA2R+ renal biopsy and had nephrotic range proteinuria >9g. He was treated with losartan and diuretics with improvement in his symptoms and decrease in proteinuria to 6g. Serum creatinine rose from baseline of 1 to 1.9 mg/dL. He was then started on high dose prednisone for IPH and cyclosporine for MN with further improvement in proteinuria to 2.6g and creatinine to 1.3 mg/dL. Anti-thrombospondin type I domain-containing 7A Ab was negative arguing against PMN. He had been trying to adhere to gluten free diet but was not consistent.

Discussion: CD is known to cause IPH and chronic anemia. It was hypothesized that chronic gastrointestinal inflammation triggers auto antibody formation against PLA2R1, which is present in duodenal and gastric cells in addition to glomerular cells. This would favor a causal relationship rather than coincidence of two idiopathic processes. Gluten free diet and steroids are the mainstay of therapy for LHS. We hope to prove that adherence to strict gluten free diet in our patient in addition to sustained low dose prednisone would lead to remission of MN without need for cyclosporine.

PO1786

Hydralazine-Induced Membranous Nephropathy

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Introduction: Hydralazine is associated with a variety of rare renal diseases including drug-induced lupus, ANCA vasculitis and membranous nephropathy (MN) with associated crescentic GN. We present a case of a patient with features of hydralazine-induced MN with some FSGS but no features of vasculitis. This would be the first such reported case to the best of our knowledge.

Case Description: This 67-year-old female with a medical history of HTN, DMT2, and CKD stage 3 initially presented to our clinic for evaluation of her renal function. Patient had increasing Cr up to 1.9 mg/dL over the course of 2 years. Her work up demonstrated modest albuminuria with several UACR results between 37.9 and 196.7 mg/g. UA demonstrated unremarkable chemistry and only 2 RBC and 1 WBC /plf. Serology showed positive ANCA 1:640 homogenous; dsDNA resulted negative; anti-histone Ab returned positive at 3.2 units (normal <1) as did her anti-MPO of 85 units (normal is <20). Of note, C3 and C4 returned normal. Patient remained asymptomatic but had rapidly worsening Cr rising from 1.9 to 2.69 mg/dL over 1 month, prompting a renal biopsy and stopping hydralazine therapy. The biopsy showed areas of scarring and FSGS on light microscopy and membranous nephropathy on EM but demonstrated none of the classic necrotizing or crescentic lesions associated with drug-induced vasculitis or any of the typical findings of lupus nephritis. Follow-up PLA2R, thrombospondin, and Hep returned negative. Age appropriate cancer screening was negative. Repeat blood work showed Cr returning to prior baseline after 1 month off hydralazine. We decided together with the patient to continue to monitor and forgo more aggressive therapy. Renal function remained baseline for the next 6 months.

Discussion: This case represents an up-to-now unreported case of hydralazine-induced MN without associated vasculitic lesions. Patient fit the classic serological findings for a drug-induced vasculitis and her renal function stabilized upon cessation of exposure to hydralazine, giving us a high suspicion for causality. Given renal decline during workup, re-exposure was not attempted. This patient never demonstrated any clinical or lab findings of MN disease: no severe proteinuria, no sequalae of nephrotic syndrome, and no associated diseases. Additionally, no lupus-like findings were appreciated on biopsy. We believe we have identified a novel association of hydralazine-induced MN.

PO1787

An Atypical Presentation of Lupus Nephritis

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Introduction: Lupus nephritis in the absence of ANA and dsDNA, and normal C4 levels is a rare, atypical presentation. To arrive at the diagnosis requires EM examination of renal biopsies and is responsive to immunosuppressive therapy. We present a report of such a case.

Case Description: A 49-year-old female was referred for asymptomatic hematuria and nephrotic-range proteinuria (4.9 g/g) in March 2014. Her creatinine (0.77 mg/dL), C4, ANA, dsDNA, and Rheumatoid factor were normal with low C3. Labs were normal for Hepatitis B, C, HIV, ANCA, RNP, and Sm antibodies. She was started on lisinopril, and initially the proteinuria improved (2.3 g/g) and renal functions were stable. Hematuria was initially suspected to be secondary to MPGN. Renal biopsy immunofluorescence showed IgG, C3, IgM, kappa/lamda, and C1q (in lesser quantitiy). EM showed deposits in subendothelial, subepithelial and mesangium. She was diagnosed with immune complex glomerulonephritis without evidence of systemic lupus. Over the next 2 years, proteinuria worsened from 1.9 to 5.7 g/g despite increasing lisinopril to maximum dosage (40 mg/day). Hematuria and low C3 levels persisted. In February 2017, creatinine worsened (1.33 mg/dL). Cellcept (1000 mg/day) was started in March; by June, there was no response. Lisinopril was stopped in May due to low BP. A second renal biopsy (November 2017) showed a lupus picture with a full house pattern (3+ IgG, 1+ IgM, 2+ C3, 3+ C1q, 2+ kappa/lambda, IgA+ tubular casts). EM showed subendothelial and scattered subepithelial deposits, and GBM duplication. She was diagnosed with Class IV Lupus Nephritis. She was started on Cytoxan (500 mg q 2 weeks x6 weeks) and prednisone (60 mg/day). She showed improvement and was started on Imuran in May 2018 for maintenance. Her proteinuria (400mg/g) and creatinine (0.93mg/dL) improved, C3 normalized, and hematuria resolved.

Discussion: Diagnosis of lupus nephritis can be missed on the basis of atypical labs and requires a high degree of suspicion and a biopsy. This case represents such an atypical presentation without systemic lupus. Initially, thought to have C3 nephritis; but later, the diagnosis was confirmed by renal biopsy and electron microscopy. The Full House immunofluorescence pattern seen in this patient is characteristically indicative of lupus nephritis, and she was responsive to immunosuppressive therapy.

PO1788

Lupus Nephritis Classification Should Consider Lupus Arteritis in the Activity Score

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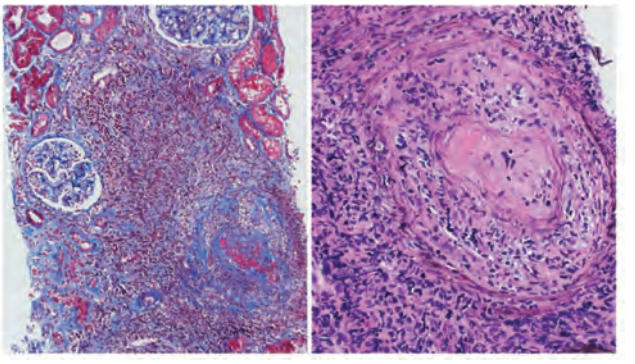
Introduction: Lupus nephritis (LN) complicates 20-49% of systemic lupus erythematosus (SLE) patients. Vascular lesions are not considered in the activity index of LN pathology classification. We report a case of LN with severe necrotizing arteritis without proliferative glomerular lesions, prompting a more aggressive intervention.

Case Description: A 36-year-old woman with known SLE with Class II LN, as well as vasculitis, resulting in multiple digital amputations presented with eight days of abdominal pain, vomiting, fever, and tea-colored urine. Labs showed creatinine of 1.4 mg/dL, microscopic hematuria, urine protein/creatinine of 5 g/g, low complements, positive anti-double-stranded DNA of 14, an elevated antinuclear antibody of 1:320, elevated Myeloperoxidase (MPO)–Antineutrophil Cytoplasmic Antibody (ANCA) of 59. She received induction therapy with intravenous (IV) methylprednisolone 1g daily x3, followed by prednisone 60 mg daily and mycophenolate mofetil (MMF) 500 mg twice daily. A repeat kidney biopsy was performed, and 12 glomeruli showed only mesangial proliferation. She was classified as International Society of Nephrology and the Renal Pathology Society (ISN/RPS) class IIIA LN based on two arteries revealing severe arteritis with transmural necrosis causing occlusion, inflammation, and rupture of the vessel walls. Consequently, we switched MMF to IV cyclophosphamide 1g/m2 monthly. Creatinine improved to 1 mg/dl on discharge and 0.9 mg/dl two months later.

Discussion: There is limited attention to non-glomerular vascular lesions among patients with LN. Prior case reports show that LN patients with vascular involvement have worse outcomes and may require more aggressive treatment. The vasculitis in this case was attributed to the MPO Antibody. Given the potential prognostic and therapeutic implications of vascular involvement in LN patients, we suggest that lupus arteritis be considered in the LN pathology classification.



PO1789

Hepatitis B-Associated Lupus-Like Nephritis

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Introduction: The spectrum of renal disease with hepatitis B virus (HBV) is broad including different glomerular lesions related to the presence of viral antigens. HBV-associated lupus-like nephritis (HBLN) is characterized by immune deposits of polyclonal immunoglobulins linked to polytypic complements in glomeruli, structures reminiscent of lupus nephritis (LN). There is a dearth of literature regarding differentiation of HBLN and LN along with differing management and outcomes.

Case Description: We report a 46-year-old male with known HBV infection with 3 weeks of progressive dyspnea and edema. The serum creatinine (SCr) rose from a baseline of 0.8 mg/dl to 5.2 mg/dl with proteinuria of 1.7 g/g and microscopic hematuria. Serology showed transiently positive ANA, negative anti ds-DNA, and low levels of C3. Hepatitis B e Ag and hepatitis B surface Ag were positive, and the viral load was 2483 IU/mL with normal liver enzymes. A renal biopsy revealed severe diffuse endocapillary hypercellularity, a "full house" immunofluorescent pattern, and numerous subendothelial and mesangial immune deposits ultrastrurally, findings consistent with a diagnosis of HBLN. The patient was started on Entecavir for treatment of hepatitis B. After 2 months of treatment, the Scr improved to 1.97 mg/dL with improvement in initial symptoms.

Discussion: Our case highlights the inherent difficulty in recognition of renal failure secondary to HBLN with associated pathology findings consistent with LN in the presence of hepatitis B infection. Although the full-house immunofluorescent pattern generally implies a diagnosis of LN, renal biopsy findings have to be interpreted in the clinical context. All the findings in renal biopsies of LN can also be seen in HBLN. Renal manifestations in both groups, including proteinuria and Scr, can be similar. Although considerably lower C3 levels in patients with lupus may suggest more widespread extrarenal disease, low C3 levels have also been reported in HBLN. The distinguishing feature between HBLN and LN is the presence of HBeAg and hepatitis B DNA. Our case is an unusual presentation of hepatitis B with renal involvement with effective diagnosis and management. While there is limited data for the treatment of HBLN with most studies excluding patients with an elevated SCr, small studies suggest first-line treatment with antiviral agents to achieve viral clearance.

PO1790

A Unique Case of Autoimmune-Mediated Cryoglobulinemic Glomerulonephritis

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Introduction: Cryoglobulinemic syndrome is a disease in which immunoglobulin components are deposited within tissues, resulting in various end-organ damage. Subtypes Type II and III contain mixed monoclonal and polyclonal immunoglobulins, thereby referred to as Mixed Cryoglobulin Syndrome (MC). MC is often associated with infections such as Hepatitis C; however, it can also be secondary to autoimmune diseases. While the most common associations are with Systemic Lupus Erythematosus and Sjogren's disease, occasionally, MC can be seen with other rheumatologic conditions. We examine a rare case of Overlap Syndrome (OS) induced cryoglobulinemic glomerulonephritis (CG).

Case Description: A 44-year-old woman with a history of OS, presented with symptoms of fatigue, generalized edema, weight gain of 20lbs, and found to have an acute kidney injury (AKI). She was admitted to the hospital with a diagnosis of decompensated heart failure. The diagnosis of OS was confirmed with elevated ANA, SSA, RNP antibodies, as well as negative dsDNA and anti-smith antibodies. Previously, she was unsuccessfully treated with methotrexate and hydroxychloroquine. She was on hydroxychloroquine monotherapy at the time of admission. During the investigation for her AKI, she was found to have hematuria and non-nephrotic range proteinuria (UPCR 2.65g/dL), raising concerns for glomerulonephritis. Subsequent renal biopsy showed autoimmune-mediated cryoglobulinemic glomerulonephritis. She was treated with a combination of methylprednisolone/prednisone and rituximab, which resulted in normalization of renal function.

Discussion: This case illustrates a patient with a history of OS with biopsy proven autoimmune mediated CG. The patient's underlying diagnosis of OS is likely the leading risk factor for renal impairment secondary to immunoglobulin deposits. Treatment

is focused on immunosuppression, including steroids, rituximab, or mycophenolate mofetil. Combination therapy with a non-steroid immunosuppressant is preferred over monotherapy with steroids. The patient was treated with steroids and rituximab, with recovery of renal function. Given the varying presentation of CG, physicians should be mindful of keeping a broad differential, particularly in patients with rheumatological history presenting with proteinuria, hematuria, and signs of renal dysfunction.

PO1791

Bartonella Buried in the Aortic Valve

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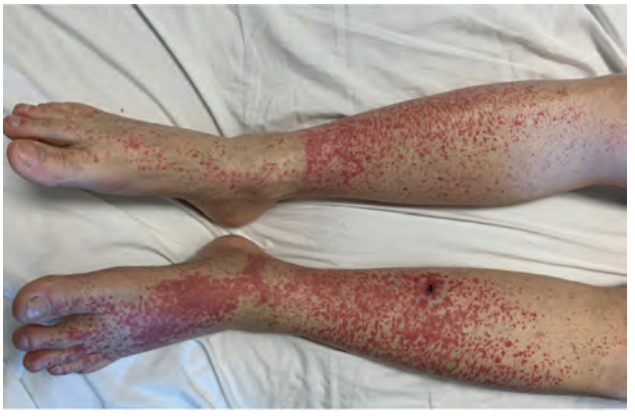
Introduction: Bartonella species are the most common cause of culture negative endocarditis in the United States. We report a case with culture negative Bartonella endocarditis masquerading as Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis.

Case Description: A 46 year old male presented with leg rash and swelling. Physical exam was notable for diastolic murmur in aortic area and a systolic murmur in the mitral area and non blanching purpura on the lower extremities. Labs showed BUN 18mg/dL, creatinine 1.54 mg/dL. Urinalysis showed non nephrotic range proteinuria and urine microscopy showed dysmorphic hematuria. ANA was 1:160, RF was 541 IU/mL, complement C3 and C4 levels were low and serum cryoglobulin was positive. ANCA titer was elevated with myeloperoxidase ANCA of 38 AU/mL and serine proteinase 3 ANCA of 580 AU/ml. Anti-Smith antibodies were 68AU/ml. Echocardiography showed severe mitral and aortic regurgitation with mitral and aortic vegetations. Ceftriaxone and vancomycin were started after blood cultures were obtained which remained negative. The aortic valve was replaced with mitral and tricuspid valve repair. Bartonella Quintana IgG titer was positive at 1:1024. Valve tissue cultures were negative and tissue PCR was positive for B. Quintana. He was eventually started on gentamycin and oral doxycycline. Creatinine 1 month later was 1.2 mg/dl.

Discussion: *Bartonella* is the most common cause of culture-negative endocarditis in the United States with a reported association with pauci- immune glomerulonephritis. In our case serological testing and valve PCR were helpful in establishing the diagnosis. In conclusion, SBE induced glomerulonephritis with false positive serology for ANCA can mimic the clinical features of ANCA associated glomerulonephritis. Intense immunosuppressive therapy can have catastrophic consequences. We recommend considering the possibility of SBE in all patient with dual positive ANCA with hypocomplementemia, positive ANA and a positive RF.



Purpuric rash present on admission.

PO1792

Clinicopathological Analysis of Renal Dysfunction due to Idiopathic Multicentric Castleman Disease in Japan

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Background: Renal dysfunction is a fatal complication of idiopathic multicentric Castleman disease. Although AA amyloidosis and glomerular endotheliopathy with severe proteinuria were reported due to this disease, human immunodeficiency virus (HIV) were positive in these previously reported cases. On the other hand, HIV-negative cases are common in Japan, and the precise renal involvement of Japanese cases has not been studied yet.

Methods: Case-series was designed for analyzing the clinicopathological features of renal dysfunction accompanied with Castleman disease. Inclusion criteria of the object is renal biopsy performed between 1990 and 2019 and the patients who were diagnosed as Castleman disease. Clinical and pathological data was collected from the electrical medical record.

Results: Eight patients were eligible to the study. Seven out of eight cases were plasma cell type, while anti-HIV antigen/antibody was negative in all cases. Laboratory data at the time of renal biopsy showed; median serum creatinine was 0.75(0.6-5.0) mg/dL, urine protein was 1.28(0.04-8.9) mg/dL. In glomerular lesion, following involvement were found: two cases of AA amyloidosis and membranous nephropathy respectively, while IgA deposition and nephrosclerosis in one case each. Nephrotic range proteinuria was found in two cases of AA amyloidosis as well as one case of membranous nephropathy. Among two cases diagnosed as membranous nephropathy, immunofluorescent analysis about IgG subclass showed that IgG1 was dominant in one case and IgG2 was in the other. IgG4 was negative in both cases. In interstitial lesion, chronic tubulointerstitial nephritis was diagnosed in one case.

Conclusions: Heterogenous glomerular lesions were found in our cohort. Previous cohort study showed that membranous nephropathy was rare, but in this study, two out of eight cases turned out to be membranous nephropathy. In addition, analysis of IgG subclass suggests that either IgG1 or IgG2 was dominant in secondary membranous nephropathy due to Castleman disease and that deposition of immunoglobulin complex could be associated to the onset of proteinuria of Castleman disease.

PO1793

Is It Systemic Lupus Erythematosus Nephritis or Not?

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Introduction: IC-MPGN (immune complex-mediated glomerulonephritis) is a histopathological finding that is associated with infection, immune-complex deposition, monoclonal gammopathies as well as autoimmune disorders such as lupus, Sjögren's, and rheumatoid arthritis. MPGN traditionally has been classified as I-III depending on the pathology findings. More recently, an alternative classification system based on the pathological process has been developed (immune complex-mediated vs complement-mediated). In cases of IF showing IgG +/- C3, a tentative diagnosis of immune-complex mediated MPGN can be made. MPGN treatment is aimed first at treating the underlying cause. In the case where a cause cannot be found, as in our case of biopsy-proven IC-MPGN with negative serologies, the underlying mechanism is not clear.

Case Description: 71-year-old female with PMHx aortic valve replacement, HTN, CKD-I presented with constitutional symptoms, and AKI on CKD with proteinuria. She was found to have biopsy-proven immune complex mediated MPGN, but the etiology was unclear due to negative: ANA, anti-Smith, anti-Ro/SS, anti-La/SSB, Hep B/C, cryoglobulins, CCP, CRP, ESR, K/L. The biopsy pattern was consistent with Lupus Type IV/V, with EM findings showing scattered sub endothelial dense deposits and full house IF staining pattern. CT abdomen/pelvis was negative. Further testing and workup for malignancy were negative. She was started on high-dose steroids for initial treatment of presumptive seronegative lupus nephritis. Serologies were repeated and all were negative. Patient showed improvement with initiation of mycophenolate + steroids; proteinuria and creatinine improved on follow-up.

Discussion: The optimal initial treatment of idiopathic/seronegative immune complex-mediated MPGN has not been established. In this case, the patient improved with aggressive steroid treatment with a tapering dose after starting mycophenolate. Proteinuria which was initially nephrotic at 14 g/g is now near 0.2 g/g.

PO1794

Role of the IgA Immune Complexes Bound to FcαRI/CD89 in IgA Nephropathy

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Background: Studies have demonstrated the pathogenic role of circulating polymers IgA immune complexes (poly-IgA ICs) in IgA nephropathy (IgAN). In this study we aim to evaluate the role of poly-IgA ICs specifically bound to FcαRI/CD89 in the kidney development of IgAN.

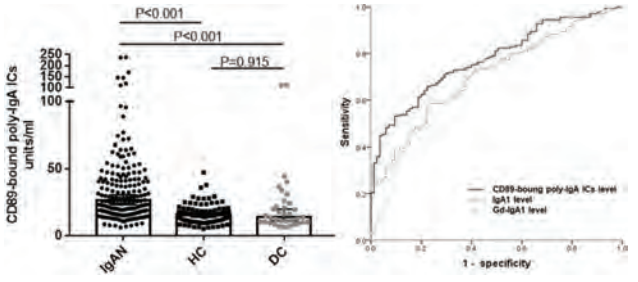
Methods: rCD89 protein was produced from a HEK293 cell expression system. A novel ELISA method that using rCD89 as the 'capturing' probe was established for detecting poly-IgA ICs. The plasma levels of poly-IgA ICs were measured in 181 IgAN patients and 35 patients with glomerular diseases of unrelated etiologies. Another 85 age-, gender-, and geographically-matched healthy individuals were enrolled as controls. rCD89-bound poly-IgA ICs were analyzed by mass spectrometry.

Results: rCD89-mounted plates specifically captured plasma poly-IgA. The levels of poly-IgA ICs in IgAN (26.67, 17.06 to 42.61 units/ml) were significantly higher than healthy controls (15.46, 10.73 to 20.04 units/ml; P<0.001) or disease controls (13.99, 10.35 to 24.22 units/ml; P<0.001). Patients with higher levels of poly-IgA ICs had lower eGFR, higher proteinuria and higher Oxford scores in E and T lesions. Accuracy parameters and concordant statistics showed good discrimination between IgAN and healthy controls for poly-IgA ICs levels (AUC, 0.777; 95% CI, 0.722–0.832; P<0.001), significantly better than IgA1 levels (AUC, 0.710; P=0.015) and galactose deficient-IgA1 levels (AUC, 0.702; P=0.048). A total of 268 proteins were identified in mass spectrometry analysis. The protein abundance of fibrinogen alpha chain, protein AMBP and C4B were higher in IgAN group.

Conclusions: Higher level of rCD89-bound poly-IgA ICs was a potential useful diagnostic biomarker in patients with IgAN which was also associated with the severity of the disease. The findings suggest that the role of CD89 in eliminating IgA ICs and it may be a new approach to improve the clinical progress of patients with IgAN.

The baseline clinical and pathological characteristics of IgA nephropathy patients

	Total	CD89-bound poly-IgA ICs low-level	CD89-bound poly-IgA ICs high-level	P value
Patients(n)	181	85	96	-
Male (%)	82(45.3)	42(49.4)	40(41.7)	0.296
Age(ys)	36.71±12.1	34.66±11.2	38.52±12.62	0.032
MAP (mmHg)	93.36±12.96	91.57±13.82	94.94±12	0.080
Scr (μmol/L)	93.08(71.25, 137.6)	85.00(66.89, 126.6)	98.94(74.08, 144.83)	0.093
eGFR(ml/min)	76.39±33.33	82.35±34.23	71.12±31.77	0.023
Proteinuria (g/d)	1.10(0.48, 2.4)	1.00(0.45, 1.92)	1.26(0.60, 2.5)	0.131
Plasma IgA1 (mg/ml)	3.44±1.41	2.69±1.08	4.1±1.34	<0.001
Plasma Gd-IgA1 (U/ml)	497.4±89	473.72±91.66	518.37±81.45	0.001
Oxford classification (%)				
M1	88(48.6)	45(52.9)	43(44.8)	0.274
E1	61(33.7)	22(25.9)	39(40.6)	0.036
S1	104(57.5)	50(58.8)	54(56.2)	0.727
T1/2	69(38.1)	22(25.9)	47(49.1)	0.002
C1/2	126(69.6)	57(67.1)	69(71.9)	0.520



Plasma levels of CD89-bound poly-IgA ICs in groups

PO1795

Racial Heterogeneity of IgA_1 Hinge Region O-Glycoforms in Patients with IgA Nephropathy

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Background: IgA1 with galactose (Gal)-deficient hinge region (HR) *O*-glycans (Gd-IgA1) plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). The microRNAs, named let7b and miR-148b, which affect IgA1 HR *O*-glycosylation, showed differences in serum levels between Caucasians and Asians, suggesting a racial difference in HR *O*-glycosylation. To understand race-specific IgA1 HR *O*-glycoform heterogeneity at the molecular level, we compared Greek and Japanese profiles of IgA1 HR *O*-glycoforms in patients with IgAN.

Methods: IgA1 from sera of 10 Japanese healthy controls (J-HC), 36 Japanese IgAN patients (J-IgAN), 16 Greek HCs (G-HC), and 23 Greek IgAN patients (G-IgAN) were purified through affinity chromatography. After neuraminidase and trypsin digestion, samples underwent liquid chromatography-high-resolution mass spectrometry, and individual profiles of IgA1 HR *O*-glycoform were quantitatively analyzed. The amounts of *N*-acetylglucosamine (GalNAc) and Gal were shown as the median number of sugar moieties per HR.

Results: Twelve variants of the IgA1 HR *O*-glycopeptide were detected in both HCs and IgAN patients. The disease-specific IgA1 HR *O*-glycoforms were 3GalNAc3Gal in Japanese ($P < 0.001$) and 3GalNAc2Gal ($P = 0.007$) and 5GalNAc3Gal ($P = 0.043$) in Greek individuals. The amount of GalNAc per HR showed a common tendency to decrease in patients from both racial groups, compared with healthy subjects, and was more prominent in G-IgAN than in J-IgAN ($P = 0.027$). The amount of Gal per HR decreased in the following order: J-IgAN, G-HC, J-HC, and G-IgAN, and was significantly lower in G-IgAN than in J-IgAN ($P = 0.001$).

Conclusions: The amount of GalNAc per HR decreased in patients of both races and was prominent in G-IgAN. The difference in GalNAc levels between G-IgAN and J-IgAN showed correspondence with previously reported serum let-7b racial differences, which were associated with the regulation of the initial glycosylation of HR. Further studies regarding upstream factors and changes downstream of GalNAc glycosylation are required to understand the pathogenesis of IgAN.

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PO1796

IgA Nephropathy Complicated with Crohn Disease: A Clinical and Pathological Study of Kidney Biopsied Cases

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Background: Intestinal immunity is closely related with the pathogenesis and progression of renal diseases, called as "entero-renal linkage". To figure out the association between IgA nephropathy (IgAN) and Crohn's disease (CD), we performed the clinico-pathological study of IgAN patients with (CD-IgAN) and without CD (NOS-IgAN).

Methods: We enrolled 29 patients diagnosed with IgAN by renal biopsy in Tokyo Yamate Medical Center from 2009 to 2017. The patients were divided into CD-IgAN (n=18) and NOS-IgAN (n=11) and investigated their clinical and pathological findings. IgA subclasses and galactose-deficient IgA1 (Gd-IgA1) on glomerulus were examined by immunohistochemistry.

Results: No significant difference in the grades of urinary protein and hematuria was observed between CD-IgAN and NOS-IgAN, but CD-IgAN had elevated serum creatinine (sCr) and lower rate in clinical remission after steroid treatment as compared to NOS-IgAN. Pathologically, CD-IgAN had remarkably higher levels of global glomerulosclerosis (%), grades of interstitial fibrosis and tubular atrophy (IF/TA) than NOS-IgAN. Immunohistochemically, IgA1 was a dominant subclass and Gd-IgA1 was frequently detected in glomerular mesangium in both groups. No difference was noted in the extents of IgA1, IgA2 and Gd-IgA1 deposition, depending on the presence or absence of CD.

Conclusions: From the results of the subclasses and galactose-deficiency of the IgA molecules, no difference was suggested in the etiology and pathogenesis between CD-IgAN and NOS-IgAN. However, advanced glomerular sclerosis and tubulointerstitial fibrosis in renal pathology and highly resistant clinical features to medical treatments in CD-IgAN suggest that the intestinal immunity and other clinical factors associated with CD may promote and activate the inflammatory process of IgAN.

PO1797

Antibody Sequencing Analysis After Flu Vaccine Response in IgA Nephropathy Patients Reveals Enhanced IgA Variable Regions of the Heavy Chains Lineage Diversity

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis in the world, is characterized by mesangial immunodeposits consisting of galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-specific IgG autoantibodies. IgG autoantibodies in IgAN patients have variable regions of the heavy chains (VH) with long complementarity-determining region 3 (CDR3) that contains a key amino-acid residue important for binding Gd-IgA1. This CDR3 modification is not due to a genetic variant of a *VH*gene in IgAN patients but it is thought to originate from somatic mutations. To determine whether IgAN patients have generally enhanced rates of *VH*somatic mutations, we have assessed responses to influenza-vaccine antigens in IgAN patients vs. healthy controls.

Methods: Peripheral blood (PB) from 4 IgAN patients and 4 healthy controls (HC) was collected 7 d after flu vaccination (i.m.), the peak of plasmablasts in PB. Plasmablasts were isolated after enrichment with CD138-coated beads. cDNA from plasmablasts was used for *VH*gene amplification with *VH*- and isotype-specific primers, and sequenced on an Illumina MiSeq. Sequences were filtered, aligned, and grouped using an in-house workflow, with further analyses performed in Matlab.

Results: Isotype-specific nucleotide mutation rates were similar in IgAN and HC plasmablasts, except for *IGHV3-7*with a higher rate in HC for IgM (p=0.01). Average nucleotide mutation rate for CDR3 was 1.6% higher in HC compared to IgAN, almost reaching significance (p=0.06). Further analysis revealed that number clonotype-specific*VH*sequences was increased for IgA in plasmablasts from HC vs. IgAN for *IGHV2-5*(p=0.02), *IGHV3-7*(p=0.04), *IGHV3-15*(p=0.02), *IGHV3-21*(p=0.01), *IGHV3-30* (p=0.01),*IGHV3-48*(p=0.03), *IGHV4-38-2*(p=0.05), *IGHV4-59*(p=0.04), and *IGHV4-61* (p=0.02).

Conclusions: Analysis of influenza-vaccine-specific immune responses showed that IgAN patients and HC exhibit similar *VH*nucleotide mutation rates. Unexpectedly, we also observed thatIgAN patients produced fewer IgA *VH*sequences than healthy controls after flu vaccination, indicating a possible disparity of IgA responses in IgAN.

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PO1798

Identification of Proteins Associated with IgA_1-Containing Circulating Immune Complexes in Patients with IgA Nephropathy

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Background: IgA1-containing immune complexes (IgA1-ICs), consisting of galactose-deficient IgA1 (Gd-IgA1) bound by IgG specific for Gd-IgA1, are central to the pathogenesis of IgA nephropathy (IgAN). We have shown that Gd-IgA1 alone is not sufficient to induce mesangial-cell proliferation and that additional serum proteins are required for IgA1-ICs to become nephritogenic. To elucidate the composition of IgA1-ICs, we have developed a novel proteomic-bioinformatic workflow to identify proteins in IgA1-ICs in patients with IgAN.

Methods: IgA1-ICs from sera of 20 patients and 20 healthy controls were isolated by lectin affinity chromatography followed by size-exclusion chromatography (SEC). Quality-control test confirmed that most IgA1-ICs and free IgA1 were captured by affinity chromatography. IgA1-ICs were separated by SEC from monomeric and polymeric IgA1. After IgA-specific protease and LC-MS sequence-grade trypsin digestion, each IgA1-IC sample was analyzed by liquid chromatography coupled on line with mass spectrometry (LC-MS). After standard proteomic database searches, LC-MS results were extensively curated by use of *Scaffold perSPECtives* to identify proteins enriched in IgA1-ICs of IgAN patients vs. healthy controls. Additional comparisons included polymeric and monomeric IgA1.

Results: Seventy-nine proteins were identified in IgA1-ICs samples from IgAN patients, with a false discovery rate of 1%. After proteomic-bioinformatic curation, we generated a list of 38 proteins with high-confidence identification that were uniquely enriched in the IgA1-ICs from patients with IgAN. Using Principle Component Analysis, we confirmed that protein content differentiated the three molecular forms of IgA1, monomeric, polymeric, and IgA1-IC. Pathway analysis indicated that proteins in IgA1-ICs were part of the complement cascade, with seemingly more enrichment in the regulation of complement, and the plasma lipoprotein pathway.

Conclusions: Our new workflow enabled targeted identification and evaluation of proteins associated with IgA1-ICs in IgAN. These proteins represent new targets to be evaluated for their roles in the formation and activity of the nephritogenic IgA1-ICs in IgAN.

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PO1799

Low Serum IgG4: A Remarkable Diagnostic Biomarker for IgA Nephropathy

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Background: Reports regarding IgG subclasses in IgA nephropathy (IgAN) were scarce. Low serum IgG4 levels in IgAN were noticed in our preliminary experiment. We aim to verify the low IgG4 levels in IgAN and investigate the related immune mechanism.

Methods: Three groups of IgAN patients were enrolled, including the newly diagnosed IgAN-N (n = 58), IgAN-F (n = 28) with a follow-up interval of (19 ± 11) months, and IgAN-10 patients (n = 27) who have been diagnosed over 10 years. Healthy individuals (n = 56) and patients with idiopathic membranous nephropathy (IMN, n = 30) were enrolled as controls. Serum IgG4, IgG, galactose-deficient IgA1 (Gd-IgA1), and urine IgG4 levels were detected by ELISA. The $IgG4^+B$, Th1, and Th2 cells were measured by flow cytometry. Receiver operating characteristic curves and logistic regression analyses were performed to evaluate the diagnostic and predictive abilities of IgG4.

Results: The serum IgG4 levels in IgAN patients with different courses, severity, and outcomes were all significantly lower than those of healthy controls and IMN (all $P < 0.001$). The cutoff value of IgG4 in differentiating IgAN from healthy individuals and IMN was respectively 0.26mg/ml (sensitivity 98.3%, specificity 82.1%, AUC 0.938, $P < 0.0001$) and 0.24mg/ml (sensitivity 96.6%, specificity 73.3%, AUC 0.869, $P < 0.0001$). The risk of IgAN in subjects with low IgG4 levels was 281 times higher than those with normal IgG4 (OR 281.11, 95%*CI* 34.33 - 2301.97, $P < 0.001$), and a negative correlation between serum Gd-IgA1 and IgG4 levels was observed in healthy controls (r = -0.240, P = 0.077) instead of IgAN-N patients (r = -0.066, P = 0.629). Similar results were obtained when IgG4/IgG was analyzed in the same patients and controls. The urine IgG4 levels [μg/(g.Cr)] in IgAN-N [798.16 (308.75, 1533.56)] were higher than healthy controls [72.87 (31.51, 201.89), $P < 0.001$], but were similar to IMN [1153.39 (378.83, 2108.40), P = 0.341]. The $IgG4^+B$/B cells (0.29 ± 0.17 vs. 0.61 ± 0.56, P = 0.017) and Th2/Th (0.54 ± 0.27 vs. 0.87 ± 0.44, P = 0.037) of IgAN were significantly lower than those of healthy controls.

Conclusions: Serum IgG4 levels of IgAN patients are generally low, and the low IgG4 level may be a risk factor for IgAN. Serum IgG4 may be a remarkable diagnostic biomarker for IgAN. Decreased $IgG4^+B$ and Th2 cells may contribute to the low IgG4 levels.

PO1800

Comparing the Lectin and Mass Spectrometry-Based Approaches to Quantify Galactose-Deficient IgA_1 in IgA Nephropathy

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Background: Abnormalities in *O*-glycosylation of circulating IgA_1 are implicated in the pathogenesis of IgAN. This was initially demonstrated by the altered binding of lectins with specificity for *O*-linked glycans and confirmed later by mass spectrometry. Nevertheless, combining and interpreting the results from these two orthogonal techniques is difficult, due to their different levels of complexity. We applied the two approaches to quantify galactose-deficient IgA_1 (Gd-IgA_1) in plasma samples of IgAN patients and matched controls. We aim to identify potential sources of discrepancy between the two analytical methods.

Methods: IgAs were affinity purified from plasma samples from 23 patients with IgAN and 36 controls. We used enzyme-linked lectin assay and the lectin from *Vicia villosa* (VVL) to measure defective galactosylation of *O*-linked oligosaccharides. Monomeric (mIgA) and polymeric (pIgA) forms of IgA_1 were size-separated by gel electrophoresis. IgA_1-containing bands were in-gel digested with trypsin, the released glycopeptides were analyzed by electrospray ionization liquid mass spectrometry.

Results: A significantly larger fraction of IgA_1 molecules in the circulation of IgAN patients exist as high molecular mass complexes, as compared with the control group (48.8 *vs* 42.8%, p=4.25E-02). The reactivity of VVL lectin with unfractionated IgA_1 was higher in the IgAN group compared with healthy controls (10.9 *vs* 9.1 A.U., p=8.60E-02). In both groups, IgA_1 binding to VVL was much stronger for pIgA than mIgA. Mass spectrometry showed that the level of Gal was higher in pIgA than in mIgA (3.66 *vs* 3.54 Gal/Heavy Chain, p=7.63E-05). However, no significant differences in glycan composition was detected between patients and controls. In all the experiments, the inter-individual differences in glycan composition were large, which may have obscured the signals from the disease-related galactose-deficient IgA_1.

Conclusions: Our results suggest that the apparent increased abundance of Gd-IgA_1 in circulation of patients with IgAN is, at least in part, attributable to a greater abundance of polymeric IgA_1 compared with controls. However, the glycosylation profile of each form of IgA_1 appeared indistinguishable in the IgAN group when compared to the corresponding form in the control group.

PO1801

Developing Molecular-Specific Biomarker Assays for IgA Nephropathy and IgA Vasculitis with Nephritis

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Background: Patients with IgA nephropathy (IgAN) develop characteristic glomerular immunodeposits containing IgA that is enriched for IgA1 glycoforms with galactose-deficient hinge-region *O*-glycans (Gd-IgA1). Blood levels of Gd-IgA1 are elevated in patients with IgAN and those with IgA vasculitis with nephritis (IgAV-N), suggesting a key role of Gd-IgA1 in pathogenesis of these diseases. In contrast, patients with IgA vasculitis (IgAV) without renal involvement do not have elevated blood levels of Gd-IgA1. These observations suggest a potential prognostic role for a minimally invasive biomarker based on profiling serum/plasma IgA1 *O*-glycoforms. Here, we describe a novel workflow to qualitatively and quantitatively assess molecular IgA1 phenotype(s) in IgAN by profiling serum IgA1. This validated approach can be extended to IgAV-N patients.

Methods: Isolation of IgA1 from sera is based on lectin-affinity chromatography followed by size-exclusion chromatography to separate IgA1 monomeric and polymeric forms and IgA1 bound in immune complexes. IgA1 *O*-glycosylation was analyzed by liquid chromatography-high-resolution mass spectrometry (LC-MS). In a pilot study, we used monomeric IgA1 from sera of 10 healthy controls and 10 IgAN patients. LC-MS runs were standardized using internal and external calibration methods.

Results: Quantitative LC-MS analysis revealed variations in the abundance of individual IgA1 *O*-glycoforms in the tested samples. We used quantitative data for 10-15 IgA1 glycoforms, expressed as relative ratios, to distinguish IgA1 from patients with IgAN vs. healthy controls. Furthermore, the LC-MS assay was standardized with internal and external calibration methods, an approach that will enable sample normalization, longitudinal studies, as well as evaluation of IgA1 from patients with IgAV-N.

Conclusions: Quantitative profiling of IgA1 clustered *O*-glycosylation can determine molecular IgA1 phenotype(s) and identify IgA1 glycoforms as biomarkers related to disease pathogenesis. These approaches are applicable to differential profiling of IgA1 from patients with IgAV-N vs. IgAV vs. healthy controls to identify pathogenic IgA1 glycoforms involved in the formation of nephritogenic immune complexes in IgAV-N.

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PO1802

Mass Spectrometric Analysis of IgA_1 O-Glycoforms Reveals the Basis of IgA_1 Galactose Deficiency Detected by Quantitative Lectin ELISA

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Background: Patients with IgA nephropathy (IgAN) have elevated serum levels of IgA1 with some hinge-region (HR) *O*-glycansdeficient in galactose (Gal; Gd-IgA1). Gd-IgA1 is recognized by IgG autoantibodies, resulting in the formation of pathogenic immune complexes. Our group has established a quantitative ELISA for Gd-IgA1 using GalNAc-specific lectins (e.g., from *Helix pomatia*; HPA). This test enabled determination of genetic basis of IgA1 Gal deficiency and provided a better understanding of IgAN pathogenesis. However, understanding of IgA1 *O*-glycosylation at a molecular-level is needed.

Methods: We used liquid chromatography with high-resolution mass spectrometry (LC-MS) to analyze and quantify *O*-glycoforms of monomeric (m) and polymeric (p) IgA1 in sera of IgAN patients (n=31) and healthy controls (HC; n=10). Total serum IgA1 was isolated by lectin affinity chromatography and m and p forms were separated by size-exclusion chromatography. Gd-IgA1 was measured by lectin ELISA. HR glycopeptides, generated by an IgA-specific protease and trypsin, were analyzed by LC-MS using LTQ Orbitrap Velos MS. LC-MS data were analyzed with the Pinnacle software.

Results: Quantitative LC-MS *O*-glycosylation profiling of IgA1 HR was performed, and results calculated as relative abundance of individual glycoforms and as ratios of Gal-containing *vs.* Gal-deficient glycoforms. Both LC-MS data and lectin ELISA confirmed that pIgA1 exhibited higher degree of Gal deficiency than mIgA1. LC-MS data provided additional insight into the molecular basis of the variability of Gd-IgA1 serum levels in IgAN patients. For example, IgA1 HR glycoform GalNAc4Gal3 was more abundant for the pIgA1 in the patients with high vs. low serum levels of Gd-IgA1 ($p<0.005$). LC-MS analysis enabled identification and quantification of individual HR glycoforms and defined the Gd-IgA1 glycoforms detected by lectin ELISA.

Conclusions: High-resolution LC-MS IgA1 glycoprofiling confirmed pIgA1 as the main form of IgA1 detected by Gd-IgA1 lectin ELISA. Furthermore, we identified several different Gal-deficient glycoforms in pIgA1, an observation that enables quantitative molecular-level assessment of Gd-IgA1 glycophenotype.

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PO1803

SeqStain: A Multiplex Staining Method for Deep Profiling of Human Kidney Tissues

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Background: Chronic Kidney Disease (CKD) is an emerging global health challenge, affecting 10-15% of the population. Lack of reliable biomarkers precludes the early diagnosis of CKD. The progression of CKD is known to be dictated by renal tissue changes. For example, in the case of Diabetic Nephropathy, disease progression is accompanied by considerable changes to the glomeruli including the thickening of the glomerular basement membrane and mesangial expansion, extracellular matrix accumulation, reduced podocyte number, inflammation of the renal tissue, the influx of immune cells which ultimately lead to tissue damage and progression to CKD. Understanding these tissue-centered events on a deeper level is imperative to reduce morbidity associated with CKD and for early diagnosis.

Methods: To aid high-level multiplex staining of these tissues by immunofluorescence, we developed a novel multiplex staining method called SeqStain. The SeqStain multiplex platform uses DNA tagged antibodies and Fab fragments to stain while endonucleases are used to achieve gentle de-staining after each round. We designed a SeqStain multiplex panel with antibodies to probe different histological regions relevant to the kidney. Antibodies or Fab fragments were tagged with DNA oligonucleotide duplex which carries multiple fluorophores. Labeled Fab fragments were pre-complexed with primary antibodies for staining.

Results: SeqStain modified antibodies and Fab fragments efficiently labeled multiple markers in tissue sections. Kidney tissues were stained with the SeqStain reagents and de-stained using endonucleases and provided a simple, gentle, and rapid technique for multiplex imaging of the tissues. The method was implemented using a custom flow chamber and allowed the labeling of tens of antigens on a single tissue section. Image alignment and analyses provided spatialomic data on multiple cell types in the tissue.

Conclusions: SeqStain method offers a robust yet gentle multiplex staining method to profile the CKD kidney tissues and comprehend the tissue-centered events that could play a role in the disease progression. Currently, we are profiling the CKD tissues in multiplex staining experiments and comparing it to healthy human kidney tissues to generate the spatial maps.

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PO1804

TLR9 Signaling Pathways in Nasal-Associated Lymphoid Tissue Have a Crucial Role in the Pathogenesis of IgA Nephropathy

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Background: The pathogenesis of IgA nephropathy (IgAN) is closely associated with dysregulation of mucosal immune system. However, it is unclear which nasal-associated lymphoid tissue (NALT) or gut-associated lymphatic tissue (GALT) is more involved in the pathogenesis of IgAN. In present study, we examined whether NALT or GALT is the major responsible site for the nephritogenic immune complexes in murine IgA nephropathy.

Methods: We examined the effect of broad-spectrum antibiotics in the IgAN onset ddY mice. In addition, we assessed disease phenotypes of the IgAN onset ddY mice housed in germ free condition (GF-ddY) and transferred to specific pathogen free (SPF) condition. The levels of aberrantly glycosylated IgA and IgG-IgA immune complexes (IC) in serum and supernatant of cultured cells purified from NALT and mesenteric lymph node (MLN) were measured using the IgAN onset and the quiescent ddY mice (each n=15). To identify dysregulation of mucosal immune response site in IgAN, NALT and GALT were immunized separately in GF-ddY mice, *i.e.*, nasally challenged with TLR9 ligand (CpG-ODN) stimulation and fecal transplantation.

Results: Broad-spectrum antibiotics depleted microbiota efficiently, resulted in ameliorating clinicopathological changes in IgAN onset ddY mice. Moreover, the GF-ddY mice did not develop IgAN, meanwhile, the GF-ddY mice showed an aggravation of renal injury with mesangial IgA deposition after transferred to SPF condition. In the IgAN onset ddY mice, the levels of aberrantly glycosylated IgA and IgG-IgA IC in serum and supernatant of cultured cells purified from NALT are significantly higher than those in the quiescent ddY mice. However, the levels of supernatant aberrantly glycosylated IgA and IgG-IgA IC produced by cultured cells purified from MLN showed no significant difference between the IgAN onset and the quiescent ddY mice. Although the GF-ddY mice nasally immunized with CpG-ODN also showed an aggravation of renal injury with mesangial IgA deposition, the GF-ddY mice which received fecal transplant did not develop IgAN.

Conclusions: Present study indicated that the dysregulation of mucosal immune response due to exogenous antigen exacerbated the pathogenesis of IgAN. TLR9 signaling pathways in NALT may be mainly involved in the pathogenesis of IgAN.

PO1805

Functional Studies of IgG Autoantibodies in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein galactose-deficient IgA1 (Gd-IgA1) is recognized by IgG autoantibodies (autoAbs), resulting in the formation of immune complexes (ICs), some of which deposit in the kidneys and induce glomerular injury. We have shown that a recombinant IgG (rIgG) autoAb derived from an IgAN patient can bind to Gd-IgA1, form ICs, and induce pathologic mesangioproliferative changes in a passive mouse model of IgAN. However, the interaction between the key elements, Gd-IgA1 and IgG autoAbs, has not been fully clarified. After solving the Fab 3-D structure, we focused on functional characterization of this rIgG autoAb.

Methods: Based on solved 3-D structure of the Fab of rIgG autoAb, we used site-directed mutagenesis to replace specific amino-acid (aa) residues in the rIgG autoAb. rIgGs were expressed in Expi293F cells and purified by affinity chromatography. ELISA was used to assess the binding of rIgGs to Gd-IgA1. Fab fragments of two selected mutants of rIgG were purified and used for hanging-drop crystallization. Liquid chromatography coupled with mass spectrometry (LC-MS) analysis was used to identify Gd-IgA1 *O*-glycoforms recognized by rIgG autoAb.

Results: We generated rIgG variants with aa replacements in several heavy-chain segments: junction of framework 1 (FR1) and complementarity-determining region 1 (CDR1) and in the CDR3. The FR1-CDR1 mutations reduced or disabled rIgGs binding to Gd-IgA1, depending on the specific aa residue used for replacement. Mutations in CDR3 completely impaired the binding of rIgG to Gd-IgA1. LC-MS analyses indicated that rIgG autoAb preferentially binds to a subset of IgA1 molecules, resulting in enrichment of hinge-region (HR) glycoforms with 4 *O*-glycans, including HR glycoform GalNAc4Gal3.

Conclusions: Our study identified specific aa residues in the FR1-CDR1 and CDR3 regions of the rIgG autoAb that are critical for Gd-IgA1 binding. The ongoing structural studies of different variants of this rIgG will elucidate the nature of autoantigen recognition by IgG autoAbs. This knowledge, together with the understanding what are the main targeted HR glycoforms, will enable the design of future therapeutic approaches based on blockade of these pathogenic IgG autoAbs in IgAN.

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PO1806

Can the Cross-Talk Between PDGF Receptor and Axl in Mesangial Cells Represent a Possible Therapeutic Target in IgA Nephropathy?

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Background: PDGF is involved in the pathogenesis of IgA nephropathy, namely in the activation of mesangial cells (MC). Our kinomic profiling revealed that receptor tyrosine kinase Axl and non-receptor tyrosine kinase ABL were the top upregulated protein-tyrosine kinases in MC stimulated by PDGF-AB. In this study, we describe crosstalk between Axl and a PDGF receptor (PDGFR-β) in human MC stimulated with PDGF.

Methods: Quiescent primary human MC were stimulated with PDGF-AB for 15 min. Cell lysates were analyzed with SDS-PAGE/Western blotting to probe for phospho-PDGFR-β, phospho-Axl, and down-stream signaling. Immunoprecipitation with antibodies specific for PDGFR-β or Axl was used to assess association of Axl and PDGFR-β. To test the role of Axl in crosstalk with PDGFR-β, the Axl/ABL inhibitor R428 and an Axl-specific siRNA knock-down (k/d) were used. Cellular proliferation was measured by BrdU incorporation ~20-h after PDGF-AB stimulation.

Results: PDGF-AB stimulated cellular proliferation of MC. PDGF-AB induced phosphorylation of multiple kinases, including Axl, PDGFR-β, Akt1, and ERK1/2 in MC. Immunoprecipitation experiments revealed association of Axl with PDGFR-β. The Axl/ABL inhibitor R428 inhibited PDGF-AB-induced phosphorylation of Axl, PDGFR-β, AKT1, and ERK1/2, and partially reduced PDGF-AB-induced MC proliferation. siRNA k/d of Axl reduced expression of Axl, but did not prevent PDGF-AB-induced phosphorylation of AKT1, ERK1/2 and PDGFR-β, and did not reduce proliferation of MC.

Conclusions: In summary, PDGF-AB induced multiple signaling events in cultured human MC that included crosstalk between PDGFR-β and Axl. MC cellular signaling induced by PDGF-AB was blocked by the Axl/ABL inhibitor R428 but not by Axl siRNA k/d. These findings suggest a role for the non-receptor tyrosine kinase ABL in a crosstalk between the two receptors. We postulate that the PDGFR-β/Axl/ABL pathway may represent a possible therapeutic target in the treatment of IgA nephropathy.

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PO1807

Galactose-Deficient IgA_1-Containing Immune Complexes Deposit with Complementary Activity in Mesangium Through Endothelial Cell Injuries

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Background: IgAN is defined by the presence of dominant mesangial IgA1 immune deposits, accompanied by C3 deposits, and deposition of IgA1 includes galactose-deficient IgA1 (Gd-IgA1). However, the pathogenic role of Gd-IgA1-containing IC with regard to mesangial immune deposits are still unclear. The endothelial surface glycocalyx modulates microvascular function. Loss of the glomerular endothelial glycocalyx is involved in albuminuria. In present study, we hypothesized that Gd-IgA1-containing IC deposit in mesangium through glomerular endothelial cell injuries.

Methods: Gd-IgA1 and recombinant anti-glycan IgG were used to form IC (Gd-IgA1-IgG IC) to inject *i.v* into nude mice. After various time intervals, mice were sacrificed and kidney was harvested to determine mesangial deposition and kidney injuries. To investigate that Gd-IgA1-IgG IC stimulation increases permeability of glomerular microvascular resulted in renal injuries, the renal microvascular endothelial glycocalyx removal was estimated by real-time glycocalyx imaging. Furthermore, human renal glomerular endothelial cells (HRGEC) were co-cultured with Gd-IgA1 alone or Gd-IgA1-IgG IC for 72 h to assess the potential capacity of these IC to activate endothelial cells.

Results: After injection of Gd-IgA1-IgG IC, but not Gd-IgA1 only induced proteinuria and hematuria in nude mice. Gd-IgA1-IgG IC deposited with murine C3 in the mesangium as well as subendothelial area of the glomerular capillaries. Furthermore, electron microscopic examination showed that injection of Gd-IgA1-IgG IC induced endothelial injuries. In fact, real-time glycocalyx imaging showed that renal microvascular glycocalyx were reduced after injection of Gd-IgA1-IgG IC in nude mice. After co-culture of Gd-IgA1-IgG IC with HRGEC, transcript levels of endothelial adhesion factors such as ICAM-1, VCAM-1 and E-selectin were significantly upregulated ($P<0.01$). Transcript levels of TNFα and IL-6, proinflammatory mediators which are able to induce the expression of adhesion factors on endothelial cells, were also increased ($P<0.01$).

Conclusions: Present data suggested that Gd-IgA1-containg IC deposition and subsequent complement activation may induce endothelial damage and overexpression of pathogenic cytokines and adhesion molecules resulting in glomerular injuries in IgAN.

PO1808

Sparsentan Protects Against Development of Albuminuria and Glomerulosclerosis in the gddY Mouse Model of IgA Nephropathy

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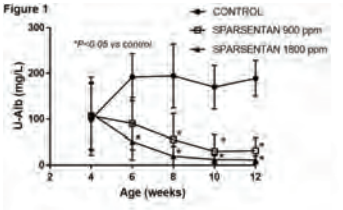
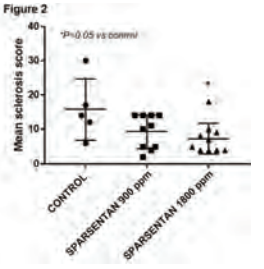
Background: gddY mice are an IgA nephropathy (IgAN) model that develops albuminuria by 8 weeks (W) of age with glomerular IgA, IgG, and C3 deposits and progressive mesangioproliferative glomerulonephritis. A previous study in the ddY mouse model (the predecessor to gddY mice) using the endothelin type A receptor (ET_AR) antagonist FR139317 resulted in amelioration of proteinuria and preservation of kidney function. Treatment of ddY mice with the angiotensin II type 1 receptor (AT_1R) blocker valsartan resulted in significant protection from glomerulosclerosis (GS) without a significant prevention in proteinuria. We examined the effect of sparsentan (SP), a dual ET_AR and AT_1R blocker, on development of albuminuria and GS in gddY mice.

Methods: 4 W old gddY mice were fed with control (C) chow (n=5) or chow containing 900 ppm (n=10) or 1800 ppm (n=10) SP (180 and 360 mg/kg/day) for 8 W. Albuminuria (U-Alb) was assessed at 4, 6, 8, and 12 W of age and plasma levels of SP were determined at 8 am and 4 pm at 6, 8, and 12 W. Kidney biopsies were taken at the end of the study at 12 W of age and 30 glomeruli/animal were scored for the percentage of GS. Serum IgA and glycosylation of IgA was measured using ELISAs.

Results: gddY mice fed SP for 8 W from 4 W of age demonstrated significantly ($P<0.05$) decreased U-Alb vs mice fed C diet (Fig 1). Development of GS in SP-fed mice was significantly ($P<0.05$) attenuated vs C diet (Fig 2). Plasma levels of SP taken at 8 am and 4 pm after 8 W of treatment were (mean±SD) 281±107 and 105±62 ng/ml respectively for 900 ppm SP and 774±674 and 304±176 ng/ml respectively for 1800 ppm SP. Weight gain in mice fed SP was not different from mice receiving C diet. There was no difference in serum levels of IgA or aberrantly glycosylated IgA.

Conclusions: 8 weeks of treatment with SP significantly attenuated increases in albuminuria and GS associated with the development of IgAN in gddY mice. If translated to the clinic, these data support SP as a new approach to the treatment of IgAN.





PO1809

Dysregulation of B-Cell Differentiation in IgA Nephropathy Model Mice

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Background: Several novel drugs targeting B cells are reported to be effective in the treatment of IgA nephropathy (IgAN). On the other hand, we have reported that the abnormal B cells expressing APRIL (A proliferation-inducing ligand) are present in tonsils of human IgAN. Given these reports, dysregulation of B cells may be involved in the pathogenesis of IgAN. To elucidate the abnormality in B cells of IgAN, we analyzed characteristics of B cells by using IgAN prone mice with (O-ddY) or without (NO-ddY) full onset of this disease. Furthermore, we recently developed a novel culture system mimicking germinal center in mucosa, by which nearly 50 % of B cells undergo class switch (CS) to IgA. Here, we aim to evaluate characteristics of B cells in O-ddY mice using this novel B cell culture system.

Methods: Splenic B cells from O-ddY or NO-ddY mice were stimulated with membrane-bound IgM and CD40 for 48h and then proliferation of B cells was evaluated by Thymidine-uptake analysis. To examine CS to IgA, naïve splenic B cells from O-ddY or NO-ddY mice were cultured for seven days under the newly developed culture system. The frequency of IgA CS was evaluated by flow cytometry.

Results: We found that naïve B cells of O-ddY proliferated more than those of NO-ddY mice in response to stimuli through CD40 and membrane-bound IgM. There was no significant difference in the frequency of class switch to IgA between splenic B cells from O-ddY mice and those from NO-ddY mice.

Conclusions: These data indicate that B cells in O-ddY mice are hyper-sensitive to stimuli by antigen and T-cell help without increasing the frequency of IgA class switch and suggest that such dysregulation of B cells may be involved in the pathogenesis of IgAN

PO1810

Novel Model for IgA Nephropathy Using Synthetic Polymeric IgA

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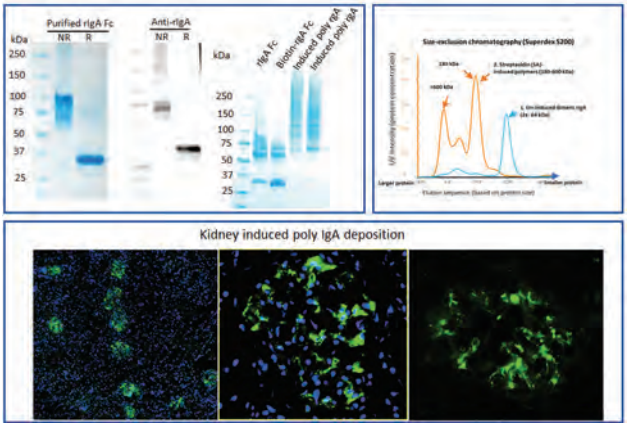
Background: IgA nephropathy (IgAN) is characterized by polymeric IgA deposition in the glomerulus. The mechanism for IgA deposition remains elusive. We constructed a recombinant IgA polymerized by streptavidin to model the initiation and development of IgAN.

Methods: To model IgA complex, we produced recombinant rat and human IgA CH2-CH3 segments. By fusing them with Avi-tag, adding biotin and tetrameric streptavidin to form 4-8-unit multimers. Both dimeric IgA and polymeric IgA constructs were IV injected in rats. Renal deposition of the IgA was detected by immunofluorescence. Polymer IgA was used to stimulate mesangial cells and IL-6 production was measured by ELISA.

Results: Through BirA enzymatic reaction, single biotin was added to the Avi-Tag at the N-terminus of IgA. The total molecular sizes of IgA with and without streptavidin were measured by size-exclusion chromatograph. As expected, uninduced IgA was a standard dimer of 65 kDa, whereas streptavidin-induced IgA formed multimers of 4-8 units, resembling poly-IgA in IgAN. These dimeric and polymeric IgA at 2 mg/kg. BW were injected in 5 week-old Wister rats. 1h, 3 hrs and 24 hrs after injection, the kidney and the liver were harvested for detection of rIgA. Exclusive IgA deposition in the glomerulus mesangial areas was found(Figure). In general, the staining intensity gradually diminished over 24 hrs period. However, rats received daily doses of the induced IgA for 2 and 5 days showed enhanced intensity of IgA deposition. In contrast, the dimeric IgA was not detectable in kidney. Furthermore, EM and PAS staining of the renal sections showed mesangial proliferation. Ex vivo stimulation of human mesangial cells also showed increased levels of IL-6 in the medium.

Conclusions: The findings indicate streptavidin-induced poly-rIgA causes specific renal mesangial deposition and mesangial cells proliferation, which can be used to study the kinetics of mesangial accumulation and clearance of IgA deposition, as a new model for investigating IgAN pathogenesis.



PO1811

Nephritic Factor Function Over Time

Christopher Culek,[1,2] Monica D. Hall,[1,2] Yuzhou Zhang,[1,2] Richard J. Smith,[1,2] Carla M. Nester.[1,2] *[1]Molecular Otolaryngology and Renal Research Laboratories, Iowa City, IA; [2]University of Iowa, Iowa City, IA.*

Background: Nephritic factors (Nef) are autoantibodies that stabilize and dysregulate the function of the C3 convertase, the cornerstone of complement amplification. Their association with renal inflammation central to the C3 Glomerulopathies (C3G) is well reported, however it is unknown whether Nefs 1) change over time, 2) correlate with serologic biomarker assessments, and/or 3) are useful for predicting risk for relapse of C3G. We aimed to create a novel assay that allows comparison of Nef properties over time. We further sought to correlate these results with an array of serologic biomarkers. We hypothesized that when Nef activity remains high, this abnormality is associated with ongoing serologic biomarker abnormalities.

Methods: The test subject was a C3G patient with disease recurrence 7 months after renal transplant. Reagent C3 convertase was formed by injecting factor B, factor D, and patient-derived IgG (versus normal pooled human IgG as a control) over a C3b-immobilized CM5 chip (Biacore X100) followed by injection of Decay Accelerating Factor (DAF) to remove unstabilized convertase. Nef-stabilized convertases were allowed to dissociate for 3600 minutes. Kinetic data were collected at five time points during dissociation. Data for each clinical time point were normalized to the amount of stabilized convertase at t=0. Serologic biomarker assays were performed as previously described.

Results: Qualitatively, test subject Nef stabilized the convertase 1.32 to 1.44 fold longer than unstabilized convertase. Between sample time point variability at 800s was less than 13%. Nef function correlated with serologic biomarker abnormalities at all 4 samples.

Conclusions: Using a novel assay, we show that Nefs isolated from a test subject remained remarkably stable over a 28-month period. In addition, the stabilizing effect of Nefs on C3 convertase consistently correlated with serologic biomarker abnormalities. We are extending this approach to additional C3G patients with and without recurrence of disease in transplant in order to provide a method for comparing Nefs over time, thereby defining the role of Nef-stabilizing function as an at-risk biomarker for C3G recurrence in transplant.

Funding: NIDDK Support

	Native		Transplant	
	10/2017	01/2018	10/2019	01/2020
Stabilization of Convertase (n= 1)	1.44	1.39	1.36	1.32
APFA (n = 50-130%)	0%	0%	24%	26%
C3 (n = 0.9-1.8g/L)	0.6	0.6	0.6	0.6
C3c (n = <1.5mg/L)	1.0	0.9	0.7	0.7
B (n = 22-50 mg/dl)	24.8	20	18.7	20.5
Bb (n = <2.2 mg/L)	2.21	2.18	1.6	1.6
C5b-9 (n = <0.3 mg/L)	0.16	0.13	0.11	0.07

PO1812

C3 Glomerulopathy Recurrence After Kidney Transplant: A Systematic Review

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Background: C3 glomerulopathy (C3G) is a recently defined entity, characterized by the dysregulation of the complement pathway, leading to deposition of C3 complement in the glomeruli, with no or few immunoglobulin deposits. While it is known that membranoproliferative glomerulopathies carry a risk of recurrence after transplant, no large-scale meta-analysis was done after 2015 to assess the precise recurrence risk and remission duration for C3 glomerulopathies. The goal of this work is to determine if there is currently enough literature specific for C3G to conduct such a metanalysis.

Methods: Our research protocol was guided by the PRISMA protocol, and the Joanna Briggs Institute Critical Appraisal Tools. A search was conducted in 3 databases using a specific search string, at the conclusion of which, 230 papers were found. The identified papers were subsequently screened by the 2 authors independently using precise inclusion and exclusion criteria. The screening resulted in the final inclusion of 6 papers, on which a qualitative synthesis was performed. The information extracted was organized on the basis of demographics, time of transplantation, disease recurrence, and disease-free period post-transplantation.

Results: Among the 6 papers selected, 2 were case series and 4 were case reports. In total, 25 patients were reported as having a recurrence of C3G. The age of the patients ranged between 7 and 60 years of age. Among the 25 patients, 11 of them were male, while 6 of them were females. The C3G subtype was determined for 25 patients, with 16 were classified as having C3GN. and 8 having DDD. The age of transplant was reported for 14 patients, ranging from 11 to 64 years old. The disease-free period between the kidney transplant and the recurrence of the disease ranged from 14 days to 91 months, with 1 case series paper only reported the median time to recurrence in months (59[27-91] for C3GN patients and 41[0-71] for DDD patients).

Conclusions: While C3G, with its 2 subtypes, have been well-defined entities for a decade, our review reveals that little research about the post-transplant evolution and recurrence of these diseases has been done. While extensive research can be found on the recurrence risks of Membranoproliferative Glomerulonephritis, we believe that with the new classification, more data on the new subtypes is necessary to guide the decision-making of clinicians and their patients.

PO1813

C3 Glomerulonephritis: A Rare Complication of Chronic Lymphocytic Leukemia

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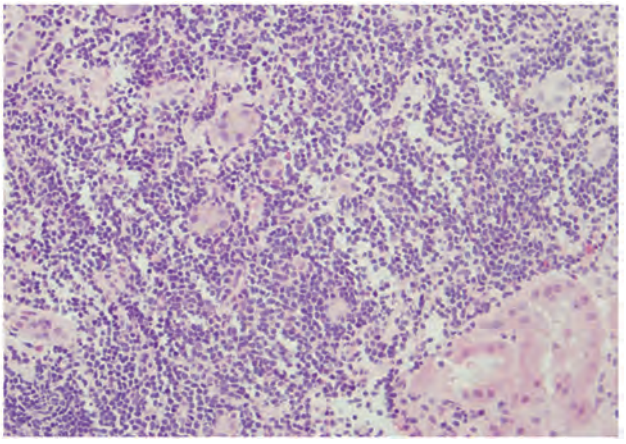
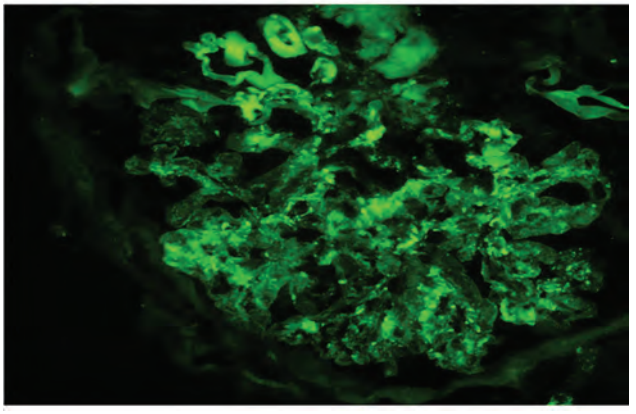
Introduction: Kidney disease develops in chronic lymphocytic leukemia (CLL) patients via multiple mechanisms including infiltration, obstruction, tumor lysis syndrome, and glomerular disease. We present a rare case of C3 glomerulonephritis (C3GN) associated with pulmonary renal syndrome that we believe was an autoimmune manifestation of CLL.

Case Description: A 76 year old male with a 15 year history of SLL/CLL, DVT, HTN, DM and Stage 3 CKD developed SOB and dry cough. At ED presentation he was in respiratory distress with BIPAP resistant hypoxia requiring intubation. Labs included Cr 7.1 mg/dL, K 5.7 mEq/L and uric acid 12.2 mg/dL CXR showed vascular congestion. Prior to developing anuria urine sediment showed RBC casts. Bronchoscopy DAH, consistent with a pulmonary renal syndrome. Patient was started on plasmapheresis, high dose steroids and CRRT. Autoimmune workup including ANA, anti GBM and ANCA was negative. Kidney biopsy showed diffuse proliferative and sclerosing glomerulonephritis with lymphocytic infiltrates consistent with involvement by patient's known CD5+, CD23+ B cell lymphoproliferative disorder. IF showed diffuse C3 staining. Steroids and

plasmapheresis were continued. Renal function improved and dialysis discontinued, with Cr at last follow up 1.9. Chemotherapy for CLL has been ordered. Lymphocytes were negative for CD3, CD10, Bcl6, and cyclin D1; with a MIB1 nuclear proliferation rate within the lymphoid infiltrates less than 5%.

Discussion: We present a case of C3GN and DAH secondary to CLL autoimmune etiology, a rare complication of CLL which usually affects the kidney by infiltration and by toxicity of the CLL treatment. Recent case reports suggest improved outcomes of CLL associated C3GN when CLL is treated.





PO1814

Fibrillary Glomerulonephritis or Complement 3 Glomerulopathy: A Rare Case of Crescentic Glomerulonephritis with C3 Dominant Glomerular Deposition and Positive DNAJB9

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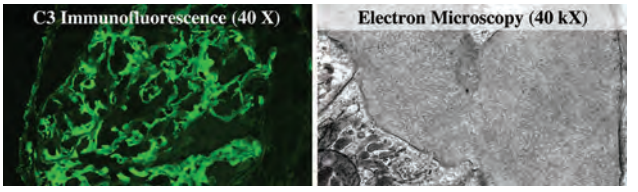
Introduction: Fibrillary glomerulonephritis (FGN) and complement 3 glomerulopathy (C3G) are two rare forms of GN. FGN is diagnosed by electron microscopy (EM) showing randomly oriented fibrils ranging in diameter from 15-25 nm. Immunofluorescence (IF) in FGN typically is IgG-predominant. C3G is diagnosed by isolated C3 (>3+ intensity) or dominant C3 (≥2 orders of intensity from other deposits) on IF. We present a rare case of crescentic GN with dominant C3 glomerular staining–consistent with C3G–but EM findings suggestive of FGN.

Case Description: A 57-year-old female with history of HTN, type 2 DM, questionable SLE (not on therapy), presented with gross hematuria & lower extremity edema. BP 113/71, pulse 88. Creatinine 1.82mg/dL (0.75 two months prior). Urinalysis with 132RBC/hpf & 51WBC/hpf. Urine Prot/Cr 24. Cultures grew mixed flora in urine & Serratia marcescens in blood, treated with ceftriaxone. Other labs included serum albumin 1.8 g/dL, ANA >12.0, SS-A >8.0, C3 202, C4 57, & HbA1c 7.3%. Anti-dsDNA, hepatitis B & C, and HIV were negative. Kidney biopsy was performed. LM: diffuse necrotizing crescentic (15 of 15) GN, focal areas of double contours. IF: dominant 3+ C3 granular stain of capillary loops, lesser 1+ IgG. Remaining IF stains negative. Testing for alternative complement dysregulation was negative. EM showed fibrillary structures within basement membranes & mesangium (mean diameter 14 nm). DNAJB9 staining was positive. Patient was treated with steroids & cyclophosphamide but became dialysis dependent.

Discussion: FGN is associated with autoimmune disease, dysproteinemia, hepatitis C, & malignancy. Our patient's EM findings & positive DNAJB9 strongly support a diagnosis of FGN likely due to an autoimmune etiology given her prior history and positive ANA, SS-A. However, the patient's IF findings of dominant C3 deposits is atypical for FGN, but rather characteristic of C3G which is caused by complement dysregulation. To the best of our knowledge, this is the first reported case of FGN to show dominant C3 glomerular deposits. Further studies are needed to determine the significance of this finding.



PO1815

A Case with Immunotactoid Glomerulonephritis with Masked Monoclonal Light-Chain Deposition Disease

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Introduction: The immunotactoid glomerulonephritis (ITG) is a rare disorder that is characterized by proteinuria, hematuria, hypertension, and kidney failure. Its diagnosis and timely treatment are important in order to decrease morbidity, conserve kidney function, and improve survival.

Case Description: An 82-year old man with a past medical history of uncontrolled hypertension and cerebrovascular disease presented with myalgia, profound weakness and persistent vomiting for 9 days. In the emergency department, his vital signs were significant for blood pressure 220/109 mmHg. BMP revealed creatinine as 3.48 mg/dl, which was 0.9 mg/dl at baseline. The patient was diagnosed with hypertensive urgency and acute kidney injury. Urinalysis showed 107/HPF red blood cells and protein >500 mg/dl. Spot urine albumin/creatinine ratio was 869.9 mg/g. Serum C3 decreased to 29.5 mg/dl (reference: 88-201) and C4 decreased to 2.5 mg/dl (reference: 16-47). Hepatitis B and C were non-reactive. Kidney biopsy was planned and pulse dose steroid, 500 mg IV daily, was prescribed for 3 days. The patient's kidney function continued to worsen and he required hemodialysis. His serum free kappa level elevated to 4.54 mg/dl (reference 0.33-1.54), lambda level was normal 2.54 mg/dl (reference 0.57-2.63), free kappa/lambda ratio elevated to 1.80 (normal 0.26-1.65). Serum immunofixation study showed IgG kappa monoclonal ab without M-spike; urine protein electrophoresis showed elevated protein level with no apparent M-spike. Initially, kidney biopsy suggested proliferative glomerulonephritis with C3 deposits with light-microscopy. However, repeat immunofluorescence was consistent with diffuse proliferative immunotactoid glomerulonephritis with "masked" monoclonal IgG1-kappa deposits. Congo red stain was negative, ruling out amyloidosis. The patient was continued on daily high-dose steroid treatment. He was referred to Hematology/Oncology for bone marrow biopsy for concern of plasma cell neoplasm or lymphoproliferative disorder. Dialysis was discontinued at the time of discharge as patient's kidney function improved with steroid treatment.

Discussion: It is important to keep ITG in the differential diagnosis as high-dose steroid or cyclophosphamide might prevent rapid glomerulonephritis progression. Treatment of underlying disease such as light-chain deposition disease might have some benefit on renal disease.

PO1816

Rare Association of Monoclonal Gammopathy of Renal Significance with Acquired Angiodema

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Introduction: Acquired angioedema(AA) due to deficiency of C1 esterase inhibitor is also abbreviated as C1INH-AAE. This rare syndrome presents with recurrent angioedema episodes, without urticaria, and sometimes is associated with B-cell lymphoproliferative disorders. Kidney involvement is rare with AA. The monoclonal immunoglobulins are secreted by a nonmalignant B-cell or plasma cell clone, causing renal damage representing a group of disorders called monoclonal gammopathy of renal significance (MGRS). We present a rare association of these two entities.

Case Description: 64 year old female patient came to the emergency department with complaints of 2 week duration waxing, waning maculopapular rashes in all extremities, chills, hoarseness of voice and lower extremity swelling. She had no family history of angiodema. Positive examination findings were rashes and bilateral pedal edema. With a normal baseline creatine, admission serum creatine was high at 2.4 mg/dl. Positive laboratory findings were very low complements level (C4> C3), low C1q level, high C1 esterase inhibitor level. Other immunological workup including serum, urine immunoelectrophoresis, kappa lambda ratio, serum immunofixation were normal. Kidney biopsy undertaken revealed monoclonal gammopathy–associated diffuse proliferative glomerulopathy. She responded well to steroids only and is in clinical remission with normal renal function.

Discussion: Paraproteinemia is characterized by clonal proliferation of B-cells and/or plasma cells resulting in overproduction of monoclonal proteins and can cause significant renal dysfunction. Paraprotein-induced renal disease can occur without malignancy, now termed as monoclonal gammopathy of renal significance. MGRS includes a wide spectrum of disorders like light/heavy chain deposition disease, C3 glomerulopathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposition(PGNMID), and primary amyloidosis. MGRS necessitates strict monitoring,

early interventions to prevent renal damage. Acquired angioedema generally presents with head and neck symptoms, mainly swollen upper airways, cheeks, and tongue. AA has low C1q levels unlike hereditary angiodema. Systemic manifestations are far common with AA than hereditary angioedema. No literature has shown an association of MGRS/PGNMID with AA and low complement levels. Further case studies needs to be done to discover any large-scale association of MGRS with AA.

PO1817

Clinical Biomarker Trend in C3 Glomerulopathy

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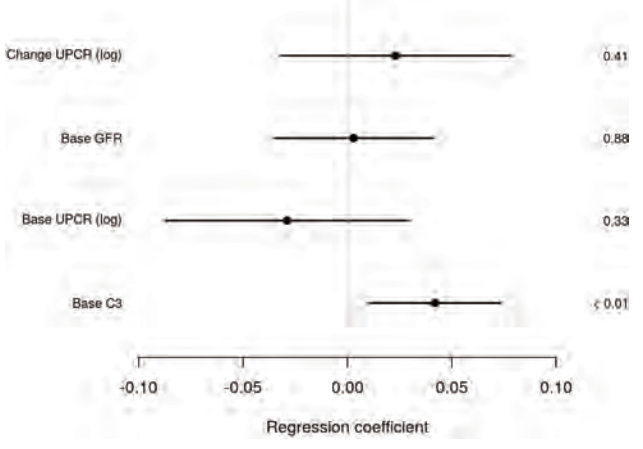
Background: There is a paucity of data defining the natural history of the clinical and complement biomarker characteristics of C3 Glomerulopathy (C3G) patients. Whether there are disease defining trends and/or relationships between the markers of disease is unknown. In a series of C3G patients, we sought to describe the trend in three commonly available markers of disease: complement C3, urine protein-to-creatinine ratio (UPCR), and GFR. We hypothesized that lower C3 levels, as a reflection of ongoing complement activity would be associated with progressive renal disease as represented by changes in UPCR and/or GFR.

Methods: All patients met the consensus, renal biopsy definition of C3G. Thirty-two native kidney disease subjects with an age ≥ 12 years and GFR ≥ 30 ml/min were included. Trends in C3, UPCR and GFR were monitored in 1-year spans. Ninety spans with matched C3, UPCR and GFR data were identified. Mean and median statistics across all spans were reported as percent change per year and standard regression analyses were used to define the relationship between variables.

Results: 54% of patients retained a C3 within 10 mg/dL of their span entry C3; 86% had a C3 within 25 mg/dL of their entry C3. In only three 1-year spans did a patient start with a low C3 and finish with a normal C3. Mean and median change in GFR per year were a decrease of 4.5% and 2.9% respectively, with the greatest GFR decreases in those spans with the lowest C3. Mean and median change in UPCR per year was a decrease of 8.3% and 10.9%. When considering baseline GFR, baseline UPCR, baseline C3 and change in UPCR, loss of GFR most closely correlated with baseline C3 (Figure, p <0.01).

Conclusions: These data indicate that C3 levels vary little from baseline over a 1 year period and that loss of GFR correlates with baseline C3. These results suggest that treatment approaches that effect an improvement in C3 may have a beneficial effect on GFR.

Funding: Commercial Support - Novartis



PO1818

A Case Series of Proliferative Glomerulonephritis with Monoclonal Immune Deposits

Deepa A. Koshti, Ramesh Saxena. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Introduction: Monoclonal gammopathy of renal significance (MGRS) comprises B-cell and plasma-cell clonal proliferative disorders that do not require treatment for the clonal disease but produce nephrotoxic monoclonal immunoglobulins (mIg) that elicit a variety of kidney manifestations. One such presentation is proliferative glomerulonephritis associated with monoclonal immune deposits (PGNMID), typically presenting as membranoproliferative glomerulonephritis (MPGN) and non-organized glomerular mIg deposits. We describe 3 unique cases of PGNMID from our institution.

Case Description: Case-1: A 16-year old female presented with abdominal pain, gross hematuria, nephrotic proteinuria, edema and normal renal function. Protein electrophoreses and bone marrow (BM) biopsy were unremarkable. Kidney biopsy showed MPGN with monoclonal IgG3 lambda deposits. She had inadequate response to B or plasma cell targeted therapies but responded very well to multitargeted therapy (mycophenolate+tacrolimus) achieving complete response. Case-2: A 39-year old woman with history of antiphospholipid syndrome and 2 miscarriages developed persistent nephrotic proteinuria after uncomplicated third pregnancy. Kidney biopsy showed membranous glomerulopathy with mesangial hypercellularity and monoclonal IgG3 lambda deposits. BM biopsy and protein electrophoresis were unremarkable. She had partial response to rituximab. She is currently being treated with plasma cell targeted therapy with good response. Case-3: A 28-year old male with nephrotic proteinuria found on routine examination. Further evaluation showed unremarkable BM biopsy and protein immunofixation. Kidney biopsy showed mesangial hypercellularity and monoclonal-IgG1 kappa deposits. He is currently being treated with rituximab.

Discussion: PGNMID is a subset of MGRS with variable histologic pattern and histological features of immune complex glomerulonephritis; however, the immune deposits are monoclonal and are seldom associated with serum M-spike. Our patients were younger than those reported in literature and had variable histologic patterns. None had M spike or clonal B or plasma cells. The response to treatment was variable. Two patients showed no response to B-cell depleting therapy. One patient did not respond to plasma-cell directed therapy, but the other did. The third patient is currently receiving B-cell depleting therapy.

PO1819

Role of SIRT1 in HIV-Associated Kidney Disease

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Background: HIV infection of kidney cells can lead to HIV-associated nephropathy (HIVAN) and aggravate the progression of other chronic kidney diseases. Thus, a better understanding of the mechanisms of HIV induced kidney cell injury is needed for effective therapy against HIV-induced kidney disease progression. We previously showed that the acetylation and activation of key inflammatory regulators, NF-κB p65 and STAT3 were increased in HIVAN kidneys. Here, we examined the key role of SIRT1 deacetylase in regulation of NF-κB and STAT3 in HIVAN.

Methods: We analyzed expression of SIRT1 in glomeruli of human and mouse HIVAN kidneys, and then we explore the role of SIRT1 on acetylation of NF-κB p65 and STAT3 and expression of HIV genes by overexpression or knock-down of SIRT1 or using SIRT1 agonist, BF175 in cultured podocytes. In vivo, we examined the effects of SIRT1 on HIVAN progression by administration of BF175 for four weeks and inducible podocyte-specific SIRT1 overexpression in Tg26. We also assessed whether miR34a was associated with SIRT1 expression.

Results: SIRT1 expression was reduced in the glomeruli of human and mouse HIVAN kidneys and that HIV-1 gene expression was associated with reduced SIRT1 expression and increased acetylation of NF-κB p65 and STAT3 in cultured podocytes. Interestingly, SIRT1 overexpression in turn reduced the expression of Nef in podocytes stably expressing the HIV-1 proviral genes, which was associated with the inactivation of NF-κB p65 and reduction in the HIV-1 LTR promoter activity. In vivo, the administration of small molecule SIRT1 agonist BF175 or inducible overexpression of SIRT1 specifically in podocytes markedly attenuated albuminuria and kidney lesions in Tg26 mice. Finally, the reduction in SIRT1 expression by HIV-1 is in part mediated through miR-34a expression.

Conclusions: These findings provide a new mechanism of SIRT1 regulation and its downstream effects in HIV-1 infected kidney cells and indicate that SIRT1/miR-34a are potential drug targets to treat HIV-related kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

PO1820

Protein Kinase R Inhibition Ameliorates Tg26 HIV-Associated Nephropathy Mouse Model

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Background: HIV-associated nephropathy (HIVAN) has become less common with widespread use of antiretroviral therapy but has not yet disappeared. Double-stranded RNA (dsRNA)-activated protein kinase (PKR) is a sensor for dsRNA in response to viral infection such caused by HIV. We previously reported that APOL1 risk alleles damages podocytes through double-stranded RNA-activated protein kinase (PKR) activation. Thus, we hypothesized that PKR activation could be an activated pathway shared in the pathology of HIV- and APOL1-mediated nephropathies. We tested this hypothesis by investigating whether PKR inhibition would ameliorate HIVAN using the well-established Tg26 mouse model.

Methods: We evaluated the kidney phenotype of Tg26 mice and wild type mice treated with or without the PKR inhibitor (C16) from 6 to 12 weeks of age. We quantified albuminuria after treatment and evaluated kidney pathology after 6-week treatment.

Results: We confirmed the activation of PKR in Tg26 mice kidney by Western blot. We saw a significant decrease in kidney disease development in the PKR inhibitor (C16) treatment group compared to the vehicle control group. Urine albumin/creatinine ratio (mg/gCr; mean [IQR]) was 668 [60-1064] in the treatment Tg26 group and 2564 [1786-5646) in the vehicle control Tg26 group (P=0.026). Kidney pathology showed fewer sclerotic glomeruli and tubular microcystic lesions in the treated Tg26 group than in the vehicle control Tg26 group.

Conclusions: PKR inhibition ameliorated HIVAN phenotype of Tg26 mouse, suggesting that PKR activation contributes to the pathophysiology of HIVAN in this model.

Funding: NIDDK Support

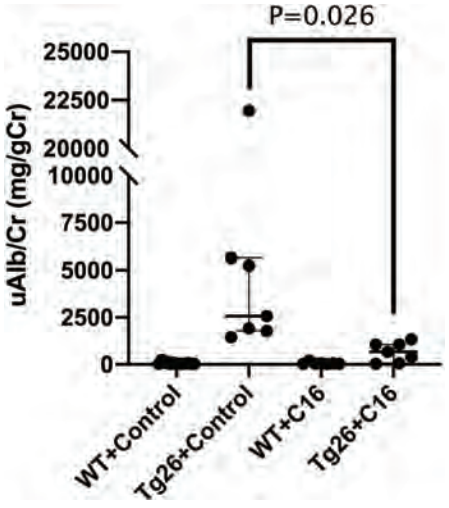

Fig: Urine albumin/creatinine ratio after treatment

PO1821

Interleukin 22 Attenuates Renal Tubular Cells Inflammation and Fibrosis Induced by TGF-β1 Through Notch1 Signaling Pathway

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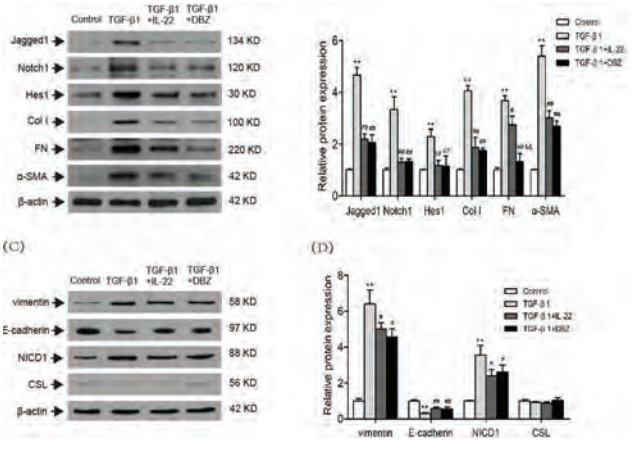
Background: Transforming growth factor-β1 (TGF-β1) is a crucial factor implicated in the development of renal inflammation and tubulointerstitial fibrosis. The cytokine interleukin 22 (IL-22) was previously reported to involve in the pathogenesis of chronic inflammatory diseases In the present study, we aim to investigate the role and mechanisms of IL-22 in renal tubular cells inflammation and fibrosis induced by TGF-β1.

Methods: HK-2 cells were treated with TGF-β1 in the presence of IL-22 or the Notch pathway inhibitor dibenzazepine (DBZ) for 48 h. Cell proliferation was determined by MTT assay, Cytotoxicity was assessed by LDH assay. Collagen I (Col I), fibronectin (FN), α-smooth muscle actin (α-SMA), vimentin and E-Cadherin were detected by western blot, proinflammatory factors (TNF-α, IL-6) and chemokines (MCP-1, RANTES) in the supernatant of cell cultures were evaluated by ELISA. Jagged1, Notch1, NICD1, and Hes1 were also detected by western blot.

Results: In our study, IL-22 (10–40 ng/ml) did not affect cell proliferation and cytotoxicity. Then IL-22 (20 ng/ml) incubation for 48 h was chosen for subsequent experiment. We found TGF-β1 increased the levels of Col I, FN, α-SMA and vimentin in HK-2 cells compared with control, and decreased E-Cadherin level, however, IL-22 restored their expressions partly. IL-22 reduced over expression of proinflammatory factors (TNF-α, IL-6) and chemokines (MCP-1, RANTES) levels induced by TGF-β1, along with down-regulation of Jagged1, Notch, NICD1 and Hes1. Fibrosis and inflammation in renal tubular cells induced by TGF-β1 could be attenuated by IL-22, and the effects were similar to DBZ treatment.

Conclusions: Collectively, our study shows that IL-22 exerts a protective role in renal fibrotic and inflammatory responses induced by TGF-β1 in vitro, which may be through inhibiting Jagged1/Notch1 signaling pathway activation.

Funding: Government Support - Non-U.S.



IL-22 reduced Notch1 pathway activation and fibrosis in HK-2 cells induced by TGF-β1.

PO1822

Urine Single-Cell RNA Sequencing in Focal Segmental Glomerulosclerosis Reveals Inflammatory Signatures in Immune Cells and Podocytes

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[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]Johns Hopkins Medicine School of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [3]University of Michigan, Ann Arbor, MI; [4]Frederick National Laboratory for Cancer Research, Frederick, MD.

Background: Individuals with focal segmental glomerulosclerosis (FSGS) typically undergo kidney biopsy only once, which limits the ability to characterize cell populations within kidney over time.

Methods: We used single cell RNA-sequencing (scRNA-seq) to explore disease-related molecular signatures in urine cells of FSGS subjects. We collected 23 urine samples from 12 FSGS subjects, and captured the urine cells using Chromium Single Cell 3' Library & Gel Bead Kit v2 (10x Genomics, Pleasanton, CA). We used Seurat package (v2) for single cell analysis, Harmony for batch correction and SingleR for annotation of cell clusters using Encode and Blueprint data. We also used Monocle2 to characterize the pseudotime trajectory of differentiation of FSGS urine monocytes from healthy peripheral blood monocytes.

Results: Using single cell transcriptomic analysis of 23 urine samples from 12 FSGS subjects, we identified immune cells, predominantly monocytes, and renal epithelial cells, including podocytes. Further analysis revealed two subtypes consistent with M1 monocytes (produce pro-inflammatory cytokines, initiate immune response) and M2 monocytes (participate in tissue repair). Shed podocytes in urine showed high expression of marker genes for epithelial-to-mesenchymal transition (EMT). We selected the 16 most highly expressed genes from urine immune cells and 10 most highly expressed EMT genes from urine podocytes as immune and EMT signatures, respectively. Using transcriptomic data from kidney biopsies from the Nephrotic Syndrome Study Network (NEPTUNE), we found that urine cell immune- and EMT-signature genes were more highly expressed in FSGS biopsies compared to minimal change disease biopsies.

Conclusions: The identification of monocyte subsets and podocyte expression signatures in FSGS subjects' urine samples suggests that urine cell profiling might serve as a diagnostic and prognostic tool in the context of nephrotic syndrome. Further, this approach may aid in the development of novel biomarkers for FSGS and for identifying personalized therapies targeting particular molecular pathways in immune cells and podocytes.

Funding: NIDDK Support, Other NIH Support - Support from Frederick National Laboratory for Cancer Research, NCI

PO1823

Retinal Drusen and Atrophy in Focal and Segmental Glomerulosclerosis: A Complement-Mediated Disease?

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Background: Retinal drusen are small yellow-white deposits typically found in age-related macular degeneration but also with dense deposit disease, lupus nephritis, IgA disease, and membranous and post-streptococcal glomerulonephritis. Drusen and glomerular immune deposits result from complement activation, are similar in composition and share a subepithelial location. Focal and segmental glomerulosclerosis (FSGS) is a heterogeneous clinicopathological entity in which immune deposits comprising IgM and C3 may be seen. This study investigated a cohort of individuals with FSGS for retinal drusen.

Methods: This was a cross-sectional observational case-control study of individuals with FSGS recruited from a general renal clinic in an Australian tertiary-care metropolitan hospital. Previous structural renal disease and glomerulonephritis were noted. Two-field colour fundus images were assessed by two trained graders for drusen count, location and size using the Wisconsin Age-Related Maculopathy Grading Grid. Central drusen counts ≥10 were considered abnormal. Retinal atrophy and pigmentation were recorded by a retinal expert.

Results: Forty-nine individuals with FSGS were compared with 49 matched controls. Mean age was 55 ± 14 years and 29 (59%) were male. One (2%) with FSGS had co-existent structural renal disease, two (4%) had thin basement membrane nephropathy and three (6%) had syndromic FSGS. Twenty-five (51%) had reached end-stage kidney failure, and 16 (33%) had transplants. Central drusen count was 9 ± 25 in FSGS and 3 ± 8 in controls with normal renal function (**p=0.02**). Central drusen counts ≥10 were present in nine patients with FSGS (18%) and four controls (8%) (p=0.23). Seven of these nine (78%) were younger than 60 years which excluded age-related macular degeneration. Medium-sized drusen (>63μm) were more common in FSGS (20, 41%) than controls (10, 20%) (**p=0.048**). Retinal atrophy was present in 9 with FSGS (18%) and no controls (**p=0.003**).

Conclusions: Drusen are more abundant and larger in FSGS than controls. Drusen reflect complement activation and their similarities in composition and subepithelial location with glomerular immune deposits suggests that some of the mechanisms underlying drusen are also relevant to FSGS. Retinal atrophy occurs more often in FSGS and may reflect podocyte loss.

PO1824

Idiopathic Glomerular Endotheliosis

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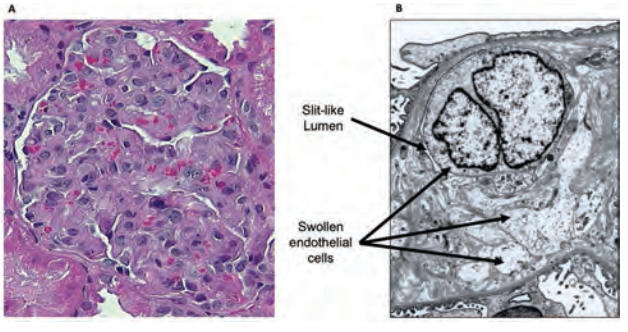
Introduction: Glomerular endotheliosis is a form of thrombotic microangiopathy (TMA) seen with preeclampsia, anti-vascular endothelial growth factor (VEGF) therapy for cancer, and some forms of Castleman's disease. We present a case without these usual conditions.

Case Description: A 31-year-old female with rheumatoid arthritis, ulcerative colitis (UC), and hypothyroidism presented with abdominal pain and emesis. Medications included adalimumab and levothyroxine. Abdominal imaging and upper endoscopy were unremarkable. Serum chemistries were initially normal. Pregnancy testing was negative. Abdominal computed tomography showed mild cecal inflammation. Fecal calprotectin was elevated. Oral budesonide was given for suspected UC flare. Symptoms worsened and she was given intravenous methylprednisolone. She developed proteinuria (up to 3.5 gm/day by 24hr urine) and worsening renal function. Serum complement was only mildy reduced - C3 (72) and C4 (10). C-reactive protein and erythrocyte sedimentation rate were elevated. Autoimmune serologies were unremarkable. Serum creatinine peaked at 5 mg/dl prompting hemodialysis. Kidney biopsy demonstrated severe glomerular endotheliosis but no other features of TMA (Figure). Pulse dose steroids were given and then daily prednisone; she had 2 sessions of plasmapheresis (PLEX). Renal function improved, attributed to steroids, and PLEX was held. At 4 weeks, she had only modest proteinuria (1.4 g/24hr) and improved renal function (serum creatinine (0.9 mg/dl).

Discussion: Glomerular endotheliosis is thought to occur due to VEGF inhibition in podocytes (by VEGF-inhibitors or by soluble fms-like tyrosine kinase in preeclampsia). Patients with endotheliosis of unknown cause have been reported to respond to immunosuppression (steroids, cyclophosphamide). Endotheliosis occurs in Castleman's disease and may improve with IL-6 inhibitors. The etiology in our patient remains unknown but she has demonstrated improvement with corticosteroids.



Hematoxylin and eosin (H&E) stain (A) and electron microscopy (B) demonstrating glomerular endothelial cell swelling and loss of capillary lumens.

PO1825

Minimal Change Disease Relapse Following Administration of an Anti-IgE Monoclonal Antibody, Omalizumab

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Introduction: Minimal Change Disease (MCD) is incompletely understood with immune cells, circulating factors, and glomerular basement membrane all considered potential precipitants. We present the first reported case of reactivation of MCD following administration of omalizumab.

Case Description: A 59-year-old lady presented with lower limb oedema two days following a second dose of Omalizumab for treatment of severe eosinophilic asthma. Her background was significant for two previous episodes of biopsy-proven MCD. Exam was significant for bilateral lower limb pitting oedema, a blood pressure of 174/86 mmHg, and proteinuria on urine dipstick. Urine PCR was 473 mg/mmol on presentation with preserved GFR. Treatment for a presumed MCD relapse was commenced with prednisolone and diuresis and omalizumab was discontinued indefinitely. Clinical and biochemical remission was achieved at 2-weeks and maintained at 6-month follow-up.

Discussion: Omalizumab is indicated as add-on therapy in patients with severe persistent allergic asthma, the primary mechanism of which is the binding of the active drug to IgE. The clinical effects of omalizumab are not accounted for solely by IgE antagonism with further immune regulatory effects hypothesised. Notably reduction in IL4, IL13, and IL8 have been described post-treatment. Immune system dysregulation, a hypothesized circulating factor, medications, and atopy are all considered to play a role in development of MCD. Studies have supported an imbalance of T-cell subpopulations and cytokines in MCD. Of note, Th2 cytokines IL4 and IL13 can interact directly with the glomerular basement membrane and are acted upon by omalizumab. In particular IL13 has been described as being related to a nephrotic syndrome in animal studies, and high levels are seen in paediatric nephrotic syndromes, with IL13 levels increasing further in remission. This is the first reported case of MCD in the context of omalizumab administration. IL13 and IL4 appear key to the hypothesised pathophysiology of MCD and mechanism of action of omalizumab. This case provides an insight into the interactions between MCD, atopy, and biologic medications, presenting MCD as a novel complication of omalizumab.

PO1826

Neurorenal Syndrome: Two Cases of Tip-Variant Focal Segmental Glomerulosclerosis Associated with Guillain-Barré Syndrome

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Introduction: Glomerular disorders have been associated with immune-mediated polyneuropathies in previous case reports. We present two cases of tip-variant focal segmental glomerulosclerosis (FSGS) associated with a variant of Guillain-Barré syndrome (GBS) in Winnipeg, Manitoba.

Case Description: Two previously healthy males aged 62- and 55-years old presented to our hospital with extremity weakness and paresthesias. They each progressed to flaccid paralysis and respiratory failure despite IV immunoglobulin (IVIG) and plasma exchange therapy (PLEX). Initial investigations were consistent with Acute Motor-Sensory Axonal Polyneuropathy (AMSAN), a variant of GBS. Nephrotic syndrome was identified after four months in case one and immediately in case two. Each patient had 20 g/day of proteinuria, preserved renal function, and histologic diagnosis of tip-variant FSGS on renal biopsy. Both cases responded to high-dose corticosteroids initially. Case one relapsed during his taper requiring re-initiation of steroids and addition of mycophenolate mofetil (MMF). He was discharged following thirteen months in hospital with complete remission of proteinuria and ongoing neurologic recovery. Case two achieved complete remission of proteinuria and was discharged after six months with ongoing neurologic recovery.

Discussion: Our cases have similar presentations and responses to therapy suggesting they may share a common circulating autoantibody reacting against shared neural and glomerular podocyte antigens. Circulating autoantibodies including anti-contactin-1 and neurofascin have previously been implicated in chronic inflammatory demyelinating polyneuropathy (CIDP), a chronic variant of GBS. Identifying the culprit immune target in primary FSGS is limited due to the absence of immune complex deposition. The timing of podocytopathy development compared to GBS is highly variable in cases reported throughout the literature. The onset and diagnosis of FSGS in Case 1 was either delayed or unrecognized illustrating the importance of educating clinicians about this neuro-renal syndrome. Although not routinely used in GBS, corticosteroids have led to favorable outcomes in our cases and those reported throughout the literature. Recognition of a co-existing nephrotic syndrome with GBS could significantly change management and impact treatment outcomes.

PO1827

Hemophagocytic Lymphohistiocytosis Presenting as Nephrotic Syndrome

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Introduction: Minimal change disease (MCD) is a podocytopathy resulting from systemic T cell dysfunction. Although frequently a primary disease, MCD can be secondary to immune dysregulation in malignancy or autoimmune disease. Hemophagocytic

lymphohistiocytosis (HLH) is a rare syndrome of excess immune activation with poorly understood renal sequelae. Here, we report a rare case of HLH-induced podocyte injury resulting in MCD.

Case Description: A 25-year-old African American male with nine-month history of progressive edema presented with tachycardia, fever and anasarca. Initial evaluation confirmed the diagnosis of nephrotic syndrome with hypoalbuminemia (1.6 g/dl) and proteinuria (15 g/24-hour). Echocardiography showed a pericardial effusion with tamponade treated with pericardiocentesis. Additional testing showed sCr 0.8 mg/dl, hypertriglyceridemia (735 mg/dl), ferritin (817 ng/dl) and EBV viral load of 43,006 copies/ml. Renal biopsy showed normal glomeruli by light microscopy with extensive foot process effacement on electron microscopy. A diagnosis of MCD was made. The patient was treated with steroids and cyclosporine. The patient was readmitted six months later with intermittent fevers, edema, pancytopenia, ferritin >3000 ng/d, hypofibrinogenemia, hepatosplenomegaly and elevated soluble IL-2R. Bone marrow biopsy showed hemophagocytosis. EBV viremia persisted (362,318 copies/ml) and he was diagnosed with chronic active EBV infection with associated HLH. Genetic testing of 15 known HLH associated genes did not identify a pathogenic mutation. HLH was treated with dexamethasone; rituximab was given once but stopped due to lack of CD19+ cells. HLH flared again during dexamethasone wean, prompting treatment with etoposide, then anakinra, without success. He achieved sufficient remission with IFN-gamma blockade with emapalumab-lzsg to undergo stem cell transplant. Three months after transplant, UPCR decreased from 20 g/g at HLH diagnosis to 1 g/g. His eGFR by cystatin C recovered to 46 ml/min/BSA from 10 ml/min/BSA prior to transplant.

Discussion: Virus-induced HLH can result in podocytopathy manifesting as MCD which can have serious sequelae including irreversible renal damage leading to chronic kidney disease, hypertriglyceridemia and pericardial effusion. This nephrotic syndrome can improve with treatment of HLH with immunosuppression or stem cell transplant.

PO1828

Case of FSGS in a Patient on Pembrolizumab

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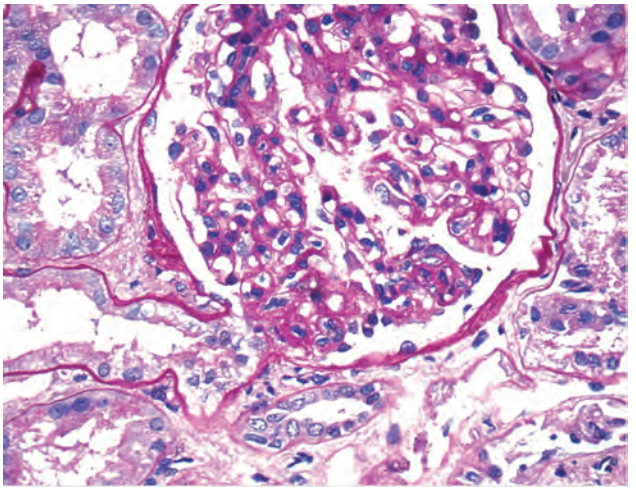
Introduction: Pembrolizumab, a humanized antibody directed against human cell surface receptor PD-1 with immune check point inhibitory and antineoplastic activities, has been reported to cause minimal change disease (MCD). Here we report a case of focal segmental glomerulosclerosis (FSGS) glomerular tip lesion (GTL) in a patient on pembrolizumab.

Case Description: A 55 year old man with a history of HTN, ex-smoker, and bladder cancer in 2014, presented with leg edema and raised creatinine. His bladder cancer was treated with cystoprostatectomy. Chemotherapy included methotrexate, vinblastine, doxorubicin, and cisplatin (2015), pembrolizumab and epacadostat (7/2016-5/2018) and guadecitabine and atezolizumab (6/2018-12/2018). Pembrolizumab was given again Dec 2018-July 2019. On physical examination he had 3+ edema up to his knees. Labs showed creatinine 1.4 mg/dl (baseline 1.0 mg/dl). Urinalysis showed proteinuria without hematuria. Urine protein excretion was 19.5 g/day. Kidney biopsy showed 8 out of 24 glomeruli were globally sclerotic. Of the remaining 16 glomeruli, 4 displayed cellular lesions of FSGS and one glomerular tip lesion (GTL). There was GBM duplication and focal endothelial swelling, suggestive of mild endothelial injury (i.e. thrombotic microangiopathy).

Discussion: Glomerular tip lesion (GTL) is a prognostically favorable variant of FSGS with presenting features intermediate between FSGS and MCD. There are reports of MCD with pembrolizumab but no reports of GTL. Given the clinical presentation and similarities between MCD and GTL, it is likely that pembrolizumab contributed to the development of GTL in this case. His FSGS was treated with steroids and pembrolizumab was withheld. His proteinuria started to improve and renal function stabilized.



Glomerular Tip Lesion of FSGS

PO1829

Collapsing Glomerulopathy in Mixed Connective Tissue Disease: Case Report

Mohammad Atari,[1] Josephine M. Ambruzs,[2] Talal Nakkar,[1] Moh'd Sharshir,[1] Osaid Saqqa,[1] Eric E. Simon.[1] *[1]Tulane University School of Medicine, New Orleans, LA; [2]arkana laboratory, Little Rock, AR.*

Introduction: Collapsing glomerulopathy (CG) is a form of podocytopathy with segmental or global wrinkling and collapse of capillary walls and overlying epithelial cell proliferation but may be distinct from other forms of focal and segmental glomerular sclerosis (FSGS). CG may be idiopathic or associated with infections, autoimmune diseases, malignancies, genetic diseases, certain drugs and in post-transplant setting. Although CG has been reported in lupus nephritis, it was rarely reported in the setting of mixed connective tissue disease (MCTD).

Case Description: A 30 y/o African American male with a history of muscle aches, nontraumatic rhabdomyolysis, evanescent skin rashes and weight loss was found to have a creatinine of 5.1 mg/dl (1.4 1 year earlier) with urine protein/creatinine ratio (uPCR) of 10,136 mg/g. CPK was 1697 U, erythrocytes sedimentation rate > 120, a positive speckled ANA of 1:640, positive anti-SSA 5.9, anti-chromatin >8, anti-sm 7.2, anti-sm RNP >8, anti-RNP >8. Kidney biopsy showed mesangial immune complex deposition, collapsing glomerulopathy and diffuse podocytopathy, immunofluorescence showed global mesangial IgG staining (3+), IgM (1+), C3 (2+), and kappa (2-3+) and lambda (3+) light chains. Electron microscopy revealed several mesangial electron-dense deposits with mild increase in mesangial matrix and hypercellularity and severe epithelial foot processes effacement without glomerular or tubular basement membrane deposits. Muscle biopsy confirmed the diagnosis of dermatomyositis. The patient was treated with pulse methylprednisolone 1 gm IV for three days followed by prolonged prednisone taper. Later, MMF was started at 500 mg bid, lisinopril 40 mg daily, hydroxychloroquine 200 mg bid and bumetanide 2 mg bid. By 4 months creatinine had stabilized at 2.6 mg/dl, uPCR was 1,824 mg/g, and CPK was 55 U.

Discussion: Here we describe a case of collapsing glomerulopathy in the setting of MCTD (SLE and dermatomyositis), with at least partial response to high dose prednisone for 16 weeks, hydroxychloroquine and late initiation of MMF. CG can present in association with autoimmune diseases including but not limited to SLE. This case represents the second such as this case of CG in the setting of MCTD and is notable for its response to immunosuppressive therapy.

PO1830

A Case of AKI with Nephrotic Syndrome After Intraperitoneal Infection with Methicillin-Sensitive *Staphylococcus aureus* (MSSA)

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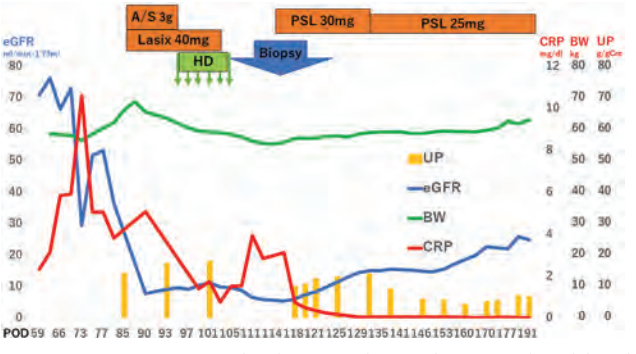
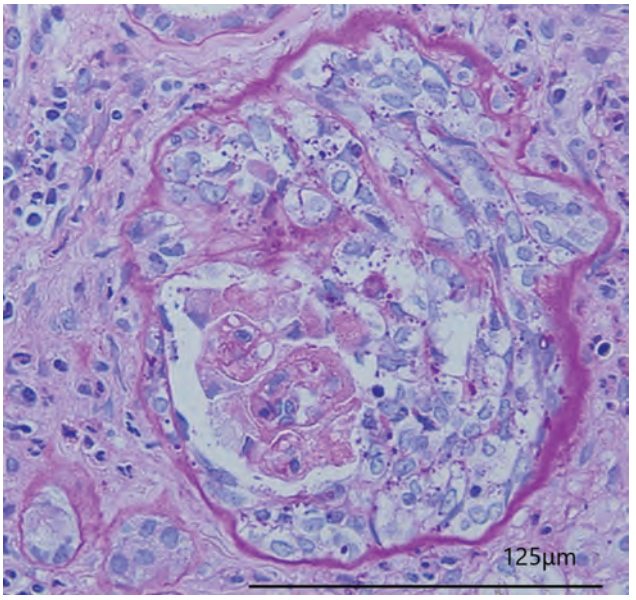
Introduction: Postinfectious glomerulonephritis (PIGN) causes acute nephritic syndrome complicated with urinary protein and hematuria after infection but rarely leads to nephrotic syndrome. The effectiveness of steroid for PIGN has been reported, but still controversial. We report a case of refractory nephrotic syndrome caused by PIGN treated with steroid.

Case Description: A 78-year-old man presenting with nausea and dizziness was admitted. He had pancreatectomy for intraductal papillary mucinous tumor two months before. He was diagnosed as postoperative pancreatic fistula with intraperitoneal infection caused by MSSA. During treatment for the infection, he presented acute kidney injury with nephrotic range proteinuria and hematuria, and required hemodialysis. Renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis with cellular crescents. He was diagnosed as nephrotic syndrome caused by PIGN after intraperitoneal infection with MSSA. Since renal failure was persistent despite infection resolution, he started steroid treatment, lead to improve kidney injury.

Discussion: Antibacterial treatment is important for treatment of PIGN, but if the improvement is still poor, steroid treatment may be effective.



Treatment coursePOD: Postoperative day, UP: Urine protein, BW: Body waight, A/S: Ampicillin sulbactam, HD: Hemodialysis, PSL : Prednisolone



PAS stain: Diffuse endocapillary proliferative glomerulonephritis with cellular crescents

PO1831

Mitochondrial Injury May Be a Ubiquitous Finding in the Pathogenesis of Various Glomerulonephritis

Byung chul Yu, Moo Yong Park, Soo Jeong Choi, Jin kuk Kim, Seung D. Hwang. *Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Gyeonggi-do, Republic of Korea.*

Background: Previous study showed that mitochondrial injury is associated with IgA nephropathy (IgAN). It is not clear whether mitochondrial injury is a unique finding in IgAN or a ubiquitous finding in various glomerulonephtiris (GN). To clarify this, we analyzed urinary mitochondrial DNA (mtDNA) levels and expression of the stimulator of interferon genes (STING) pathway activated by mtDNA leakage in various GN.

Methods: We prospectively enrolled age-sex matched healthy volunteers (HV) and biopsy-proven IgAN, minimal change disease (MCD), acute tubulointerstitial nephritis (ATIN), and minor glomerular abnormalities (MGA) (n=30, 8, 10, and 7 each, respectively). Urinary copy number of the mtDNA genes cytochrome-c oxidase-3 (COX3) and nicotinamide adenine dinucleotide dehydrogenase subunit-1 (ND1) were measured by quantitative polymerase chain reaction. We analyzed STING expression in prostatic cancer specimen as control and kidney tissues obtained from each GN patients by immunohistochemistry staining.

Results: $\log_{10}$ND1/nDNA and $\log_{10}$COX3/nDNA were significantly higher in IgAN ($p<0.001$, $p=0.002$), MCD ($p<0.001$, both), ATIN ($p<0.001$, both), and MGA ($p<0.001$, both) compared with HV (Figure 1). Although there was a difference in signal intensity and site of kidney structures, positive staining for STING was observed in the kidney tissue of each GN patients. Characteristically, STING was strongly stained in the tubulointerstitium for ATIN and in the distal tubule for MGA (Figure 2).

Conclusions: Elevated urinary mtDNA copy numbers and STING activation were observed in various GN. These results suggest that mitochondrial injury would be a ubiquitous finding in the pathogenesis of various GN.

Funding: Government Support - Non-U.S.

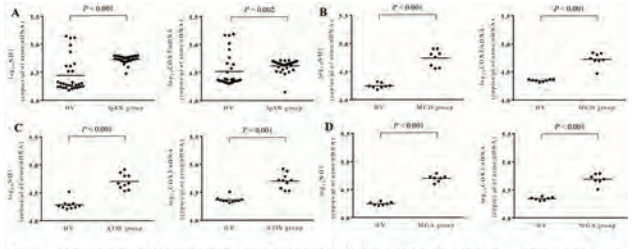


Figure 1. Urinary mitochondrial DNA copy number of patients with IgAN (A), MCD (B), ATIN (C), MGA (D), and HV. Data were analyzed by Mann-Whitney test. ATIN, acute tubulointerstitial nephritis; COX3, cytochrome-c oxidase-3; HV, healthy volunteers; IgAN, IgA nephropathy; MCD, minimal change disease; MGA, minor glomerular nephritis; ND1, nicotinamide adenine dinucleotide dehydrogenase subunit-1.

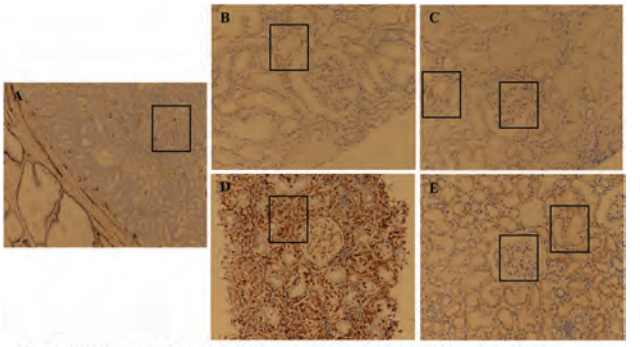


Figure 2. STING expression in prostatic cancer tumor specimen as control and kidney tissues in various glomerulonephritis. All images were captured at 40x magnification. Prostatic cancer tumor (A) and kidney tissues in patient with IgA nephropathy (B), minimal change disease (C), acute tubulointerstitial nephritis (D), and minor glomerular abnormalities (E) were stained for STING expression by immunohistochemistry staining.

PO1832

Single-Cell Transcriptomic Profiling Reveals Aberrant Signaling Responses to Tfh Cytokines in IgA_1-Secreting Cells from IgA Nephropathy Patients

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Background: IgA nephropathy (IgAN), a common primary glomerulonephritis, is characterized by glomerular IgA1 immunodeposits enriched for galactose-deficient IgA1 (Gd-IgA1). These immunodeposits are likely derived from Gd-IgA1-containing immune complexes that are elevated in the circulation of IgAN patients. Gd-IgA1 is produced by IgA1-secreting cells due to abnormal expression of several glycosyltransferases in IgAN. Furthermore, some cytokines can enhance production of Gd-IgA1 by IgA1-secreting cells from IgAN patients but not those from healthy controls. We hypothesize that pro-inflammatory factors, such as those identified by GWAS or produced during episodes of synpharyngitic hematuria in IgAN patients, may further dysregulate IgA1-secreting cells and lead to enhanced Gd-IgA1 production.

Methods: As an experimental model, we used T-follicular helper (Tfh) cell-derived cytokines (IL-4, IL-6, IL-21, CD40L) to stimulate for 30 min immortalized Ig-producing cells derived from peripheral blood of IgAN patients and healthy controls. Then, single-cell transcriptomic analysis was performed. IgA1 splice variants were integrated into the hg38 reference genome to identify IgA1-secreting cells and the data analyzed using Seurat and Alteryx workflow. siRNA knock-down (k/d) was used to confirm involvement of candidate regulatory elements in cytokine-mediated overproduction of Gd-IgA1. Production of Gd-IgA1 was assessed after 72 h.

Results: Single-cell transcriptomics identified discrete populations of IgA1-secreting cells with differential*C1GALT1*expression after Tfh-cytokine stimulation. Furthermore, these subpopulations exhibited reduced expression of cytokine-signaling regulatory elements, *SOCS3*,*SOCS1*, *PTPN2*, and *PTPN11*($p = 0.07, 0.04, 0.02, 0.07$), indicating dysregulation of cytokine-signaling JAK/STAT pathways in IgAN-derived cells. Involvement of SOCS3 in Gd-IgA1 production was further supported by the observation that *SOCS3*siRNA k/d increased Gd-IgA1 production in healthy-control cells ($p = 0.01$).

Conclusions: Single-cell transcriptomics with stratification of IgA1-secreting cells based on *C1GALT1*expression and siRNA k/d experiments revealed that aberrant regulation of Tfh cytokine signaling was associated with enhanced Gd-IgA1 production in IgAN.

Funding: NIDDK Support, Private Foundation Support

PO1833

The NefIgArd trial: The Effect of Nefecon® (Budesonide) in Patients with Primary IgA Nephropathy at Risk of Developing ESRD

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Background: The gut-associated lymphoid tissue (GALT) has been identified as the potential source of poorly *O*-galactosylated immunoglobulin A (IgA) 1 that triggers the formation of nephritogenic immune complexes in IgA nephropathy (IgAN). The NEFIGAN trial (NCT01738035), which assessed the safety and efficacy of a novel targeted-release formulation of budesonide (NEFECON®), highlighted the potential of selectively targeting GALT in patients with IgAN. After 9 months' treatment, urine protein–creatinine ratio (UPCR) was reduced by 29.3% in the NEFECON® 16 mg/day group vs placebo. Estimated glomerular filtration rate (eGFR) decreased by 4.7 ml/min/1.73 m^2 in the placebo group, but with no deterioration seen with NEFECON® 16 mg/day. The incidence of patient-reported adverse events was similar in all groups. Based on these data, the phase 3 NefIgArd study was designed to assess the efficacy and safety of NEFECON® 16 mg/day in patients with IgAN at risk of end-stage renal disease.

Methods: NefIgArd is a randomized, double-blind, placebo-controlled trial with two parts, recruiting a total of 360 patients across 150 nephrology clinics in 20 countries. Patients must be aged ≥18 years with biopsy-confirmed primary IgAN, proteinuria >1 g/24 h and eGFR 35–90 ml/min/1.73 m² (CKD-EPI) despite optimized renin–angiotensin system blockade. Part A of the study, comprising the first 200 dosed patients, will form the basis for submission for accelerated/conditional regulatory approval to the FDA and EMA. The primary outcome will assess the effect of NEFECON® 16 mg/day on UPCR at 9 months vs placebo, consistent with the 2019 Kidney Health Initiative White Paper "Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy". Part B is a post-approval confirmatory trial to validate the surrogacy of the Part A UPCR endpoint. For this purpose, and based on the 2018 NKF/FDA/EMA workshop supporting eGFR slope as an endpoint for full approval, the primary outcome will assess the effect of NEFECON® on a 2-year eGFR-based endpoint vs placebo.

Results: In 2019 the 200 patients needed for Part A were randomized, with top-line data expected in Q4 2020.

Conclusions: Randomization will continue until 360 patients are reached for Part B, which is expected to report in 2022.

Funding: Commercial Support - Calliditas

PO1834

Effect of Hydroxychloroquine in Patients with IgA Nephropathy with Insufficient Responses to Immunosuppressive Therapy: A Retrospective Case-Control Study

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Background: Hydroxychloroquine, a well-known immunomodulator, has recently been used in IgA nephropathy (IgAN) due to its antiproteinuric effects. We aimed to verify the effect of HCQ in patients with IgAN whose proteinuria remained above 1 g/d after conventional immunosuppressive (IS) therapy

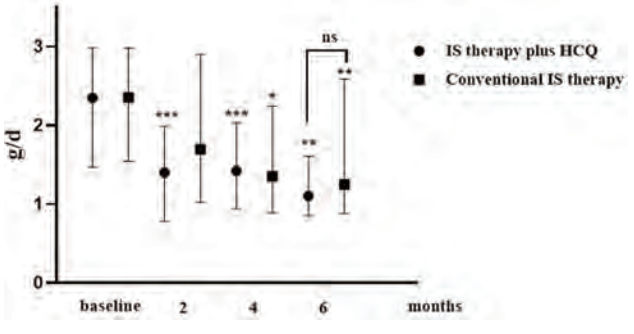
Methods: This was a retrospective case-control study. Twenty-six patients with IgAN who received HCQ and had insufficient responses to IS therapy (corticosteroid (CS) therapy with/without IS agents) were included. 26 matched historical controls who received conventional IS therapy were selected by propensity score matching. The clinical data from 6 months were compared

Results: Proteinuria at baseline was comparable between the "IS therapy plus HCQ" and "conventional IS therapy" groups (2.35 [interquartile range (IQR), 1.47, 2.98] vs. 2.35 [IQR, 1.54, 2.98] g/d, p=0.920). There was a significant reduction in proteinuria in patients with IgAN with HCQ treatment (2.35 [IQR, 1.47, 2.98] vs. 1.10 [IQR, 0.85, 1.61] g/d, p=0.002). The percent reduction in proteinuria at 6 months was similar between the two groups (-39.81% [-66.26, -12.37] vs. -31.99% [-67.08, -9.14], p = 0.968). The cumulative frequency of patients with a 50% reduction in proteinuria during the study was also comparable between the two groups (53.8% vs. 57.7%, p= 0.780). No serious adverse events were observed during the study

Conclusions: HCQ could further reduce proteinuria in patients with IgAN who had insufficient responses to conventional IS therapy

Proteinuria of enrolled patients

	IS therapy plus HCQ N=26	Conventional IS therapy N=26	P-value
Proteinuria level before IS therapy (g/d)	2.52(1.66,5.60)	2.27(1.54,4.36)	0.727
Baseline Proteinuria (g/d)	2.35(1.47,2.98)	2.35(1.54,2.98)	0.920
Proteinuria at months 6(g/d)	1.10(0.85,1.61)	1.24(0.87,2.58)	0.312



Proteinuria of patients during the follow-up. The dots represent the median value, the bars represent the 25th and 75th percentiles. Each Month's was compared with "Baseline" respectively. * p < 0.05; ** p < 0.01; *** p < 0.001

PO1835

IgA Nephropathy Study: A Multicentric Study in Portugal

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Background: In the last decade, an attempt to correlate the histopathological lesions with renal prognosis in IgA Nephropathy (IgAN) was developed in order to identify patients that benefit from IS therapy.

Methods: A multicentric, longitudinal and retrospective (2007-2019) study was developed in Portugal: adult patients with histological diagnosis of IgAN. Biopsy date defined study entrance and data was collected.

Results: 167 patients were analyzed. The coorte was divided in 2, according the use of steroid therapy: 105 in group of no steroids (noCST) and 62 in the group with steroids (wCST). Endocapillary hypercellularity (29% vs 16%, p=0.049) and crescents 34% vs 10%, p<0.001), were significantly more frequent is wCST group. Median time until the beginning of steroids was 55 days (IQR 7-251), and tmedian duration was 195 days (IQR 96-239). Follow up time was 39 months (IQR 15.1-65.8), significantly superior in wCST group (56.6 vs 29.8 months, p=0.004). No difference between groups considering infections, AKI, CV disease or death. Renal survival at 7 years was 70% at noCST group and 85% at wCST group, p=0.184. Multivariable analysis identified HT (OR 3.81), proteinuria (OR 2.80) and crescents (OR 2.72) as significant factors associated with steroids use. Table 1 defines the independent predictors for ESRD (Cox regression analysis). When we analyze the steroids effect on renal survival, we saw that the average time until renal replacement therapy (RRT) was 47.7 months (IQR 34.6-60.7) in noCST group and 81.6 months (IQR 63.8-99.3) in wCST group. The average treatment effect with steroids was 33.9 months (11.9-55.9, p=0.002), that means that if we treat all, this was the time that we could delay beginning of RRT.

Conclusions: In this group of patients, use of steroids was an independent predictor for delaying CKD progression and the beginning of RRT. HT, degree of proteinuria and crescents presence were significant predictors for its use. In spite of the controversy about the use of steroids therapy in IgAN, this study showed their effectiveness without risk increase.

	HR (95% CI)	P
Steroids	0.318 (0.120-0.842)	0.021
IFTA (by unit)	2.105 (1.207-3.671)	0.009
Crescents, by unit	2.438 (1.309-4.543)	0.005
Endocapilar hypercelullarity	1.032 (1.001-1.065)	0.044
eGFR (mL/min)	0.990 (0.980-0.999)	0.032
Age (years)	0.991 (0.982-0.999)	0.041

PO1836

Corticosteroid Therapy Improves Renal Prognosis in IgAN Patients with Crescent

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Background: IgA nephropathy (IgAN) has been identified as having an inflammatory basis leading to the biological rationale of immunosuppressive therapy. However, little is known about the clinical indication of immunosuppressive therapy related to each histological finding. Recently, Haas et al reported that the crescent lesion is an independent predictor for renal survival in IgAN especially with no immunosuppressive therapy. We assessed the effect of corticosteroid therapy on renal survival of IgAN with crescent based on the Japanese dataset used in the recently published IgAN prediction tool from multinational multi-ethnic cohort (Barbour SJ, JAMA Intern Med. 2019), given it was almost all corticosteroids.

Methods: We extracted the 566 Japanese adults with biopsy-proven IgAN patients (male 45.9%, median age 34.7) from original cohort. Baseline characteristics were evaluated at the biopsy, and clinical data including serum creatinine, urinary findings, use of RAS blockers (RASB) and corticosteroid therapy and tonsillectomy were collected at every visit. The outcome was defined as 50% decline in eGFR or end-stage kidney disease. Cox proportional hazard models were used to investigate the association between corticosteroid therapy and renal survival with adjustments of confounders including the Oxford classification. Treatment options were included in the model as time-dependent covariates.

Results: At biopsy, median eGFR and proteinuria and proportions of the patients with crescent were 73.2ml/min/1.73m², 0.67g/day, and 59.9%, respectively. During a median follow-up of 3.79 years, 57 patients (10.1%) reached the outcome. RASB and corticosteroid were used in 377 patients (66.6%) and 368 patients (65.0%), respectively. 241 (42.6%) patients were performed tonsillectomy. Hazard ratio (HR) of corticosteroid

therapy was reversed by presence of crescent (no crescent: HR 1.75 95% confidence interval [CI] 0.72-4.23, presence of crescent: HR 0.26 95%CI 0.11-0.61), indicating the interaction between corticosteroid therapy and presence of crescent (p<0.001). Tonsillectomy had also a favorable effect on renal survival (HR 0.43 95%CI 0.20-0.91).

Conclusions: Present findings revealed that corticosteroid therapy improved renal survival in Japanese IgAN patients with crescent and are thus suggestive for the indication of this therapy.

PO1837

Vitamin D Deficiency and Outcome of IgA Nephropathy in North Indian Patients

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Background: Vitamin D has been shown to be beneficial in reducing proteinuria in patients with chronic kidney disease (CKD). IgA Nephropathy (IgAN) is one of the leading causes of CKD in India and worldwide. Asians, especially Indians develop more severe IgAN. We conducted this study to evaluate 25-hydroxy vitamin D (25(OH)D) level as a prognostic marker for disease progression and outcomes in a cohort of Indian patients with IgAN.

Methods: In this retrospective cohort study, demographic and clinical data of Indian adult patients with biopsy proven IgAN, diagnosed between 2015 and 2019, was obtained. Patients with a minimum follow-up of 6 months were included for analysis. A 25-(OH)-vitamin D assay was performed on serum samples collected at the time of kidney biopsy. 25-(OH) D levels <10 ng/mL were considered as deficient.

Results: Of the 105 patients included in the study, 69.5% were males. The mean age was 34.0±10.6 yrs. The mean baseline creatinine and 24 hr proteinuria was 1.37±0.51mg/dL and 3.12±2.45 g/day, respectively. The mean baseline vitamin D levels were 15.88±11.85 ng/mL. 39% patients were 25(OH)D deficient. The median duration of follow up was 23.5 months (range: 6 – 56 mon). Eleven patients (10.5%) progressed to end stage renal disease (ESRD) during follow-up. Vitamin D deficiency was not significantly associated with progression to ESRD (p=0.61) or proteinuria remission (0.83). Risk for ESRD was reduced in patients with lower baseline creatinine levels (p=0.00) and patients on ACE inhibitors (p=0.03). Remission of proteinuria was more common in patients with lower baseline creatinine levels (p=0.006) and normotensive patients (p=0.03). Baseline creatinine (HR = 14.40; 95% CI, 1.02 – 202.15), 24 hr proteinuria (HR = 0.03; 95% CI, 0.00–0.85) and disease remission (HR = 0.01; 95% CI, 0.00–0.32) were predictors of risk for ESRD.

Conclusions: Vitamin D deficiency is common in Indian patients with IgAN. Baseline vitamin D deficiency did not affect outcomes of IgAN.

Funding: Government Support - Non-U.S.

PO1838

Long-Term Beneficial Effects of Tonsillectomy on Patients with Immunoglobulin A Nephropathy

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Background: Tonsillectomy may treat immunoglobulin (Ig) A nephropathy (IgAN) by reducing the levels of galactose-deficient IgA1. Hence, we aimed to analyze the long-term effects of tonsillectomy as an initial treatment and a treatment at any time in their lives on patients with IgAN.

Methods: In this retrospective cohort analysis, 1147 patients with IgAN were grouped according to whether or not they had undergone tonsillectomy at any time in their lives (Study 1) or within 1 year after renal biopsy (Study 2). The patients who underwent tonsillectomy (T1) and who did not undergo tonsillectomy (T0) were propensity score matched, and the 20-year renal survival rates were evaluated until the serum creatinine level doubled (primary endpoint) and end-stage renal disease was reached (secondary endpoint).

Results: In both studies, the groups' clinical data, histological data according to Oxford classification, and treatments such as immunosuppressants and inhibitors of renin-angiotensin systems were similar after propensity score matching (Study 1, n=179/each group (T1 vs. T0); median age: 31.0 vs. 30.0 years, p=0.53; mean arterial pressure: 90.0 vs. 88.0 mmHg, p=0.72; median eGFR: 76.1 and 79.1 mL/min/1.73m^2, p=0.46; median proteinuria: 0.72 vs. 0.82 g/day, p=0.71) (Study 2: n=143/each group (T1 vs. T0); median age: 30.0 vs. 30.0 years, p=0.414; mean arterial pressure: 86.3 vs. 88.7 mmHg, p=0.56; median eGFR: 81.0 vs. 81.5 mL/min/1.73m^2, p=0.98; median proteinuria: 0.77 vs. 0.62 g/day, p=0.48). In Study 1, the renal survival rates at the primary and secondary endpoints were significantly higher in T1 than in T0 (primary endpoint: 82.1 vs. 63.3%; p=0.002) (secondary endpoint: 98.1 vs. 76.3%; p= 0.002). In Study 2, the renal survival rate at the primary endpoint tended to be higher and the renal survival rate at the secondary endpoint was significantly higher in T1 compared with T0 (primary endpoint: 97.5 vs. 81.5%; p=0.063; secondary endpoint: 98.9 vs. 88.7%; p=0.04). Multivariate Cox regression analyses showed that immunosuppressants and tonsillectomy prevented disease progression (hazard ratio, 0.27; p=0.04). Complications associated with tonsillectomy occurred in 7.8% of the patients.

Conclusions: Among patients with IgAN, tonsillectomy at any time of life or soon after renal biopsy prevents disease progression, and it is relatively safe.

PO1839

Rituximab in IgA Vasculitis with Aggressive Glomerulonephritis: A Real-Life Experience

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Background: IgA-vasculitis (IgAV) is a systemic small vessels vasculitis characterized by deposition of underglycosylated IgA1 immune complexes. Presently, no treatment is specifically recommended in IgAV Glucocorticoids (GC) have been traditionally thought to be effective in tempering systemic symptoms, but did not show long-term benefits either in reducing flares or progression of kidney disease. Recently Rituximab (RTX) has been proved to be effective in a few case series of adults with IgAV. Aim of the study: to evaluate the effectiveness of RTX as first line therapy in induction and maintenance of remission of adults with IgAV with biopsy-proven crescentic glomerulonephritis.

Methods: We reviewed the clinical records of patients (pts) with adult-onset IgAV treated with RTX at our Center. Patients included 8 males and 4 females, mean age 45 years with mean follow-up duration of 31 months. All pts had a biopsy proven IgAV- severe nephritis. Pts received 4 weekly doses of RTX given alone (8 pts) or in combination with CS (4 pts). Disease activity was evaluated by BVAS version 3 at the onset and at 1, 6 and 12 months and at the end of follow up. Complete remission (CR) was defined as BVAS of 0.

Results: Eleven pts (91.7%) achieved a clinical response at 6 months. 10 pts had a CR while 1 pt had a partial response and was given an additional dose of RTX after 12 months from induction due to persistent proteinuria (1gr/24 hrs), despite systemic remission. He achieved a CR 6 months later. One patient did not respond to RTX and was switched to MMF. Among the 10 pts with CR, 1 patient needed maintenance doses of RTX every 6 months due to relapse of palpable purpura; 1 relapsed after 15 months and received a new induction course showing a CR again. Significant decrease in 24-hour proteinuria, BVAS, and CRP level was detected. RTX was generally well tolerated. One patient, who had a CR with RTX alone died after 6 months of follow-up for cardiovascular cause.

Conclusions: This extended experience confirms our initial results supporting the use of RTX in the treatment of IgAV with severe renal involvement. Indeed, RTX proved to be effective and safe for induction and maintenance of long-lasting remission. Present data also suggest that RTX is not only effective for severe and refractory IgAV, but can be also proposed as a first line therapy.

PO1840

External Validation of International IgA Nephropathy Prediction Tool in a Singapore Cohort (EXIST Study)

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Background: IgA Nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide, including in Singapore. Although IgAN may lead to end-stage kidney disease (ESKD), the risk of progressive kidney function decline is extremely heterogeneous; a reliable risk prediction model is important to inform both patients and physicians of renal prognosis and to guide clinical treatment decisions. A newly validated International IgAN prediction tool has been published recently and we aim to externally validate this model in our Singapore cohort.

Methods: We validated the predictive performance of the two full models (with or without race) derived from the International IgAN Prediction Tool study in our IgAN patient dataset over 11 years (Jul 2009 to Oct 2020) using external validation of survival prediction models (Royston and Altman). The discrimination and calibration of the models were tested using the R^2_D measure, C statistics, Akaike Information Criterion (AIC), and calibration plot.

Results: The study included 119 patients; mean age of 43.3 (± 16.66) years; 62 (52.1%) were male; 90 (75.6%) Chinese, 12 (10.1%) Malay, 7 (5.9%) Indian and 10 (8.4%) other ethnicity. Complete case analysis was done with 93 patients. The 5-year risk of the primary outcome (50% reduction in estimated glomerular filtration rate or ESKD) was 15.0%. Oxford T2 histologic score was removed from the full model analysis as the number of observations is low (n=2). The original study reported AIC of 6338 for full model with race, 6379 for full model without race, vs 107.35, and 111.90 respectively in our study. The R^2_D for the full models with and without race when applied to our validation cohort were 39% and 32% respectively, both were similar or better than the R^2_D for the same models applied to the original derivation and validation cohorts (26.3%, 25.3%, and 35.3%, respectively). The C statistics for the full model with race was 0.858 (95% CI, 0.687-1.000), without race was 0.811 (95% CI, 0.599-1.000), comparable to the C statistics from the original derivation and validation analysis. Both full models were well-calibrated in our cohort, with good agreement between predicted and observed risk of the primary outcome at 5 years post-biopsy.

Conclusions: The 2 full models with or without race were shown to be validated in our multi-ethnic Singapore IgAN cohort for predicting disease progression.

PO1841

Associations of Genetic Variants Contributing to Gut Microbiota Composition in IgAN

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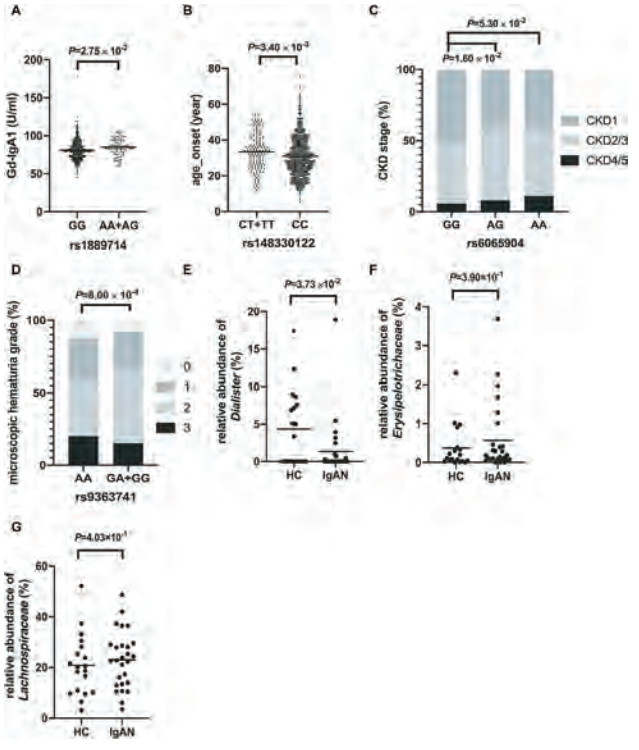
Background: Gut microbiota is observed to be associated with IgAN, as immune response in the gut is assumed to be one of the triggers of its development. And because the microbial composition is heritable, we hypothesize that genetic variants controlling gut microbiota composition may associate with susceptibility to IgAN or clinical phenotypes.

Methods: 175 gut-microbiome-associated genetic variants were retrieved from GWAS Catalog. Genetic associations were examined in 1511 patients with IgAN and 4469 controls. Sub-phenotype associations and microbiome annotations were undertaken for better understanding how genes shaped phenotypes. Likely candidate microbes suggested in genetic associations were validated using 16s rDNA sequencing in 29 patients with IgAN and 20 controls.

Results: Nine genetic variants associated with susceptibility to IgAN (*P* values from 4.13×10^{-2} to 1.39×10^{-3}). The rs1889714-AA/AG risk genotypes associated with higher serum levels of Gd-IgA1 (**A**). Other significant findings included the associations between rs148330122-CC risk genotype and early age of onset (**B**), rs6065904-AA/AG risk genotypes and worse kidney function (**C**), rs9363741-GG/GA risk genotypes and severer hematuria (**D**). Besides, rs1889714-AA/AG risk genotypes associated with decreased abundance of beneficial *Dialister*; whereas rs6065904-AA/AG and rs9363741-GG/GA risk genotypes associated with increased abundance of detrimental *Erysipelotrichaceae* and *Lachnobacterium*, respectively. 16S rDNA sequencing data validated the decreased *Dialister* (**E**), and a tendency of increased *Erysipelotrichaceae* and *Lachnospiraceae* abundance in faeces from IgAN (**F/G**).

Conclusions: Our results provided supporting evidence that gut microbiota in IgAN was affected by host genetics and shed light on candidate bacteria for future pathogenesis studies.

Funding: Government Support - Non-U.S.



PO1842

IgA Nephropathy: Quantifying Remission Duration on Clinical Outcome

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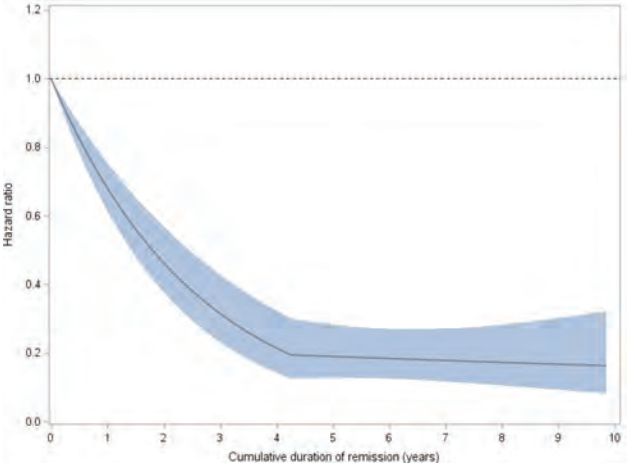
Background: A relative reduction in proteinuria has been proposed as a surrogate outcome for therapeutic trials in IgA nephropathy (IgAN). We sought to quantify the association between duration of proteinuria remission and the risk of disease progression in IgAN.

Methods: In this retrospective international cohort of adult patients with biopsy-proven IgAN, we defined remission based on: (i) a ≥25% reduction in proteinuria from the peak value after biopsy; (ii) an absolute reduction in proteinuria to <1g/day; (iii) peak proteinuria prior to remission ≥1g/day. The total duration of first remission was treated as a time-varying exposure using longitudinal proteinuria measurements. Time-dependent Cox proportional hazards models were used to quantify the association between duration of remission and the primary outcome (ESKD or 50% reduction in eGFR).

Results: Of 1864 patients who entered a first remission, 274 (14.7%) experienced the outcome during median follow-up of 3.9 years. The relationship between duration of proteinuria remission and the primary outcome was non-linear (Figure). Each 3 months in sustained remission up to 51 months was associated with an additional 9% reduction in the risk of disease progression (HR 0.91, 95% CI 0.89-0.93). Each additional 3 months in remission beyond 51 months was associated with a non-significant risk reduction (HR 0.99, 95% CI 0.96-1.03). Results were robust to multivariable adjustment and consistent across subgroups including immunosuppression exposure.

Conclusions: We observed a non-linear dose-response relationship between the duration of proteinuria remission and the risk of disease progression in IgAN. When considering proteinuria as a surrogate outcome, our findings illustrate the need to consider the duration of remission in addition to the magnitude of proteinuria reduction when evaluating the anticipated impact on long-term clinical endpoints.



PO1843

Results of a Phase 1 Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers

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Background: IgA nephropathy (IgAN) is an autoimmune disease with no approved treatments[1]. Key steps in IgAN pathogenesis are the production of galactose-deficient IgA1 (Gd-IgA1), the generation of anti-Gd-IgA1 autoantibodies and the formation of immune complexes resulting in kidney inflammation and damage[2]. Patients with IgAN have elevated levels of A proliferation-inducing ligand (APRIL) which regulates B cell differentiation and proliferation[3]. In a study of patients with IgAN, those with high plasma APRIL levels had elevated levels of Gd-IgA1 and proteinuria and lower eGFR[3]. BION-1301, a first-in-class humanized anti-APRIL antibody, was well-tolerated with no dose-limiting toxicities in a Phase 1/2 first-in-human study in multiple myeloma[4]. This 3-part Phase 1 trial characterizes the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BION-1301 in healthy volunteers (HV) and patients with IgAN.

Methods: (NCT03945318) Parts 1 and 2 are double-blind, randomized, placebo-controlled single and multiple ascending dose studies, respectively. Part 1 enrolled 36 HV in 5 dose cohorts, randomized in a 3:1 ratio to receive a single dose of BION-1301 or placebo delivered by IV infusion. Part 2 enrolled 27 HV in 3 dose cohorts, randomized in a 2:1 ratio to receive 3 doses of BION-1301 or placebo delivered by IV infusion every two weeks. Part 3 assesses a multiple dose regimen in patients with IgAN and is currently enrolling.

Results: BION-1301 was well-tolerated with low incidence of non-neutralizing ADAs in HVs. The PK profile was well behaved with a half-life supporting monthly dosing. Durable target engagement, suppression of IgA and IgM, and to a lesser extent IgG were observed following BION-1301 administration. IgG values remained in normal ranges with no increase of infections post-treatment. Updated data will be presented including B cell immunophenotyping of HVs and results from patients with IgAN, if available.

Conclusions: BION-1301, an anti-APRIL antibody, offers a pharmacodynamic window to exploit IgA suppression while tempering impact to IgG. BION-1301 may provide a novel approach to address the pathophysiology of IgAN.

Funding: Commercial Support - Aduro Biotech

PO1844

Clinical Significance of Intensity of Galactose-Deficient IgA1 Deposition in Patients with IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) have a crucial role in the pathogenesis of IgA nephropathy (IgAN). It was reported that Gd-IgA1 specifically deposit on glomeruli of primary IgAN using Gd-IgA1-specific monoclonal antibody (KM55 mAb). However, the association between intensity of Gd-IgA1 deposition and histological severity and clinical parameters are not clear.

Methods: We performed immunostaining with anti-IgA and KM55 mAbs in 74 patients who were diagnosed as IgAN at Juntendo University Hospital. We quantified the intensity of glomerular Gd-IgA1 by Image J software, and analyzed its association with histological findings. We also analyzed the association of intensity of glomerular Gd-IgA1 with serum levels of Gd-IgA1 and creatinine, urinary Gd-IgA1 and proteinuria.

Results: Glomerular Gd-IgA1 was positive in all 74 primary IgAN cases, we divided into high-intensity (n=45) and low-intensity groups (n=29) by Image J software. In the Gd-IgA1 high-intensity group, acute lesions such as cellular crescents are dominant compared with low-intensity group ($P=0.01$). Moreover, the levels of proteinuria and urinary Gd-IgA1 were significantly high compared with Gd-IgA1 low-intensity group ($P<0.05$). Next, we analyzed the pathogenic significance of merge ratio of glomerular IgA and Gd-IgA1. Interestingly, levels of proteinuria and urinary Gd-IgA1 were correlated with high merge ratio of glomerular IgA and Gd-IgA1.

Conclusions: Present study suggested that high intensity of glomerular Gd-IgA1 deposition is associated with histological severity, especially acute lesions. Moreover, levels of proteinuria were correlated with high merge ratio of glomerular IgA and Gd-IgA1. Thus, glomerular Gd-IgA1 staining may be considerable index for therapeutic intervention.

PO1845

Glomerular Galactose-Deficient IgA_1 Expression Analysis in Pediatric Patients with Glomerular Diseases

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Background: Galactose-deficient IgA1 (Gd-IgA1) has been identified as a key molecule in the pathogenesis of IgA nephropathy (IgAN). Using a Gd-IgA1-specific monoclonal antibody (KM55), glomerular Gd-IgA1 deposition has been detected in patients with IgAN and IgA vasculitis with nephritis (IgAV-N), but not other glomerular diseases. However, this specificity is controversial and there are currently no studies in pediatric cases.

Methods: We conducted a retrospective, multicenter study to examine double-immunofluorescence staining of IgA and Gd-IgA1 (KM55) in 60 pediatric patients with various glomerular diseases.

Results: Glomerular Gd-IgA1 deposition was detected in all cases of IgAN (n=17/17) and IgAV-N (n=6/6), and in patients with immunocomplex-mediated glomerulonephritis, including lupus nephritis (n=9/9), membranoproliferative glomerulonephritis (n=3/4), and membranous nephropathy (n=1/1). However, Gd-IgA1 was negative in patients with non-immune related glomerular diseases with IgA deposition, including idiopathic nephrotic syndrome (n=6/6), oligomeganephronia (n=2/2), Alport syndrome (n=1/1), dense deposit disease (n=1/1), and crescentic glomerulonephritis (n=1/1). Both IgA and Gd-IgA1 were negative in patients with idiopathic nephrotic syndrome (n=5/5), membranoproliferative glomerulonephritis, membranous nephropathy, oligomeganephronia, Alport syndrome, C3 glomerulonephritis, poststreptococcal acute glomerulonephritis, and hemolytic uremic syndrome (n=1/1 each).

Conclusions: Gd-IgA1-positivity in patients with IgAN and IgAV-N was consistent with previous reports. However, Gd-IgA1 was also positive in patients with IgA-positive immunocomplex-mediated glomerulonephritis. KM55 may have the potential to distinguish incidental IgA deposition in pediatric cases. We speculate that Gd-IgA1 may be involved in the pathogenesis of these immune-related diseases, or KM55 may recognize IgA-related immunocomplex nonspecifically.

PO1846

Urinary Exosomal MicroRNAs Are Potential Diagnostic and Prognostic Biomarkers in IgA Nephropathy Patients

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Background: Micro-RNAs (miRNAs) are small non-coding RNA molecules which regulate disease pathophysiology by modulating target gene expression. miRNAs are derived from tissues and biofluids such as serum, saliva, and urine. Recently, emerging evidence suggests urinary exosomal miRNAs as non-invasive biomarkers of various kidney diseases. However, few studies investigated clinical relevance of miRNA in IgA nephropathy (IgAN). In this study, we evaluated urinary exosomal miRNA expression and analyzed its clinical significance in patients with IgAN.

Methods: Urine samples were collected from 93 patients with biopsy-proven IgAN and 14 normal controls. We identified mRNA differential expression of renal tissue between IgAN and normal subjects in the gene expression omnibus dataset, and selected 884 glomerular and 67 tubulointerstitial genes through meta-analysis. We then used the miRTarBase, TargetScan, micorRNA database to predict potential miRNA targets. Finally, 11 urinary exosomal miRNAs were selected. We observed urinary exosomal expression of miRNAs and analyzed their diagnostic and prognostic accuracy for IgAN.

Results: The expression of miR-16-5p, miR-26b-3p, miR-29a-3p, miR-29c-3p, miR-126-3p, miR-199a-3p, miR-615-3p, and miR-29b-3p were significantly upregulated in IgAN patients as compared with normal controls. miR-16-5p, miR-26b-3p, miR-29a-3p, miR-29c-3p, miR-126-3p, miR-199a-3p, and miR-29b-3p have good diagnostic accuracy of IgAN (area under curve of the receiver operating characteristic curve > 0.8). Baseline renal function significantly correlated with miR-16-5p, miR-29a-3p, miR-199a-3p, miR-199b-5p, miR-335-3p, and miR-615-3p. During follow-up period, 43 (46.2%) IgAN patients experienced adverse renal outcomes defined as a greater than 25% reduction in estimated glomerular filtration rate (eGFR), decline in eGFR category from the value determined at the time of renal biopsy, or start renal replacement therapy. miR-16-5p, miR-29a-3p, miR-199a-3p, and miR-335-3p were independently associated with increased risk of adverse renal outcomes.

Conclusions: Urinary exosomal miRNAs might be potential non-invasive biomarkers for diagnosis and prediction of disease progression of IgAN. Further studies are needed to clarify our results and ascertain the underlying mechanisms.

PO1847

Urinary Sediments Could Differentiate the Endocapillary Proliferative Lupus Nephritis and Endocapillary Proliferative IgA Nephrology

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Background: The role of manual urine sediment examination in the diagnosis and prognostication of endocapillary proliferative glomerulonephritis remains to be elucidated. This study aims to investigated the differences of urinary sediment findings between lupus nephritis and IgA nephropathy with endocapillary proliferative glomerulonephritis and further evaluated associations of leukocyturia with disease activity, pathological features and prognosis.

Methods: The urinary sediment of 126 patients, including 92 patients with lupus nephritis and 34 patients with IgA nephropathy, with a renal biopsy-proven endocapillary proliferative glomerulonephritis were examined in the morning before renal biopsy according to a standardized method. The urinary elements investigated including various cells, casts and crystals. The associations of the level of leukocyturia and disease activity, pathological features and prognosis were further analyzed.

Results: In the patients with endocapillary proliferative glomerulonephritis, normal to mild leukocyturia (≤12/HPF), and moderate to severe leukocyturia (>12/HPF) were found in 52(41.27%) and 74 (58.73%) patients, respectively. The proportion of moderate to severe leukocyturia, the frequency of urinary white blood cells casts and waxy casts were significantly higher in endocapillary proliferative lupus nephritis patients compared with endocapillary proliferative IgA nephropathy patients ($P<0.001$, $P=0.020$, $P=0.010$, respectively). In the proliferative lupus nephritis group, the levels of leukocyturia was significantly correlated with serum creatinine (r=0.288, $P=0.005$), eGFR (r=-0.284, $P= 0.006$), serum C3 (r=-0.275, $P= 0.009$), SLEDAI scores (r=0.383, $P=<0.001$) and glomerular leukocyte infiltration (r=0.285, $P= 0.002$). A multivariate analysis showed that leukocyturia was identified as an independent risk factor for renal outcome in proliferative lupus nephritis (HR: 1.456, 95% CI: 1.083-1.957, $P=0.013$) but not in IgA nephropathy (HR: 1.069, 95% CI: 0.494-2.312, $P=0.866$).

Conclusions: Urinary sediments of the endocapillary proliferative lupus nephritis and endocapillary proliferative IgA nephrology differed in many aspects. Leukocyturia could reflect the disease activity and prognosis of endocapillary proliferative glomerulonephritis, especially in lupus nephritis.

PO1848

A Single-Center Retrospective Study of Thrombotic Microangiopathy

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Background: Thrombotic microangiopathies (TMAs) are a rare group of clotting disorders of various origin, including infectious, idiopathic, autoimmune or drug-induced. This group shares common clinical manifestations that include low red blood cell and platelet counts. Although the disease is rare but treatable if clinician is aware about its manifestations. To increase the awareness and understand the disease better we conducted a retrospective study to characterize and assess TMAs in our institution

Methods: An observational retrospective study of patients with a diagnosis of TMA at Westchester Medical Center in the past 5 years was conducted. Data was collected from electronic medical records. Demographic, clinical and therapeutic variables were extracted, tabulated and analyzed

Results: A total of 43 patients with a diagnosis of TMA were identified and included in the study. The cohort had a mean age of 39.9 years; 20 were male and 23 females. As shown in **Table 1**. Thrombotic thrombocytopenia purpura (TTP) (n=14, 32%), systemic lupus erythematosus (SLE) (n=5, 11.6%), and hemolytic uremic syndrome (HUS) (n=5, 11.6%) are the most common etiologies. Other identifiable etiologies were atypical HUS (9%), use of calcineurin inhibitors (9%), acute myeloid leukemia (4.6%). About 6.9% cases didn't have any identifiable cause (6.9%). Patients with TTP had a mean age of 48 years, mean platelet count of 17 k/mm3, and most were female (71%). Fifty-seven percent had hematuria, 21% proteinuria and 85% had schistocytes in the blood smear

Conclusions: Most common cause of thrombotic Microangiopathies is TTP which is what we found in our institution. It is essential to aware about the manifestation of this disease since early recognition and prompt treatment is the key for better outcome

Table 1

Etiology	TTP	SLE	HUS
Number of cases	14	5	5
Mean age, years	48	30	16
Mean platelets count (k/mm3)	17	105.4	53.8
Hematuria, %	57	80	100
Proteinuria, %	21	80	100
Schistocytes, %	85	60	100

TTP, thrombotic thrombocytopenia purpura; SLE, systemic lupus erythematosus; HUS, hemolytic uremic syndrome

PO1849

Changing Prognostic Factors and Sustainability in Thrombotic Microangiopathy Patients: A Need for a Multidisciplinary Team

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Background: Thrombotic microangiopathy (TMA) is associated with a higher risk of dead and chronic renal replacement therapy (CRRT). Eculizumab is highly effective but also expensive. We evaluate the economic burden of the TMA, the cost of CRRT, Eculizumab, and the impact of a multidisciplinary team (MDT) after two years of its implementation.

Methods: It is a retrospective study. We evaluate the risk of i) dead and ii) CRRT need. The cost (euros) for hospitalization at the floor and intensive care unit admission, CRRT and Eculizumab at the pre-MDT implementation (from January 2008 to May 2016) in comparison with the post-MDT period (from May 2018 to Dec 2018). Clinical outcomes: i) risk of death and ii) risk of CRRT need. To determine the cost per patient-year, we calculated the total number of days of hospitalization, the entire months on dialysis or in kidney transplant program (KTx) and the milligrams of Eculizumab used at any period. The total amount divided by the whole years of observation and finally and by the mean number of patients per year diagnosed at any period. The number of patients-year we determined considering the incidence density (ID: cases/1,000,000 person-year). Patients with ADAMTS-13 deficiency were excluded.

Results: Forty-two patients were included. ID increased from 2.3 cases/1,000,000 person-years (n=20) to 11.7 cases/1,000,000 person-year (n=22). Comparing with the pre-MDT period, the number of patients who died increased from 3(15%) to 7(32%), P=0.20; while the risk for CRRT decreased from 9(45%) to 0, P<0.01 [relative risk (95%CI) for no CRRT requirements: 0.55 (0.37 to 0.81)]. One (5%) and three (14%) patients died under futility consideration at the pre- and post-MDT period, respectively (P=0.60). From all the patients who died, only one was in acute dialysis program while 7 showed neurologic damage. The mean cost per patient-year changed from 319,931 to 150,878 euros from the pre- to post-MDT period.

Conclusions: The implementation of an MDT shows a change in the natural history of the disease, where neurological damage emerges as a risk factor associated with mortality instead of CRRT needs. TMA patients represent a remarkable economic burden, representing an essential challenge for the health system sustainability that could be improved by an MDT.

PO1850

Does Kidney Histology Predict Renal Response or Complement Status in Atypical Hemolytic Uremic Syndrome?

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Background: Atypical Hemolytic Uremic Syndrome (aHUS) is diagnosed based on clinical evidence of microangiopathic hemolytic anemia, thrombocytopenia and renal failure and histologic evidence of thrombotic microangiopathy (TMA). However, these characteristics are not specific and cannot differentiate aHUS from other causes. Whether specific histologic lesions of TMA can predict complement mutation status (CM +/-), guide treatment, or predict renal outcomes has not been explored. Here, we evaluate the potential of using kidney histology to predict CM status and renal response in aHUS.

Methods: A retrospective analysis of aHUS patients (N=35) who achieved a hematologic response after treatment with anti-C5 therapy was conducted. Clinical and demographic data were recorded and two blinded Nephropathologists scored native kidney biopsy findings independently. Seventeen histologic lesions of TMA were scored. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Association between morphology scores and CM status (n=29), renal response (n=27) and other categorical characteristics were tested using chi-squared or Fisher's exact test as appropriate. Unpaired t-test was used for continuous variables. Significance level was set at $\alpha \leq 0.05$.

Results: In this cohort, 13/29 (45%) were CM+. Of the 17 histologic variables studied, only glomerular intracapillary fibrin differentiated CM+ from CM- (0% vs 30%, P=0.04). Histologic features were also similar between patients who achieved renal response (RR) and non-responders (NR). Although not statistically significant, NR had a higher percentage of global glomerulosclerosis (38 vs 16%, P=0.07) and concentric fibrous intimal thickening (onion skinning) (70% vs 29%, p=0.08) compared to RR.

Conclusions: Glomerular intracapillary fibrin was the only histologic variable different in CM+ versus CM- TMA. When present, this variable may suggest patients with TMA will be CM-. Percentage of glomerulosclerosis and presence of fibrous intimal thickening was higher in NR compared to RR but this did not reach statistical significance. A larger study is needed to determine the value of these features in predicting complement mutation status and renal response in aHUS.

PO1851

Comparative Efficacy of Ravulizumab and Eculizumab in the Treatment of Atypical Hemolytic Uremic Syndrome: An Indirect Comparison Using Clinical Trial Data

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease that can cause organ damage or death if not suitably treated. Eculizumab (ECU), a C5 inhibitor, was approved to treat aHUS in 2011. Ravulizumab (RAV), approved in 2019, was engineered from ECU to reduce dosing frequency (every 8 weeks [for patients weighing ≥20 kg] vs 2 weeks, respectively) and minimise treatment burden. Both drugs have established safety and efficacy via pivotal single armed studies. We indirectly compared the efficacy of RAV vs ECU using clinical trial data.

Methods: Patient-level data from a pivotal RAV trial (NCT02949128) and pivotal ECU trials (NCT00844428, NCT01194973) for adults with aHUS without kidney transplant were used. Propensity scores were calculated based on baseline characteristics (dialysis status, estimated glomerular filtration rate [eGFR], platelet count and serum lactate dehydrogenase), with stabilized inverse probability weighting used to balance groups while preserving sample size. Outcomes were changes in clinical characteristics at 26 weeks, and evaluated between groups using appropriate statistical tests at a 5% significance level.

Results: In all, 85 patients (46 RAV, 39 ECU) were included for analysis. Baseline characteristics were balanced after weighting, with no significant difference between groups in any clinical or patient-reported characteristics. At 26 weeks, outcomes were improved from baseline in both groups, including reduced prevalence of dialysis, and increased mean eGFR and mean platelet count, with no significant differences between groups (**Table**).

Conclusions: After balancing patient characteristics between study groups, no significant differences were seen between outcomes for ECU and RAV at 26 weeks.

Funding: Commercial Support - This study was sponsored by Alexion Pharmaceuticals, Inc.

Representative clinical characteristics at baseline and 26 weeks.

Clinical characteristic	Patients receiving ravulizumab (n=46)*	Patients receiving eculizumab (n=39)	*P* value	Differences between groups (95% confidence interval)
Patients receiving dialysis (%) At baseline At 26 weeks	52 22	53 8	0.998 0.070	0 (-21 to 21) -15 (-30 to 1)
eGFR (mL/min/1.73m^2; mean [SD])† At baseline At 26 weeks	16.7 (16.6) 55.4 (40.8)	16.6 (12.4) 51.4 (30.8)	0.986 0.619	0.0 (-6.3 to 6.3) -4.0 (-19.8 to 11.8)
Patients experiencing an improvement of ≥15 mL/min/1.73m^2 in eGFR from baseline at 26 weeks (%)	59	64	0.662	5 (-16 to 26)
Platelet count (x10^9/L; mean [SD]) At baseline At 26 weeks	118 (85) 243 (81)	118 (65) 244 (65)	0.979 0.953	0 (-33 to 32) 1 (-31 to 33)

*For eGFR and platelet count, n=43 at 26 weeks.

† eGFR defined as 10 mL/min/1.73m² for those on dialysis.

PO1852

C3 Inhibition with Pegcetacoplan Targets the Underlying Disease Process of C3 Glomerulopathy (C3G) and Improves Proteinuria

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Background: C3G is a rare renal disease in which C3 overactivation leads to the accumulation of C3 breakdown products in the glomeruli. Progression to end-stage renal disease occurs in up to 50% of patients (pts) within 10 years of diagnosis; no therapies target the underlying pathophysiology of C3 activation. The study aims to assess whether pegcetacoplan (APL-2; Apellis Pharmaceuticals, Waltham, MA), a C3 inhibitor, targets C3G complement dysregulation and reduces proteinuria.

Methods: This phase 2 open-label study was designed to evaluate preliminary efficacy and safety of pegcetacoplan in pts with complement-mediated glomerulopathies. Pts with C3G who were ≥16 years old, with proteinuria >750 mg protein/g creatinine, and eGFR ≥30 mL/min/1.73 m² were eligible for inclusion. Pegcetacoplan was administered as 360 mg daily subcutaneous infusions with transition to 1080 mg twice weekly from Week 24. The primary endpoint was change in proteinuria from baseline to Week 48, measured by 24-hour urine protein-to-creatinine ratios (uPCR). Serum C3, albumin, and creatinine as well as safety were also evaluated.

Results: Eight C3G pts were enrolled in the study. Three pts were excluded from efficacy analyses for self-reported non-compliance or interrupted study drug administration. Data showed a greater than 65% reduction in 24-hour uPCR from baseline to Week 48. Serum albumin and C3 increased, and serum creatinine was stable (Table). No serious or severe adverse events were reported and no TEAEs led to discontinuation.

Conclusions: These data suggest that pegcetacoplan targets the underlying pathophysiology of C3G, resulting in proteinuria reduction with stable renal function. Pegcetacoplan also appeared to be well-tolerated. Further studies are warranted to investigate the therapeutic potential of pegcetacoplan in the treatment of C3G.

Funding: Commercial Support - Apellis Pharmaceuticals, Inc.

	24-hour uPCR, mg/mg Mean (SE) [range] N = 5	Serum albumin, g/dL Mean (SE) [range] N = 5	Serum C3, mg/dL Mean (SE) [range] N = 5	Serum Creatinine, mg/dL Mean (SE) [range] N = 5
Baseline*	3.48 (0.82) [1.74, 6.55]	3.50 (0.30) [2.91, 4.01]	83.60 (20.42) [51.00, 116.00]	1.48 (0.50) [0.55, 2.92]
Week 48	0.93 (0.23) [0.24, 1.69]	4.08 (0.24) [3.50, 4.60] #	252.00 (52.82) [182.00, 407.00] #	1.32 (0.30) [0.50, 2.49] #

*Last result prior to initial dose; #Local lab data used for 1 pt due to COVID-19 related constraints

PO1853

C3 Glomerulonephritis Associated with Monoclonal Gammopathy: A Retrospective Case Series Study from a Single Institute in China

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Background: To analysis the demographic and clinicopathological features and renal outcomes of Chinese patients with C3GN in the setting of monoclonal gammopathy.

Methods: Patients with renal biopsy-proven C3 glomerulonephritis and detectable serum and/or urine monoclonal Ig from 2006 to 2018 in Peking University First Hospital were included, clinical data, renal pathology type, treatment and prognosis were collected.

Results: Nineteen patients were enrolled, accounting for contemporaneous 26.7% of C3GN patients. The mean age was 55 years old, and average eGFR at biopsy 48.42ml/min/1.73m². The IgG was the most common isotype of monoclonal Ig on immunofixation electrophoresis. Eleven patients had nephrotic ranged proteinuria and hypoalbuminemia. Kidney biopsies revealed a relative prominent MPGN pattern. Two patients had concurrent TMA-like renal injuries. The median renal survival was 24 months. Median renal survival was 12, 12, and 34 months, respectively in patients receiving conservative therapy, immunosuppressant therapy, and clone-targeted chemotherapy, without statistical significance. Plasma exchange therapy only improved one patient's renal outcome.

Conclusions: The clinicopathological features of Chinese patients with C3GN combined with monoclonal gammopathy are consistent with the previously reported population. Renal prognosis of these patients is poor, and immunosuppressant therapies show no advantage over supportive therapy in renal prognosis, while the benefit of clone-targeted chemotherapy is still requiring investigation.

Funding: Government Support - Non-U.S.

PO1854

The Prognostic Value of Chronic Histopathological Lesions in Monoclonal Immunoglobulin Deposition Disease: A Clinicopathological Analysis of Patients from a Single Institution

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Background: Kidney is the most common involved organ in monoclonal immunoglobulin deposition disease (MIDD), which could lead to end stage renal disease (ESRD). Few studies have evaluated the association between the irreversible chronic histopathologic lesions and clinical features, and its prognostic value in renal outcomes in MIDD.

Methods: A series of 20 patients with MIDD and 20 patients with renal AL amyloidosis proven by renal biopsy between January 2001 and December 2018 were reviewed retrospectively. The degree of chronic changes including glomerulosclerosis, interstitial fibrosis, and arteriosclerosis were semiquantitatively scored and the overall chronic lesions were also graded based on the grading system proposed in 2017. The association between histopathologic lesion and clinical manifestations, and the correlation with risk of progression to ESRD were investigated.

Results: MIDD patients presented more significantely overt ischemia-related global glomerulosclerosis and a more severe tendency of interstitial fibrosis(Figure 1). The significantly higher extent of overall chronic changes was also seen in MIDD compared with AL amyloidosis, which was independently correlated with worse baseline estimated glomerular filtration rate (β coefficient (95% CI): -4.618(-8.238-0.999), *P*=0.017). And the overt interstitial fibrosis predicted the increased risk of developing ESRD in MIDD.

Conclusions: The extent of overall chronic changes and the overt interstitial fibrosis provide information both about baseline manifestation and renal survival. Carefully grading and evaluating the chronic changes in MIDD may help guiding the treatment and accessing the renal outcomes.

Figure1.Comparison of overt histopathological lesions between AL and MIDD at kidney biopsy

Histopathological score	MIDD	AL	P-value
Overt segmental glomerulosclerosis (≥2)	2(10%)	5(25)	0.407
Overt global glomerulosclerosis (≥3)	5(25%)	0(0%)	0.047
Overt nodular glomerulosclerosis (≥3)	7(35%)	3 (15%)	0.144
Overt tubular atrophy/interstitial fibrosis (≥3)	9(45%)	5(25%)	0.185
Overt arteriosclerosis (≥2)	7(35%)	10(50%)	0.337
Overt overall chronic changes (≥5)	13(65)	3(25)	0.011

Figure 1. Comparison of overt histopathological lesions between AL and MIDD at kidney biopsy

PO1855

Development of Atypical Hemolytic Uremic Syndrome in a Patient with Complement 3 Glomerulonephritis

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Introduction: Uncontrolled hyperactivity of alternative complement pathway has been implicated in development of two distinct pathological processes, namely C3 glomerulonephritis (C3GN) and atypical hemolytic uremic syndrome (aHUS). Here we present a unique case which initially started as C3GN on kidney biopsy and progressed to aHUS.

Case Description: 68-year-old female presented with progressive weakness and palpitations over a month. She denied any fever, chills, dysuria, chest pain, dyspnea or abdominal pain. Her past medical history was significant for hypertension and coronary artery disease, with no family history of end stage renal disease. On admission, her medications included amlodipine for hypertension, levothyroxine for hypothyroidism and intermittent steroids for gouty arthritis. On exam, her vital signs revealed tachycardia with heart rate 119 beats/min and hypotension with blood pressure 97/59 mmHg. Exam was significant for dry mucosa and irregular heart rate. Initial laboratory evaluation was significant for acute kidney injury (AKI), with creatinine (Cr) of 2.6 (baseline Cr of 1.2). Urinalysis demonstrated 21-50 RBC/hpf and urine protein/Cr of 12.5 g/g. A renal biopsy was performed which showed endocapillary proliferation with dominant staining for C3 in the mesangium and along the capillary wall, consistent with C3GN. The patient was started on prednisone 60 mg daily.

Hemodialysis was initiated for uremic symptoms. Complement function test was consistent with ongoing complement dysregulation at C3 convertase level and C5 convertase level without the presence of autoantibodies towards complement proteins. 2 months after her kidney biopsy, she developed worsening anemia and thrombocytopenia, elevated lactate dehydrogenase and undetectable haptoglobin. Direct coombs test was negative, peripheral smear showed schistocytes, ADAMTS13 level was 65%, consistent with diagnosis of atypical hemolytic uremic syndrome. Patient was started on Eculizumab therapy with stabilization of hemoglobin and platelets but remains dialysis dependant.

Discussion: In our growing understanding of alternative complement pathway, it is thought that dysregulation at fluid state is associated with C3GN, while solid state dysregulation is associated with widespread endothelial injury leading to aHUS. Our patient developed both pathologies, suggests further research is needed in understanding the details of complement system.

PO1856

Acute Renal Failure from Thrombotic Microangiopathy: Is IgA Vasculitis to Blame?

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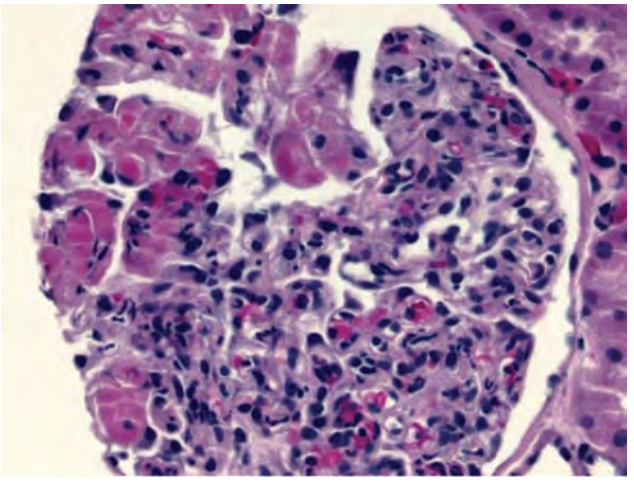
Introduction: Thrombotic microangiopathy (TMA) has been associated with several cases of IgA nephropathy. In most cases the clinical significance of the TMA is uncertain. We describe a case of acute renal failure in a patient with systemic IgA vasculitis, who was found to have severe renal-limited TMA treated with eculizumab for the possibility of underlying complement dysregulation.

Case Description: A 34 year old male presented with abdominal pain and bloody bowel movements, and was found to have extensive duodenitis. Infectious testing of stools was negative, though he later tested positive for H. pylori. While hospitalized he developed acute kidney failure, with creatinine rising from 1.5 to 11.7 within four days. Urine sediment demonstrated granular casts consistent with acute tubular injury, though he also had white cell casts for which acute interstitial nephritis was considered. Blood counts were normal on admission, but he developed anemia and thrombocytopenia with mildly positive markers of hemolysis (haptoglobin 25, LDH 269, no schistocytes). Serum complements were profoundly low (C3 33, C4 9). A kidney biopsy revealed severe TMA. Given the rapidity of progression to renal failure requiring dialysis, he was started on eculizumab for a presumed atypical hemolytic uremic syndrome (aHUS). Since he did not have evidence of active hemolysis, he was not started on plasmapharesis. Kidney biopsy demonstrated proliferation and expansion of the mesangium with IgA deposition. Endoscopy was later performed with biopsy consistent with systemic IgA vasculitis, for which he was started on steroids. Abdominal symptoms improved and he was discharged home. He continues on eculizumab with normalization in complements, but without improvement in renal function.

Discussion: There have been case reports of complement factor dysregulation resulting in both IgA vasculitis and TMA. Given the extent and acuity of renal failure in this case, we treated our patient with eculizumab for presumed aHUS.



PO1857

Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID): A Report of Two Cases Managed with Renin-Angiotensin-Aldosterone System (RAAS) Inhibition Alone

Marianna Vynnyk, Maria V. DeVita, Jordan L. Rosenstock. *Lenox Hill Hospital, New York, NY.*

Introduction: PGNMID is a relatively rare disorder with monoclonal immunoglobulins (Ig) deposition in glomeruli that resembles immune complex glomerulonephritis (GN), after exclusion of other related disorders such as amyloidosis and cryoglobulinemia. The pathogenesis and management of PGNMID remains uncertain, especially if no systemic clonal disorder is found, which is frequently the case. Some groups have recommended anti-plasma cell or anti-B cell therapy in most if not all cases, even if a clone is not identified. We present two cases of PGNMID that were managed with RAAS blockade alone and whose renal disease remained stable over 6 and 10 years of follow up.

Case Description: Two cases were identified who had prolonged follow up with PGNMID and no immunosuppressive treatment. Charts were reviewed retrospectively and data collected from time of biopsy until most recent follow up. Case 1 is a 25 year old obese black woman with recent onset of hypertension who presented with serum creatinine (sCr) 1.4mg/dl. Urinalysis (UA) showed 1+ protein and no blood. 24hr urine protein was 296mg. Renal biopsy (done as she had positive antiphospholipid antibodies) revealed PGNMID (IgG kappa) with diffuse mesangial proliferation and focal sclerosing GN with focal fibrous crescents. There was no evidence of thrombotic microangiopathy. Serum and urine immunofixation (IF) were negative for monoclonal protein. Bone marrow biopsy was unremarkable. The patient was treated with angiotensin-receptor blocker (ARB) without immunosuppressive therapy. Six years later the most recent sCr was 1.5mg/dl and urine protein-creatinine ratio (PCR) was 1100mg/g. Case 2 is a 41 year old white woman who presented with sCr 0.6mg/dl. UA had 3+ protein and no blood. 24hr urine protein was 2.3g. Renal biopsy showed PGNMID (IgG kappa) with mesangial and endocapillary proliferation. Serum and urine IF were negative for monoclonal proteins. Bone marrow biopsy was not done. The patient was treated with an angiotensin-converting enzyme inhibitor (ACEI) alone. After ten years of follow up, her sCr was 0.7mg/dl, and urine PCR was 632mg/g.

Discussion: We report 2 cases of PGNMID with stable renal function and proteinuria after 6 and 10 years of RAAS therapy alone. This suggests that not all patients with PGNMID may require immunosuppression.

PO1858

Use of Pronase-Treated Paraffin Immunofluorescence to Unmask a Reclusive Glomerular Disease

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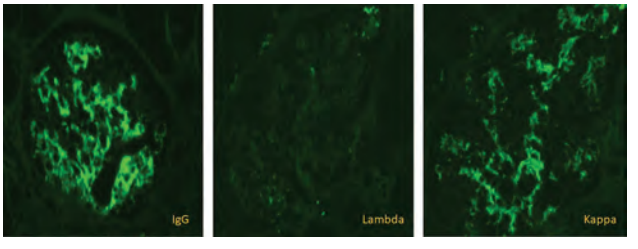
Introduction: Interpretation of renal biopsy depends on light, IF and electron microscopy. Direct IF on unfixed frozen tissue sometimes fails to pick up immunoglobulins. Treatment of paraffin embedded formalin-fixed tissue with pronase renders such Igs more amenable to detection. We present a case of a young woman where use of this "unmasking" technique allowed the correct diagnosis to be made.

Case Description: A 24 YO WF presented to our GN Clinic with intermittent edema, proteinuria and hematuria noticed about a year ago. Her creatinine was 1.5 mg/dl. Urine Pr/Cr ratio was 1.8 g/g. Her ANA was 1:320 but the rest of the antibody panel was negative. C3 and C4 were normal. Lupus Anticoagulant, beta 2 GPI, anticardiolipin IgG and IgM were positive. Screens for paraproteins and relevant viruses were negative. Renal Biopsy: 20/31 glomeruli were globally sclerotic. Intact glomeruli showed mesangial proliferation and hypercellularity. IF showed C3+ but all other stains were negative. IF on pronase digested, paraffin embedded tissue stained IgG, C3 and kappa with no lambda. Stain for SAP was positive. EM showed numerous mesangial deposits, some sub-epithelial but no sub-endothelial deposits. Based on above, she was diagnosed with Membranous like glomerulopathy with masked IgG-kappa deposits. Her age, race, gender, Ab profile as well as biopsy findings all supported the diagnosis. She was started on immunosuppression therapy to attempt salvage of renal function and delay progression.

Discussion: Refinement in IF techniques has expanded our diagnostic ability and mechanistic understanding of glomerular disease. Use of paraffin embedded tissue for IF after pronase treatment helps discover Ig deposits not picked up by traditional IF. This can prove critical in correctly diagnosing glomerular disease, as exemplified in this case. This patient could have been misdiagnosed as C3 glomerulopathy based on traditional IF. Unmasking IgG-kappa deposits allowed us to correctly diagnose her with a rare disease, MGMID. This technique expands our ability to correctly diagnose glomerular disease and should be applied routinely.



IF on Paraffin Embedded Tissue

PO1859

Fibrillary Glomerulonephritis: A Case Series with Clinical Features and Outcomes

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Background: Fibrillary glomerulonephritis (FGN) is a rare cause of chronic glomerulonephritis with a poor prognosis. We evaluated a series of patients with FGN, most of whom were treated with rituximab, low-dose cyclophsophamide, and prednisone (RCP).

Methods: Patients were included if they had FGN treated at Massachusetts General Hospital between 2008 – 2020 with a minimum of six months of follow up. The primary outcome was achievement of remission, defined as serum creatinine that remained stable, improved or increased <25% of the original value after treatment, and a 50% reduction in proteinuria at the end of follow up.

Results: We identified 11 consecutive patients with FGN. ANCA-associated vasculitis (n = 3), rheumatoid arthritis (n = 1), chronic hepatitis C (n = 1), and monoclonal B lymphocytosis (n = 1) were concurrently present. At the start of therapy, the median (IQR) serum creatinine, eGFR, and protienuria was 2.31 mg/dL (1.25 – 4.69), 30 mL/min/1.73 m^2 (11 – 68), and 6.6 g/g (1.5 – 8.4), respectively. Of the 11 patients, 10 were treated with RCP, and one patient with rituximab monotherapy. The median (IQR) follow-up was 2.6 years (2.0 – 3.9). Seven of 11 patients achieved remission. Of the 4 patients who did not achieve remission, one received pre-emptive transplantation, two initiated hemodialysis, and one had > 25% rise in serum creatinine not reaching ESRD. Five serious adverse events occurred over 33 patient years.

Conclusions: Remission was achieved in most patients with FGN treated with rituximab, low-dose cyclophosphamide, and prednisone. Larger studies evaluating this regimen are warranted.

Patient	Age	Gender	Race	Cr (mg/dL)		eGFR		Proteinuria (g/g)		Albumin (g/dL)		Additional Diagnosis	Treatment	# of RTX doses	Years of CBCD	Outcome
				Baseline	Last F/u	Baseline	Last F/u	Baseline	Last F/u	Baseline	Last F/u					
1	51	M	AA	1.70	3.91	33	19	7.2	8.1	2.8	2.8	HCV, HIV[a]	CBCD[c]	14	3.8	ESRD
2	78	F	W	1.37	0.98	37	55	19.0	0.4	2.1	-	-	RCP[d]	7	2.3	Remission
3	66	F	W	4.69	4.44	9	9	0.3	4.2	3.0	3.2	AAV	RCP	13	6.0	ESRD
4	85	F	W	3.57	1.58	11	29	1.5	0.2	3.5	4.4	MBL	RCP	4	2.3	Remission
5	48	M	W	1.25	1.38	68	56	9.3	3.5	3.6	3.7	-	RCP	21	4.9	Remission
6	64	M	W	1.52	2.71	25	23	0.6	1.2	3.8	3.2	-	RCP	11	3.9	Remission
7	64	F	W	5.60	1.66	7	32	0.7	0.3	3.4	4.5	AAV	RCP	9	3.2	Remission
8	38	M	W	5.40	3.97	12	16	8.4	14.2	2.5	3.3	-	RCP	2	0.6	ESRD
9	55	M	W	0.98	1.12	86	73	7.1	2.9	3.4	3.8	-	RCP	9	2.6	Remission
10	71	M	W	0.98	1.12	77	69	2.5	0.4	4.2	4.5	AAV	RCP	6	2.6	Remission
11	60	M	W	2.31	3.68	30	21	4.6	6.3	4.2	4.2	RA	RCP	3	0.6	Cr rise

Abbreviations: AAV anti-neutrophil cytoplasmic antibody-associated vasculitis, AA African-American, CBCD continuous B cell depletion, Cr creatinine, DM diabetes mellitus, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, F/u follow-up, HCV hepatitis C virus, HIV human immunodeficiency virus, MBL monoclonal B lymphocytosis, RA rheumatoid arthritis, RCP rituximab-cyclophosphamide-prednisone, RTX rituximab, W white

Table 1. Baseline characteristics

[a]Calculated by CKD-EPI Creatinine Equation (2009); reported as mL/min/1.73m^2
[b]Patient 1 had an undetectable HIV viral load with antiretroviral therapy; however, he had treatment-naive chronic HCV with viremia.
[c]Continuous B cell depletion is defined as scheduled rituximab infusions to maintain B cell depletion (total B cell count <5 cells/µL).
[d]RCP is defined as rituximab-induced continuous B cell depletion, low-dose oral cyclophosphamide for 8 weeks, and a rapid prednisone taper.

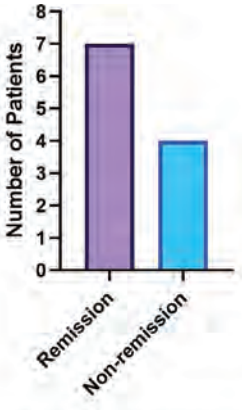

Figure 1. Primary outcome of renal disease. The primary outcome was achievement of remission, defined as serum creatinine that remained stable, improved or increased <25% of the original value after treatment, and a 50% reduction in proteinuria at the end of follow up. Non-remission was defined as serum creatinine increased >25% of the original value after treatment, failure to achieve a 50% reduction in proteinuria, or development of ESRD (dialysis initiation or transplantation).

PO1860

An Atypical Case of Fibrillary Glomerulonephritis

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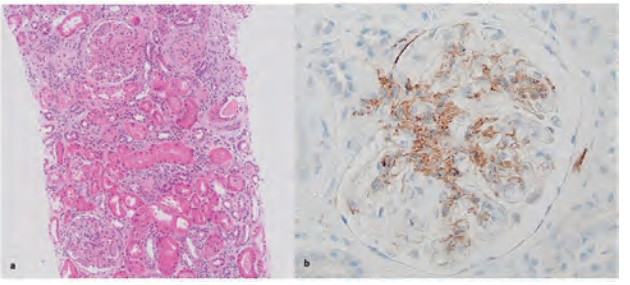
Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease with multiple disease associations such as hepatitis C, malignancy, and dysproteinemia. Despite these known associations, little is known about the interaction between FGN and other comorbidities. We present a case of FGN that presented years after successful treatment of hepatitis C infection (HCV).

Case Description: The patient is a 72 year old male with history of HCV. He was treated with ledipasvir/sofosbuvir and achieved a sustained virologic response however developed liver cirrhosis and underwent a liver transplant 2 years later. Histological examination of his liver explant was positive for hepatocellular carcinoma however he did not demonstrate any systemic involvement. 1 year after his transplant, he was noted to have a progressively worsening serum creatinine (1.37mg/dl from 0.97mg/dl) and new nephrotic range proteinuria (5.7 gram protein/gram creatinine). Autoimmune serology including ANCA, ANA, and monoclonal protein testing was negative. Complement levels were normal. He underwent a kidney biopsy which demonstrated focal endocapillary hypercellularity (figure 1a), segmental glomerular sclerosis, and mild mesangial and capillary wall staining for IgG, kappa, and lambda, with less C3. Electron microscopy demonstrated mesangial, subendothelial and few isolated subepithelial and intramembranous deposits with a vague fibrillar appearance. DNAJB9 staining was later performed and was positive, confirming a diagnosis of FGN (Figure 1b). After diagnosis of FGN, he underwent extensive malignancy screening which was unrevealing.

Discussion: FGN has a known association with HCV infection. Case series reported positive HCV serology in around 15% of patients with FGN, but none reported FGN after HCV eradication. DNAJB9 staining is specific for FGN and helps establish the diagnosis especially when histology does not demonstrate the classical membranoproliferative or mesangioproliferative patterns of glomerular injury.



PO1861

Fibrillary Glomerulonephritis Treated with Rituximab: A Case Report

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Introduction: Fibrillary Glomerulonephritis (FGN) is a rare primary glomerular disease first described by Rosenmann and Eliakim in 1977 present in 0.5 to 1% of native kidney biopsies defined by haphazardly arranged fibrils 10 to 30 nm in thickness deposited in the mesangium, glomerular basement membranes or both. Initially, FGN was considered to be idiopathic. However, approximately one-third have a history of malignancy, monoclonal gammopathy, autoimmune disease, hepatitis C infection or an IgM glomerular deposit disease. Prognosis is generally poor with 50% of patients developing ESRD within 6 years of presentation. The most common form of treatment is steroids with or without a second agent usually Cyclophosphamide or Rituximab. To date, there is no convincingly effective treatment but published case series reports clinical response referred to as "nonprogression" defined by stable renal function in those treated with Rituximab.

Case Description: Our patient is a 49-year old Filipino female, hypertensive, diagnosed case of Immune Complex-Mediated Glomerulonephritis presenting with elevated blood pressure and nephrotic-range proteinuria. Initial adjustment of her anti-hypertensive regimen controlled her blood pressure. Subsequently, she developed resistant hypertension and increasing proteinuria. Creatinine increased to 2.1 mg/dL from a baseline of 1 mg/dL in 12 months. A second renal biopsy was done showing fairly widespread podocyte foot process effacement and mesangial fibrillary deposits measuring 13 nm in mean diameter suggestive of Fibirillary Glomerulonephritis. Patient was worked up for an underlying malignancy, autoimmune disease and infectious causes but none turned out positive. At this time, proteinuria has increased to 7596.05 grams from 1622.08 grams with a creatinine clearance of 39.80 ml/min/1.73 m^2. After discussing with the patient, she was given Rituximab as four weekly doses of 375 mg/m^2 intravenously. After five months, there was significant reduction in proteinuria at 1734.32 grams with stable creatinine clearance of 31.99 ml/min/1.73 m^2.

Discussion: In general, FGN prognosis is poor and majority of patients progress to ESRD. Treatment options are currently limited and conclusions regarding immunosuppressive therapy cannot be drawn from limited published data. Rituximab may offer benefit particularly in patients with relatively normal baseline renal function.

PO1862

Cryoglobulinemia After Hepatitis C Virus Eradication

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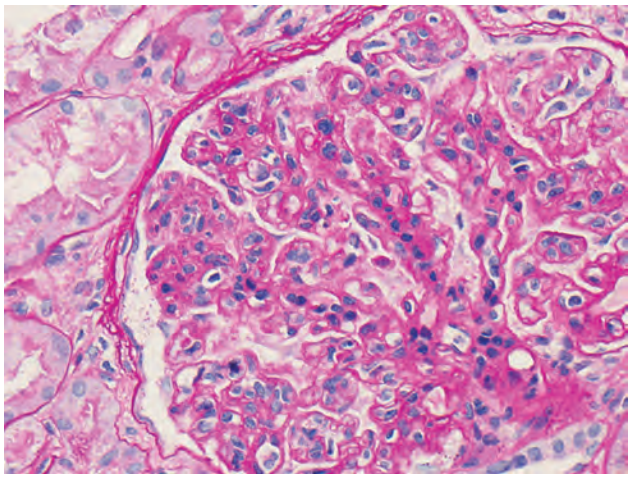
Introduction: Mixed cryoglobulinemia (cryo) is often caused by HCV infection. Major clinical manifestations are arthralgias, myalgias, palpable purpura, peripheral neuropathy and glomerulonephritis (GN). Diagnostic evaluation may reveal the presence of serum cryoglobulins, rheumatoid factor (RF) and hypocomplementemia. If diagnosis is uncertain tissue biopsy with histologic confirmation may be useful. The treatment of patients with HCV-related cryo GN involves eradication of HCV infection with direct-acting antiviral agents (DAAs) and immunosuppression for more severe systemic disease. Some patients develop persistent or relapsing disease despite a sustained virologic response (SVR) with DAAs rarely leading to life-threatening manifestations.

Case Description: We report a case of a 76-year-old female with chronic HCV infection treated with DAAs with SVR for years referred to nephrology clinic for evaluation of CKD and nephritic syndrome. She also reported pain and a purpuric papular rash on her legs. Labs showed hypocomplementemia and high levels of RF. Cryo was suspected, but repeated testing of serum cryoglobulins was negative. Renal biopsy showed membranoproliferative GN with endocapillary hypercellularity and intracapillary "cryo-plugs" by LM, and IgM dominant with kappa greater than lambda capillary loop and mesangial staining by IF, and subendothelial and mesangial deposits by EM. These findings suggest cryo GN. Patient was treated with a prednisone taper and rituximab. She had a rapid improvement in renal function, complete remission of proteinuria and normalization of complement levels.

Discussion: Mixed cryo should be considered in the differential diagnosis in the appropriate clinical setting in patients with HCV infection even after treatment and prolonged SVR. To detect serum cryoglobulins blood should be collected in a prewarmed tube without anticoagulant. Inadequate technique may lead to false-negative results.



Renal Biopsy. Cryoglobulinemic Glomerulonephritis

PO1863

Clinico-Biological Characteristics and Treatment of Hepatitis B Virus-Related Mixed Cryoglobulinemia: Current Clinical Evidence

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Background: Hepatitis B virus(HBV)-related mixed cryoglobulinemia (MC) was considered to be a rare disease, presented as mild clinical symptoms just like purpura to severe organ damage such as glomerulonephritis. We aimed to clarify the clinico-biological characteristics and treatment of HBV-related MC.

Methods: We reported a case of HBV-related MC, enrolled 41 HBV-related MC cases from literature, and summarized demographic, clinical, laboratory, treatment and outcome data of the 42 HBV-related MC cases. Meanwhile, the Asian and European group, patients in remission and refractory were compared. Kidney involvement, death and time to death were included for survival analysis.

Results: Of the 42 HBV-related MC, Mean age was 53±14 years, and 47.6% patients were male. Extrahepatic clinical manifestations mainly included cutaneous lesions, kidney involvement, peripheral neuropathy, articular involvement, which accounted for 78.6%, 54.8%, 35.7%, 19.0%, respectively. 87.1% (27/31) patients had low serum C4, and 92.6% (25/27) patients' rheumatoid factors(RF) were positive. Renal pathology showed membranous proliferative glomerulonephritis, the capillary lumen disclosed hyaline thrombi and electron microscope found microtubular substructure. 36 (85.7%) patients received antiviral therapy. Corticosteroids were used in 22 (52.4%) patients, immunosuppressive agents were given to 13 (31.0%) patients, and plasma exchange (PE) were used in 9 (21.4%) patients. At the end of follow-up, 52.4% (22/42) patients were in remission, 47.6% (20/42) patients had refractory disease, and 11.9% (5/42) patients died. The patients who had cutaneous necrosis, peripheral neuropathy and kidney involvement were more likely to have refractory disease but without statistical difference. The Asian group showed more kidney involvement than the European group (P=0.001), but the European group had more peripheral neuropathy (P=0.037). The Asian group showed a higher mortality than the European group(P=0.048). Univariate analysis showed kidney involvement had correlation with overall survival (log rank P=0.034).

Conclusions: Extrahepatic clinical manifestations of HBV-related MC were varied. Anti-HBV treatment, corticosteroids, immunosuppressive agents and PE were useful for some patients. The patients with kidney involvement may be related to poor prognosis.

PO1864

Membranoproliferative Glomerulonephritis (MPGN) Associated with Epstein Barr Virus (EBV)

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Introduction: Immune complex-mediated MPGN has been commonly associated with viral infections including Hepatitis B, C, HIV and Hantavirus. We present a rare case of EBV associated MPGN successfully treated conservatively.

Case Description: A 19-year old female, previously healthy, presented with fatigue, sore throat and periorbital swelling for 3 weeks. Vitals were stable on presentation. Her EBV IgM and IgG serologies were positive while CMV was negative. UA showed proteinuria (>300mg/dL) and microscopic hematuria. Albumin was 2.9 g/dL. Spot urine protein to creatinine ratio was 2.6g/g. Urine sediment was bland. SCr was 0.72 mg/dL. Extensive serological work up was negative. Renal biopsy showed mesangial hypercellularity, double contours of capillary loops with intramembranous, subendothelial and subepithelial immune type electron dense deposits. Immunofluorescence revealed segmental globular to coarsely granular staining in the glomerular capillary walls for IgG (3+), IgA (1+), IgM (3+), kappa (2+), lambda (3+), C3 (1-2+), C1q (3+), and C4 (1+). Mesangial regions showed segmental granular staining for IgG (1+), kappa (1+), lambda (1+) and C4 (1+). She was treated with furosemide 20mg daily as needed for swelling and lisinopril 5mg daily. Her symptoms resolved within 2 weeks of initiating treatment. She self-discontinued her medications after 4 months. On 6 month follow up, she remained asymptomatic and urine protein was undetectable.

Discussion: Infectious Mononucleosis (IM) is caused by EBV. EBV primarily infects human B cells via the CD21 receptor and may infect renal tissue since the CD21 molecule has been detected in proximal tubular cells of kidneys. Further, acute EBV infection may cause immune-mediated response with deposition of immune complexes and subsequent glomerulopathy. Renal involvement is reported with 3-16% cases of acute IM. Common renal lesions include acute tubulointerstitial nephritis, membranous nephropathy, minimal change disease and vasculitic lesions. MPGN is a rare presentation of EBV and should be considered in patients with IM and proteinuria. Previous case reports have suggested that nephrotic syndrome in patients with an acute EBV infection is usually self-limiting. Our case report also suggests that MPGN associated with EBV may have a relatively benign course.

PO1865

Infection-Related Glomerulonephritis Mimicking Lupus Nephritis

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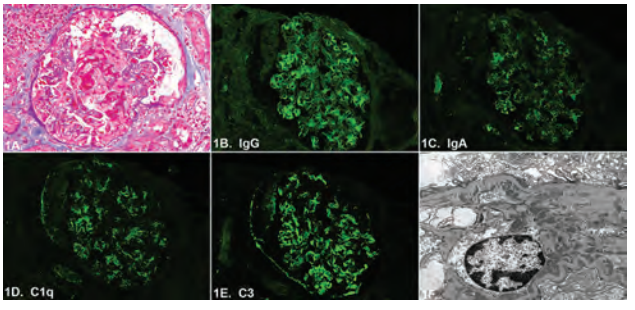
Introduction: Differentiating infection vs auto-immune related GN is crucial in order to avoid inadvertent immunosuppressive therapy that can be harmful and even lead to fatal consequences. This case illustrates the dilemma of medical management in lupus like-GN

Case Description: A 66 year old man with mitral valve prolapse, was found to have elevated creatinine of 3.59 mg/dl from a baseline of 1 mg/dL. He complained of leg rash and dark urine. His rash was symmetric and non blanchable petechiae. Urine sediment showed 20 dysmorphic RBC per high-power field and RBC casts. Urine protein/creatinine ratio was 1.35 g/g. Serum creatinine peaked at 10.4 mg/dl. Hemodialysis was begun. Further testing was significant for pancytopenia, low complements (C3 was 40 mg/dl, C4 10 mg/dl) and positive MPO-ANCA. Kidney biopsy was performed (Fig 1). On light microscopy 2 glomeruli were globally sclerotic. One glomerulus showed crescentic and necrotizing lesion. There was diffuse ATN. Some tubules showed red blood cell casts. Interstitial inflammation was mild. Direct IF showed a full house pattern with bright IgG, IgM, kappa, lambda, C1q, C3 and mild to moderate IgA staining. EM identified few mesangial and subendothelial deposits with a single subepithelial hump. During his hospitalization, streptococcus bacteremia was documented. Echo showed mitral valve vegetation. In setting of bacterial endocarditis, the Biopsy is consistent with infection related glomerulonephritis (IRGN).

Discussion: Crescents as well as ANCA positivity have been described in IRGN. However a full-house immunostaining pattern is not typical of IRGN and has never been reported in IRGN. Instead, this is typical of lupus- like GN. The patient didn't have positive ANA, however he developed pancytopenia and hypocomplementemia which can be manifestations of both SLE even at an old age as well as infection. The dilemma is that auto-immune mediated GN warrants immunosuppressive therapy which is contraindicated in IRGN. Our patient received penicillin and underwent mitral valve replacement His kidney function gradually improved and dialysis was discontinued after 4 months.



PO1866

Hypocomplementemic Urticarial Vasculitis: Interstitial Nephritis with New Microtubular Deposits and Successful Response to Rituximab

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Introduction: HUV is caused by antibodies to C1q complement and has many features of systemic lupus and cryoglobulinemia. Different patterns of GN often occur such as the mesangial GN, MPGN or membranous GN but interstitial nephritis has never been described.

Case Description: A 57 year old female in 2007 developed recurrent hives, angioedema, leucocytoclastic vasculitis on skin biopsy & 5 g proteinuria with RBC casts. C1q complement was 2 mg/dL, C3 20 mg/dL, C4 6 mg/dL & C1q antibody was 35 mg/mL (NL<10). All other serology and cryos were negative. Serum creatinine was 0.6mg/dL.

Her 1st renal biopsy showed mesangial proliferative GN with +3 IF for IgG, IgA, C1q & EM deposits in the mesangial, subendothelial, subepithelial locations & interstitial inflammation. Parallel microtubular structures, 25 nm wide with hollow cores, were present in interstitial capillaries and hilar arterioles but not in the glomeruli. Tubular basement membranes & peritubular capillaries were +3 positive for IgG & C1q with granular deposits on EM. She failed prednisone, mycophenolate & cyclosporin, but after 4 weekly doses of Rituximab 375 mg/m^2 she rapidly went into remission within 2 months which was sustained for 6 years. HUV flared in 2016 with new onset nephrotic syndrome, hives, angioedema, COPD & AKI. Serum creatinine was 2.2 mg/dL & urine total protein/creatinine ratio was 8.7 with RBC casts. C1q was 4 mg/dL, C3 38 mg/dL, C4 4 mg/dL & C1q antibody > 100 mg/ml. A 2nd renal biopsy showed diffuse endocapillary proliferation with membranous GN similar to lupus Class IV & V and interstitial inflammation. IF was +3 for IgG, IgA, C1q and kappa and lambda in the same locations as biopsy 1. Tubules & peritubular capillaries were positive for IgG & C1q, peritubular capillaries had 25 nm hollow microtubule structures as before. Rituximab was initiated at 375 mg/m^2 for 4 doses. It induced a complete renal remission after 3 months with a serum creatinine of 0.6 mg/dL & urine total protein of 210 mg.

Discussion: We conclude: In addition to glomerulonephritis HUV can cause interstitial nephritis with +IF for IgG & C1q. HUV causes unique microtubular structures in the interstitium but not the glomeruli. Rituximab rapidly induces clinical renal remission in HUV.

PO1867

Unusual Aggregation of Different Glomerulopathies in a Family Resolved by Genetic Testing

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Introduction: Glomerulonephritis (GN) is a major cause of chronic kidney disease (CKD) in children. The conventional approach to diagnosis of GN includes clinical evaluation and in most cases kidney biopsy to make a definitive diagnosis. However, in many cases, clinical presentations of different GNs can overlap leading to uncertainty in diagnosis and management even after renal biopsy. In this report we identify a family with clinical diagnoses of post infectious glomerulonephritis (PIGN) and IgA nephropathy in a parent and two children. Renal biopsies were inconclusive and we were only able to make final diagnoses in each of the family members after genetic testing and reverse phenotyping.

Case Description: A previously healthy 7 year old male presented to the emergency department with hematuria, fever, and sore throat. Apart from being obese, his physical examination was unremarkable. Laboratory data was remarkable for microscopic hematuria and non-nephrotic range proteinuria. C3/C4 complements, ASO, anti-DNase b, anti-dsDNA, ANCA, and anti-GBM titers were all normal. A presumptive diagnosis of PIGN was made. However, he had persistent hematuria and proteinuria over the next 10 months. Further history at follow up revealed a history of IgA nephropathy in his mother and CKD of unclear etiology in his maternal grandfather. Renal biopsy was initially reported to be consistent with IgA nephropathy. However, because of the family history we carried out genetic testing and identified a rare hemizygous variant [c.3437G>A (p.Gly1146Glu)] in the gene *COL4A5*. COL4A staining was performed on the prior biopsy and staining pattern was consistent with COL4A5 disease. We confirmed that his mother also carried the same variant and she also has a history of hearing loss. Incidentally, his older brother presented a few weeks later with AKI and classical features of PIGN. His renal biopsy was consistent with PIGN and genetic testing in him was negative for the *COL4A5* variant found in his brother and mother.

Discussion: This case highlights the utility of genetic testing and reverse phenotyping in resolving clinical diagnosis in families with unusual constellations of different glomerulopathies. We propose that clustering of different glomerular disease phenotypes in a family should be an indication for genetic testing.

PO1868

Unusual Case of Histiocytic Glomerulopathy in the Setting of Sarcomatoid Malignancy

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Introduction: We present a case of histiocytic glomerulopathy and pauci-immune ANCA negative glomerulonephritis (GN) in the setting of sarcomatoid malignancy.

Case Description: An 83-year-old female presented to our hospital for evaluation of abdominal pain. Her vital signs were normal and her physical exam was only significant for mid-abdominal tenderness on palpation. Aortic angiography revealed occlusion of the superior mesenteric artery, celiac artery and left renal artery, in addition to a mass engulfing the celiac artery. She later developed acute kidney injury (AKI) with creatinine rising to 1.5mg/dl from baseline of 1.2mg/dl. Work up reveled bland urine sediment and 24-hour urine protein of 3.4g/day. Further laboratory studies revealed anti myeloperoxidase of 19.4u/ml, anti-proteinase 3 of 10.3u/ml, negative C-ANCA and P-ANCA, and normal complement levels. Renal biopsy showed focal crescentic and endocapillary proliferative GN comprised of mostly of CD68-positive foamy histiocytes, pauci-immune, with segmental C3 staining, as well as severe arterial fibrointimal hyperplasia with scattered intimal histiocytes and lymphocytes, consistent with arteritis and acute tubular injury with foci of prominent tubular vacuolization. Contrast induced nephropathy was thought to be the cause of AKI. Celiac mass biopsy showed sarcomatoid malignancy.

Discussion: Histiocytic glomerulopathy poses a diagnostic challenge as it has many possible underlying causes with different pathophysiology. Kaur and Sethi described 5 entities with histiocytic/foamy glomerular change on the kidney biopsy: crystal-storing histiocytosis, histiocytic glomerulopathy associated with macrophage-activating syndrome, thrombotic microangiopathy, lecithin-cholesterol acyltransferase deficiency and lipoprotein glomerulopathy. Our patient does not fulfill criteria for either of these entities. Small and large vessel vasculitis is well described as neoplastic and paraneoplastic phenomena, including both immune complex–mediated and ANCA-associated (pauci-immune). Pauci-immune GN is a rare and aggressive cause of AKI with 10% of the cases being ANCA-negative. Few case reports linked ANCA-negative pauci-immune GN to non-small cell lung cancer. To our knowledge this is the first case of histiocytic glomerulopathy, ANCA-negative pauci-immune GN and arteritis in the setting of sarcomatoid malignancy.

PO1869

Bilateral Renal Infarctions: A Perplexing Presentation of Polyarteritis Nodosa

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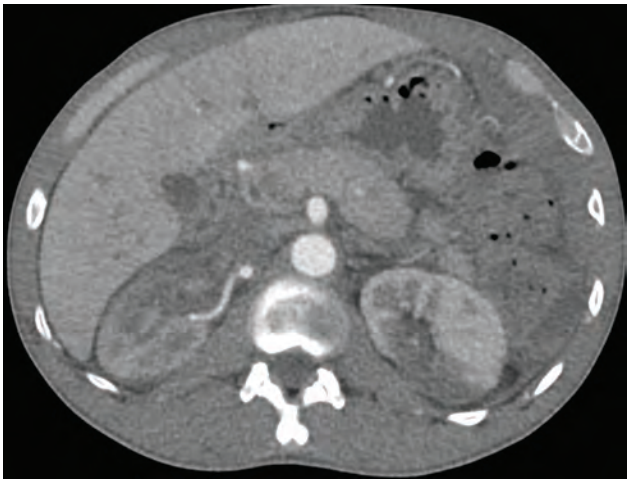
Introduction: Classic polyartertis nodosa (c-PAN) is an autoimmune necrotizing vasculitis with predilection for medium-sized vessels. Although c-PAN can be associated with renal involvement, acute renal failure or extensive renal infarctions are exceedingly uncommon. We report a rare case of c-PAN manifested by bilateral renal infarctions on initial clinical presentation.

Case Description: A 40 year old man with no known medical issues presented to the emergency department with encephalopathy in the setting of one month of reported myalgia, fevers, chills, night sweats, and unintentional ten lb. weight loss. Upon physical examination, his vitals were 95.1°F, 101 beats/min, 145/101 mmHg, with no evidence of trauma or skin abnormalities. His lab results were notable for Cr 1.83 mg/dL, AST 247 U/L, ALT 136 U/L, Hbg 12.6 g/dL, WBC 24.1x10^9/L, and UA with hematuria and proteinuria. An extensive workup was completed, and his HIV, Hepatitis B and C, ANCA, Cardiolipin Ab, DRVVT, and ANA results were negative. TEE was normal. His ESR was 116 mm/hr, and he had transient worsening of his Cr (2.96 mg/dL) and Hbg (6.7 g/dL). CT/CTA revealed bilateral renal infarctions with perinephric and retroperitoneal hematomas, right renal artery aneurysm, thrombosis of one of three left renal arteries, and splenic hematoma, while MRI demonstrated a small parietal hematoma and thoracic intrathecal/epidural hemorrhage. He was initiated on monthly cyclophosphamide and prednisone. One month later, he had symptomatic resolution and a Cr of 1.89 mg/dL.

Discussion: Given his fulfillment of five American College of Rheumatology (ACR) criteria, he was diagnosed with c-PAN as a constellation of clinical findings can be used, and biopsy results are not always necessary, especially given the risk of hemorrhage. Although it is a rare condition, it is important to remain cognizant and consider c-PAN in the differential due to its significant implications and the importance of timely treatment.



Right Renal Artery Aneurysm and Renal Infarctions

PO1870

Clinical Predictors of Response to Rituximab in the Nephrotic Syndrome Study Network (NEPTUNE) Cohort

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Background: Rituximab, an anti CD20 monoclonal antibody, is one of the alternative medications offered to children and adults with Nephrotic syndrome. Despite the growing knowledge regarding this medication, there are still concerns regarding long-term safety that need to be considered prior to initiation of therapy. Given these risks there is a need to identify characteristics of patients who will respond best to rituximab therapy.

Methods: We identified all patients who received rituximab within NEPTUNE, a prospective study of adults and children with glomerular disease enrolled at the time of first biopsy or at initial presentation. Remission was defined as UPCR<0.3 mg/mg

after rituximab initiation. Kaplan-Meier plots and log-rank tests were used to compare the probability of response among various levels of demographic and clinical variables.

Results: Of 734 patients enrolled in NEPTUNE, 57 (34 adult, 23 pediatric) received rituximab after enrollment and were eligible for analysis. In the adult cohort, average age at initiation was 45.8 (SD=15.4), majority were male (79%) and white (88%) and diagnosed with membranous nephropathy (MN) (74%). In the pediatric cohort, most had Minimal change disease (MCD) disease on biopsy or nephrotic syndrome not specified (not biopsied) (NSNS) (83%), mean age was 6.96 yrs (SD=4.25), 57% were male, and 74% were white. Remission was achieved in 18 (53%) adults and children 19 (83%) respectively, with median time to remission of 25.4 months and 4.8 months respectively. Probability of achieving remission was higher in patients with MCD/NSNS compared to MN (p<0.001, Figure). Among patients with MCD/NSNS, probability of remission was higher in <6 yrs. vs. ≥6 yrs. and adults (p=0.036).

Conclusions: Rituximab response rate in patients with MCD/NSNS were higher and quicker than in those with MN. Young children with MCD/MSNS had the highest rates of response. Future work is now targeted at identifying additional biomarkers (specifically lymphocyte profile) to predict response to rituximab.

Funding: NIDDK Support, Private Foundation Support

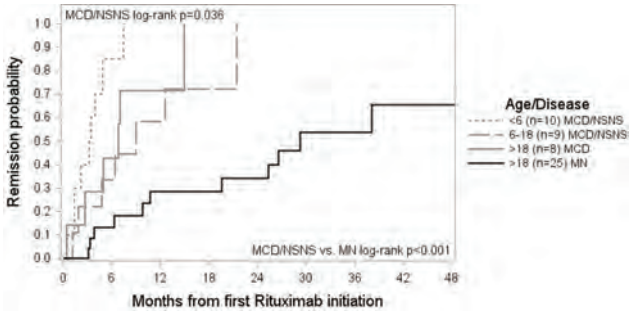

Figure: Remission probability by age and disease diagnosis.

PO1871

Tobacco Exposure in the Nephrotic Syndrome Study Network (NEPTUNE)

Linda Wang,[2] Kevin E. Meyers,[1] Christine B. Sethna.[2] NEPTUNE Cardiovascular Working Group *[1]The Children's Hospital of Philadelphia, Philadelphia, PA; [2]Cohen Children's Medical Center, Queens, NY.*

Background: Tobacco exposure is associated with cardiovascular disease (CVD) risk and chronic kidney disease (CKD) progression. Risks of tobacco exposure in proteinuric glomerulopathies are not known. The objectives were to describe the prevalence of tobacco exposure and determine the longitudinal associations between tobacco exposure and CVD risk factors and kidney outcomes in adults and children with proteinuric glomerulopathies in NEPTUNE.

Methods: Tobacco exposure was self-reported at study enrollment as non-smoker, active smoker, past smoker and passive smoker. Baseline characteristics were compared by t-test, ANOVA and chi square. Using adjusted generalized estimating equations and time-varying Cox survival analysis, tobacco exposure was analyzed for association with blood pressure (BP), lipids, urine protein:creatinine ratio (UPCR), glomerular filtration rate (eGFR), complete remission (UPCR <0.3), kidney failure (eGFR <15 or Kidney Replacement Therapy [KRT]) and CKD progression (40% eGFR decline and eGFR <90, or KRT).

Results: Included were 371 adults (45.9±16.0 yrs.; 60.6% M; 23.0% black, eGFR 66.4 [IQR 42, 91]) and 192 children (9.8±5.0 yrs; 57.3% M; 39.4% black, eGFR 93.1 [IQR 78,114]) with median 45 (IQR 27,55) months of follow up. Among adults, there were 14.6% active smokers, 29.1% past smokers and 4.9% passive smokers. In children, percentages were 0.5%, 1.6%, and 16.7%, respectively. In adults, there were significant differences in age, sex, race, and employment among groups. In children, non-smokers were significantly older than passive smokers (10.1±4.9 vs 8.0±4.9, p<0.01). Tobacco exposure was associated with greater total cholesterol in adults and UPCR in children in adjusted models (Table).

Conclusions: In NEPTUNE, tobacco exposure was associated with higher levels of cholesterol in adults and proteinuria in children.

Funding: NIDDK Support

Table. Association of Tobacco Exposure with Cardiovascular Risk Factors and Kidney Outcomes in Adjusted Regression Models*

Reference Non-Smokers	Adult Active Smokers			Pediatric Passive Smokers		
	OR (95% CI)		p value	OR (95% CI)		p value
Hypertensive BP	0.51 (0.22, 1.16)		0.11	1.26 (0.84, 1.90)		0.26
Dyslipidemia	1.29 (0.78, 2.13)		0.32	Failed to Converge		
	β (95% CI)		p value	β (95% CI)		p value
Systolic BP (mmHg)	1.26 (-1.21, 3.72)		0.32	0.383 (-1.88, 2.61)		0.75
Diastolic BP (mmHg)	0.43 (-2.05, 2.91)		0.73	0.01 (-2.00, 2.01)		0.99
HDL (mg/dl)	0.00 (-3.75, 3.75)		1.00	1.34 (-6.04, 8.71)		0.72
LDL (mg/dl)	7.12 (-4.01, 18.24)		0.21	-6.79 (-29.78, 16.21)		0.56
Triglycerides (mg/dl)	3.41 (-31.02, 37.84)		0.58	-21.86 (-59.13, 15.40)		0.25
Total Cholesterol (mg/dl)	17.91 (0.06, 35.76)		0.049	-38.85 (-87.21, 9.51)		0.12
UPC (g/g)	0.39 (-0.09, 0.87)		0.12	1.23 (0.13, 2.33)		0.03
eGFR (ml/min/1.73m^2)	3.06 (-2.96, 9.07)		0.32	4.13 (-2.52, 10.78)		0.22
	HR (95% CI)		p value	HR (95% CI)		p value
Complete remission	N=184	0.86 (0.70, 1.05)	0.13	N=127	1.00 (0.79, 1.27)	0.98
CKD progression	N=82	1.24 (0.91, 1.68)	0.17	N=36	0.71 (0.48, 1.04)	0.08
Kidney failure	N=30	0.82 (0.51, 1.32)	0.41	N=2	-	-

* Models were adjusted for age, sex, weight status, black race, glomerular diagnosis, UPC, log eGFR and steroids. Exceptions: UPC model did not include UPC, eGFR model did not include eGFR. Kidney Failure adjusted only for age and sex due to N of outcome in adults. Kidney failure not performed in children due to small N. CKD progression in children adjusted for age and sex due to N.

PO1872

Validating a Computable Phenotype for Nephrotic Syndrome in Children and Adults Using PCORnet Data

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Background: Primary nephrotic syndromes (pNS) are rare diseases which can be a barrier to adequate sample size for observational patient-oriented research. A computable phenotype may be powerful in identifying patients with these diseases for research while leveraging data from millions of patients in the PCORNet Common Data Model (CDM).

Methods: A comprehensive algorithm of ICD-9 and ICD-10 codes indicative of pNS was developed based on prior work in the University of Michigan Health System. Cases of pNS were defined as subjects that were seen for at least one encounter with more than 1 NS code, and did not have codes for diabetes mellitus, systemic lupus erythematosus, or amyloidosis. Non-cases were individuals not meeting case criteria who were seen in the same calendar year and within 2 years of age of a case. The algorithm was executed against the PCORNet CDM at 3 institutions from Jan 1, 2009 to Jan 1, 2018, where a random selection of 50 cases and 50 non-cases were reviewed by a nephrologist, for a total of 150 cases and 150 non-cases reviewed. The classification accuracy (sensitivity, specificity, positive and negative predictive value, F1 score) of the computable phenotype was determined.

Results: The algorithm identified a total of 2,708 patients with NS from 4,305,092 distinct patients in the CDM at all sites. For all sites, the sensitivity, specificity, PPV, and NPV of the algorithm were 99.1%, 81.0%, 76.7%, and 99.3%, respectively. The accuracy of the algorithm was 88.0% with an F1 score of 86.5%. The most common cause of false positive classification was secondary FSGS (17/35), followed by class V lupus nephritis (9/35).

Conclusions: While prior computable phenotypes for glomerular diseases have used IMO and SNOMed codes, this computable phenotype had good classification in identifying both children and adults with pNS utilizing only ICD-9 and ICD-10 codes, which are universally available. This may facilitate future screening and enrollment for research, however further refinements to the algorithm or addition of natural language processing may help better distinguish primary and secondary FSGS.

Funding: NIDDK Support, Other U.S. Government Support

2 x 2 Computable Phenotype Classification Table

		True Status	
		Primary NS	Not primary NS
Predicted Status	Primary NS	115	35
	Not primary NS	1	149

Data from all 3 health systems

PO1873

Family History of Diabetes Is Associated with Progression of Kidney Disease: The CureGN and CRIC studies

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Background: Family history (FHx) of complex traits may reflect shared genetic/environmental risk. We studied associations of FHx with presentation patterns, comorbidities and renal disease progression in a prospective cohort of primary GN and one of non-GN chronic kidney disease(CKD).

Methods: The Cure Glomerulopathy Network(CureGN) is a prospective multi-center study of patients(N=2474-median age 29 years)with biopsy-proven GN. Associations of self-reported FHx of diabetes(DM), cancer(C), clotting disorders(CD), and autoimmune diseases(AD) with eGFR and comorbidities prevalence were studied with multivariable regression models. We investigated associations of FHx and end-stage renal disease/50%eGFR decline(ESRD/50%eGFR) with multivariate Cox models. The Chronic Renal Insufficiency Cohort (CRIC) Study, a multi-center prospective study of 3939 adult(median age 59 years)CKD patients, was used for replication.

Results: FHx of DM predicted lower eGFR at diagnosis(p=0.002) in CureGN. Figure 1 summarizes associations of FHx of complex traits with comorbidities in CureGN. FHx of DM was associated with higher odds of DM(OR 1.56, 95%CI 1.16-2.09, p=0.003)in the subgroup of CRIC with no DM at baseline. After adjustment for relevant covariates, FHx of DM was associated with higher risk of the composite outcome of ESRD/50%eGFR reduction in both CureGN (HR 1.43, 95%CI 1.06-1.94, p=0.02) and CRIC (HR 1.15, 95%CI 1.01-1.31, p=0.038).

Conclusions: FHx of complex traits are associated with specific comorbidities. FHx of DM identifies patients with lower eGFR and disease progression. In conclusion, FHx could be an additional parameter for risk stratification and management of CKD.

Funding: NIDDK Support

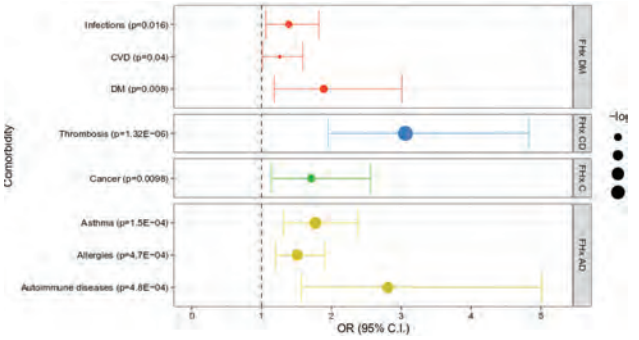

Figure1:FHx and comorbidity prevalence in CureGN. CVD: cardiovascular disease.

PO1874

Proteinuria Selectivity Index as a Predictor for Response to Therapy in Nephrotic Syndrome

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Background: Minimal change disease (MCD) is the most frequent cause of primary nephrotic syndrome (NS) in Japan. The response to steroid therapy is highly sensitive, and remission rates are over 90% in patients with MCD. However, recurrence rates are also high. Selectivity index (S.I.) of proteinuria using clearance ratio of IgG to transferrin is commonly used for initial examination to differentiate MCD. Whereas, there is no useful index of predictor for response to therapy in nephrotic syndrome. In present study, we evaluated clinical markers to predict the treatment response.

Methods: Of the 94 patients with NS who were performed renal biopsy in our hospital from 2013 to 2019, 60 patients with primary nephrotic syndrome were divided into complete remission group and incomplete remission group by initial treatment response. We examined whether clinical markers including eGFR, serum albumin and S.I. can predict initial treatment response. We further examined the association between S.I. and risk of relapse in patients with MCD.

Results: Forty-five of sixty patients with primary NS were complete remission group. In complete remission group, the incidence of MCD, idiopathic membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis (MPGN) were 75%, 16%, 7%, and 2%, respectively. The S.I. was significantly lower in the complete remission group than in the incomplete remission group (P<0.01). And, the S.I. in the complete remission group was less than 0.2 in any underlying diseases. Thus, regardless of the primary underlying disease, NS patients with low S.I. may have high remission rate after initial prednisolone (PSL) therapy. In patients with MCD, the relapse group showed the higher level of urine IgG and transferrin compared with the remission maintenance group (P<0.05), although the level of S.I. was the same degree. The remission rate and recurrence rate were not correlated with age, levels of serum albumin, creatinine, eGFR, IgG or urinary protein.

Conclusions: Regardless of the causal diseases of NS, the patients with S.I. less than 0.2 have good response to PSL treatment. Moreover, it is suggested that S.I. as well as levels of urinary IgG and transferrin may be useful to assess the risk of recurrence in patients with MCD.

PO1875

Fractional Excretion of Total Protein in Nephrotic Syndrome

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Background: Lower estimated glomerular filtration rate (eGFR) and higher proteinuria are the most sensitive predictor of the development of progressive renal insufficiency in various glomerular diseases. Fractional excretion of total protein (FETP) calculated by dividing the total protein clearance by the creatinine clearance is tightly associated with both proteinuria and GFR. However, few studies have analyzed in glomerular diseases the FETP to evaluate their relationship with renal function and histologic lesions. This study aimed to evaluate the relationship between FETP and the clinical features and histologic lesions and to assess whether FETP predicts outcome in nephrotic syndrome (NS).

Methods: Subjects who exhibited NS with a histological diagnosis were retrospectively analyzed at the Jikei University School of Medicine Hospital, Tokyo, Japan, during biopsy performed between 2002 and 2018. We analyzed 24-h urinary protein excretion, FETP, and other clinicopathological findings at kidney biopsy. The FETP was determined by the standard clearance technique based on 24-h urine collection: FETP = (urinary total protein / serum total protein) / (urinary creatinine / serum creatinine) × 100.

Results: A total of 113 subjects with NS were identified (Age 53.7 ± 17.3 [mean ± SD] years old; Male 71.7%, eGFR 57.6 ± 27.7 mL/min/1.73m^2; urinary protein excretion 7.02 ± 3.67 g/day; minimal change nephrotic syndrome [n = 41]; focal segmental glomerular sclerosis [n = 10]; membranous nephropathy [n = 36]; diabetic nephropathy [n = 26]). FETP was significantly associated with eGFR (ρ = -0.65, P <0.01), urinary protein excretion (ρ = 0.58, P <0.01), interstitial fibrosis and tubular atrophy (ρ = 0.24, P <0.05), and glomerulosclerosis (ρ = 0.24, P <0.05). Interestingly, patients with diabetic nephropathy showed the highest level of FETP with the poor renal outcome, while membranous nephropathy revealed the lowest level of FETP.

Conclusions: These results suggest that FETP would be a useful marker combining the two predictors of the decline of renal function in NS showing increased glomerular protein permeability and decreased glomerular filtration function.

PO1876

Prediction of Morphological Lesions Using Various Glomerular Filtration Rate Equations in Patients with Primary Glomerulonephritis

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Background: Glomerular filtration rate (GFR) is generally accepted best overall index of kidney function. However, it remains controversial to use GFR as a marker of morphological lesions. **Aim.** To assess GFR equations as a predictor of chronic morphological lesions in patients with glomerulonephritis (GN).

Methods: 100 patients [48 female, age Me 39 (27; 54) years] with biopsy proven primary GN were included in the study (9%–minimal change disease, 28%–focal segmental glomerulosclerosis, 26%–membranous nephropathy, 37%–IgA-nephropathy). Serum creatinine was measured by enzymatic, serum cystatin C - immunoturbidimetric methods. GFR was estimated using creatinine clearance (CCr), MDRD, CKD-EPICr, CKD-EPICysC, CKD-EPICrCysC, full age spectrum (FASsCr) equations. Glomerulosclerosis (GS) was assessed quantitatively, tubulo-interstitial fibrosis (TIF), tubular atrophy (TA) - semi-quantitatively (0-lesions absent; 1-mild focal lesions; 2-moderate lesions; 3-diffuse lesions). All patients were separated consistently in two groups according to the degree of each morphological lesion: “mild” (GS<25% or TIF/TA=0-1), “severe” (GS≥25% or TIF/TA=2-3).

Results: Independently of estimating equation, GFR positively correlated (p<0,001) with GS, TIF, TA and was higher in patients with “mild” GS, TIF and TA (p<0,001). Based on the results of ROC-analysis patients were separated (p<0.001) in two groups using all equations according to the degree of morphological lesions (“mild” or “severe” GS, TIF and TA). Using comparison of AUC we found the significant difference between CCr and CKD-EPICr, CKD-EPICysC, CKD-EPICrCysC, between MDRD and CKD-EPICr, CKD-EPICrCysC equations in prediction of TIF, between CKD-EPICrCysC and FASsCr - in prediction of GS and no difference for all equations in prediction of TA (Fig. 1).

Conclusions: Independently of estimating equation, GFR is a good marker of morphological lesions in patients with primary GN. Our data shows that CKD-EPI equations, especially CKD-EPICrCysC, provide the highest diagnostic value in prediction GS and TIF.

Funding: Government Support - Non-U.S.

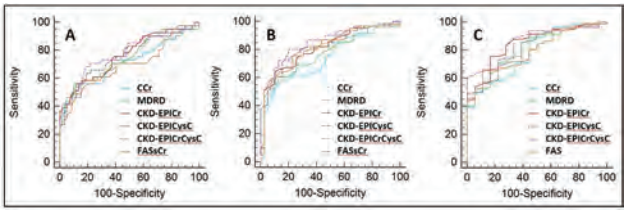

Fig. 1. ROC-curves of GFR equations for: A – GS; B – TIF; C – TA

PO1877

Fluid Overload and Markers of Cardiovascular Damage in Severe Nephrotic Syndrome

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Background: The purpose of the study was to evaluate the dimension of body water compartments and markers of cardiovascular damage in patients with severe nephrotic syndrome (SNS) defined as nephrotic range proteinuria and hypalbuminaemia ≤ 2.5 g/dl.

Methods: 40 patients with SNS and eGFR >30 ml/min/1.73m² formed the study group (SNSG) and 40 healthy volunteers without SNS matched according to age, sex, height, body mass, kidney function formed the control group (CG). Body water compartments were assessed using Body Composition Monitor, Fresenius Medical Care. For statistical analysis Spearman's correlation coefficients, chi² or Mann-Whitney U tests were used (Statistica v 13.1).

Results: SNSG included 28 males and 12 females, the mean daily proteinuria was 10.5±5.0 g. The groups are described in the table. In SNSG significantly higher hsTnT, NT-proBNP and extracellular water(ECW) were observed in comparison to CG. Intracellular water (ICW) was significantly lower in comparison to CG. Total body water (TBW) did not differ between the groups. Overhydration (OH) was higher in SNSG than in CG. Significant, positive correlation was observed between OH and NT-proBNP (R=0.56, p<0.0001) as well as hsTnT (R=0.60, p<0.0001). We did not observed significant correlation between ECW and NT-proBNP or hsTnT.

Conclusions: In SNSG fluid retention was associated with the increase in ECW and the decrease in ICW whereas TBW was the same in both groups. Such constellation can indicate for intracellular underhydration which was not describe so far. OH, which is a derivative of ECW, correlated with markers of cardiovascular damage and can be important for patients with resistant SNS and influence their prognosis.

Clinical characteristic of the study groups

	Severe Nephrotic Syndrome Group (SNSG)	Control Group (CG)	P
Gender	M: 28 (50%) F: 12 (30%)	M: 29 (72.5%) F: 11 (27.5%)	1.000
Age [years]	55 (30-64)	44 (30-64)	0.736
Height [cm]	170 ± 10	173 ± 10	0.173
Body weight [kg]	80.0 ± 15.5	77.5 ± 14.5	0.473
eGFR [ml/min/1.73m2]	73 ± 36	82 ± 27	0.382
Serum albumin [g/dl]	2.0 ± 0.4	4.6 ± 0.5	<0.0001
hs-TnT [ng/l]	18 (8-40)	6 (3-13)	0.0001
NT-proBNP [pg/ml]	294.8 (94-1033)	47.1 (33-168)	0.0003
TBW [L]	39.8 ± 8.6	38.8 ± 7.7	0.603
OH [L]	4.2 (3.0-6.6)	0.3 (-0.2-0.6)	<0.0001
ECW [L]	20.9 ± 5.2	17.4 ± 3.3	0.001
ICW [L]	18.9 ± 4.7	21.4 ± 4.8	0.034

PO1878

Glomerular Filtration Barrier Dysfunction in an RNA Virus-Induced Glomerulopathy Resembles Findings of Common Nephrotic Syndromes

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Background: Virally induced kidney dysfunction is highlighted by the alarming incidence of SARS-CoV-2 associated acute renal disease including nephrotic syndrome (NS). Plasma levels of soluble urokinase plasminogen activator receptor (suPAR) are elevated in COVID patients and provide prognostic insights. SuPAR is also involved in proteinuric kidney diseases such as focal segmental glomerulosclerosis in which podocytes effacement/injury is a common feature. Hantavirus-induced hemorrhagic fever with renal syndrome (HFRS) represents another RNA virus-induced disease with acute kidney injury and NS. The exact pathophysiology of proteinuria is, however, unclear. We hypothesized that hantavirus infection results in podocyte injury and a dysfunctional glomerular filtration barrier (GFB), similar to findings in common NS.

Methods: Renal biopsy specimens were analyzed by light and electron microscopy. Urinary nephrin and serum suPAR were measured over time in 26 patients with HFRS and 18 healthy controls.

Results: Hantavirus patients showed significantly increased urinary nephrin, immunoglobulin G (IgG), a1-microglobulin (a1-MG) and serum suPAR concentrations compared to healthy controls. Furthermore, nephrin and IgG levels were significantly higher in patients with severe than with mild proteinuria. Differences in a1-MG levels, however, disappeared after normalization to urinary creatinine. Urinary nephrin levels as a marker for podocyte damage correlated strongly with biomarkers of non-selective glomerular proteinuria. Interestingly, suPAR correlated significantly with urinary nephrin, IgG and albumin levels, suggesting suPAR as a potential pathophysiological mediator in GFB dysfunction in response to RNA virus infection. The main finding in microscopy analyses was a focal foot process effacement. Proteinuria and kidney dysfunction recovered autonomously in all patients.

Conclusions: Hantavirus infection causes a podocyte injury leading to GFB dysfunction. A better understanding of transient virally induced proteinuria syndromes and their often self-limiting disease character may generate new therapeutic approaches for NS.

PO1879

Nephrotic Syndrome from the Age of 65 Years: Epidemiological, Clinical, and Renal Biopsy Data

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Background: This study aims to evaluate epidemiological, clinical, and renal biopsy data of patients aged 65 or over with nephrotic syndrome, admitted in a University Hospital.

Methods: Retrospective cohort study of renal biopsies performed from 2012 to 2017, considering the age 65 years or over, with diagnosis of nephrotic syndrome, under follow-up at the Nephrology Department of the Hospital das Clínicas of the University of São Paulo.

Results: In these period 103 renal biopsies were performed in patients aged 65 or over, 45 (43.68%) of them were indicated by the diagnosis of nephrotic syndrome. These 45 patients had mean age of 70.60±5.24 years old, 60% male, laboratory data at diagnosis were median serum creatinine of 2.02±1.53 mg/dl, hemoglobin of 11.34±1.41 g/dl, serum albumin of 2.23±0.83 g/dl and proteinuria of 6.95±4.64 g/day. Only minor complications of renal biopsy were observed and occurred in 6.6% of cases. The most frequent histological lesion was Membranous Nephropathy in 13 cases (28.88%), followed by Renal Amyloidosis AL in 9 cases (20%), Focal Segmental Glomerulosclerosis (FSGS) in 8 (17.77%) highlighting that 4 patients had the Collapsing Form, Minimal Change Disease (MCD) occurred in 7 cases (15,55%) and the remaining 8 had others glomerular diseases. In Table 1 has the comparison between patients data according the glomerular disease. [Table]

Conclusions: Renal biopsy was a safe procedure and provided confirmation that Membranous Nephropathy was the most common histological lesion followed by Amyloidosis AL in aged 65 or over. Highlights the Collapsing glomerulopathy founded in 8.88% of the patients none of them associated with HIV or other disease. Minimal Change Disease was the only cause of nephrotic syndrome with acute tubular necrosis in this population, while FSGS had less vascular lesions at renal biopsy.

Funding: Private Foundation Support

Comparative data on diagnosis and after 6 months of follow up according glomerular disease.

Variable	Membranous Nephropathy n = 13	Amyloidosis n = 9	FSGS n = 8	MCD n = 7	P value
Age (years)	70.46±4.46	72±1.97	68,50±4.03	74±8.73	0.33
sCr (mg/dL) Inicial Final	1.45±0.84 1.77±0.89	2.30±2.17 5.69±2.29	2.01±0.86 2.75±2.41	1.75±1.23 1.20±0.47	0.36 0.02
Proteinuria (g/day) Inicial Final	7.49±4.41 3.03± 0.75	9.14±5.13 24.18±18.53	8.02±3.93 5.99±3.75	8.28±8.14 0.99±1.23	0,77 0.007
Histology ATN Vascular lesions TI fibrosis	0 (0%) 9 (69.2%) 3 (23%)	0 (0%) 9 (100%) 2 (22.2%)	0 (0%) 8 (100%) 3 (37.5%)	3 (42.8%) 7 (100%) 0 (0%)	0.002 0.04 0.37

sCr – serum creatinine; ATN acute tubular necrosis; TI tubules and interstice

PO1880

Clinical Characteristics, Treatment Patterns, and Outcomes of Children and Adults with Biopsy-Proven Minimal Change Disease from the Cure Glomerulonephropathy Network Study (CureGN)

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Background: The age of Minimal Change Disease (MCD) onset spans all ages. We analyzed the CureGN multi-center observational cohort study to elucidate differences in natural history and treatment patterns by age of MCD onset.

Methods: 567 participants enrolled within 5 years from kidney biopsy were available. Continuous variables are described as median [25,75 percentile] or n[%]. Univariate comparisons were performed using chi-square tests and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. eGFR was winsorized to 120 ml/min in repeated measures models used to assess eGFR over time.

Results: Comparisons by age group are shown in the Table. There were modest differences in the racial/ethnic composition and weight. Severity of proteinuria was similar at disease onset [6.1 vs 6.5, p-value=0.5] but higher in adults at biopsy (6.6 vs. 3.4, p-value=<0.001). At biopsy, eGFR was higher in children than adults (127.7 vs 88.6, p-value<0.001), and were more likely to have received immunosuppression prior to biopsy (58% vs. 18%, p-value<0.001). Compared to children, adults were more likely to report a history of HTN (29% vs 43%, p-value<0.001). Children were more likely to have frequently relapsing/steroid dependent disease than adults (51% vs. 29%, p-value <0.0001) and higher steroid resistant disease than adults (17% vs. 12%, p-value <0.0001). Over a median of 29.1 months follow up, ESKD occurred in 13 (2%) participants (8 children; 5 adults) and deaths occurred in 3 (1%) (1 child, 2 adult).

Conclusions: Significant sociodemographic and clinical differences exist between adult-onset versus pediatric onset MCD at the time of biopsy. These differences are most likely due to differences in treatment and biopsy practices relative to symptom onset.

Funding: NIDDK Support

TABLE

	Pediatric at Disease Onset (n=354)	Adult at Disease Onset (n=191)	P-value
Female, n(%)	140 (40%)	115 (60%)	<0.001
Age at Disease Onset (years)	4 (2-8)	43 (28-58)	
Age at Biopsy (years)	5 (4-11)	44 (29-58)	
Race, n(%)[a]			0.02
White/Caucasian	224 (63%)	134 (70%)	
Black/African American	69 (19%)	25 (13%)	
Asian	25 (7%)	23 (12%)	
Other	21 (3%)	4 (2%)	
Hispanic or Latino Ethnicity, n(%)[b]	44 (13%)	16 (8%)	0.2
Private Insurance Status, n(%)	143 (40%)	136 (71%)	<0.001
UPCR at Biopsy*	3.4 (0.5-8.6)	6.6 (2.8-10.06)	<0.001
UPCR at Diagnosis*	6.6 (2.1-12.2)	6.1 (2.4-10.0)	0.5
eGFR (mL/min/1.73m^2) at Biopsy**	128 (103-166)	88 (60-108)	<0.001
eGFR (mL/min/1.73m^2) at Diagnosis**	119 (95-154)	89 (59-109)	<0.001
Serum albumin (g/dL) at Biopsy***	2.4 (1.8-3.2)	2.2 (1.7-2.8)	0.07
Serum albumin (g/dL) at Diagnosis***	1.8 (1.4-2.4)	2.2 (1.7-2.8)	<0.001
Overweight/obese at Enrollment	188 (54%)	127 (69%)	<0.001
Hypertension History at Enrollment , n(%)	102 (29%)	82 (43%)	<0.001
Steroid Response Classification at Enrollment			<0.0001
Infrequently Relapsing	30 (8%)	29 (15%)	
Frequent Relapsing/Steroid Dependent	180 (51%)	55 (29%)	
Steroid Resistant	61 (17%)	22 (12%)	
Multi-drug resistant	7 (2%)	8 (4%)	
Untreated	20 (6%)	14 (7%)	
Unknown	56 (19%)	63 (33%)	
Any Immunosuppression prior to biopsy	202 (58%)	33 (18%)	<0.001
Corticosteroids prior to biopsy	170 (49%)	29 (16%)	<0.001
Calcineurin inhibitor prior to biopsy	41 (12%)	2 (1%)	<0.001
Rituximab prior to biopsy	8 (2%)	3 (2%)	0.8
Mycophenolate prior to biopsy	21 (6%)	2 (1%)	0.006

a. 3% missing, 22 pediatric and 4 adult; b. 2% missing 7 pediatric and 2 adult;
*missing at biopsy: 128 (36%) pediatric and 69 (36%) adult, missing at diagnosis: 221(62%) pediatric and 87 (46%) adult onset participants
**missing at biopsy: 81 (23%) pediatric and 50 (26%) adult, missing at diagnosis: 208(59%) pediatric and 89 (47%) adult onset participants
***missing at biopsy: 98 (28%) pediatric and 60 (31%) adult, missing at diagnosis: 215(61%) pediatric and 91 (48%) adult onset participants.
****Fishers exact test. GFR estimated using CKiD bedside (pediatric) and CKD-Epi (adults) equations, GFR's from both equations were averaged for participants between ages 18-26. UPCR collected from either a 24 hour, a 1st morning or a spot urine, depending on availability.

PO1881

Clinical Characteristics of Acute Glomerulonephritis with Presentation of Nephrotic Syndrome at Onset in Children

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Background: Acute glomerulonephritis (AGN) is a common disease in children, which placed a huge burden on developing countries. Prognosis of it may not always good. However, the clinical characteristics of AGN with nephrotic syndrome (NS) at onset were not fully clarified.

Methods: 113 cases were analyzed retrospectively. Clinical data, pathological results and prognosis between AGN with NS (AGN-NS) and AGN without NS (AGN-no-NS) were compared.

Results: 20 (17.7%) of 113 patients were AGN-NS. The patients with AGN-NS were more likely to have hypertension (55.0% vs. 25.8%) and acute kidney injury (AKI) (50% vs. 17.2%). The AKI was significantly related to the manifestation of AGN-NS in children (OR=3.812, *P*=0.040). Compared with the AGN-no-NS, the immunosuppressive treatments were more common in AGN-NS. A severer pathological grade was significantly related to the lower C3 fraction, estimated glomerular filtration rate (eGFR) and AKI, but not the performance of AGN-NS. There was no difference in prognosis between two groups.

Conclusions: The AKI was significantly associated with AGN-NS. The prognosis of AGN-NS and AGN-no-NS in our study was almost good. Given the fact that AGN-NS patients more likely to use the immunosuppressive therapy, the long-term outcome of AGN-NS is worth a further research.

PO1882

Estimation of Childhood Nephrotic Syndrome Incidence: Data from the Atlanta Metropolitan Statistical Area and Meta-Analysis of Worldwide Cases

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Background: There is limited epidemiological data on childhood idiopathic nephrotic syndrome (NS) in the United States. We estimated contemporary childhood NS incidence estimates in a racially and ethnically diverse U.S. population, and performed a meta-analysis of published reports to examine differences by race and ethnicity and changes over time.

Methods: Children 1-17 years-old diagnosed with NS in the Atlanta MSA between 1/1/2013 and 12/31/2018 were identified by chart review using practice data from the only pediatric nephrology practice in the region. Annual incidence rates were calculated by dividing the number of cases by population data provided by the Georgia Department of Public Health. We also performed a literature review for published childhood NS incidence and calculated pooled incidence estimates using random-effects regression models. Incidence estimates by race and ethnicity were compared by computing pooled estimates within each subgroup and testing for significant heterogeneity between subgroup estimates. We also reviewed U.S. incidence over time comparing pooled incidence estimates before and after 1984.

Results: 175 children aged 1-17y were diagnosed with NS between 2013-2018 in the Atlanta MSA. Incidence by race and ethnicity from the Atlanta MSA and meta-analysis demonstrated highest incidence in Asian children, followed by those of African descent, Hispanics and Caucasians (Table 1). Incidence in the U.S. was stable over time.

Conclusions: Risk for childhood NS development differs by race and ethnicity without changes over time. Future studies need to evaluate the underlying genetic and environmental factors associated with NS incidence.

Table 1. Incidence of childhood idiopathic nephrotic syndrome

Subgroup	Atlanta MSA, 2013 – 2018 (mean, 95% Confidence Interval)	Incidence Rate Ratio (p value)	Worldwide Meta-analysis (median, 95% Confidence Interval)	Q (p value)[a]
Overall	2.13 (1.83-2.47)	–	2.26 (1.99-2.54)	–
Caucasian	1.60 (1.24-2.02)	Reference	1.83 (1.52-2.14)	Reference
African Descent	2.47 (1.94-3.10)	1.55 (0.01)	3.53 (2.93 -4.12)	24.57 (<0.001)
Asian	5.04 (3.20-7.57)	3.15 (<0.001)	7.14 (4.73-9.54	18.37 (<0.001)
Hispanic [b]	2.13 (1.40-3.10)	0.99$ (>0.99)	–	–
	US incidence (median, 95% Confidence Interval)			Q (p value)[a]
Prior to 1985	2.05 (1.85-2.25)			Reference
After 1985	2.26 (2.14-2.37)			Q= 3.02 (0.082)

[a]Test of heterogeneity

[b]Compared to non-Hispanics

PO1883

Steroid Treatment for the First Episode of Childhood Nephrotic Syndrome: Comparison of the 8- and 12-Week Regimen Using an Individual Patient Data Meta-Analysis

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Background: Steroids are the cornerstone of the treatment of childhood nephrotic syndrome. The optimal duration for the first episode remains a matter of debate. The aim of this study is to determine whether the 8 weeks ISKDC regimen (prednisolone 4 weeks 60mg/m^2 daily, 4 weeks 40mg/m^2 on alternate days) is equally effective as the 12 weeks APN regimen (prednisolone 6 weeks 60mg/m^2 daily, 6 weeks 40mg/m^2 on alternate days).

Methods: An individual patient data (IPD) meta-analysis of randomized controlled trials reporting on prednisolone treatment for a first episode of childhood nephrotic syndrome was conducted. European trials aimed at investigating the ISKDC and/or APN steroid regimen were selected. Statistical models were adjusted for relevant covariates.

Results: Four trials included European patient cohorts treated according to the ISKDC and/or APN steroid regimen. IPD of two trials were available (PREDNOS, UK, 2019, n=109 and Nephrotic Syndrome trial, the Netherlands, 2013, n=62). Baseline characteristics did not significantly differ between the two treatment groups, with the exception of ethnicity. A significant difference was found in the time to first relapse after cessation of steroid treatment between the 8 and 12 weeks treatment group (p 0.04). The incidence of frequent relapsing nephrotic syndrome (FRNS) was similar in the two groups (p 0.75). Interestingly, a significant difference was found in the incidence of steroid dependent nephrotic syndrome (44% [8 weeks] vs 24% [12 weeks], p 0.01). Overall, relapse rate ratios were 51% higher in the 8 weeks group compared to the 12 weeks group (p 0.01). Finally, children below 4 years of age seem to have a significantly lower survival time (time to first relapse and time to FRNS) compared to children of 4 years and older (p 0.02 and p 0.003).

Conclusions: The results of this IPD meta-analysis suggest that the 8 weeks regimen for a first episode of nephrotic syndrome is not equally effective as the 12 weeks steroid regimen. Although less steroids for the first episode would be beneficial in terms of steroid toxicity in the short term, these results suggest patients treated with a 12 week steroid regimen may have a less complicated disease course.

Funding: Private Foundation Support

PO1884

Targeted B-Cell Depletion with Rituximab in Adult Relapsing Minimal Change Disease

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Background: Case series suggest use of rituximab is effective in treating adults with relapsing Minimal Change Disease (MCD). We previously reported rituximab to increase time in remission, however, the majority of patients did have further relapses. We thus studied the efficacy of retreatment with rituximab on B cell repletion for 2 years to prevent relapse.

Methods: Adult patients with recurrent MCD relapses were identified and treated with rituximab and monitored for lymphocyte depletion (total B-lymphocyte <10) with pre-emptive re-dosing after reconstitution was observed.

Results: 16 patients (8 female, 8 male) started B cell targeted maintenance rituximab for up to 2 years. At start of the maintenance period, 14/16 were on immunosuppression, tacrolimus (7) steroids (3), or both (4), stopped at a mean of 6.4 months (range 2-16 months). 15/16 patients re-dosed after reconstitution was observed. 1/16 received 6 monthly rituximab, without waiting for lymphocyte reconstitution, due to a history of rapidly relapsing disease. 16/16 achieved lymphocyte depletion post rituximab. 3/16 relapsed during the 2 year treatment period, 1/3 was B cell deplete at relapse, 2/3 were B cell replete at relapse having been deplete on their previous blood test. As of May 2020, 10/16, have completed 2 years treatment, with a mean follow up post treatment of 6.6 months (range 1 to 13.). Of these 3/10 have subsequently relapsed at mean time of

3.3 months (range 1-5), 2/3 were B cell replete at relapse. Rituximab was generally well tolerated, with no significant hypogammaglobinaemia or hospital admissions observed.

Conclusions: Targeting B cell depletion with rituximab is effective in maintaining remission of MCD. However, relapse can occur rapidly post repletion of lymphocytes, so frequent monitoring of lymphocyte subsets is required to ensure early retreatment upon reconstitution. An alternative strategy maybe pre-emptive rituximab dosing at fixed intervals. Even after 2 years of maintenance therapy, B cell repletion is still associated with relapse. Further work is needed to compare maintenance strategies and to determine the optimal length of time of maintenance rituximab.

PO1885

Belimumab for the Treatment of Frequently Relapsing Nephrotic Syndrome: The BELNEPH Study

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Background: A pathogenic role of B cells in pediatric idiopathic nephrotic syndrome (INS) has been suggested by the therapeutic efficacy of B-cell depletion, which however can impair immune memory. Belimumab treatment affects B-cell survival and differentiation but preserves the established immune memory. Its efficacy has been proven in other immune-mediated diseases, such as systemic lupus erythematosus and membranous nephropathy.

Methods: In this open-label, prospective, single-arm study, 5 children with frequently-relapsing INS who were on alternate-day prednisone only were enrolled. Belimumab was administered at 10 mg/kg i.v. on day 0, 14, 28 and then every 4 weeks for up to 12 months. Concomitant prednisone treatment was gradually tapered up to recurrence of NS if it occurred. Safety, efficacy and laboratory blood and urine parameters were monitored for the duration of the study.

Results: Four patients completed the primary endpoint (6 months) and 2 patients completed the study. Infusions were well tolerated. One patient experienced a pulmonary infection which required hospitalization 2.3 months after the first infusion. Four patients experienced a first relapse within 6 months (1.9, 2.5, 2.6, 3.3 months after starting treatment) and 1 patient 8.1 months from first infusion. Three patients discontinued the study due to the frequency of relapses (≥2) after 5.2, 9.2, 9.6 months, respectively, and were started on another steroid-sparing agent. The study was discontinued due to apparent lack of effectiveness. $CD19^+$ B cells decreased during the follow-up, with a nadir at 6 months (8.6% of lymphocytes vs 19.1% at baseline, $p<0.01$). Naïve B cells started to significantly decrease after 1 month (7.7% vs 12.4% at baseline, $p<0.05$) and continued to decline during the follow-up. In contrast, no significant impact was observed on memory B cells, which became the most representative B-cell subset already at 1 month (43.5% of B cells vs 27.3% at baseline, $p<0.01$), with an initial shift toward a switched subset (57.4% and 59.0% of memory B cells at 3 and 6 months, respectively, vs 48.3% at baseline, $p<0.01$). Serum IgG, IgA and IgM levels were not significantly modified.

Conclusions: Belimumab treatment in children with frequently-relapsing INS failed to modify disease course. Persistence of circulating memory B cells supports their pathogenic role in INS.

Funding: Private Foundation Support

PO1886

GFB-887, a TRPC5 Inhibitor, Is Safe and Well Tolerated and Engages the TRPC5 Target, Leading to Reductions in Urinary Rac1 in Healthy Subjects

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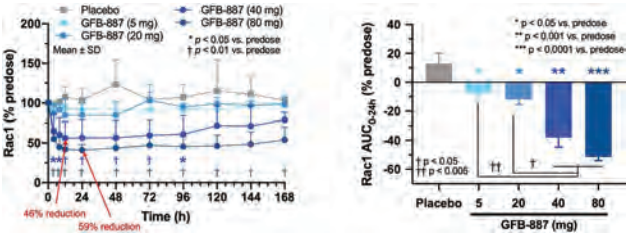
Background: Activation of the TRPC5-Rac1 pathway is a key driver of podocyte injury in focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and diabetic nephropathy (DN). Inhibition of the TRPC5 ion channel may be a potential therapeutic target for these disorders. GFB-887 is a sub-type selective, small molecule TRPC5 ion channel inhibitor that has been shown in preclinical models to prevent podocyte damage mediated by Rac1 activation. This is a first-in-human study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending doses (SAD) of GFB-887 in healthy subjects.

Methods: This is a phase 1, double-blinded, randomized, placebo-controlled, study in healthy subjects. The objectives were to characterize safety, tolerability, PK profile, and effects on urinary Rac1 after single oral doses of GFB-887. Subjects were randomized to either GFB-887 or placebo (8:2) in 5, 20, 40, 80,160, 320, and 900 mg SAD cohorts. Each subject received a single dose, had 24-hour urine collection pre and post-dose, and followed for 28 days post-dose.

Results: 70 healthy subjects (median age 43 years, 86% male, 56% Caucasians, 42% African Americans) were dosed with GFB-887. The most common adverse event (AE) was headache. All AEs were mild and non-serious. There were no clinically significant changes in ECGs, vital signs or laboratory results. Blood pressure was modestly and asymptomatically reduced at the highest doses. C_{max} and AUC of GFB-887 increased with higher doses in a less than dose proportionally manner through 900mg. Urinary Rac1 was significantly reduced from baseline with increasing doses of GFB-887.

Conclusions: Single doses of GFB-887 were well tolerated with a favorable PK profile in healthy subjects. GFB-887 exhibits dose-dependent reduction in urinary Rac1, a regulator of podocyte cytoskeletal structure and motility, indicating that GFB-887 engages and inhibits the TRPC5-Rac1 pathway. The safety and efficacy of GFB-887 is currently being evaluated in patients with FSGS, MCD, and DN (NCT04387448).

Funding: Commercial Support - Goldfinch Bio



PO1887

Phase 1 Study of N-Acetylmannosamine (ManNAc) for Glomerular Disease

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Background: ManNAc is an uncharged monosaccharide and precursor of N-acetylneuraminic acid (NeuAc, sialic acid). It provides anionic charges to proteins, including those constituting the glomerular filtration barrier. Glomerular hyposialylation is common in nephrotic diseases and may contribute to podocyte foot process effacement and increased protein permeability. ManNAc showed benefit in nephrotic mouse models.

Methods: We performed a phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of single and multiple doses of ManNAc in nephrotic subjects (NCT02639260). Seven subjects were enrolled, 6 with focal segmental glomerulosclerosis and 1 with membranous nephropathy. Urine protein/creatinine ratio was 1.3 to 9.9 l g/g and estimated glomerular filtration rates were 29 to 89 ml/min/1.73m2. Six subjects completed a 11-day inpatient stay, receiving a 3 g single ManNAc dose, followed by 5 days 1.5 g twice daily. One subject received a single dose of 6 g ManNAc.

Results: ManNAc administration was well-tolerated. There were no serious adverse events. Most subjects (5 of 6) that received ManNAc twice daily showed a marked reduction in urine PCR (26-54%), which correlated with the degree of glomerular hyposialylation. Baseline plasma ManNAc levels in nephrotic subjects with normal eGFR were similar to those in subjects with normal renal function, but baseline plasma free NeuAc levels were elevated in nephrotic subjects with lower eGFR. This is consistent with NeuAc having high glomerular permeability and little tubular reabsorption. Plasma ManNAc levels peaked 2-4 h after dosing and returned to baseline after ~12h. Plasma free NeuAc levels peaked ~10h after dosing, remained elevated beyond 48h, and continued to increase during twice daily dosing, particularly in subjects with low eGFR. There appeared to be no adverse effects with increased free sialic acid levels, but confirmation is needed. These data support twice daily dosing, with reduced doses for subjects with low eGFR.

Conclusions: Oral ManNAc was safe and well tolerated in glomerular disease subjects. ManNAc supplementation showed a trend towards proteinuria reduction, possibly linked to the degree of glomerular hyposialyation. A phase 2 study is planned, to include assessment of longer-term pharmacokinetics, efficacy and safety.

Funding: NIDDK Support, Other NIH Support - NHGRI, Commercial Support - Escala Therapeutics

PO1888

Efficacy and Safety of ACE Inhibitor and ARB Therapies in Primary FSGS Treatment: A Systematic Review and Meta-Analysis

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Background: Use of ACEi and/or ARB (RASi) as conservative management to control proteinuria in primary and genetic focal segmental glomerulosclerosis (FSGS) follows guideline recommendations based on other proteinuria-related kidney diseases. There is lack of consensus about the efficacy and safety of RASi therapies in primary and genetic FSGS, thus this systematic review aims to assess the benefits and risks of RASi therapies on renal outcomes in these patients.

Methods: English-language studies were searched in MEDLINE, Embase and Cochrane Central Register of Controlled Trials, from inception to April 2019. Cohort studies assessing efficacy (response to treatment and indicators of renal function) and safety outcomes in primary and genetic FSGS were selected. Study results were summarized as Ratio of Means (ROM) between baseline and follow-up measurements, or as Hazard Ratio (HR) using random effects models.

Results: We selected 30 studies of which only 5 were controlled trials. Only 8 assessed RASi as monotherapy while the rest studied them in combination with other drugs, mainly immunosuppressants (IS). On average, a 32% reduction on proteinuria (ROM=0.68; 95% CI: 0.47-0.98) and no change on CrCl (ROM=0.95; 95% CI: 0.77-1.16) from baseline to variable follow-up periods was observed in patients treated with RASi therapy alone. A reduction of 72% in proteinuria was observed when RASi were combined with other drugs, mainly IS (ROM=0.24, 95% CI: 0.08-0.75). Published data did not allow to evaluate the eGFR ROM between follow-up and baseline and the

effect on the risk of reaching ESRD of RASi therapy alone. Only one controlled study reported adverse effects of RASi as monotherapy. Overall, the available evidence exhibits considerable heterogeneity in cohort baseline characteristics and study design.

Conclusions: This review supports the tendency to observe a reduction of proteinuria in patients treated with RASi, and demonstrates the lack of strong evidence to quantify their effect on eGFR and their long-term impact on renal survival. The current lack of properly controlled studies in primary FSGS stresses the need for larger and better designed clinical trials to better understand the effect of RASi.

Funding: Commercial Support - Retrophin, Inc.

PO1889

Efficacy and Safety of Immunosuppressive Therapy in Primary FSGS: A Systematic Review and Meta-Analysis

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Background: Focal segmental glomerulosclerosis (FSGS) is a rare condition which can lead to decline in renal function and progression to ESRD. Immunosuppressants (IS) are often used to treat primary FSGS. However, their efficacy and safety is not clearly established. The objective of this work was to assess the current knowledge on the clinical effectiveness and safety of IS in the treatment of primary FSGS.

Methods: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched for English-language studies on primary FSGS from inception to 2019. Clinical outcomes of interest were changes from baseline in proteinuria, and renal function (eGFR or CrCl) and survival (ESRD, renal failure, doubling of creatinine, or author reported). When possible, study results were summarized using random effects models as Ratio of Means (ROM) between follow-up and baseline measurements or as Hazard Ratio (HR).

Results: We included 100 articles. Substantial heterogeneity was observed in patient baseline characteristics and study design. Most studies assessed treatment with corticosteroids alone or combined with other drugs, mainly other IS. On average, patients treated with IS showed a reduction of proteinuria (14 studies, ROM=0.34; 95% CI 0.25-0.46). Pooled studies showed a lower CrCl at the end of the follow-up compared to baseline (ROM=0.77; 95% CI 0.71-0.83). In contrast, eGFR measurements suggested no change from baseline to follow-up (16 studies, ROM=0.92; 95% CI 0.84-1.01). IS therapy had uncertain effect on reducing the risk of reaching ESRD (HR=0.79; 95% CI 0.47-1.32). Hypertension and infections were the most commonly reported AEs.

Conclusions: This systematic literature review supports that patients treated with IS have on average, a reduction in proteinuria between baseline and varying follow-up periods. Reported changes from baseline to follow-up in CrCl and eGFR are contrasting and effect of IS on renal survival is uncertain. However, due to lack of properly controlled studies, it is hard to attribute how much of these outcome are due to IS treatment effect, stressing the low certainty evidence currently available in the literature and the need for better designed studies to reliably assess the effect of IS on primary FSGS patients.

Funding: Commercial Support - Retrophin, Inc.

PO1890

The Epidemiological Comparison Between North American and Japanese FSGS/Minimal Change Disease Patients

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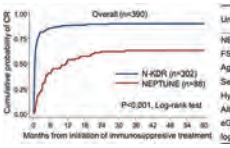
Background: Few studies directly compared the presentation and treatment response of nephrotic syndrome (NS) considering the racial and ethnic differences of different countries.

Methods: NEPTUNE is a prospective cohort study of NS across 23 North American centers. Nagoya Kidney Disease Registry (N-KDR) is a Japanese retrospective cohort in Nagoya area. Nephrotic FSGS/MCD adults who received immunosuppressive therapy (IST) were included. Demographics and laboratory data of the patents were compared. Time to complete remission (CR: UPCR<0.3) from the start of IST were evaluated using Kaplan-Meier method. The common predictors for CR among both cohorts were evaluated by Cox proportional hazard model and selected using a backward stepwise method.

Results: Eighty-eight NEPTUNE and 302 N-KDR cases were eligible. The median of follow-up was 35 and 47 months in NEPTUNE and N-KDR, respectively. In NEPTUNE, 20.7% were African Americans and 26.1% were Hispanic. NEPTUNE had higher proportion of FSGS (55.7 vs. 16.2%, p<0.001). N-KDR cases were older (55 vs. 43 years, p<0.001) and showed more rapid NS onset (0.8 vs. 1.5 months, p=0.004). NEPTUNE cases demonstrated lower level of UPCR (4.20 vs. 8.00, p<0.001) and hypoalbuminemia (2.6 vs. 1.8 mg/dL, p<0.001). In both cohorts, >85% started on steroid monotherapy. In NEPTUNE, only 1% of patients changed within first 28 days as compared to 10% of N-KDR patients. N-KDR cases showed higher proportion of CR in overall sample (89.7 vs. 62.5%, p<0.001), FSGS (67.4 vs. 42.9%, p=0.015) and MCD (94.1 vs. 87.2%, p=0.113). Multivariate analysis showed associations of FSGS (HR=0.65, 95%CI: 0.52-0.81), hypertension (HR=0.64, 95%CI: 0.45-0.90), serum albumin (HR=0.62, 95%CI: 0.45-0.85) and eGFR (HR=1.24, 95%CI: 1.17-1.32, for 10 mL/min/1.73m^2) with time to CR. There were significant interactions between the cohort and hypertension (p=0.008), albumin (p=0.030) and eGFR (p<0.001).

Conclusions: Adult nephrotic FSGS/MCD in the North American cohort showed diverse ethnical background and less severe NS. Japanese patients had a higher rate of response to the IST. FSGS, hypertension, higher albumin, and lower eGFR were considered as shared predictors of poor treatment response between both cohorts.

Funding: NIDDK Support, Other NIH Support - NCATS



Univariate		Overall			NEPTUNE			N-KDR		
		HR	[95%CI]	P-value	HR	[95%CI]	P-value	HR	[95%CI]	P-value
NEPTUNE	(vs. N-KDR)	0.32	[0.23-0.42]	<0.001						
FSGS	(vs. MCD)	0.50	[0.43-0.59]	<0.001	0.52	[0.40-0.69]	<0.001	0.57	[0.48-0.69]	<0.001
Age	(every10)	0.96	[0.91-1.02]	0.23	1.14	[0.96-1.36]	0.123	0.83	[0.78-0.89]	<0.001
Sex	(male)	1.26	[1.01-1.57]	0.043	1.58	[0.93-2.69]	0.091	1.28	[1.00-1.63]	0.048
Hypertension		0.46	[0.36-0.58]	<0.001	0.70	[0.41-1.19]	0.181	0.43	[0.33-0.55]	<0.001
Albumin		0.70	[0.59-0.81]	<0.001	0.93	[0.68-1.27]	0.66	0.81	[0.65-1.01]	0.063
eGFR	(every10)	1.10	[1.08-1.14]	<0.001	1.06	[0.98-1.15]	0.168	1.17	[1.12-1.22]	<0.001
log_UPCR		1.08	[0.96-1.22]	0.21	0.73	[0.59-0.90]	0.004	0.82	[0.68-1.01]	0.064

PO1891

Long-Term Renal Outcomes in Focal Segmental Glomerulosclerosis

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Background: Focal Segmental Glomerulosclerosis (FSGS) is a glomerular disease defined by pathognomonic histopathology but is caused by multiple mechanisms of disease, not all of which have been fully elucidated. Therefore, the reported renal prognosis, treatment strategies, and treatment response has varied significantly in previous small case series. We sought to analyze long term renal survival and associated risk factors in the largest cohort over the longest period of follow up described to date.

Methods: We performed a retrospective cohort study on all previous and current active duty military with biopsy proven FSGS. Potential cases were identified through query of the military electronic medical record for International Classification of Diseases 9 and 10 codes (581.1, 582.1, and N04) and then confirmed by comprehensive chart review. Extensive data collection was performed and then analyzed using STATA 16.

Results: We identified 348 patients with biopsy proven FSGS with a mean follow up of 9.5 years. The majority were black, male, and under 40 years old. Progression to end stage kidney disease (ESKD) was 14%, 25%, and 35% at 5 years, 10 years, and 15 years after diagnosis, respectively. More patients with nephrotic range proteinuria progressed to ESKD (20%, 31%, and 49% at 5, 10, and 15 year follow up, respectively) than non-nephrotic range proteinuria (13%, 20%, and 31% at 5, 10, and 15 year follow up, respectively), and no significant proteinuria (6%, 14%, and 23% at 5, 10, and 15 year follow up, respectively); p=0.04. Overall progression to stage 3 chronic kidney disease (CKD3) was 32%, 40% and 50% at 5, 10, and 15 years after diagnosis, respectively. Full remission from initial treatment was associated with a substantial reduction in progression to ESKD (2%, 4%, and 7% at 5,10, and 15 years follow up, respectively) compared to partial remission (12%, 21%, and 30%) and no remission (27%, 45%, 63%), p<0.001.

Conclusions: We present the largest cohort of biopsy proven FSGS cases over the longest follow up period to date. Approximately one third of all FSGS patients develop ESKD and one half developed CKD3 within 15 years. Proteinuria significantly increased the risk of progression to ESKD. Achieving a full or partial remission after initial treatment significantly decreased the risk of progression to ESKD.

PO1892

Cellular Senescence Is Associated with Faster Progression of Renal Disease in Adults with Focal Segmental Glomerulosclerosis: A 6-Year Prospective Cohort Study

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Background: A current hypothesis is that an acceleration of cellular senescence, a state of irreversible cell cycle arrest mediated by cyclin-dependent kinase inhibitors, is involved in impaired renal repair and in the progression of renal diseases. The functional role of the senescent changes observed in patients with glomerular diseases are unknown and if senescence is really associated with more disease progression is still not understood.

Methods: The hypothesis that cell senescence represents a proximate mechanism by which the kidney is damaged in focal segmental glomerulosclerosis (FSGS) was investigated in 26 consecutive kidney biopsies from FSGS patients (Age 50 ± 3, M/F 12/14, eGFR 72 ± 3.7, proteinuria 2.3 ± 0.6) who were incident in a Northern Italy Nephrology Centre. All biopsies were classified as the not otherwise specified (NOS) FSGS subtype.

Results: Cell senescence (p16INK4A, SA-b-galattosidase stains) was upregulated both in glomeruli (mainly in podocytes) and tubule cells in FSGS as compared to controls (p<=.05-0.01). Tubular p16INK4A correlated with tubulointerstitial fibrosis. Baseline proteinuria, eGFR, interstitial fibrosis and p16INK4A expression in the tubular compartment were associated with eGFR loss at follow up (6.5 ± 2 years). In multiple regression analysis, loss of renal function was predicted by interstitial fibrosis and tubular p16INK4A only. No association with faster eGFR decline was observed for SA-b-galattosidase stain.

Conclusions: These results indicate that an elevated cell senescence rate at the time of initial biopsy represents an independent predictor of progression to ESRD in adult patients at an early stage FSGS.

PO1893

Clinicopathologic Characterization of Focal and Segmental Glomerulosclerosis in a Dominican Republic Sample

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Background: There are limited recent epidemiological and clinicopathological behavior reports on FSGS in the Caribbean population. The aim is to identify clinical characteristic, epidemiological trend and treatment response of patients with diagnosed FSGS and their different variants in a Dominican Republic sample

Methods: Cross-sectional study of performed transcutaneous native kidney biopsy taken in an interval date from years 2018-2019 of two separate nephrology consult from Dominican Republic. Diagnosed FSGS biopsy reports availability and biochemical laboratories (creatinine, BUN, 24h Proteinuria, cholesterol, triglycerides, hematuria) within the date of biopsy were analyzed. Histopathological analysis of foot process effacement (FPE) degree reported and nephrotic syndrome (NS) presentation was correlated to primary or secondary cause of FSGS. Also, description of FSGS variants response to the different treatments implemented at the time of data collection, overlapping comorbidities and serology were taken in notice

Results: 49 biopsies were analyzed with FSGS. NOS variant was the most common (72%), tip lesion (6%) and collapsing (6%), with no reported perihilar or cellular variants and (16%) reported as unsampled biopsy of FSGS. Biopsy with diffuse FPE (>80%) 24 presented with nephrotic syndrome and 8 did not (p= 0.010). Remission in biopsy with described diffuse foot process effacement (DFPE) with unidentified cause 32% had complete remission (CR) (serum albumin >3.5g/dl or <300 mg/24h protein), 16% had partial remission (PR) (≥50% reduction basal proteinuria, subnephrotic proteinuria), and 20% did not remitted at a ≥ 6 month period (p=0.921). Steroids and calcineurin inhibitors treatment were significantly associated with CR in FSGS with DFPE with unidentified cause (p=0.029, p=0.014 respectively)

Conclusions: Biopsies analyzed in a 2 year period presented NOS as the most common variant while perihilar or cellular variants were not reported. In the sample studied the degree of FPE was associated to NS presentation. The use of steroids and calcineurin inhibitors in suitable patients is significantly associated with remission of disease. The FPE degree on biopsy, clinical manifestations of patients and history represent the best tools for correct diagnose and treatment

PO1894

Differentiating Focal and Segmental Glomerulosclerosis

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Background: FSGS is a histological pattern of kidney injury associated to broad causes and pathogenesis. FSGS can be primary, genetic or secondary to other conditions. Differentiating these subclasses is crucial for management and prognosis, but there is no biomarker for it and genetic testing is not suitable for all patients. Herein, we present a series of patients with FSGS classification based on clinical and histological criteria comparing outcomes.

Methods: In a retrospective analysis of 359 kidney biopsies were identified patients with FSGS histological diagnosis. Primary and secondary FSGS were identified based on clinical and histological data. Genetic FSGS was considered if they present at least one of the following:a)nephrotic syndrome (NS) resistant to corticosteroids;b)NS with normal serum albumin;c)NS with focal foot process effacement or d)non-nephrotic proteinuria with diffuse foot process effacement. Each group was divided in immunosuppression treatment (IST) or only supportive treatment (ST) groups. Renal and survival outcomes were assessed.

Results: Among 66 FSGS patients, 65% were males, 71% non-black, 74% had HTN, 26% diabetes; median eGFR 26.5mL/min/1.73m^2 (IQR 15.3-48.8), 24h-UProt 4.4g (IQR 2.5-7.6). Globally, 38% (n=25) progressed to ESKD and mean time to RRT was longer in IST group (p=0.37). According to the applied criteria 52% (n=34) were classified as having secondary FSGS, 23% (n=15) primary and 25% (n=17) as genetic FSGS. Among primary FSGS patients 40% received IST. In ST group 25% progressed to ESKD in a median time to RRT of 24 months (SD±31.7) *vs* 13% in 66mo (SD±93.3) in IST group. Among secondary FSGS, 17.6% received IST. Of them, 50% developed ESKD in 31.7mo (IQR SD±28.6) *vs* ST group with 46% progression to ESKD in 12mo (SD±28.7). From the genetic group 59% were in IST group and 30% progressed to ESKD in 12mo (SD±27.1) *vs* ST group with 29% ESKD in 42mo (SD±27.1).

Conclusions: FSGS etiology is not straightforward in most patients. Since IST can be inappropriate and potentially harmful in some FSGS subclasses, it is crucial to identify patients who are likely to benefit from such therapies, in order to obtain better outcomes. Most of genetic forms of FSGS do not respond to IST and have a rapid progression to ESKD. Therefore, in a suspicion of a genetic cause a genetic screening should be performed for appropriate management.

PO1895

APOL1 High-Risk Genotype Is Highly Prevalent Among Brazilian Patients with Collapsing Glomerulopathy, an Association That Manifests from Adolescence to Early Middle Adulthood

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Background: Collapsing glomerulopathy (CG) is associated with fast progression to ESKD. CG has been linked to specific infections, drugs and immune disorders, the *APOL1* high-risk genotype (HRG) and monogenic pathogenic variants.

Methods: 70 Brazilian patients of all ages with the diagnosis of idiopathic CG were submitted to *APOL1* genotyping and 51 of them to broad genetic evaluation through whole exome sequencing, a 62-gene panel directed to glomerulopathies or Sanger sequencing. Based on retrospective analyses of medical records, the frequency and clinical impact of HRG were analyzed.

Results: Thirty-three (47.1%) patients harbored an HRG. Monogenic pathogenic or likely pathogenic variants were identified in 5 *APOL1* low-risk genotype (LRG) individuals, affecting the *COL4A5* (2 cases), *COQ2*, *MYH9*, and *PLCE1* genes. Gender distribution did not differ between the HRG and LRG groups. Patients with HRG were less often self-declared Caucasian than LRG individuals (36.4% vs 89.2%, p<0.001). While the age of disease onset was not significantly different between the HRG and LRG groups [21 (17-33) vs 25 (18-31) years, p=0.755], patients harboring HRG manifested the disease from adolescence to early middle adulthood (10-44 years) more frequently than LRG individuals (97% vs 70.3%; OR=13.54, CI 2.01-150.00; p=0.004). HRG patients reported more often family history of renal disease than individuals with LRG (36.4% vs 10.8%, p=0.01). HRG patients, however, did not differ from individuals with LRG or with monogenic/likely monogenic etiologies with respect to hematuria, hypertension and eGFR decline. The transplant rate did not differ between patients with HRG and individuals with LRG without identified Mendelian disease, whereas the rate of disease relapse in the graft was significantly lower in the first group (0 vs 33.3%, p=0.02).

Conclusions: *APOL1* HRG is highly prevalent among Brazilian patients with CG, suggesting a common role of second hits in genetic-environmental interaction in the pathogenesis of this glomerulopathy. Our findings strongly suggest that HRG-associated CG is a disease that manifests primarily from adolescence to early middle adulthood.

PO1896

Collapsing Glomerulopathy and Vascular Lesions

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Background: Collapsing Glomerulopathy (CG) has usually been associated with rapidly progressive renal failure. Some authors have found that vascular injury could be associated with poor outcomes. The goal of the study was to compare patients with and without vascular lesion on renal biopsy

Methods: A retrospective analysis was performed on all CG cases diagnosed by kidney biopsy between 1996 and 2019 at the University of Sao Paulo. Clinical and laboratory data were collected at baseline and at the end of follow up. We excluded cases of chronic viral infection(8 HIV, 4 HCV, 2 HBV) drugs, any suspected immune-mediated disease(4 SLE) and diabetes(3). We analyzed histological, clinical and follow-up data and compared patientes with and without vascular lesions in biopsy.

Results: Clinical features of the groups with and without vascular lesions are summarized in Table 1. There was no significant difference in gender, albumin, proteinuria, among the two groups. Moreover, the immunofluorescence of the renal biopsies showed no difference in IgM and C3 deposits in glomeruli. Patients with vascular lesions were older and presented with worse renal function.

Conclusions: Vascular lesion in CG is associated with worse renal function and it is more prevalant in older adults.

Clinical Features of the groups with and without vascular lesions

	With Vascular Lesion(32)	Without Vascular Lesion (47)	P value
Age(years)	37.0±3.0	27.4±1.53	0.002
Male(n,%)	13(38)	25(48)	0.37
Creatinine (mg/dL)	3.2±0.39	1.8± 0.17	0.001
CKD-EPI baseline	45.0±6.9	64.5± 6.5	0.050
Proteinuria g/day	6.7±0.97	7.9±0.98	0.369
Albumin (g/dL)	2.4 ±0.17	2.0 ± 0.13	0.06
IgM positive (%)	27(55)	38(68)	0.296
C3 positive (%)	19(67)	27(71)	0.784
Interstitial fibrosis (n, %)	33(93)	52(80)	0.091
Creatinine at the end mg(dL)	5.1±1.0	5.9±1.6	0.64
Follow up (months)	28±10	61±11	0.04
CKD-EPI at the end	30±5.2	45±7.6	0.15

Data Showed as mean (±SD)

PO1897

The Dual Endothelin/Angiotensin II Receptor (ET_AR/AT_1R) Antagonist Sparsentan Slows Renal Disease, Improves Lifespan, and Attenuates Hearing Loss in Alport Mice: Comparison with Losartan and Atrasentan

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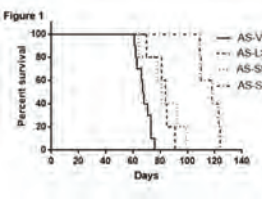
Background: In Alport syndrome (AS), ET_AR activation is important in renal and inner ear pathologies. Previously, sparsentan (SP) was shown to prevent increases in proteinuria, glomerulosclerosis, and glomerular basement membrane dysmorphology in AS mice. Here we compare the effect of SP, the AT_1R antagonist losartan (LS), and the ET_AR antagonist atrasentan (ATR) on lifespan and proteinuria, and of SP and LS on hearing loss and inner ear pathology.

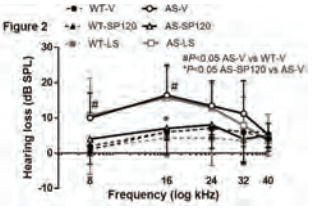
Methods: Wild type (WT) and AS mice were gavaged daily with vehicle (V), 60 or 120 mg/kg of SP (SP60, SP120), LS (20 mg/kg; 3-4 W) or LS (10 mg/kg from 4 W), or ATR (7.5 mg/kg females or 10 mg/kg males) in the drinking water. Two studies were conducted: early intervention for hearing from 3-8.75 W (V, SP120 and LS), and for lifespan with treatment from 3 W (V) or from 4 W (SP60, SP120, LS or ATR). Urinary protein/creatinine ratio (UP/C) was assessed weekly. The auditory brainstem response (ABR) was used to assess hearing ability and sensitivity to noise at 8-8.75 W. The cochleae were preserved and strial pathology determined by transmission electron microscopy.

Results: SP120 significantly ($P<0.05$) increased median lifespan compared to any other group (Figure 1). At 8 W, only SP120 significantly ($P<0.05$) attenuated the increase in UP/C compared to V (UP/C mg/mg mean±SD: 47±16 V; 31±6 LS; 42±18 ATR, 61±44 SP60; 20±3 SP120). UP/C at 11 W in SP120 mice was significantly attenuated ($P<0.05$) vs. LS mice. SP120 significantly improved post-noise ABR thresholds at 16 kHz vs. V mice ($P<0.05$), LS had no effect. Dysmorphology of the stria vascularis was noted in LS but not SP120-treated mice.

Conclusions: SP120 in AS mice extended lifespan beyond that of mice treated with SP60, LS, or ATR and attenuated noise-induced hearing loss compared to LS. Sparsentan may therefore offer a novel, dual-therapeutic approach in AS by reducing both renal injury and hearing loss.

Funding: Commercial Support - Retrophin, Inc.





PO1898

Long-Term Outcomes of Tacrolimus Treatment for Idiopathic Membranous Nephropathy

Aikaterini K. Nikolopoulou,[1] Sarah Gleeson,[1] Rakesh Dattani,[1] Marie B. Condon,[1] Tom Cairns,[1] Jeremy B. Levy,[1] Liz Lightstone,[2] Stephen P. McAdoo,[1] Frederick W. Tam,[2] Charles D. Pusey,[2] Megan Griffith.[1] *[1]Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Imperial College London Faculty of Medicine, London, United Kingdom.*

Background: Tacrolimus (TAC) is effective for the treatment of membranous nephropathy (MN).

Methods: Retrospective study of longterm outcomes of 111 patients (pts) with MN treated with TAC from January 2000 to June 2018.

Results: Demographics:table 1. Treatment: 91/111 TAC monotherapy, 20/111 dual therapy with mycophenolate + TAC. All pretreated with ACEi/ARB. Median follow up (FU) 68 months (IQR 33-115). 93/111 pts (84%) reached Partial Remission (uPCR reduction by 50% and <300mg/mmol) at 5.1 months (median, IQR 2-11). 76/111 (69%) also reached Complete Remission (uPCR<50mg/mmol) at 15.2 months (9.3-24). 18/111(16%) did not respond to initial treatment with TAC.3/18 progressed to ESRD rapidly, 9/18 were treated with Rituximab (RTX), 4/18 with cyclophosphamide (CYP) and steroids. Only 4 achieved remission, all in the RTX group. 2 lost to FU. 48/93 (51%) of pts that achieved remission relapsed after 22 months (14-34) (Figure 1) following withdrawal or reduction of immunosuppresion. 28/48 were retreated with TAC and all achieved remission, 15/48 treated with RTX, remission in 11/15. 3/48 treated with CYP and steroids (2/3 remission, 1 lost to FU). No treatment in 2. 11/28 cases retreated with tacrolimus had a second relapse. At 3 months on TAC there was a reduction of eGFR from baseline (90ml/min) to 78 ml/min (48-99, p<0.001),(Figure 2). Renal function stabilised thereafter during the follow up period to 10 years. 10(9%) pts reached ESRD and 5/10 within 12 months from diagnosis;these pts had a lower baseline eGFR 48ml/min (23-61).

Conclusions: TAC can be an effective treatment for MN with a relatively rapid response. Lack of response to TAC and low eGFR at presentation are associated with non-response to alternative immunosuppression and ESRD. Relapse is common often necessitating repeat immunosuppression. Most pts maintain eGFR in the longterm.

Funding: Clinical Revenue Support

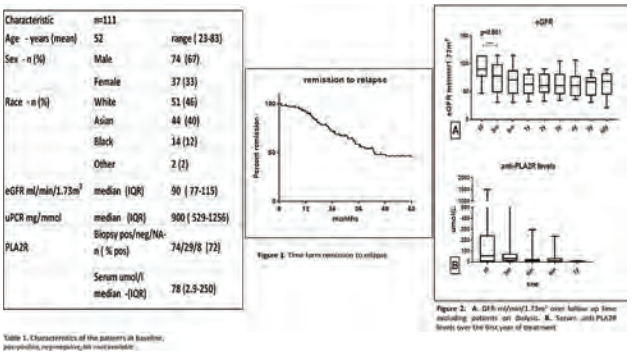


Table 1. Demographics. **Figure 1**. Time from remission to relapse. **Figure 2. A.** eGFR and **B.** anti-PLA2R levels over time

PO1899

Etiology, Histology, and Prognosis of Primary and Secondary Membranous Nephropathy in Young Patients Under 50 Years Old: A 35-Year, Two-Center Experience

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Background: Membranous nephropathy (MN) is often diagnosed in older age group; its mean age of onset is 50-60 years old. Although retrospective analyses on young patients with primary MN have been published, clinicopathologic characteristics of primary MN and secondary MN combined in young patients have not been reported.

Methods: All patients diagnosed with MN in the age under 50 years old by a kidney biopsy performed between January 1985 and December 2019 at Toranomon Hospital and Toranomon Hospital Kajigaya were retrospectively analyzed. All patients with glomerular membranous changes presumed to be due to subepithelial deposits were included except for cases with classic membranoproliferative glomerulonephritis.

Results: 37 patients met the criteria. 19 of them (51%) had nephrotic syndrome, 17 (46%) had urinary protein excretion less than 3.5 grams per day, and one (3%) had no proteinuria. To evaluate renal biopsy specimens, light microscopy was performed in all cases, fluorescence microscopy in 36 cases and electron microscopy (EM) in 28 cases. 14 patients (38%) were diagnosed with primary MN, 22 patients (59%) with secondary MN, and one patient (3%) with de novo MN post-transplantation. Secondary MN were due to lupus erythematosus (27%), mixed connective tissue disease (14%), Sjögren's syndrome (3%), hepatitis B (11%), bucillamine use (3%), and graft versus host disease (GVHD) after peripheral blood stem cell transplantation (3%). Mean and median follow-up period was 14.9 and 12.0 years, respectively. At the end of follow-up, only two patients out of the 37 patients reached end-stage renal disease, and 33 patients (89%) observed serum creatinine level lower than 1.5 mg/dL. 21 patients achieved complete remission (CR). Among 27 cases who underwent EM, cases with subendothelial deposits had smaller CR rate (3/11 cases) than those without subendothelial deposits (12/16 cases), which was statistically significant ($\chi2=6.01$, $p=0.014$). The CR rates of cases with mesangial deposits (12/21 cases) and those without mesangial deposits (3/6) was not significantly different ($\chi2=0.096$, $p=0.76$).

Conclusions: The prognosis of renal function was fairly good in patients with MN in the age under 50 years old. Cases with coexisting subendothelial deposits showed lower CR rate than the rest.

PO1900

A Target Antigen-Based Approach to the Classification of Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is caused by circulating auto-antibodies against podocyte surface antigens, identified as M-type-phospholipase–A2-receptor (PLA2R) in 70-80% and thrombospondin-type-1-domain-containing-7A (THSD7A) in 2-5% of patients. Secondary MN occurs in the context of malignancy, autoimmune disease, infection, paraproteinemia or medication. Some patients with PLA2R-associated MN have a current or previously diagnosed associated condition, but it remains unclear whether it is causally related or coincidental. A few THSD7A-associated MN cases have a strong etiologic link with active malignancy, while in others malignancy appears coincidental. Exostosin 1/exostosin 2 (EXT1/EXT2) are recently discovered target antigens in patients with MN, the majority of whom have auto-immune disease. These recent findings blur the traditional distinction between primary and secondary MN.

Methods: To describe the phenotypes of PLA2R-, THSD7A- and EXT1/EXT2-associated MN, 201 adult patients with biopsy-proven MN were classified using serology, immunostaining and mass spectrometry. Clinical, biochemical and follow-up data were examined for associated disease and its relationship with MN.

Results: PLA2R-associated MN (n=161) occurred predominantly in middle-aged white males, with 72% presenting without associated disease. Only 1 case of THSD7A-associated MN was identified, with a concomitant malignancy. EXT1/EXT2-associated MN (n=8) was identified in younger females and was strongly linked with active auto-immunity. The majority of patients who were negative for all three target antigens (n=27/31, 87%) presented with associated disease, mainly malignancy and auto-immunity.

Conclusions: In conclusion, the historical primary-secondary dichotomy has substantial limitations when applied to MN. We propose a terminology combining the target antigen involved in pathogenesis and the associated clinical diseases in order to classify MN and guide clinical decision making.

Funding: Private Foundation Support

PO1901

Noninvasive Diagnosis of Primary Membranous Nephropathy Using Anti-Phospholipase A2 Receptor (PLA2R) Antibodies: A Validation Study

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Background: Kidney biopsy is the current gold standard to diagnose membranous nephropathy (MN). Approximately 70-80% of patients with primary MN have circulating anti-PLA2R antibodies. We sought to validate our previous work showing that in a proteinuric patient with preserved renal function (eGFR >60ml/min/1.73m^2) and no associated conditions (e.g. autoimmunity, malignancy, infection, drugs, paraproteinemia) a positive anti-PLA2R antibody test by simultaneous ELISA and IFA, is a valid strategy to make a non-invasive diagnosis of primary MN (Bobart et al. KI 2019; 95: 429-438).

Methods: The medical records of all Mayo Clinic patients with positive serum anti-PLA2R antibody tests by both ELISA and IFA between July 2018 and April 2020 were reviewed.

Results: A total of 1522 anti-PLA2R antibody tests were ordered in 1112 unique patients, yielding 128 positive results. We excluded previously reported patients (n=33), renal transplant recipients (n=5), no biopsy available (n=18), and pediatric cases (n=2). In all 70 remaining patients, the primary biopsy diagnosis was MN. Associated disease was identified in 28 cases (autoimmunity = 10, malignancy = 6, NSAID = 4, Hepatitis = 3, monoclonal protein = 5). Of the 42 patients with negative work up for secondary causes, 32 (76%) had preserved renal function. One patient had fibrin thrombi and neutrophils in the capillary loops, and one patient had 1 glomerulus with focal glomeruar basement membrane duplication. Neither of these findings altered diagnosis or management. Among the 10 patients with eGFR <60 ml/min/1.73m^2, additional findings that altered the treatment plan included acute interstitial nephritis (n=1) and superimposed diabetic nephropathy (n=1).

Conclusions: The study extends our previous observations that in patients with preserved renal function and no evidence of secondary causes or diabetes, a positive PLA2R test by simultaneous ELISA and IFA confirms the diagnosis of MN.

PO1902

Association Between Anti-Complement Factor H Antibodies and Renal Outcome in Primary Membranous Nephropathy

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Background: The complement factor H (CFH) regulates activation of the alternative complement pathway. Autoantibodies against CFH have been involved in progressive renal dysfunction in a case with primary membranous nephropathy (MN) (Ronco P. et al. N Eng J Med 2018;379: 2479-81). However, the prevalence and the roles of anti-CFH antibodies in the clinical outcome of MN remains unclear.

Methods: We investigated retrospectively 36 Japanese patients with primary MN (23 males, 13 females; age 64.5 [59-72] years old) and 18 healthy normal controls (8 males, 10 females, age 31 [27-38] years old). Serum anti-CFH antibody titers were measured by enzyme-linked immunosorbent assay (Vidia Vestec, Czech Republic) to evaluate the association between anti-CFH antibody titers and the clinical outcome of MN patients.

Results: Anti-CFH antibody titers were significantly higher in MN patients as compared with normal controls [4.69 (3.69-6.38) RU/mL vs. 0.0 (0.0-0.0) RU/mL, p <0.001]. Twenty-eight patients were classified into the anti-CFH antibody positive group. The other 8 patients were classified into negative group. According to the Kaplan-Meier method, no significant difference was observed in the complete or incomplete remission rate of proteinuria, the incidence of renal dysfunction judged by the 30% reduction of estimated glomerular filtration rate (eGFR) and 50% elevation of serum creatinine (s-Cr) levels between the anti-CFH antibody positive group and the negative group of MN patients, however. In MN patients, anti-CFH antibody titer was selected an independent unfavorable predictor of renal dysfunction in Cox proportional hazards analysis adjusted by age, gender, sCr levels, proteinuria (g/gCr), anti-CFH antibody titer and immunosuppressive therapy (adjusted hazard ratio (HR) 1.344, 95% confidence intervals (CI) 1.038 to 1.741, p=0.025 for 30% reduction of eGFR; adjusted HR 1.930, 95% CI 1.108 to 3.363, p=0.020 for 50% elevation of sCr).

Conclusions: These data suggested that anti-CFH antibodies may be involved in the deterioration of renal function in primary membranous nephropathy.

PO1903

Concurrent Anti-Glomerular Basement Membrane Nephritis and Membranous Nephropathy

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Background: Anti-GBM nephritis is an uncommon entity with a rapidly progressive course. The concurrence of anti-GBM nephritis with membranous nephropathy (MN) is rare and poorly understood. We report a single center case series of this dual glomerulopathy with emphasis on presenting features, course, and outcome.

Methods: A total of 12 cases of combined anti-GBM nephritis and MN were identified from the archives of the Columbia Renal Pathology Laboratory over the past 18 years. Presenting clinical, histopathologic and laboratory data with follow up were obtained by chart review.

Results: The cohort of 12 cases included 7 men and 5 women with age range 18-81 years. The most common presenting feature was AKI (mean creatinine 9.3 mg/dL), with one patient having pulmonary symptoms. Positive anti-GBM serology was available at presentation for 11 cases, 5 with titers > 100 au/mL, and all were ANCA negative. Of those tested the majority were PLA2r negative. Patients were predominantly Caucasian (N = 9). All patients required hemodialysis (HD) at presentation, and two patients, a 20-year-old woman and an 81-year-old woman had renal recovery with the later having a stable creatinine of 2.0 mg/dL 11 months later. Treatment regimens included the following: cyclophosphamide, plasmapheresis, and prednisone (N=9); cyclophosphamide and prednisone (N=1), prednisone and plasmapheresis (N=1) and rituximab alone (N=1). Two patients died, both on HD, one 16 years later from unknown cause and one 3 months after presentation from sepsis. Analysis of the 12 renal biopsies showed combined linear and granular staining of GBMs for IgG, with crescents involving 23-100% of glomeruli, and fibrinoid necrosis involving 15-100%. The two patients who recovered renal function had fewer total crescents (82% crescents, and 23%, respectively) and less fibrinoid necrosis (15% and 31%) compared to the subgroup without recovery respectively, on kidney biopsy.

Conclusions: Combined anti-GBM and MN is a rare entity presenting with severe AKI requiring dialysis. Renal recovery is uncommon. High percentage of crescents are consistent with poor outcomes. Treatment and course are dominated by anti-GBM nephritis. The MN component is predominantly PLA2R negative, and further studies into pathogenesis are needed.

PO1904

Recurrent Membranous Post Transplantation: Histopathology, Treatment, and Outcomes

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Background: Membranous nephropathy(MN) recurs in 30-45% of transplants. Reported recurrence rates are higher in centres that perform surveillance biopsies. Optimal treatment is unknown. We examined recurrent MN in our cohort in terms of their histopathology, treatment and outcomes.

Methods: Patients with MN as the cause of their ESRF who were later transplanted were identified from an in-house database. Further data was collected from the electronic health record.

Results: 36 patients with a diagnosis of MN were transplanted. Mean follow up was 6.4 ± 4.2 years. 41.6% had a rejection episode (mean time from transplant 0.42±0.15 years). Overall there was 22% graft loss (mean time 6.5± 3.7 years), 11% deaths (8.6± 2.3 years from transplant) and 6% deaths with functioning grafts (mean time 6.9± 2.3 years). Mean eGFR at 3 months and 1 year were 48.1 ±18.5 and 48.1±14.5 ml/min. 30/36 patients had at least one biopsy following transplantation. Of those whose biopsies did not show recurrence, the mean time to the most recent biopsy was 2.9± 2.7 years (range 0.02-9.3) 8/36 patients (22%) had recurrent MN, 7 detected on indication biopsy and 1 on surveillance biopsy. The mean time to recurrence was 1.9±1. years (range 0.09-4.46 years). Granular C4d staining of the capillary wall was detected in 6/8 biopsies prompting immunofluorescence and electron microscopy, leading to the diagnosis of recurrent MN. Histological anti-PLA2R staining was positive in 3/8 biopsies. 2/8 patients had donor specific antibodies. In the 4 patients with clinically significant proteinuria rituximab was used to treat with a complete or partial response in all patients (mean time 22.5±16 months [range 4.4-43.8 months]). There are no significant differences in rejection, graft loss, death or death with functioning graft between those with recurrence and those without recurrence in our cohort.

Conclusions: Recurrent MN was frequent but not associated with increased allograft failure in our programme, with the use of rituximab in selected cases. Granular C4d staining of the glomerulus in transplant patients with MN could prompt further investigation with immunofluorescence and electron microscopy to look for recurrent disease.

PO1905

Secondary Polycythemia Associated with Membranous Nephropathy

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Introduction: Polycythemia has been recognized as a common occurrence in certain renal diseases such as cystic diseases of the kidney, renal cancer, tuberous sclerosis and hydronephrosis. However, polycythemia in association with membranous nephropathy has rarely been reported. Here we report a case of secondary polycythemia from membranous nephropathy. Although the mechanism of this phenomenon is unclear, decreased effective circulating volume leading to hypoxemia and thereby polycythemia seems to be the most likely explanation

Case Description: 37-year old white male with Hypertension, OSA using CPAP, tobacco use was admitted with 40-lb weight gain and anasarca. 24-hour urine collection revealed 17-gram protein excretion with serum albumin of 1.1 and marked hyperlipidemia. Kidney biopsy revealed membranous nephropathy. Staining for PLA2R and THSD7a were negative within the glomerular deposits. Evaluation for secondary causes of membranous nephropathy was negative for ANA, RPR/syphilis antibodies, Hepatitis, HIV, ANCA, Anti-GBM Ab and normal C3,C4 levels. CT of torso was negative for overt malignancy or hepatosplenomegaly. Patient's hemoglobin ranged between 16.5– 18.5 G/dl (hct 52-60%). Serum erythropoietin level was 12.3 IU/L (Normal 5-30IU/L) with corresponding hemoglobin of 18.2 G/dl. JAK2 exon12, V617F mutations were negative. Hematology evaluation concluded that primary polycythemia is unlikely. Patient received 2 doses of 1 Gm Rituximab given 2 weeks apart. Patient was placed on Apixaban for prophylactic anticoagulation. Follow up labs to evaluate response to therapy are currently pending. It is yet to be seen if polycythemia resolves with remission of membranous nephropathy.

Discussion: Polycythemia is seldom seen in patients with membranous nephropathy. We postulated that hypoxia induced by decreased renal perfusion is the main trigger for polycythemia. However, it is puzzling as to why more patients with membranous nephropathy are not polycythemic. This leads us to believe that there might be some unique processes leading to polycythemia in membranous nephropathy, as in this patient, which might need further investigation. Polycythemia would further enhance the risk of thromboembolism in such patients whose risk of hypercoagulability is already high in setting of severe hypoalbuminemia. Hence, prophylactic anticoagulation should strongly be considered in these patients.

PO1906

Membranous Nephropathy Preceding the Recurrence of Thymoma

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Introduction: Membranous nephropathy secondary to neoplastic processes is a recognized phenomenon, and it may be the first finding that leads to the diagnosis of the underlying malignancy. Here, we describe a case of secondary MN in a patient with a history of recurrent thymoma that led to a prompt evaluation for malignancy, which did not appear on PET imaging until a few months later.

Case Description: We describe the case of a 62 year old man with myasthenia gravis (on IVIG), history of thymoma with recurrence in 2017 and March 2019 requiring multiple surgeries and adjuvant chemoradiation. There was no evidence of disease in October 2019. Subsequently, he presented in December 2019 with anasarca, acute kidney injury and nephrotic syndrome (proteinuria greater than 9 g per day). He underwent diuresis and a kidney biopsy which was notable for secondary membranous nephropathy with negative PLA2R antibody. A PET-CT was performed in December 2019 which did not show any evidence of FDG avidity or active malignancy. In February 2020, he presented with worsening anasarca and a myasthenic flare, for which he was treated with steroids, five sessions of plasma exchange and rituximab. In order to search for possible recurrent thymoma, he had another PET-CT which found a new FGD avid focus in the left second rib, which was biopsied and consistent with recurrent thymoma. He was then treated with radiation therapy.

Discussion: When a patient is diagnosed with secondary membranous nephropathy without an identifiable cause, it is recommended to perform general screening for cancers. In order to compare conventional screening with PET imaging, Z Feng et al compared two groups of patients with different screening approaches. In this study the PET imaging group identified 5 cases of malignancy among 49 patients, while the conventional screening only identified 1 case of malignancy among 75 patients. While PET imaging may be the optimal imaging for undiagnosed malignancy or recurrent malignancy in patients with newly diagnosed membranous nephropathy, this case presentation suggests that thymoma recurrence with nephrotic syndrome may precede a positive result on PET imaging. Reference: Z Feng, S Wang, Y Huang et al. "A follow-up analysis of positron emission tomography/computed tomography in detecting hidden malignancies at the time of diagnosis of membranous nephropathy" Oncotarget 2016. 7(9): 9645-9651

PO1907

A New Approach to De Novo Minimal Change Disease in Pregnancy

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Introduction: Although proteinuria in pregnancy is common and usually due to preeclampsia, nephrotic range proteinuria especially early in pregnancy, warrants investigation and treatment. We present the first case of minimal change disease (MCD) presenting in pregnancy, treated only with tacrolimus.

Case Description: A previously well 20 year old G1P0, presented at 9 weeks gestation with 3 weeks of oedema and shortness of breath. Examination revealed marked oedema. Investigations: creatinine 44umol/L (55-110), albumin 7g/L (35-50), urine PCR 1456mg/mmol. A fetal scan confirmed a viable pregnancy. A renal biopsy was performed which demonstrated MCD. She was started on tacrolimus in addition to enoxaparin, frusemide and aspirin. At 12 weeks she had melena with a haemoglobin drop. There was no active bleeding on endoscopy and she had no further episodes in pregnancy. She was managed by the renal and joint renal-obstetric clinic throughout pregnancy. She was maintained on tacrolimus alone (levels 5-8ug/L). Her albumin rose and PCR fell throughout pregnancy. By 34 weeks her albumin was 28g/L and uPCR was 128 mg/mmol. Fetal growth was normal on serial growth scans. She did not develop preeclampsia. Labour was induced at 39 weeks and she had a normal vaginal delivery of a 3194g healthy baby

Discussion: There have only been 4 previous reports of de novo MCD in pregnancy all of whom were treated with steroids. In our patient who presented early in pregnancy with marked oedema and heavy proteinuria a kidney biopsy was performed. Kidney biopsy should be performed when the benefit of obtaining a diagnosis outweighs the risks of the procedure. In pregnancy the risks are increased (7% versus 1% outside pregnancy). Biopsy during the 1st trimester is safest. Corticosteroids are often used to treat MCD outside pregnancy. Prednisone is safe is pregnancy as the fetal dose is minimal. However, there is a risk of maternal complications including gestational diabetes and weight gain. The recent MinTac trial of prednisolone and tacrolimus in patients with MCD found no difference in remission rates at 8, 16 or 26 weeks and no difference in relapse rates. We achieved partial remission in this heavily nephrotic patient with use of tacrolimus alone allowing us to avoid steroid adverse effects, which was especially important after her GI bleed. We believe tacrolimus is a valuable option for treatment of MCD in pregnancy.

PO1908

Tiopronin-Induced Minimal Change Disease: The Third Reported Case

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Introduction: Cystinuria, a rare inherited metabolic disorder characterized by defective proximal tubule cystine transport, manifests predominantly in childhood or young adulthood with renal colic and recurrent nephrolithiasis, often requiring urologic intervention. Insoluble cystine in the urine precipitates into hexagonal crystals that can coalesce into larger, recurrent calculi, with associated higher risk of chronic kidney disease. Prevention of stone formation is the primary goal, using conservative non-pharmacologic approaches and if unsuccessful then pharmacologic. Since its approval in 1986 tiopronin (TP), a thiol compound that forms a soluble mixed disulfide tiopronin-cysteine complex, has been used to increase urine cystine solubility. Adverse effects of TP most commonly are cutaneous and mucosal. Reports of TP-induced nephrotic syndrome (NS) are rare, especially due to minimal change disease (MCD).

Case Description: A 19-year-old male with cystinuria and bilateral nephrolithiasis requiring extensive urologic interventions was on TP 300 mg bid for 6 months, when he presented to the Emergency Department with foamy urine, decreased urine output and anasarca. Labs showed elevated urine protein:creatinine ratio 9.2 (UPCR), low serum albumin 1.6 mg/dL and elevated cholesterol. ANA, ANCA, anti-GBM, HBV, HCV, HIV, C3, C4, and cryoglobulins were negative. Renal biopsy demonstrated MCD. He was not treated with steroids. TP was discontinued and UPCR 2 months later was 0.21 and albumin 2.3, with complete resolution of symptoms. He was referred to Metabolic Stone Clinic to discuss alternative treatment options.

Discussion: Only 31 cases of TP-induced NS have been reported to date, the majority membranous glomerulonephritis (GN), with fewer cases of mesangioproliferative or membranoproliferative GN and only two cases of MCD. Although the exact mechanism is unclear, TP is speculated to play an antigenic role interfering with podocyte function. TP induced NS is not necessarily dose-dependent, with no relationship between mean daily dose and toxicity. The highest prevalence occurs in the first six months and is self-limited upon cessation of TP, without need for immunosuppressives. Clinicians should be aware of the rare but severe occurrence of NS due to TP. A weekly dipstick for protein may help in early detection.

PO1909

Recurrent Nephrotic Syndrome in Podocyte Infolding Glomerulopathy: Remission with Rituximab

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Introduction: Podocyte infolding glomerulopathy (PIG) is a recently recognized entity. The sentinel paper showed that it is associated with autoimmune disorders and is often responsive to corticosteroids (CS). We present a case of PIG with recurrent nephrotic syndrome (NS) who is maintaining remission on Rituximab off of CS.

Case Description: A 61-year old woman with type II diabetes mellitus, inflammatory bowel disease (IBD), and uveitis presented in 2009 with proteinuria. Kidney biopsy was read as focal segmental glomerulosclerosis (FSGS). She was treated with angiotensin converting enzyme inhibitor (ACE I) and prednisone, and proteinuria remitted. In 2012, an increase in proteinuria promped repeat biopsy resulting in a diagnosis of membranous glomerulonephritis. Anti-PLA2R was negative. ACE I and prednisone were continued and proteinuria remitted. In 2014, she developed nephrotic syndrome (NS). Repeat biopsy was read as showing FSGS. Prednisone 1 mg/kg/day induced remission. When prednisone was tapered, NS flared. She did not remit with high dose prednisone and at 8 weeks developed acute kidney injury (AKI). Tacrolimus was added and proteinuria and creatinine (cr) improved. Steroids were tapered over several months. On Humira for IBD and tacrolimus (level 11 mg/dl), NS and AKI flared 1 year later with urine protein:creatinine (UP/C) of 2 and cr 2.1 mg/dl. Prednisone was restarted. Intravenous cyclosphosphamide was started, steroids were tapered, and Humira was discontinued. Within 5 weeks, proteinuria worsened (UP/C 29) and cr rose to 4 mg/dl. Renal biopsy demonstrated foot process invagination yielding a diagnosis of PIG. At trial of cyclosporine was stopped at 1 week due to drug intolerance. Mycophenolate mofetil (MMF) in combination with prednisone and tacrolimus was started. MMF caused severe diarrhea. In September of 2019, 4 weekly doses of Rituximab 375 mg/m^2 followed by 1 gram doses at 4 month intervals were administered. Proteinuria remitted and creatinine improved to 1 mg/dl. She remains in remission off of steroids and on lower dose tacrolimus now for 11 months.

Discussion: This case is the first to describe the effectiveness of Rituxan as rescue and maintenance therapy following failure of other IS regimens in a patient with recurrent NS due to PIG. Rituxan should be considered in refractory cases of PIG to induce and maintain remission and allow for steroid sparing.

PO1910

Glomerular Tip Lesion FSGS: A Rare Case of Nephrotic Syndrome in African Americans

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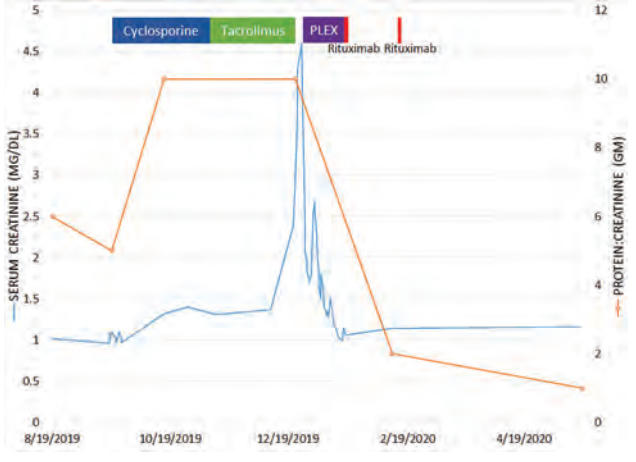
Introduction: Nephrotic syndrome caused by focal segmental glomerular sclerosis (FSGS) in African Americans is known to have a poor prognosis and frequent treatment failure. Tip variant FSGS connotes good prognosis, usually responsive to calcineurin inhibitor (CNI) and steroid. We present a case of CNI resistant tip lesion FSGS requiring plasma exchange (PLEX) and rituximab

Case Description: A 25-year-old African-American male, initially presenting to outpatient clinic for edema associated with proteinuria. He had a past medical history of seizure disorder controlled with zonisamide. He trialed hydrochlorothiazide and furosemide without success. His urine showed nephrotic range proteinuria with 6g/g creatinine on spot urine. Outpatient workup was unrevealing, and was managed with enalapril and torsemide. He eventually had worsening edema and shortness of breath, prompting ED visit. Biopsy was performed which showed FSGS, tip variant. He was discharged on cyclosporine and increased diuretic. Cyclosporine caused gastrointestinal upset, and so patient switched to tacrolimus. He again had increasing swelling, and re-presented to hospital. He was found to have acute kidney injury, and 10g/g creatinine despite therapeutic tacrolimus levels. Patient trialed stress dose steroids but serum creatinine rose to 4.44. He started PLEX for 10 treatments, and then transitioned to rituximab. During treatment with PLEX patient creatinine quickly downtrended, and after second dose of rituximab as an outpatient he was back to baseline. He lost 30 kg with resolution of his edema. Patient then tapered off steroids, and will continue on rituximab alone.

Discussion: Glomerular tip lesion is more common in European Americans and associated with a favorable outcome compared to other subtypes of FSGS. Resistance to one immunosuppressive treatment is not always associated with resistance to other treatment modalities. PLEX and rituximab should be considered in glomerular tip lesion in African Americans



PO1911

Utility of Immunofluorescent Intensity of IgG3 and Phospholipase A2 Receptor-to-IgG4 Ratio to Presume the Prognosis of Patients with Membranous Nephropathy

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Background: Membranous nephropathy (MN) is likely to show the long-term course and is a frequent glomerulonephritis in the elderly. For this reason, effective use of immunosuppressive drugs in a short period of time is desirable. In this study, we aimed to investigate the factors that could predict treatment responsiveness, using the treatment outcome in a short period of time, and retrospectively analyzed patients with MN in our hospital.

Methods: We included 66 patients who underwent renal biopsy and were diagnosed with MN in our hospital between April 2009 and December 2017. The percentage reduction in proteinuria one month after initiation of steroids, immunosuppressants, and ARBs was set to the endpoint. Intensity of immunofluorescent siaining (IF) was scored according to the criteria of Japanese Scoiety of Nephrology. Hematuria was quantified by 7-grade scoring of RBC numbers in high powered microscopic field.

Results: The intensity of IF (IgG subclass, PLA2R, THSD7A) was numerically evaluated and used for the analysis. The mean age of the patients included in the analysis was 66.4±11.7 years and baseline eGFR 63.9±18.7 ml/min, baseline urine protein was 7.05±5.45 g/gCr. Multiple parameters in high responder (HR, n=39) that resulted in less than 50% of urine protein after one month and low responder (LR, n=27) that remained proteinuria more than 50% were compared. Baseline urine protein and scored baseline hematuria were both higher in HR group (urine protein: 6.95 in HR vs 3.86 g/gCr in LR, p=0.003; hematuria: 1.0 in HR vs 0.0 in LR, p=0.036), but there was no difference in baseline eGFR (70.5 in HR vs 60.4 mL/min in LR, p=0.087). The mean dose of prednisolone was also not different between the two groups (18.6 in HR vs 14.0 mg/day in LR, p=0.451). In IF, significant differences were observed between the two groups in the scored staining intensity of IgG3 and the staining intensity ratio of PLA2R to IgG4 (PLA2R-to-IgG4 intensity ratio:PGIR) were both lower in HR group (IgG3: 0.0 in HR vs 0.5 in LR, p=0.049; PGIR: 0.58 in HR vs 1.00 in LR, p=0.029).

Conclusions: From the result of the present examination, staining intensity of IgG3 and intensity ratio of PLA2R to IgG4 might be helpful to predict better therapeutic responsiveness in addition to the baseline proteinuria and hematuria.

PO1912

Graves Disease and Nephrotic Syndrome

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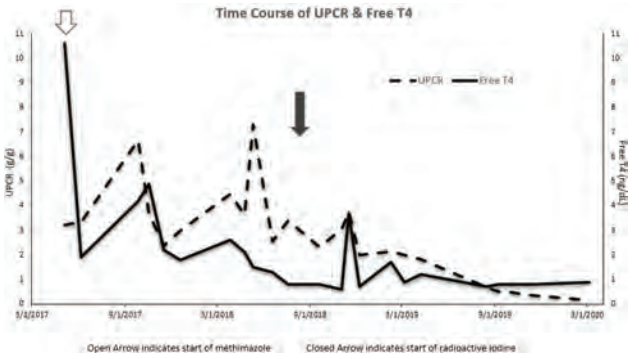
Introduction: Disorders of the thyroid and kidney may co-exist. Isolated case reports of Graves' disease associated with various glomerular diseases, including membranous nephropathy, membranoproliferative GN, fibrillary GN, and minimal change disease have been published. A patient with membranous nephropathy and Graves' disease who had improvement but not resolution of proteinuria after treatment with radioactive iodine has been described (Sasaki et al. CEN Case Rep. 2014; 3(1): 90-93). We report a case of nephrotic syndrome associated with Graves' disease which completely resolved after treatment of the thyroid disease with radioiodine.

Case Description: A 33-year-old healthy female was seen for evaluation of proteinuria discovered during a routine life insurance evaluation. BP was normal, and she had trace-1+ lower extremity edema. Urinalysis showed 3+ protein, 1 red blood cell and 1 white blood cell per high power field. Urinary albumin/creatinine ratio was 4010 mg/g. Serum albumin was 2.7 g/dL. Renal function was normal. Tests for hepatitis B and C, HIV, RPR, ANA, C3, C4, cryoglobulins, immunofixation, and free light chains were normal. Renal biopsy was planned but the patient missed the biopsy date. Subsequently she returned to clinic complaining of neck swelling. Exam revealed tachycardia, palpable goiter, 1+ pedal edema, no tremor. She reported heat intolerance, occasional diarrhea, insomnia, diaphoresis, and weight loss for the past month. A thyroid panel showed TSH <0.01 UU/mL (0.40-4.60 UU/mL), free T3 >2000 pg/dL (230-420), and free T4 10.6 ng/dL (0.8-1.7). TSH receptor and thyroid peroxidase antibodies were present. The patient was treated with methimazole and tapering steroids. She refused thyroid surgery and ultimately underwent two sessions of radioactive iodine treatment. After this treatment, nephrotic syndrome went into complete remission (Figure).

Discussion: Although relatively uncommon, Graves' disease needs to be considered as a reversible cause of nephrotic syndrome.



PO1913

Treatment of Systemic Lupus Erythematosus with or Without Nephritis with the Immunoproteasome Inhibitor KZR-616: Initial Results of the MISSION Study

Mary K. Farmer,[1] Samir V. Parikh,[2] Richard Furie,[3] Christopher Kirk,[1] Ken Harvey,[1] Darrin Bomba.[1] *[1]Kezar Life Sciences, Inc, South San Francisco, CA; [2]The Ohio State University, Columbus, OH; [3]Northwell Health, Great Neck, NY.*

Background: Immunoproteasome inhibition demonstrated therapeutic potential in preclinical models of systemic lupus erythematosus (SLE) and lupus nephritis (LN). KZR-616 is a first-in-class selective immunoproteasome inhibitor, which has been safe and well tolerated in early clinical trials. One hundred subjects across 2 healthy volunteer studies, with dosing of KZR-616 up to 75mg SC, achieved target levels of immunoproteasome inhibition at doses ≥30mg. Here we report safety, tolerability and exploratory efficacy data from the Phase 1b portion of MISSION (KZR-616-002; NCT: NCT03393013), a clinical trial in which KZR-616 was administered to patients with active SLE with or without LN.

Methods: In this open-label dose-escalation study, SLE patients (per SLICC classification criteria) with SLEDAI ≥4 despite stable background therapy received KZR-616 at doses of 45mg (Cohort 1), 60mg (Cohort 2), or 60mg following a step-up dose (Cohorts 2a, 2b, 2c) SC weekly through Week 13 (W13) with 12 weeks of follow-up.

Results: To date, 39 patients with SLE, including 2 patients with active proliferative LN, have enrolled in MISSION. The majority of TEAEs have been mild or moderate with injection site reactions the most common TEAE. Tolerability has improved with an initial step-up dosing regime, subsequent doses and the introduction of a lyophilized formulation. To date, no patients have discontinued from cohorts after implementation of these protocol modifications. Multiple measures of disease activity improved from Baseline to W13 and persisted through W25; no patients worsened over 13 weeks. KZR-616 administration resulted in improvements in multiple serologic markers as well as reduced expression of inflammatory gene expression modules. Both patients with biopsy-proven active proliferative LN had reductions in proteinuria.

Conclusions: KZR-616 has been safe and tolerated at a target dose of 60 mg weekly. Step-up dosing, use of select pre-medications, and/or introduction of a lyophilized preparation have increased its tolerability. The administration of KZR-616 resulted in improvement across multiple disease activity measures as well as serologic markers, including improvement in proteinuria in patients with active proliferative LN. MISSION is an on-going study now focused on patients with LN.

Funding: Commercial Support - Kezar Life Sciences, Inc

PO1914

Rituximab as Maintenance Therapy in Lupus Nephritis

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Background: Rituximab (RTX) has been shown to be effective in refractory lupus nephritis (LN) in some studies. Minimal literature exists on using RTX as maintenance therapy for LN.

Methods: We performed a retrospective review of 21 patients (pts) with biopsy-proven LN who received RTX. We analyzed clinical data at baseline (pre-RTX) and up to 36 months (mo) of follow-up.

Results: Of 21 pts, 7 received RTX as part of first-line treatment, 7 for refractory LN and 7 for relapsing LN. All continued RTX (1gm q4-6 mo) as maintenance therapy. 15/21 (71%) pts were on RTX monotherapy (excluding prednisone and plaquenil) at 12 mo, 14/16 (88%) at 24 mo, and 11/13 (85%) at 36 mo. 17/19 (89%) had continuous B cell depletion at 12 mo, 13/14 (93%) at 24 mo, and 11/12 (92%) at 36 mo. At 12 mo, 16/21 (76%) achieved complete or partial remission. Median UPCR (g/g) decreased from 2.95 at baseline to 0.61 at 12 mo, 0.42 at 24 mo and 0.21 at 36 mo. 16/21 (76%) pts were on prednisone ≤5mg/day at 12 mo, 13/16 (81%) at 24 mo, and 10/13 (77%) at 36 mo. Over 36 mo, 2 pts had LN relapses while on RTX alone, and later progressed to ESRD. 2 pts developed hypogammaglobulinemia.

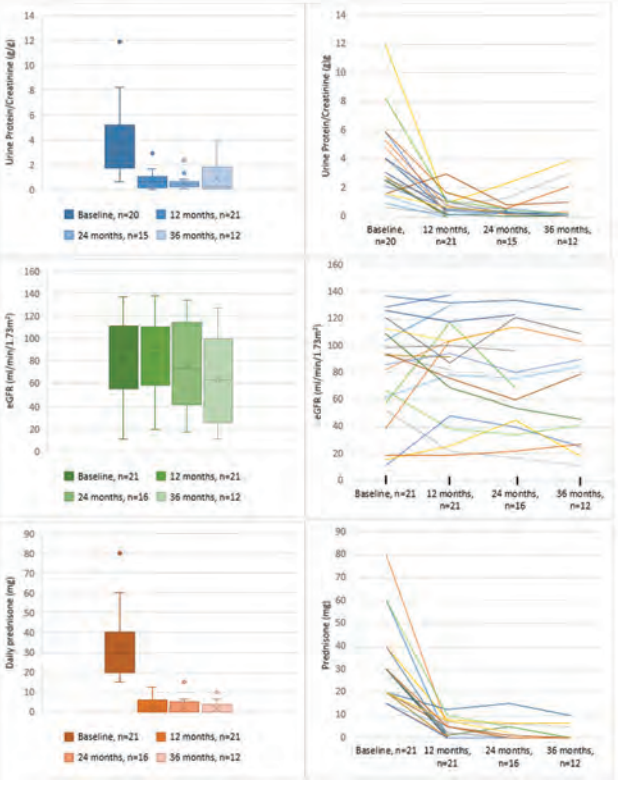
Conclusions: RTX monotherapy appears promising as maintenance therapy in LN. Given favorable renal outcomes and steroid-sparing effect, larger studies studying this effect may be warranted.

Definitions Table

Complete Remission	Normal creatinine (creat) (if abnormal at baseline (BL)), or creat <115% of BL (if normal at BL); inactive urinary sediment (<5 red blood cells (RBC)/hpf and 0 RBC casts); and UPCR <0.5 g/g
Partial Remission	Creat ≤115% of BL; RBCs/hpf ≤50% above BL and 0 RBC casts; and ≥50% decrease in the UPCR to <1.0 (if BL UPCR ≤3.0) or to ≤3.0 (if BL UPCR >3.0)
Relapse	Active urine sediment (RBC casts or >5 RBCs/hpf), rise in UPCR, or rise in creat, after achieving CR or PR.

Table 1. Baseline characteristics of 21 patients with lupus nephritis treated with Rituximab.

Data presented as n(%) or mean ± SD	Overall (n=21)	First-line therapy (n=7)	Refractory LN (n=7)	Relapsing LN (n=7)
Sex (female), n (%)	19 (90)	6 (86)	6 (86)	7 (100)
Age at time of first rituximab, years	32.6 ± 11.7	33.6 ± 12.3	27.1 ± 8.4	37.3 ± 13.4
Race				
- Caucasian	10 (48)	4 (57)	3 (42)	3 (43)
- African American	3 (14)	1 (14)	2 (29)	0 (0)
- Other	8 (38)	3 (43)	2 (29)	4 (57)
LN duration prior to RTX, months	22.1 ± 37.6	0.6 ± 0.8	15.3 ± 15.1	50.4 ± 53.7
LN Class III	1 (5)	0 (0)	0 (0)	1 (14)
LN Class IV	11 (53)	6 (86)	2 (29)	3 (43)
LN Class V	4 (19)	1 (14)	2 (29)	1 (14)
LN Class II	1 (5)	0 (0)	1 (14)	0 (0)
LN Mixed (Class III+IV, III+V, IV+V)	4 (19)	0 (0)	2 (29)	2 (29)
Creatinine (mg/dL)	1.42 ± 1.09	1.96 ± 1.50	0.86 ± 0.17	1.42 ± 0.98
Spot UPCR (g/g)	3.8 ± 2.7	5.14 ± 4.03	2.91 ± 1.13	3.27 ± 1.70
Albumin (g/dL)	3.01 ± 0.67	2.73 ± 0.72	3.07 ± 0.54	3.34 ± 0.72
eGFR by CKD-EPI (ml/min/1.73m2)	72.63 ± 32.04	63.71 ± 44.85	103.14 ± 20.11	77.43 ± 38.18
Concomitant therapies at first RTX				
- Cyclophosphamide	11 (52)	6 (86)	4 (57)	1 (14)
- Mycophenolate mofetil	7 (33)	1 (14)	2 (29)	5 (71)
- Glucocorticoid	21 (100)	7 (100)	7 (100)	7 (100)
- Plaquenil	5 (23)	1 (14)	3 (43)	1 (14)



Results

PO1915

Therapeutic Effect of Belimumab in Lupus Nephritis with Impaired Renal Function

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Background: To investigate the nephroprotective effect of belimumab (BEL) in SLE with mildly impaired renal function and proteinuria.

Methods: We studied 28 patients in the maintenance phase of SLE who was treated with BEL for more than 6 months. The median duration of treatment was 14 months. The patients were divided into those with reduced eGFR less than 60 ml/min/1.73 m2 (n=5; R group) and those with normal renal function (n=23; N group), and the effects of BEL were compared 6 months after treatment. In addition, the effect of BEL on lupus nephritis was investigated in patients with urinary protein of 0.2 g/gCr or more.

Results: The patients consisted of 26 females and 2 males, and the median age was 41 years. After BEL treatment, urinary protein decreased in both groups, 0.45 to 0.20 g/gCr in N group and 0.32 to 0.17 g/gCr in R group. The eGFR changed from 88.6 to 87.7 and from 50.8 to 61.2, while dsDNA antibodies (IU/mL) decreased from 54.9 to 30.5 and from

23.2 to 9.04, respectively. The doses of prednisolone (mg/day) decreased in both groups. The IgG level decreased from 1377 to 1204 (mg/dL) in N group and from 1009 to 865 in R group. In 18 patients with urinary protein of 0.2 g/gCr or more, proteinuria significantly decreased from 0.54 to 0.20 to 0.23 (g/gCr) and dsDNA antibody improved from 67 to 34 to 35.1 (IU/mL) at 3 and 6 months after BEL therapy.

Conclusions: BEL may improve SLE activities and also renal function in patients with renal insufficiency as effectively as in those with normal renal function, although hypogammaglobulinemia comparably develops in both groups.

PO1916

A Multicenter Double-Blinded Preclinical Randomized Controlled Trial (pRCT) on Jak1/2 Inhibition in Lupus Nephritis

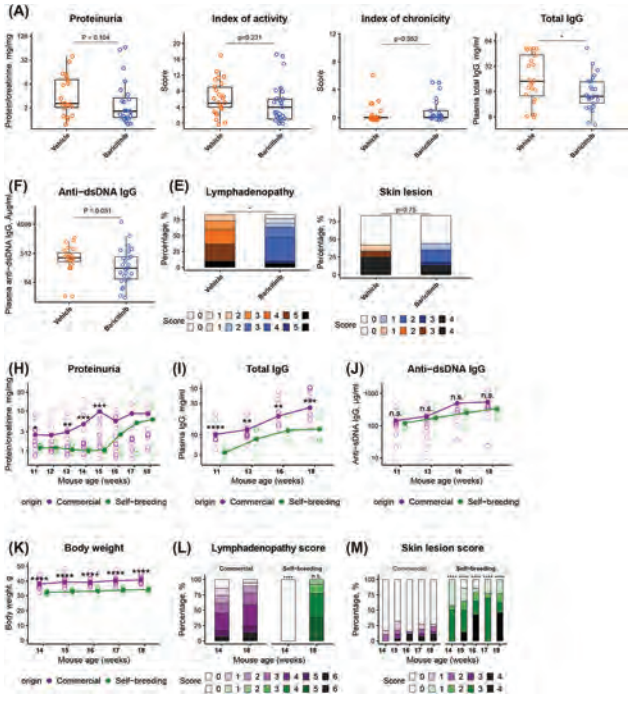
Yutian Lei,[5] Bettina Sehnert,[6] Reinhard E. Voll,[6] Conxita Jacobs Cachá,[4] Maria Jose Soler,[4] Maria Dolores Sanchez-Nino,[3] Alberto Ortiz,[3] Roman D. Bülow,[2] Peter Boor,[2] Hans J. Anders.[1] *[1]Division of Nephrology, Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany; [2]Institute of Pathology and Department of Nephrology, RWTH University of Aachen, Aachen, Germany; [3]IIS-Fundacion Jimenez Diaz, School of Medicine, Universidad Autonoma de Madrid, Fundacion Renal Iñigo Alvarez de Toledo-IRSIN and REDINREN, Madrid, Spain; [4]Nephrology Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Nephrology Research Group, Vall d'Hebron Research Institute (VHIR) and REDINREN, Barcelona, Spain; [5]Division of Nephrology, Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany; [6]Department of Rheumatology and Clinical Immunology, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany.*

Background: We conducted the first multicenter double-blinded pRCT in the field of nephrology and tested the Jak1/2 inhibitor baricitinib in experimental lupus nephritis.

Methods: We conducted a pRCT at two Spanish and two German academic sites. One site included MRL/lpr mice from their own breeding colony and the other sites purchased MRL/lpr mice from the Jackson lab. Eligibility criteria included female and 13-14 weeks old. Mice were randomized at a 1:1 ratio and orally dosed with 20 mg/kg/d baricitinib or vehicle for 4 weeks. Samples were assembled for blinded analyses, including histology, which was assessed by an independent pathology institute. The primary endpoint was proteinuria.

Results: A total of 55 mice were randomly assigned to the vehicle (n=28) and baricitinib group (n=27). Baricitinib-treated mice showed a trend towards decreased proteinuria, but this did not reach statistical significance (p=0.104). In contrast, plasma total IgG and lymphadenopathy score were significantly improved in the baricitinib group. In the vehicle group, at the initiation of treatment, self-breed mice had less proteinuria, less plasma total IgG, and worse skin lesion compared to commercial-source mice.

Conclusions: In a pRCT, targeting Jak1/2 with baricitinib for 4 weeks had no significant effect on the primary end-point proteinuria in MRL/lpr mice, whereas total plasma IgG and lymphadonpathy score significantly improved. Mice of different origins had different lupus phenotypes and increased the variability. Placebo controlled multicenter trials are feasible in animal models of lupus, however, standard deviations may increase due to multiple factors, which requires higher numbers of animals.



PO1917

Management of Lupus Nephritis (LN) with Voclosporin: An Update from a Pooled Analysis of 534 Patients

Brad H. Rovin,[1] Samir V. Parikh,[1] Robert B. Huizinga,[2] Neil Solomons,[2] Simrat Randhawa.[2] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Aurinia Pharmaceuticals Inc, Victoria, BC, Canada.*

Background: Voclosporin (VCS) is a novel calcineurin inhibitor (CNI) with a favorable metabolic profile and a consistent, predictable dose response potentially eliminating the need for therapeutic drug monitoring. VCS significantly improved renal response (RR) in patients with LN in two pivotal trials. Compared to MMF (target dose 2g/day) and prednisone (rapid taper), the addition of VCS 23.7 mg BID increased renal response by 25% in the Phase 2 AURA-LV (OR: 3.21; 95% CI: 1.68, 6.13; $p < 0.001$) and 18% in the Phase 3 AURORA (OR: 2.65; 95% CI: 1.64, 4.27; $p < 0.001$) studies at one year. To provide more information on VCS treatment effect we analyzed an integrated data set from AURA-LV and AURORA.

Methods: The two pivotal trials were of similar design, conducted in comparable patient populations and defined similar key outcome measures. The integrated data set included an intent to treat (ITT) population of 266 control and 268 VCS 23.7 mg/BID patients. Here we report key integrated data of interest including renal response, defined as: ● UPCR ≤ 0.5 mg/mg ● eGFR ≥ 60 mL/min or no decline > 20% from baseline ● ≤10 mg prednisone 8 weeks prior to endpoint measurement ● No rescue medications

Results: RR at one year was 43.7% for VCS vs 23.3% for control (OR 2.76, 95% CI: 1.88, 4.05; $p < 0.0001$), and at 6 months (VCS 31.7%; control 20.3%), [OR: 2.01; 95% CI: 1.34, 3.01; $p = 0.0008$]. In addition, 1-year RR for Hispanic patients was 37.9% in VCS arm vs 19.4% control. As expected, the largest estimated eGFR change from baseline for VCS vs control-treated patients occurred early, at week 4, (-5.6 mL/ min, $p < 0.0001$) which decreased to -3.7 mL/min by week 52 ($p = 0.0012$). Mean change from baseline of eGFR in the VCS arm at week 52 was -1.0 mL/min (p=ns). Finally, serious adverse events were similar between groups (22.8% VCS vs 18.8% control).

Conclusions: This integrated analysis provides further support to the efficacy of VCS seen in both AURA-LV and AURORA including in Hispanic patients, a high-risk LN patient population. Furthermore, VCS' expected impact on mean eGFR as a CNI was mild over the course of one year.

Funding: Commercial Support - Aurinia Pharmaceuticals, Inc.

PO1918

Use of Therapeutic Drug Monitoring Does Not Add Clinical Value for Voclosporin in Patients with Lupus Nephritis

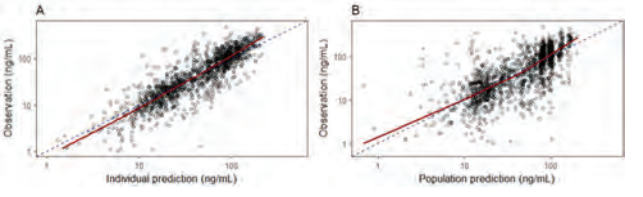
Teun van Gelder,[2] Robert B. Huizinga,[1] Jan Noukens,[3] Laura J. Lisk,[1] Neil Solomons.[1] *[1]Aurinia Pharmaceuticals Inc Victoria, Victoria, BC, Canada; [2]Universiteit Leiden, Leiden, Netherlands; [3]Curare Consulting, Leiden, Netherlands.*

Background: In a phase III clinical trial in patients with active lupus nephritis (LN), patients treated with 23.7 mg voclosporin bid in combination with MMF, achieved renal response rates of 40.8% vs. 22.5% for the control arm (OR 2.65; $p < 0.001$). The dose of voclosporin (VCS) was adjusted in response to decreases in eGFR. The objective of the present analysis was to evaluate the potential added value for therapeutic drug monitoring (TDM) in the LN patient population

Methods: Pharmacokinetic (PK) data was analyzed from patients with LN treated with VCS. Based on a population PK model, the influence of various covariates on the disposition of voclosporin was evaluated. Calcineurin inhibition (CNI) was estimated using concentration data in the LN population and previously measured inhibition. Obtained exposure were put into perspective of renal response and the established safety margin

Results: Sex, body weight, race, age, serum albumin, total bilirubin and eGFR demonstrated no significant or clinically relevant effect on the PK parameters. VCS has linear PK, and the goodness-of-fit plots (Figure 1 a/b) indicate that the model adequately describes observed and predicted concentrations of VCS. A strong correlation between VCS concentration and calcineurin inhibition is observed. VCS inhibits calcineurin in a dose-dependent manner up to maximum of 64 mg bid. In healthy subjects, a 96 mg bid dose was considered to be the upper limit of tolerability though did not present any safety concerns. At the 4-fold lower therapeutic dose of 23.7 mg bid, CNI was estimated to be 15.7% at C_{trough} and 58.1% at C_{max}. In a quartile exposure analysis, no relationship with the odds ratio for renal response was observed and favored VCS in all quartiles

Conclusions: At a therapeutic dose of 23.7 mg bid, sex, body weight, race, age, serum albumin, total bilirubin and eGFR demonstrated no clinically relevant effect on VCS PK parameters. The linear PK profile of VCS allows the use of a pharmacodynamic approach instead of a pharmacokinetic approach, in which the dose of VCS is adjusted in response to decreases in eGFR. These data suggest that TDM is unlikely to be of added benefit to patient management



PO1919

Clinical Outcomes in Lupus Nephritis by Renal Response Status: A Retrospective Analysis of the Hopkins Lupus Cohort

Michelle Petri,[1] Qinggong Fu,[2] Yulia Green,[3] Anuradha Madan,[4] Daniel W. Goldman,[1] Selin Cooper-Blenkinsopp.[5] *[1]Johns Hopkins University School of Medicine, Baltimore, MD; [2]GlaxoSmithKline, Upper Providence, PA; [3]GlaxoSmithKline, Uxbridge, United Kingdom; [4]GlaxoSmithKline, Collegeville, PA; [5]GlaxoSmithKline, Stevenage, United Kingdom.*

Background: A retrospective analysis of the Hopkins Lupus Cohort (a prospective, longitudinal study of patients [pts] with systemic lupus erythematosus) reported that renal response (complete/partial/none) at 24 months post-diagnosis of lupus nephritis (LN) predicts long-term renal survival.[1] Here, we compare long-term renal survival and chronic renal insufficiency-free survival in pts with and without a renal response (RR) to standard LN therapy, as defined by primary endpoint in the Phase 3 BLISS-LN study (GSK Study BEL114054; NCT01639339).

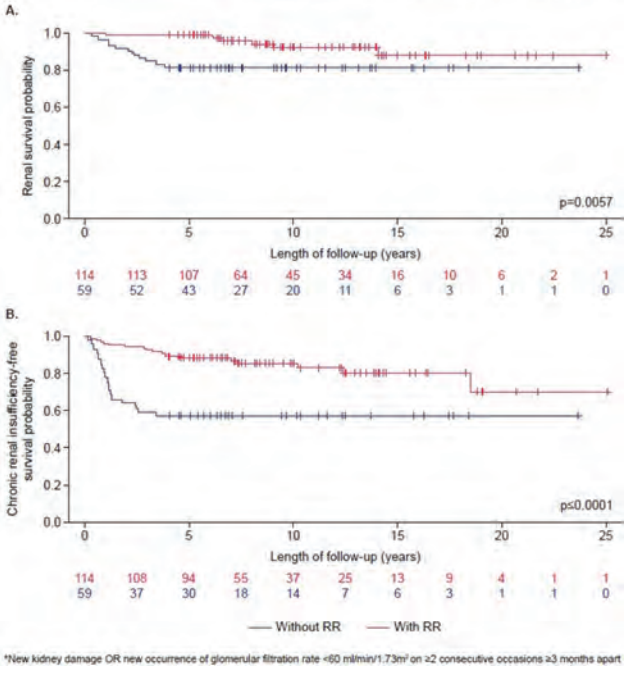
Methods: This retrospective analysis (GSK Study 213039) of the Hopkins Lupus Cohort included pts with biopsy-proven class III, IV, or V LN. Endpoints were: long-term renal survival (no end-stage renal disease [ESRD] and/or mortality) and long-term chronic renal insufficiency-free survival by RR status at 24 months post-biopsy, both assessed by Kaplan–Meier plots with log-rank test and Cox proportional hazards regression.

Results: 173 pts with LN were included; 91.3% were female and mean (SD) age at biopsy was 36.2 (11.8) years. At 24 months post-biopsy, 114 (65.9%) pts achieved RR. Pts with RR at 24 months were less likely to experience an ESRD/mortality event and chronic renal insufficiency (**Figure**), even after adjusting for covariates (HR [95% CI] 0.33 [0.13, 0.87], p=0.0255; and HR [95% CI] 0.26 [0.14, 0.47], p<0.0001, respectively).

Conclusions: Achieving BLISS-LN primary endpoint defined RR at 24 months post-biopsy is associated with long-term renal survival and chronic renal insufficiency-free survival in pts with LN. [1]Davidson JE, *et al. J Rheumatol* 2018;**45:**671–7.

Funding: Other NIH Support - The Hopkins Lupus Cohort is funded by NIH grant R01-AR069572, Commercial Support - GSK

Figure. Renal survival (A) and chronic renal insufficiency–free survival* (B) by RR status at 24 months



*New kidney damage OR new occurrence of glomerular filtration rate <60 ml/min/1.73m² on ≥2 consecutive occasions ≥3 months apart

PO1920

Predictors of Doubling of Serum Creatinine at the Time of Biopsy in a Lupus Nephritis Cohort

Jaime (James) A. Vondenberg, Saeed K. Shaffi. *University of New Mexico, Albuquerque, NM.*

Background: Lupus nephritis is associated with significant morbidity and it is imperative to study the factors associated with renal survival. We study the determinants of doubling of serum creatinine in a predominantly Hispanic cohort.

Methods: We identified patients with biopsy-proven lupus nephritis from the biopsy registry that comprises of biopsies performed between 2002-2016. Demographic, clinical, and biochemical variables were obtained from the registry and electronic medical records. We studied the factors associated with the doubling of creatinine by performing univariate Cox proportional hazard analysis. All significant associations (p <0.05) were studied in a multivariate Cox regression model. Patients were censored upon death or the last follow-up.

Results: Out of 62 patients with biopsy-proven lupus nephritis, 53 (85.5%) were female. Whites, Hispanics, and Native Americans comprised 35.5, 30.6, and 16.1% of the cohort, respectively while 56% of the participants identified ethnically as Hispanic. Mean biopsy age, serum creatinine, and spot urine Protein/Creatinine were 34.5 (SD 15.3) years, 1.34 (SD 0.83) mg/dl, and 4.2 (SD 4.9) g/g, respectively. Class IV (48.4%) and III (16.1%) were the most prevalent lupus classes. Median (IQR) follow-up was 474.5 (1170) days. On multivariate analysis, higher age at biopsy was associated with decreased risk of doubling of serum creatinine (Figure 1). A higher spot urine Protein/Creatinine and C4 level at the time of biopsy were associated with increased risk of doubling of serum Cr.

Conclusions: Previous studies have shown that biochemical markers at the time of kidney biopsy are a poor prognostic marker of renal outcomes in lupus nephritis. In this study, demographic, biochemical, and histological markers failed to predict doubling of serum creatinine. The age and the level of proteinuria at the time of kidney biopsy were associated with doubling of serum creatinine.

Figure 1: Predictors of doubling of serum Creatinine

Univariate Analyses		
Variables at the time of biopsy	**Reference/ Interpretation**	**Hazard Ratio for doubling of serum Cr (95% CI)**
Hispanic	Not Hispanic	0.40 (0.28-0.57)
Age at Biopsy (years)	1-year increment	0.90 (0.88-0.92)
Male	Female	0.28 (0.10 – 0.77)
SSA/RO +	Negative	2.39 (1.95 -2.92)
SSB/LA +	Negative	2.39 (1.95-2.92)
Anti-Smith +	Negative	2.39 (1.95-2.92)
C4 (mg/dL)	1-unit increment	0.99 (0.98-0.99)
CRP (mg/dL)	1-unit increment	0.71 (0.62 – 0.82)
ESR	1-unit increment	0.98 (0.98-0.99)
Urine Protein/Creatinine (g/g)	1 gm increment	1.11 (1.09 -1.12)
Urine RBC (RBC/HPF) ≥3	Normal (<3 RBC/HPF)	0.00 (0.00-INF)
Multivariate Analyses		
Age at Biopsy	1-year increment	0.78 (0.74-0.82)
C4	1-unit increment	1.16 (1.14-1.19)
Urine Protein/Creatinine (g/g)	1 gm increment	1.13 (1.10- 1.16)

PO1921

Lupus-Related Renal Disease Increases Inpatient Mortality: Analysis of the National Inpatient Sample

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Background: The aim of this study is to analyze the difference in outcomes of Systemic Lupus Erythematosus (SLE) with and without lupus-related renal disease. The primary outcome was inpatient mortality, while secondary outcomes were hospital length of stay (LOS) and total hospital charges.

Methods: Data were abstracted from the National Inpatient Sample (NIS) 2016 and 2017 Database. NIS is the largest inpatient admission database in the USA. The NIS was searched for adult SLE hospitalizations with and without lupus-related renal disease as principal or secondary diagnosis using ICD-10 codes. Multivariate logistic and linear regression analysis was used to adjust for confounders for the primary and secondary outcomes respectively. STATA software was used to analyze the data.

Results: There were over 71 million discharges included in the combined 2016 and 2017 NIS database. 355,740 hospitalizations were for adult patients, who had either a principal or secondary ICD-10 code for SLE. 51,875 (14.6%) and 303,865 (85.4%) of these hospitalizations were for SLE with and without lupus-related renal disease respectively. 7,060 adult SLE hospitalizations (2%) resulted in inpatient mortality. 1,110 (2.14%) of the deaths occurred in SLE with lupus-related renal disease vs 5950 (1.96%) without lupus-related renal disease (P=0.228). The adjusted odds ratio (AOR) for inpatient mortality for SLE with lupus-related renal disease compared to those without lupus-related renal disease was 1.38 (95% CI 1.17-1.63, P<0.0001). SLE with lupus-related renal disease hospitalizations had a mean increase in adjusted LOS of 1.14 days (95% CI 0.95-1.34, P<0.0001) compared to SLE without lupus-related renal disease. Hospitalizations for SLE with lupus-related renal disease had an increase in adjusted total hospital charges of $15,910 (95% CI 13,085-18,736, P<0.0001) compared to SLE without lupus-related renal disease.

Conclusions: Hospitalizations for SLE with lupus-related renal disease have increased inpatient mortality, LOS, and total hospital charges compared to those without lupus-related renal disease. SLE patients with lupus-related renal disease require a multidisciplinary approach involving the rheumatologist and nephrologist to optimize outcomes.

PO1922

Analysis of Characteristics and Risk Factors of Sepsis in Patients with Lupus Nephritis

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Background: Patients with lupus nephritis are at high risk of infection due to intrinsic immune dysregulation and treatment with glucocorticoids and immunosuppressants. Infection is a common complication in patients with lupus nephritis and is a major determinant of in-hospital mortality. Sepsis are the most frequent causes of infection-related mortality. In this research, we study the clinical characteristics and related risk factors of sepsis in patients with lupus nephritis according to a retrospective analysis.

Methods: A retrospective study was carried out for 322 hospitalized patients with lupus nephritis in Sun Yat-Sen Memorial Hospital from 2010 to 2019. The infected group consisted of 140 patients (The infected patients were subdivided into septic group and non-septic group according the sepsis criteria) while the non-infected group consisted of 182 patients without infection. Baseline data including sex, age, disease duration, hospitalization duration, associated organ involvement, use of glucocorticoid and immunosuppressants.

Results: Compared to the non-infected group, longer hospitalization duration(14 vs. 9d,P<0.05), pulsed methylprednisolone treatment within 1 month(10.7% vs. 1.6%,P<0.05), cyclophosphamide(22.9% vs. 14.3%,P<0.05), and calcineurin inhibitors(18.6% vs. 10.4%,P<0.05), and higher dose of oral corticosteroid(15 vs. 10mg,P<0.05)can be seen in the infected group (P<0.05). Compared to the non-septic group, higher proportion of male(21.2% vs. 8.0%,P<0.05), higher SELDAI score(9.0 vs. 6.0,P<0.05), higher proportion of pulsed methylprednisolone treatment within 1 month(13.5% vs. 10.7%,P<0.05)and higher dose of oral corticosteroid(20.0 vs. 15.0mg,P<0.05)can be seen in the septic group (P<0.05). About the laboratory results, lower level of platelet(129.0 vs. 194.5×10^9/L,P<0.05)and lymphocyte(0.6 vs. 0.9×10^9/L,P<0.05), while higher level of serum creatine(134.0 vs. 88.0μmol/L,P<0.05), C reactive protein(43.8 vs. 12.3mg/L,P<0.05)and erythrocyte sedimentation rate(60.0 vs. 45.5mm/h,P<0.05) can be seen in the septic group. Multivariate Logistic regression analysis revealed that male and pulse methylprednisolone treatment within 1 month were independent risk factors of sepsis in patients with lupus nephritis (P<0.05).

Conclusions: Male and pulse methylprednisolone treatment within 1 month were independently associated with sepsis in patients with lupus nephritis.

PO1923

An Evaluation of Costs Associated with Overall and Renal-Specific Organ Damage in Patients with Systemic Lupus Erythematosus in the United States

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Background: Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory, autoimmune disease affecting multiple organ systems, and characterized by fluctuating disease activity (flares). The combination of flares and SLE treatment toxicity increases the risk of organ damage (OD), including renal OD. Despite the high prevalence of OD and the associated poor disease prognosis, real-world studies on the economic impact of OD, especially renal OD, in SLE are limited.

Methods: This retrospective analysis (GSK Study 208380) used the IQVIA PharMetrics Plus Database to identify patients with SLE and OD during 01/01/09–06/30/18. Patients with OD were identified using International Classification of Diseases (ICD)-9/10 codes derived from the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.[1] Inclusion criteria: ≥18 years of age; continuous enrollment 12 months both pre and post index (index: date of first observed OD medical claim); ≥1 inpatient (IP) or ≥3 outpatient (OP) claims within 6 months for an OD-related diagnosis code; ≥1 IP or ≥2 OP claims separated by ≥30 days for SLE (ICD-9: 710.0 or ICD-10: M32.X) prior to the OD index date. Patients with renal-specific OD at index were noted. Patient characteristics were identified in the 12-month pre-index period and all-cause healthcare costs (2018 US$) were reported in the 12-month pre- and post-index periods. Results were analyzed with descriptive statistics.

Results: A total of 8952 patients met OD criteria and 486 (5.4%) had renal-specific OD. Patients were 92% female, mean (standard deviation [SD]) age was 46.4 (12.2) years, and mean (SD) Charlson Comorbidity Index was 2.0 (1.1). Mean (SD) all-cause healthcare costs increased from $15,746 ($29,637) to $26,998 ($57,982) in pre- versus post-index periods, respectively. In patients with renal-specific OD, mean (SD) all-cause healthcare costs increased from $16,131 ($22,914) to $36,905 ($72,188) in pre- versus post-index periods, respectively.

Conclusions: In patients with SLE and OD, annual costs increased after OD diagnosis. A similar increase in annual costs was observed for patients with renal-specific OD at index. [1]Gladman DD and Urowitz MB. *Lupus.* 1999;8:632–7.

Funding: Commercial Support - GSK

PO1924

Characteristics of Lupus Nephritis in a Cross-Sectional Study of Hispanic and Native American Patients in New Mexico

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Background: In patients with lupus, nephritis develops in ~50% of patients, and is associated with significant morbidity. Therefore, it is important to characterize the demographic and biochemical variables associated with lupus nephritis. In this cross-sectional study comprised of many Hispanics and Native Americans, we investigate the demographic and biochemical variables at the time of lupus nephritis diagnosis.

Methods: We identified 62 patients with lupus nephritis from the University of New Mexico kidney biopsy registry that contains biopsies from 2002-2016. Demographics, comorbidities, outcomes, therapies, and laboratory data typically followed in lupus patients (complements, spot urine protein/creatinine (Pr/Cr) ratio, urine RBCs, serologies, etc) were collected from the registry and medical charts.

Results: 62 patients were included, 53 females and 9 males. White, Hispanic, and Native American races accounted for 35.5%, 30.6%, and 16.1% of the cohort, while 56.6% of patients identified ethnically as Hispanic. 3 patients had no labs. Overall mean age at the time of renal biopsy was 34.5 (SD 15.3) years old. Laboratory data among ethnicities is shown in Figure 1. Class IV was the most common classification in the whole cohort (48.5%), for Hispanics (56.7%), and Non-Hispanics (30%). Antibody status was similar among all ethnicities: ANA positive (95%; 80% titer ≥ 1:80), anti-dsDNA positive (73%), anti-Smith positive (56%), and SS-A positive (56%). The most common comorbidities were hypertension (n=46) and depression (n=16). For induction therapy, most Hispanics received low dose cyclophosphamide (CYC) (41%), and Non-Hispanics received mycophenolate mofetil (MMF) (35%). For maintenance therapy, both Hispanics (37%) and Non-Hispanics (35%) most often received MMF. 7 patients progressed to ESKD, by ethnicity: 5 Hispanic and 2 Unavailable (1 African American).

Conclusions: The lupus cohort predominantly consisted of females and class IV nephritis. Many patients of Hispanic ethnicity identified as White with respect to race. At the time of lupus nephritis diagnosis, antibody status, serum creatinine, and urine spot protein/creatinine ratio were similar among ethnicities. Hispanics were more likely to progress to ESKD. The most commonly used induction therapy was low dose CYC followed by MMF, and the most common maintenance therapy was MMF.

PO1925

The ISN/RPS 2016 Classification Predicts Renal Prognosis in Patients with First-Onset Class III/IV Lupus Nephritis

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Background: Lupus nephritis (LN) is a life-threatening complication of systemic lupus erythematosus. The 2003 pathological classification of LN by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) was revised in 2016; it quantitatively evaluates the interstitium in addition to the glomeruli. To date, the clinical utility of the 2016 classification has not been fully investigated.

Methods: We performed a retrospective multicenter cohort study and investigated the utility of the 2016 classification—including the activity index (AI), chronicity index (CI), and each pathological component to predict CR or renal function decline defined as 1.5-fold increase in serum creatinine levels (sCr)—and compare with that of the 2003 classification. Adult patients with first-onset class III/IV LN who were newly prescribed any immunosuppressants were consecutively enrolled from January 2004 to December 2014 and observed until July 2016.

Results: We enrolled 91 patients (number of female, 65; median age [interquartile rage: IQR], 47 [30–62] years old; median estimated glomerular filtration rate (eGFR), 64 [IQR: 45–84] ml/min/1.73 m^2; median proteinuria, 1.9 [IQR: 0.9–4.6] g/gCr). During the observation period (median, 51 [IQR: 23–77] months), 35 patients achieved CR, and 16 developed 1.5-fold increase in sCr. The A or A/C subclasses based on the 2003 classification were not associated with clinical outcomes. After adjustments for eGFR and urinary protein levels, higher CI and interstitial inflammation scores were associated with failure to achieve CR (adjusted hazard ratios (HR) [95% confident interval (CI)]: 0.75 [0.64–0.88], 0.39 [0.25–0.61], respectively). Similarly, higher CI and higher interstitial fibrosis and lower hyaline deposit scores were associated with renal functional decline (adjusted HR [95%CI]: 1.24 [1.01–1.53], 2.66 [1.43–4.93], 0.45 [0.21–0.97], respectively).

Conclusions: We demonstrated the utility of CI and importance of assessing interstitial regions in predicting renal prognosis. The 2016 classification can predict the clinical outcomes more precisely than the 2003 classification.

Funding: Commercial Support - Chugai Pharmaceutical Co

PO1926

Resolution of Immune Deposits in the Glomeruli of Patients with Lupus Nephritis (LN)

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Background: Patients with proliferative LN have severe glomerular immune injury that resolves over time with treatment. The extent of resolution has been assessed by the NIH activity index (AI) in patients who have had a repeat kidney biopsy during maintenance immunosuppression, and many patients do achieve an AI=0, so-called histologic remission. The fate of glomerular immune complexes in treated LN patients has not yet been characterized. This study examined the immunofluorescence (IF) patterns in biopsies obtained during LN therapy.

Methods: A cohort of Hispanic LN patients (n=89) was studied. All patients had biopsy-proven (Bx1) proliferative (Class III, IV±V) LN, and were treated with corticosteroids plus cyclophosphamide or MMF for 6 months and then switched to MMF for maintenance therapy. After a median of 42 (range 30-52) months patients had a second protocol biopsy (Bx2) to determine if they had achieved histologic remission (AI=0) or had persistent histologic activity (AI≥1). Kidney biopsies were evaluated by standard IF microscopy (IgG, IgA, IgM, C3, C1q), and semi-quantitatively graded on a scale of 0-3 (not present-bright).

Results: cyclophosphamide (48%). These patients had a median serum creatinine of 0.7 mg/dl (0.5-2.2) and proteinuria of 0.2 g/d (0-0.8). The 26 patients who had persistent histologic activity at Bx2 had a median AI of 2 (1-6), serum creatinine of 0.75 mg/dl (0.6-1.1), and proteinuria of 0.2 g/d (0.1-0.9) and about half had been treated with MMF. No residual IF was present in 30% of patients with an AI of 0, but was present in all patients who had an AI≥1. IF for IgG became negative in 46% of patients with an AI=0 between Bx1 and Bx2, but in only 7.7% of patients with AI≥1 (P=0.0005). Similarly, IF for C3 became negative in 84% of patients with AI=0, compared to 31% of patients with AI≥1 (P<0.0001). After a median of 23 months (11-39) 7 patients who had been in histologic remission suffered an LN flare. None of these patients had had complete resolution of IF on Bx2. In contrast, no patient with an AI=0 and an absence of IF on Bx has had an LN flare during a follow-up of 44 months (19-105).

Conclusions: About one third of patients with LN can achieve histologic and immunologic kidney remission. These patients appear to have an outstanding long-term kidney prognosis.

Funding: Clinical Revenue Support

PO1927

Vasculopathy Associated with Lupus Nephritis (Severity and Outcomes)

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Background: Lupus nephritis (LN) is common in patients with systemic lupus erythematosus. Classification, prognosis, and treatment considerations of LN relays mainly on kidney biopsy features. Although few observational studies showed LN with vasculopathy has more severe course, literature reviews are scarce and mostly from Asian populations. The goal of the study was to shed more light on severity and response to Immunosuppression (IS) therapy in this subgroup of LN.

Methods: This was a single center retrospective chart review of LN patients from 2010-2019. Inclusion criteria were adult patients with native kidney biopsy proven LN documented in chart. Patients with systemic thrombotic microangiopathy (TMA) or possible secondary cause of renal TMA (other than SLE) were excluded. Two groups were identified for comparison, LN without vasculopathy (WOV) and LN with vasculopathy (WV). Vasculopathy was defined from kidney biopsy as vascular sclerosis (at least moderate), vascular immunoglobulins deposits, vasculitis, or TMA. Creatinine (Cr), albumin (Alb), urine protein-creatinine ration (UPCR), end-stage renal disease (ESRD) and treatment regimens were compared, p-values are calculated by Mann Whitney, chi square and ANOVA of repeated measures.

Results: There were 431 patients with LN, 65 patients qualified for the study. patients with LN-WOV (n=38), and LN-WV (n=27). Racial demographics: 49=black (75%),14=white (21%), 1=Hispanic, 1=Asian. Females 57 (88%). Median age 37 years. Average follow-up 3.5 years. Induction IS regimen for LN-WOV was mycophenolate mofetil (MMF) in 52%, Cyclophosphamide (CYC) in 11%, and Rituximab (RTX) in 15%. In LN-WV induction IS regimen was MMF in 52%, and CYC in 23%. At baseline, mean values of Cr 1.7 mg/dL, Alb 2.5 g/dL and UPCR 3.7 g/g for LN-WOV and LN-WV were similar (p = 0.38, 0.37, 0.53, respectively). At 6 and 12 months of follow-up, mean values of Cr, Alb, and UPCR remained similar (p = 0.59, 0.49, and 0.64 for 6 months, and 0.34, 0.41, 0.53 for 12 months). No difference was found in ESRD events: 7 (18%) in LN-WOV and 5 (18%) in LN-WV, p=0.86.

Conclusions: In our cohort, both groups of LN-WOV and LN-WV showed no statistical difference in the severity of presentation, nor in response to IS therapy assessed at 6 and 12 months follow-up of Cr, Alb, and UPCR, and ESRD. Hence, LN-WV was not associated with ominous outcomes or more resistance to IS.

PO1928

Urine Epidermal Growth Factor Levels Are Associated with Kidney Prognosis in Lupus Nephritis

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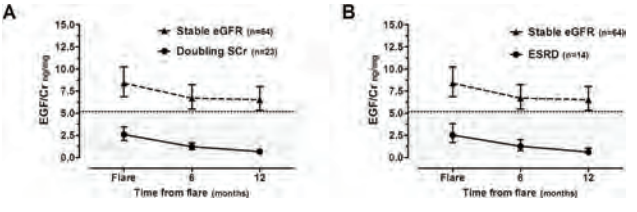
Background: Epidermal growth factor is a protein specifically synthesized in the kidneys. EGF urine levels have been associated with progressive chronic kidney disease. This study evaluated the role of urine epidermal growth factor (uEGF) as a biomarker of chronic kidney damage in lupus nephritis (LN).

Methods: Through a proteomic approach we identified uEGF as a biomarker of interest in an LN discovery cohort. The expression of uEGF was characterized in two large multiethnic LN cohorts, and the association between uEGF at flare and long-term outcomes assessed in a subset of 120 patients. The expression of uEGF over time was observed in two longitudinal LN cohorts in which serial urine samples were collected.

Results: The proteomic analysis showed lower uEGF in patients with active LN than in normal controls. The peptide sequence was consistent with the proEGF isoform, and this was confirmed by immunoblotting. These findings were verified by ELISA. Patients with active LN had a significantly lower levels of uEGF than patients with active non-renal lupus, patients with inactive lupus, and kidney donors. Urine EGF was inversely correlated with the kidney biopsy chronicity index (r=-0.67, p<0.001). Multivariate survival analysis showed that uEGF at flare was associated with the time to doubling of serum creatinine (HR 0.88, 95% CI 0.77-0.99, p=0.045). In patients who progressed to doubling of serum creatinine (Figure 1A) and end-stage kidney disease (Figure 1B), uEGF was lower at flare and then decreased over the 12 months following flare. A uEGF cutoff <5.3ng/mg identified all patients who progressed to end-stage kidney disease.

Conclusions: Urine EGF levels correlate with histologic kidney damage. Low uEGF levels at flare and decreasing uEGF levels over time are associated with adverse long-term kidney outcomes.

Funding: Other NIH Support - NIH - NIAMS



Urine EGF course in patients with stable kidney function compared to patients who progressed to doubling of serum creatinine (A) or end-stage kidney disease (B).

PO1929

Idiopathic Hypokalemia in Lupus Nephritis: A Previously Unrecognized Entity

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Background: The lupus nephritis (LN) population at Parkland Hospital is among the largest in the country. During the course of usual care in this population, we encountered a phenomenon of unexplained hypokalemia that has never been previously described. Here we begin to phenotype this cohort by comparing it to a group of LN controls as well as LN with distal renal tubular acidosis (RTA).

Methods: From our population of 403 LN patients followed in the Parkland Health and Hospital System, we identified a cohort of 20 patients with idiopathic hypokalemia (HK). This cohort is compared to 90 LN controls (control) and 10 LN patients with distal RTA (RTA). In contrasting the three groups, the Chi-squared test or Fisher's exact test were used for categorical data and the one-way ANOVA or Kruskal-Wallis test was used for continuous measures. For paired comparisons of continuous variables between the groups, the student's t-test was employed

Results: The HK cases had lower mean serum potassium compared to control and RTA (3.24 vs 4.06 vs 3.75 mmol/L, respectively; P< 0.001). The mean serum bicarbonate was normal in HK and control but lower in RTA (25.83 vs 25.20 vs 19.28 mmol/L, respectively; P< 0.001). The urine pH was abnormally high only in the RTA group (6.13 vs 6.22 vs 6.68; P= 0.012). The mean serum magnesium was modestly lower in HK compared to control-nml and control-RTA (1.75 vs 1.97 vs 1.97 mg/dL; P= 0.002) There were differences in serologic markers of autoimmunity. Compared with control, both HK and RTA were more likely to be seropositive for anti-SSA (P= 0.002 and 0.015, respectively). In contrast, compared to controls, only HK expressed a higher rate of anti-RNP seropositivity (P= 0.002) and only control-RTA had a higher rate of anti-SSB positivity (P= 0.044).

Conclusions: A syndrome of idiopathic hypokalemia was revealed in 20/403 (5%) of patients within our lupus nephritis population and is distinct from the RTA that is

known to rarely occur in lupus. This phenomenon has not been previously described. We speculate that idiopathic hypokalemia is the result of a novel target of autoimmunity in lupus affecting renal tubular potassium transport.

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PO1930

Outcomes of Lupus-Related Glomerular and Tubulointerstitial Disease: Analysis of the National Inpatient Sample

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Background: The study aims to compare the differences in outcomes of hospitalizations for Systemic Lupus Erythematosus (SLE) with glomerular and tubulointerstitial related renal disease. The outcomes compared were inpatient mortality, hospital length of stay (LOS), and total hospital charges.

Methods: Data were abstracted from the National Inpatient Sample (NIS) 2016 and 2017 Database. NIS is the largest inpatient hospitalization database in the United States (U.S). The NIS was searched for adult SLE hospitalizations with lupus-related glomerular and tubulointerstitial disease as principal or secondary diagnosis using ICD-10 codes. The analysis was done using STATA. Multivariate logistic and linear regression analysis was used accordingly to adjust for confounders for the outcomes.

Results: There were combined 71 million discharges included in the 2016 and 2017 NIS database. 51,875 hospitalizations were for adult patients, who had either a principal or secondary ICD-10 code for SLE with lupus-related renal disease. 51,525 (99.3%) and 350 (0.7%) of these hospitalizations were for SLE with lupus-related glomerular and tubulointerstitial disease respectively. The mean age for SLE with lupus-related glomerular disease was 40.6 vs 44.2 years for lupus-related tubulointerstitial disease (P=0.084). 7,060 adult SLE hospitalizations resulted in inpatient mortality. 1,110 (2.14%) of the deaths occurred in SLE with lupus-related glomerular disease. The number of deaths for lupus-related tubulointerstitial disease was less than 10, hence it was omitted during the analysis by STATA. SLE with lupus-related glomerular disease had similar LOS (6.8 vs 6.7 days, p=0.865) and total hospital charges ($79,718 vs $83,006, p=0.961) compared to those with tubulointerstitial disease.

Conclusions: SLE with glomerular disease makes up the vast majority of SLE with lupus-related renal disease hospitalizations. Almost all the in-hospital deaths of SLE patients with lupus-related renal disease occurred in SLE with glomerular disease. LOS and total hospital charges were similar between hospitalizations for SLE with lupus-related glomerular and tubulointerstitial diseases.

PO1931

Lupus Podocytopathy Systematic Review

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Background: Patients with lupus, can present with a renal lesion distinct from the ones described by the ISN/RPS classification of lupus nephritis called lupus podocytopathy. Lupus podocytopathy has been described as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) in patients with SLE with or without mesangial involvement but without proliferative or membranous lupus nephritis features. We have gathered the available data on lupus podocytopathy and analyzed it to provide a comprehensive report in this review.

Methods: We searched electronic databases including pubmed and google scholar, using keywords related to lupus podocytopathy and synonyms and treatment from inception to December 2019. Articles retrieved were screened for relevance, including reference list of retrieved. We included cohort studies, case series, and retrospective studies. Individual case reports were excluded.

Results: The search identified 8 studies, of which 6 were included with a total of 107 patients. The patients were predominantly female (88%). The average age was 35 years. Studies done outside of China had predominantly African-American patients 72.5%. The average serum creatinine was 2.06 mg/dL. The average proteinuria was 6.5 g/day. Four studies reported monotherapy corticosteroids, and three studies reported varied treatments. The average follow up was 3.7 years. Complete remission was reported to be 67% from 3 studies. Four studies reported relapse rate of patients, and it accounted to 72.5% of patients.

Conclusions: Our study is the first systematic review of lupus podocytopathy. The strength of this study is the merger of data from known studies in lupus podocytopathy which is a rare but important disease entity in lupus patients with renal disease. The treatment and possible prognosis of lupus podocytopathy patients are different from proliferative and membranous lupus nephritis, and physicians should be aware of this process. Patients can be spared from unwarranted immunosuppressive medications and their side effects. Greater collaborations and biopsies are needed to learn more about this interesting disease process.

Study	Initial Scr(mg/dL	Avg Proteinuria(g)	MCD	FSGS	Mes Prolif	Tx with CS	Tx with CS + CYC	Tx with CS+ CNI	Tx with CS + MMF	Avg f/up (years)	Remission (n)	Relapse (n)
Cobb et al	3.6	5.6	8	10	0	15	1	1	1	5.9	NA	NA
Wang et al	1.7	3.1	9	4	0	NA	7	0	0	3.5	0	13
Salvatore et al	5.3	8.0	NA	NA	NA	12	0	0	0	1.9	6	6
Hu et al	0.69	6.0	13	9	29	50	Yes	Yes	Yes	5.1	NA	37
Dube et al	1.8	9.6	7	0	5	7	0	0	0	NA	4	3
Kraft et al	3.8	7.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

PO1932

Extended Follow-Up of Patients Recruited to a Randomized, Controlled Trial of Rituximab vs. Azathioprine, After Rituximab Remission Induction for Patients with Relapsing ANCA-Associated Vasculitis

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Background: RTX is an effective remission induction therapy in AAV. However, the effect of RTX is not sustained, and relapse rates are high, especially in patients with a history of relapse. The RITAZAREM trial was an international, open-label, randomized, controlled trial of patients with AAV with relapsing disease comparing the efficacy, after induction of remission with RTX, of repeat dose RTX or AZA as relapse prevention strategies.

Methods: Patients with relapsing AAV received induction therapy with RTX and glucocorticoids (GC). If remission was achieved by month 4, patients were randomized 1:1 to receive RTX (1000 mg every 4 months for 5 doses) or AZA (2 mg/kg/day) as maintenance therapy for 24 months. Patients continued to be followed until at least 36 months after enrolment, with a primary outcome of time to disease relapse. The final patient reached month 36 in the trial in November 2019.

Results: 190 patients were enrolled and 170 randomized at month 4 (85 to RTX; 85 to AZA): median age = 59 years (range 19-89); prior disease duration = 5.3 years (0.4-38.5); 123/170 (72%) with anti-PR3 ANCA, 47/170 (28%) with anti-MPO ANCA; 104 (61%) enrolled after a severe relapse, 66/170 (39%) after a non-severe relapse; GC induction regimen: 48/170 (28%) higher-dose, 122/170 (72%) lower-dose; 114 (67%) patients had prior renal involvement. We previously presented the results demonstrating the superiority of rituximab over azathioprine during the maintenance treatment period. Results of the follow up phase of the study after discontinuation of maintenance therapy will be presented at the 2020 meeting.

Conclusions: The results of the extended phase of RITAZAREM will examine the long-term impact of B cell depletion in patients with AAV on sustaining remission beyond the treatment period, clinical or biomarker factors associated with risk of relapse, and post-treatment safety of prolonged use of rituximab, including a focus on hypoimmunoglobulinemia.

Funding: Other NIH Support - The VCRC is funded through collaboration between NCATS, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and has received funding from the National Center for Research Resources (U54 RR019497)., Commercial Support - Genentech/Roche

PO1933

Renal Disease During Maintenance Treatment in ANCA-Associated Vasculitis (AAV) Remains a Problem and Glucocorticoid Use Is High

Peter A. Rutherford, Dieter K. Goette. *Vifor Pharma Ltd, Glattbrugg, Switzerland.*

Background: AAV is a relapsing remitting long term condition and patients are at risk of organ damage from active AAV and therapy in particular glucocorticoids (GC). The remission maintenance phase of AAV is critical for good long term renal outcomes. This retrospective study examined the pattern of renal disease during the maintenance phase in AAV patients managed in routine clinical practice

Methods: 1478 AAV patients managed by 493 EU physicians (61% Nephrologists) who completed induction therapy for organ/life threatening AAV and initiated therapy between 2014-16 were studied. Data were collected from when maintenance was determined to begin by the physician and then after 6, 12, 18 and 36 months

Results: 49% had GPA; mean age 54.2 years and 56% male. 49% had incident AAV and 51% were studied from relapse. 70% received cyclophosphamide/GC and 30% received rituximab/GC with 28% plasma exchange. Physicians defined time of start of maintenance as mean of 5.7 months from diagnosis. Over 36 months from maintenance start 38% patients had relapse (26% 1, 8% 2, 3% 3 and 1% 4). Only 22% had no comorbidity at diagnosis, hypertension and renal impairment were common. eGFR CKD stage changed over tme - stage 5 (8% to 11%), stage 4 (12 to 8%), stage 3 (43 to 37%) and stage2/1 (38 to 46%) – mean at 36 months of 53.3 ml/min. Hypertension and renal impairment were frequent comorbidities and renal related AEs were often reported. Many patients stayed on GCs and renal impairment and hypertension as well as active/chronic vasculitis activity were more frequent in patients remaining on GCs throughout maintenance. Renal function worsened in 24% patients and 46% were still receiving steroids vs 35% and 37% of those with improved or unchanged renal function ($p< 0.05$)

Conclusions: This study demonstrates relapse remains a problem iin AAV and many patients still receive long term GCs. Worsening renal disease is a challenge and associates with higher GC exposure suggesting ongoing renal inflammation and/or chronic damage. New therapeutic approaches are needed to improve renal outcomes

Funding: Commercial Support - Vifor Pharma

	Diagnosis - incidence or relapse	36 months
Receiving GCs %	71	39
Hypertension – comorbidity % All patients, No GC, Constant GC use	48	50, 39, 57
Renal impairment – comorbidity % All patients, No GC, Constant GC use	9	19, 13, 24
Adverse events		
Worsening eGFR %		10
Rising proteinuria %		4
Hypertension (new or worsening) %		18
Active or chronic renal vasculitis activity % All patients, No GC, Constant GC use		36, 28, 46

PO1934

Cost-Effectiveness of Maintenance Therapy with Azathioprine vs. Rituximab (Tailored or Fixed-Schedule) in Adults with Generalized ANCA Vasculitis in Colombia

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Background: Azathioprine has been the drug of choice for maintenance therapy in patients with generalized ANCA vasculitis. However, recent studies show that rituximab, a high-cost biological agent, which can be administrated in two different schedules, might be more effective, so it is necessary to know the cost- effectiveness. Our goal was to compare the cost-effectiveness of the 3 maintenance schemes: standard therapy with azathioprine; fixed-dose rituximab and rituximab tailored according to CD19 lymphocyte level and ANCA titres, from the perspective of the Colombian healthcare system.

Methods: We designed a 5-year annual cycle Markov model with the following stages: remission, minor relapse, mayor relapse and death. Transition probabilities were obtained from a systematic review of the literature (Scopus and Pubmed). Following national guidelines for economic studies, costs, in 2018, 1USD = 2.956 Colombian pesos (COP), were estimated based on national drug registries, and official tariff manuals for procedures and other resources. Main outcome was quality-adjusted life years (QALY), using lupus nephropathy as a proxy; values were obtained from Tufts CEA Registry and validated by local expert panel through a modified Delphi technique. Cost-effectiveness threshold was three-times per capita GDP (USD 17253). Discount rate was 5%. Univariate and probabilistic sensitivity analyses were performed.

Results: Overall discounted 5-years costs were USD 1356 for azathioprine; USD 4750 for tailored rituximab and USD 6162 for fixed rituximab. QALY gains were 2.94, 3.63 and 3.64, respectively. Both tailored and fixed rituximab were cost-effective (cost per QALY gained: USD 4.919 and USD 6.865 respectively), but tailored dosing was preferable due to its lower cost. Sensitivity analyses did not modify these results significantly.

Conclusions: To our knowledge this is the first economic evaluation that compare azathioprine with tailored and fixed rituximab regimens as a vasculitis maintenance treatment in adults with ANCA generalized. Due to its lower effectiveness azathioprine should not be the first line of treatment. Tailored rituximab should be a better option than fixed schedule due to its lower cost with similar effectiveness.

PO1935

Use of Subcutaneous IgG to Treat Hypogammaglobinemia in ANCA-Associated Vasculitis

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Background: Intravenous immunoglobulin (IVIG) has been used to treat ANCA vasculitis (AAV) patients with recurrent infections as a result of hypogammaglobinemia induced by treatment regimens such as rituximab. Subcutaneous immunoglobulin (SCIG) has a better safety and tolerability profile. We characterized the clinical features, treatment and outcomes of AAV patients treated with SCIG).

Methods: We conducted a retrospective chart analysis of 187 patients in our AAV database to identify patients with recurrent infections and hypogammaglobinemia subsequently treated with SCIG. Patient demographics, clinical characteristics, treatment and immunological parameters were assessed.

Results: Of the 187 patients identified with AAV, 6 were treated with SCIG. All were Caucasian, PR3 positive and majority (n=4) were females. All patients had pulmonary involvement, and regimens of cyclophosphamide (CYC) and/or rituximab (RTX) were employed for induction and remission. Ig levels (IgG, IgM, IgA) were reduced in all patients. CD19/CD20 B cells were depleted, and CD3/4/8 and NK cells were preserved in all patients. The majority of patients(n=4) experienced recurrent URIs, 3 had shingles, in addition to other infections(table 1). All patients had no discernible IgG antibody response to pneumococcal vaccine. Mean duration between first rituximab administration and initiation of SCIG was 6.4 years. Four patients continued to receive RTX every 6 to 12 months while 2 patients remained in remission off RTX for over 2 yrs. IgG levels normalized and none of the patients had recurrence of infections after initiation of SCIG

Conclusions: These data, albeit preliminary, is one of the first series that demonstrates SCIG can be a safe and reliable alternative to IVIG in AAV patients with recurrent infections secondary to hypogammaglobinemia. Our data also suggest that SCIG may have immunomodulatory effects to maintain disease remission in AAV

Table 1. Treatment regimens for ANCA Associated Vasculitis Prior to Commencement of SCIG

Patient ID	Induction	Maintenance	RTX details	IgG level prior to SCIG (mg/dL)	Duration of RTX cessation prior to SQIG (months)
1	S + CYC + PLEX + RTX	AZA	Induction 375mg/m^2 q week x 4	299	95
2	S + RTX	RTX	7 courses of induction 375mg/m^2 q week x 4 for initial disease and 6 relapses Maintenance q 6 months	484	RTX continued
3	S + CYC	RTX	Induction 375mg/m^2 q week x 4 1 dose 500mg for recurrence	318	10
4	S + CYC	RTX	Maintenance 1000mg q 6 months	393	RTX continued
5	S + RTX	RTX	Maintenance 1000mg q 6 months	213	RTX continued
6	S + CYC	RTX	Maintenance 1000mg q 1year	289	RTX continued

PO1936

Glucocorticoid Maintenance Therapy and Severe Infectious Complications in ANCA-Associated Vasculitis

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Background: Although treatment and outcomes in anti-neutrophil cytoplasmic autoantibody associated vasculitis (AAV) have been improved over the last decades, intensified immunosuppressive burden is concurrently associated with life-threatening adverse effects which are the main cause of death during the first year after disease onset. Our study evaluates the impact of cyclophosphamide (CYC) induction dose and glucocorticoid maintenance dose and duration on patient outcomes with an emphasis on infectious complications.

Methods: A total of 130 AAV patients from two different German Vasculitis Centers diagnosed between 2004 and 2019 treated with CYC for induction therapy and glucocorticoids ± mycophenolate mofetil or azathioprine for maintenance therapy were included in this study. We evaluated the impact of CYC dose for induction therapy and glucocorticoid dose and treatment duration for maintenance therapy on time to relapse, kidney function, infectious complications, irreversible physical damage and mortality. Patients were separated into four groups: <3g versus ≥3g cumulative CYC dose and <7.5mg after 6 months versus ≥7.5mg glucocorticoids after 6 months.

Results: The baseline demographic and disease characteristics were comparable between groups. Cumulative CYC dose had no impact on relapse rate, kidney function, infectious complications or mortality. Patients receiving ≥7.5mg glucocorticoids after 6 months had an increased rate of infectious episodes per patient (0.6 vs. 1.7; p<0.001). Urinary tract infection (p=0.007), pneumonia (p=0.003) as well as opportunistic pneumonia (p=0.022) and sepsis (p=0.008) appeared more frequently. Especially pneumonia during the first 24 months after disease onset (hazard ratio, 3.0 [95% confidence interval (CI), 1.5–6.1]) led to more death by infections (p=0.034). Patients ≥65 years with ≥7.5mg glucocorticoids after 6 months were at particular risk for infectious complications. Glucocorticoid maintenance therapy had no impact on relapse rate or kidney function after the last follow-up.

Conclusions: An extended glucocorticoid maintenance therapy may induce severe infectious complications leading to an increased frequency of death by infection, has no effect on time to relapse and should therefore be critically revised throughout the aftercare of AAV patients.

PO1937

Country Differences Exist in the Treatment of ANCA-Associated Vasculitis (AAV), but High-Dose and Prolonged Glucocorticoid Use Is Observed Across Europe

Peter A. Rutherford, Dieter K. Goette. *Vifor Pharma Ltd, Glattbrugg, Switzerland*.

Background: European AAV guidelines recommend remission induction therapy with combination of high dose glucocorticoids (GC) and rituximab (RTX) or cyclophosphamide (CYC) and maintenance therapy with either RTX or azathioprine (AZA). This retrospective study examined the pattern of prescribing, including the use of GCs, across Europe in AAV patients managed in routine clinical practice

Methods: 1478 AAV patients managed by 493 physicians in France, Germany, Italy, Spain and UK who completed induction therapy for organ or life threatening AAV (49%

incident and 51% relapsing) and initiated maintenance therapy between 2014-16 were studied. Data were collected at the time maintenance was determined to begin by the physician and then after 6, 12, 18 and 36 months.

Results: AAV type varied with more GPA in Germany (52%) and UK (56%) compared to France (47%), Italy (47%) and Spain (40%). Proportion of patients with severe progressive disease varied - 41% Italy to 48% France. Induction therapy varied with lowest use of IV GC and rituximab (RTX) and highest cyclophosphamide (CYC) use in the UK. Maintenance was defined by clinicians as approximately 6 months following treatment start and GCs were used similarly across all countries with less RTX and less GC used in UK and more AZA in Germany and UK. At 36 months prescribing patterns were similar and a variable proportion of patients (13% Germany to 30% France) stopped therapy but with approximately 25% patients not in full remission

Conclusions: AAV treatment prescribing patterns vary across Europe particularly RTX, driven by economic as well as case mix differences. GC use is high across all countries with high GC use (including IV at induction) and prolonged use over 36 months being common. Sustained remission rates could be improved and there is need for more targeted therapies to reduce reliance on GCs

Funding: Commercial Support - Vifor Pharma

% patients	Germany	France	Italy	Spain	UK
Remission Induction					
GC Oral	10	13	7	11	15
GC IV then oral	65*	56	61*	65*	53
RTX	36*	33*	31*	29	23
CYC (IV, oral)	69 (53,16)	67 (55,12)	68 (47*,21)	71 (58,12)	78 (61,17)
Maintenance start					
GC total, > GC 7.5mg/day	67, 66	62, 63	71, 66	56*, 61	67, 45
RTX	22	35	17	22	10*
Azathioprine	43*	24	28	29	47*
MMF	6*	14	21	21	24
CYC	22*	13	18	17	9
Full/partial remission	50, 45	52, 40	30, 61	40, 53	45, 49
eGFR < 45 ml/min	36	43	42	36	42
Maintenance 36 months					
GC total, > GC 7.5mg/day	45, 31	35, 29	46, 24	27, 39*	40, 21
RTX	22	19	9	19	6*
Azathioprine	41*	16	19	20	38*
MMF	7*	9	17	19	18
CYC	12*	4	3	6	1
Full/partial remission	77,21	74,21	70,24	75,24	73,23
eGFR < 45 ml/min	49	34	30	24	35

AAV prescribing (*p<0.05 vs respective highest/lowest country)

PO1938

Validation of a Clinical-Pathologic Renal Risk Score in ANCA-Associated Glomerulonephritis: The US Experience

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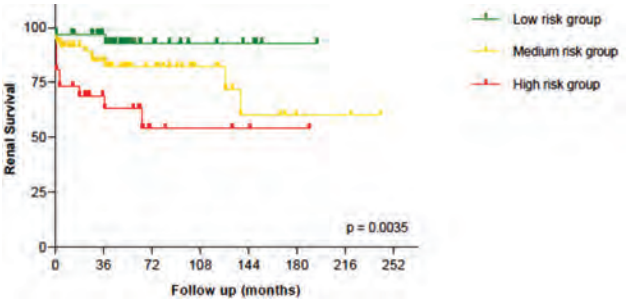
Background: The prognostication of renal disease in the setting of ANCA associated vasculitis (AAV) continues to pose a significant clinical challenge given lack of validated clinical and pathologic correlates. A risk score has been developed by a German consortium (Brix et al Kidney International 2018), to stratify risk of AAV-related renal disease progression to ESKD. We applied this risk score in our cohort of AAV patients to ascertain its reproducibility.

Methods: A single center retrospective cohort study was performed reviewing 148 renal biopsies of patients with AAV GN. Data for score calculation was available of 119 patients with a median follow up of 58 months (IQR 28 – 97 months). Three parameters were used in the risk prediction score: (1) # of normal glomeruli (N0 >25%, N1 10-25%, N2 <10%), (2) tubular atrophy and interstitial fibrosis (T0 <25%, T1 >25%) and (3) eGFR at the time of diagnosis (G0 >15, G1 <15). A weighted assignment of points to each parameter was as follows: N1 [4], N2 [6], T1 [2], G1[3], and the resulting aggregate risk score used to classify predicted ESRD risk was low (0), intermediate (2 to 7), or high (8 to 11 points).

Results: In the cohort of 148 patients, median age was 63 years and mean eGFR at diagnosis was 27.7. Seventy-six were MPO, 57 were PR3 positive and 15 were ANCA negative. With regards to risk stratification, 34 were in low risk category, 59 in the medium risk category and 26 patients in the high-risk category. Overall, 23 patients (19.3%) progressed to ESKD with 2 (5.9%), 11 (18.6%), 10 (38.5%) in low, medium and high risk groups, respectively. A Kaplan-Meier survival curve (Figure1) demonstrates worsening of renal survival across the risk groups (p=0.0035).

Conclusions: This AAV renal risk score was able to reliably predict risk for progression to ESKD. A further analysis revalidating cut-offs and risk score points would likely refine the score improving its prediction accuracy.



PO1939

Clinical Features and Outcomes of Anti-Neutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Chinese Elderly and Very Elderly Patients

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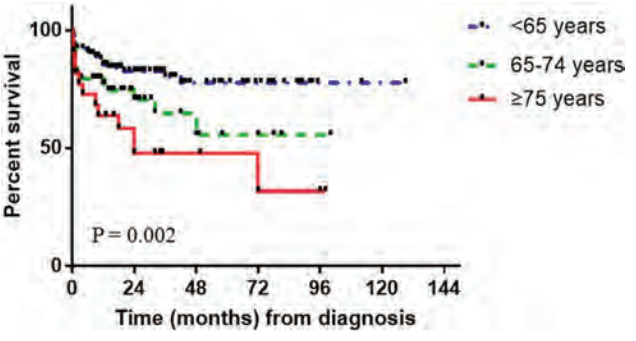
Background: Anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV) is predominantly a disease of the elderly, and the incidence increases with age. However, there are few data focusing on the clinical features in elderly-onset AAV, especially in very elderly-onset AAV in China. The aim of this study was to explore whether elderly-onset AAV shows any specific clinical features and outcomes in Chinese patients.

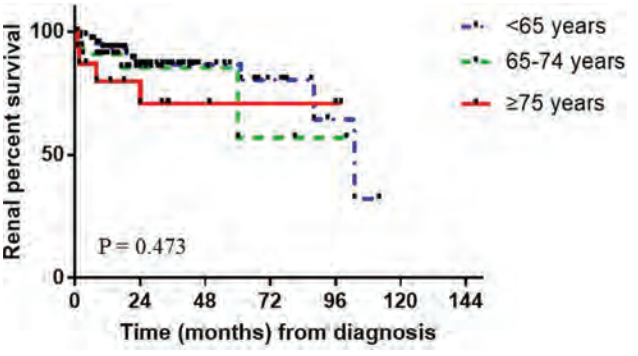
Methods: We performed a retrospective study in Xiangya Hospital, a mixed tertiary medical center in south China. A total of 177 patients presenting with AAV were included between January 1, 2010 and December 31, 2017. Patients were divided into younger group (age<65 years) and older group (age≥65 years) which was sub-divided into elderly group (age 65-74 years) and very elderly group (age≥75 years).

Results: We found patients in the very elderly group had more chest and cardiovascular involvement (P =0.033 and P =0.017). Older AAV patients had less renal involvement and lower serum C4 level (P =0.013 and P =0.003). Very elderly AAV patients had lower platelet counts. Patients in the younger group had a higher level of BVAS among three groups (P <0.05 younger group vs. very elderly group; P <0.05 younger group vs. elderly group). There were no significantly difference in the proportion of ESRD patients among the three groups (P =0.473). Patients in the very elderly group had the poorest patient survival (P = 0.002).

Conclusions: Older AAV patients had less renal involvement, lower serum C4 level and BVAS. The very elderly group got the most chest and cardiovascular involvement and had lower platelet counts. Older age is associated with higher mortality in AAV patients.

Funding: Government Support - Non-U.S.





PO1940

Validation of the Renal Risk Score for ANCA-Associated Glomerulonephritis in a National Irish Cohort

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Background: Histopathological examination is currently the gold standard for diagnosis of ANCA-associated glomerulonephritis (AAV GN). However, the commonly used Berden score is inconsistent at predicting renal outcomes across different cohorts. Furthermore, treatment related morbidity remains a major problem. Brix et al. recently published a clinico-pathologic score to predict End-Stage Kidney Disease (ESKD), using 3 parameters to stratify patients into 3 risk groups. Parameters include: percentage normal glomeruli (N0 >25% = 0 points, N1 10 to 25% = 4, N2 <10% = 6), percentage tubular atrophy and interstitial fibrosis (T0 ≤25% = 0, T1 >25% = 2), and estimated glomerular filtration rate at the time of diagnosis (G0 >15 ml/min/1.73 m2 = 0, G1 ≤15 ml/min/1.73 m2 = 3). The ultimate aim is to utilise this to personalise treatment, enabling the optimal balance of toxic immunosuppression for every patient.

Methods: The Rare Kidney Disease (RKD) registry is an Irish national longitudinal, multi-centre, cohort study which includes 567 AAV patients, to date, diagnosed using the European Medicines Agency Algorithm (1990-2019). Patients with Granulomatosis with polyangiitis (GPA) or Microscopic polyangiitis (MPA), with biopsy proven AAV GN and positive PR3 or MPO serology were included in our validation of the renal risk score.

Results: 248 patients, of whom 43 (17.3%) developed ESKD and 35 (14.1%) died, over a median follow up of 32 months (interquartile range, IQR 5 – 69.5 months), were identified. Outcome data and histopathologic details were available for 205 patients. Forty-five patients were in the lowest risk group (group 1) - two (4.4%) of which developed ESKD. Eight (8.6%) of the 93 patients in the middle risk group (group 2) reached ESKD. Sixty-seven patients were in the highest risk group (group 3) and 28 (41.8%) of them required permanent renal replacement therapy. Kaplan Meier survival analysis demonstrated a difference in renal outcome between the 3 risk groups ($p < 0.0001$).

Conclusions: The proposed renal risk score accurately predicts ESKD in patients with AAV GN, in our national Irish cohort. The next step is to further refine the predictive cut-off values for the 3 clinico-pathologic parameters using a regression tree analysis.

PO1941

Hypocomplementemia Is Associated with More Severe Renal Disease and Worse Renal Outcomes in Patients with ANCA-Associated Vasculitis: A Retrospective Cohort Study

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Background: The complement system has been recently proposed to play an important role in the pathogenesis of ANCA associated vasculitis (AAV). Real life data assessing its predictive role in renal outcomes are limited. In this study, we evaluated the value of serum and kidney deposited C3 in predicting renal outcomes in patients with AAV.

Methods: In this retrospective study, patients with AAV were categorized according to their baseline serum C3 levels as hypo- or normo-complementemic and to those with positive or negative kidney biopsy immunofluorescence (IF) for C3. Clinical, serologic, treatment and histopathologic characteristics, as well as prognosis between the 2 groups were compared.

Results: Forty-seven patients (51% men) were enrolled with a mean age at diagnosis of 65 years and were followed up for a median period of 56 months. At baseline, 23% (11/47) of the patients were hypocomplementemic (C3 <75 mg/dL). These patients were older (74 vs. 65 years, p=0.013), had higher creatinine levels (4.9 vs. 2.2 mg/dL, p=0.006), were more often hemodialysis dependent (64% vs. 19%, p=0.009) and progressed more often to ESRD (55% vs .11%, p=0.01) compared to normo-complementemic patients (n=36). On multivariate analysis, serum Cr at diagnosis (HR=16.8, 95%CI: 1.354-208.62, p=0.028) and low serum C3 (HR=2.492; 95% CI: 0.537-11.567, p=0.044) were independent predictors for ESRD. Among 25 patients with kidney biopsy data, those with positive IF staining for C3 (56%, n=14) had more often a mixed histological pattern (72% vs. 27%, p=0.033), low serum C3 levels (42% vs. 18%, p<0.001) and serious infections during follow-up (57% vs. 18%, p=0.047) compared to those with negative (n=11) IF staining.

Conclusions: The subgroup of patients with AAV and low C3 levels at diagnosis (23%) have more severe renal disease and outcomes (ESRD) compared to patients with normal C3 levels. This should be taken into account in therapeutic and monitoring strategies.

PO1942

Clinical Features and Treatment Outcomes of Patients with Pauci-Immune Vasculitis with and Without a Medical History of Autoimmune Disease

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Background: A proportion of patients with **p**auci-immune vasculitis (PIV) report a past medical history (PMH) of other autoimmune disorder prior to the diagnosis of vasculitis. The purpose of this study was to identify the differences, if any, between patients with PIV with or without a PMH of other autoimmune disease prior to the onset of vasculitis.

Methods: Among 304 patients with biopsy proven PIV at any site, detailed information regarding their PMH was available in 235 patients (77.3%). Of these, 60 (25.5%) reported a PMH of other autoimmune disorder including Sjogren syndrome, Crohn's disease, autoimmune thyroiditis, psoriasis, rheumatoid arthritis, and scleroderma.

Results: The clinical characteristics and outcomes of the two groups are displayed in [table 1].

Conclusions: Patients with a PMH of other autoimmune disorder prior to the diagnosis of PIV were predominantly P/MPO-ANCA positive, had less impaired kidney function at presentation and a lower probability of relapse after achieving remission, compared to patients without a PMH of autoimmunity.

Characteristic Mean (sd) or N(%)	Patients with a PMH of autoimmune disease N=60	Patients without a PMH of autoimmune disease N=175	p-value
Age (years)	53.9 (±16.03)	51.2 (±15.08)	0.88
Gender (Male)	26 (43.3)	99 (56.5)	0.67
ANCA type			
P/MPO-ANCA	35 (58.6)	73 (42)	0.03
C/PR3-ANCA	23 (37.9)	88 (55)	0.61
Negative	2 (3.3)	3 (1.8)	0.47
Clinical phenotype			
Microscopic polyangiitis	32 (53.4)	71 (40.6)	0.09
Polyangiitis with Granulomatosis	13 (22.4)	81 (46.6)	0.0012
Renal limited disease	14 (24.1)	23 (13.1)	0.057
Organ involvement			
Kidney	42 (70)	142 (80.9)	0.8
Pulmonary	(20) 33.3	78 (44.5)	0.14
Ear nose throat	8 (13.3)	55 (31.2)	0.009
Serum creatinine at biopsy (mg/dl)	2.3 (±19.94)	5.1 (±3.96)	<0.0001
Outcome			
Remission	89.2 %	85.5 %	0.5
Treatment resistance	10.7 %	15.2 %	0.41
Relapse	16 %	34.2 %	0.017
ESKD	11.1 %	13.4 %	0.66
Relapse by ANCA type			
PR3-ANCA patients	19 %	47.7 %	0.02
MPO-ANCA patients	10.7 %	18.35 %	0.37

PO1943

Low Serum C3 at Diagnosis of Pauci-Immune Glomerulonephritis Is Associated with More Advanced Kidney Impairment and Worst Renal Prognosis

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Background: Recent evidence supports the notion that complement activation plays a critical role in pauci-immune (PI) vasculitis pathogenesis. The aim of this study was to investigate if the clinical, serological and laboratory characteristics and treatment outcomes of patients with PI glomerulonephritis (GN) with low serum complement levels at diagnosis differ from those of patients with complement values within the normal range.

Methods: In a retrospective design we studied patients with biopsy proven PIGN with available serum complement measurements at diagnosis, or during a relapse, prior to initiation of immunosuppressive therapy. All patients were tested for antineutrophil cytoplasmic antibodies (ANCA) at presentation. Fisher's exact tests and Wilcoxon rank sum tests were used to compare the characteristics by serum C3.

Results: Of 96 patients included in the study, 22 (22.9%) had low serum C3 at diagnosis. Comparison of clinical, serological and laboratory characteristics and outcomes between the two groups is shown in [table 1].

Conclusions: Almost one quarter of patients with biopsy proven PIGN had low serum C3 at diagnosis in this cohort. These patients had more advanced renal impairment, required acute dialysis more frequently and were more likely to end up in end-stage kidney disease compared to patients with serum C3 within the normal range.

Characteristic Mean(sd) or N(%)	PIGN with low serum C3 N=22	PIGN with normal serum C3 N=74	p value
Age (years)	60.4(±13.1)	58.3 (±15.6)	0.42
Gender (male)	12 (57.1)	35 (47.3)	0.45
BVAS	16.6 (±5.35)	17.7 (±5.75)	0.89
ANCA type			
P/MPO-ANCA	14(63.6)	44(59.45)	0.71
C/PR3-ANCA	6 (27.3)	25 (33.8)	
Negative	2 (9.1)	5 (6.75)	
Clinical phenotype			
Microscopic Polyangiitis	11(50)	29 (39.2)	
Polyangiitis with Granulomatosis	5 (22.7)	17 (22.9)	0.38
Kidney limited disease	6 (27.3)	28 (37.8)	
Serum creatinine (mg/dl)	8.25 (±3.8)	2.875 (±1.9)	<0.0001
Peak serum creatinine (mg/dl)	10.8 (±3.3)	2.9 (±1.7)	<0.0001
Patients requiring acute dialysis	10 (±47.6)	13 (±17.5)	0.004
Outcome			
Remission	13(59.1)	55(74.2)	0.17
ESKD	9(40.9)	10 (13.6)	0.006

PO1944

Serum and Urinary Metabolites Discriminate Disease Activity in ANCA-Associated Glomerulonephritis

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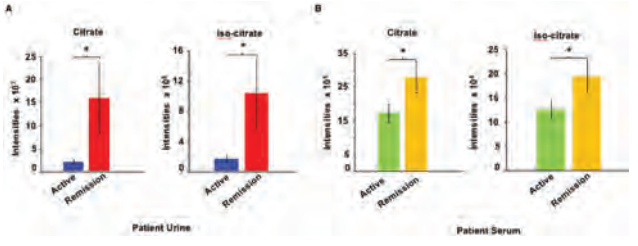
Background: Relapse of disease and treatment related morbidity due to lack of a reliable biomarker for disease activity continue to be a significant issue in patients with ANCA associated vasculitis (AAV). Renal biopsy is currently gold standard for reliable detection of active disease. Metabolomics have been used to successfully discern disease activity in a number of autoimmune diseases. We sought to investigate the use of serum and urinary metabolomics to discriminate disease activity in ANCA associated GN

Methods: Ten patients with AAV renal disease had paired serum and urine supernatant sample collections during active and remission phases of disease. Active renal disease was defined by presence of hematuria >5 RBC/hpf, urinary RBC casts or an increase in serum creatinine > 30% or < in eGFR by 25% or biopsy proven GN. The samples were then subjected to targeted metabolomics data acquisition using a Thermo scientific Q Exactive plus Orbitrap Mass Spectrometer Plus with a Vanquish UPLC at our metabolomics facility.

Results: The mean age in this cohort was 61 years, with 6 patients each being male and Caucasian. Nine patients had biopsy proven renal disease, with clinical diagnosis in one. Mean BVAS and mean GFR was 17 and 28 respectively. Intensities of urinary citrate and iso-citrate are significantly higher in the remission group compared to the active group (Fig 1A). Similar trend of higher citrate and iso-citrate intensities present in serum of patients in remission versus active disease (Fig 1B). There was a disproportionately high intensity difference in citrate and iso-citrate levels in serum and urine samples compared to other metabolites of the TCA cycle implying involvement of additional metabolic pathways.

Conclusions: This study indicates that serum and urinary citrate and iso-citrate may be utilized to monitor disease activity in AAV and emerge as an alternative to kidney biopsy.



PO1945

Renal Involvement in Granulomatosis with Polyangiitis Does Not Increase Inpatient Mortality Compared with No Renal Involvement

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Background: The aim of this study was to analyze the difference in outcomes of Granulomatosis with polyangiitis (GPA) with and without renal involvement. The primary outcome was inpatient mortality, while secondary outcomes were hospital length of stay (LOS) and total hospital charges.

Methods: Data were abstracted from the National Inpatient Sample (NIS) 2016 and 2017 Database. NIS is the largest inpatient admission database in the United States. The NIS was searched for adult GPA hospitalizations with and without renal involvement as the principal or secondary diagnosis using ICD-10 codes. Multivariate logistic and linear regression analysis was used to adjust for confounders for the primary and secondary outcomes respectively. STATA software was used to analyze the data.

Results: There over 71 million discharges included in the combined 2016 and 2017 NIS database. 23,670 hospitalizations were for adult patients, who had either a principal or secondary ICD-10 code for GPA. 8,265 (34.92%) and 15,405 (65.08%) of these hospitalizations were for GPA with renal and without renal involvement respectively. Inpatient mortality occurred in 1,010 GPA patients (5.1%). 425 (5.1%) of the deaths occurred in GPA with renal involvement vs 585 (3.8%) without renal involvement (p=0.0287). The adjusted odds ratio (AOR) of inpatient mortality for GPA with renal compared to without renal involvement was 1.14 (95% CI 0.84-1.56, p=0.406). GPA with renal involvement hospitalizations had a mean increase in adjusted mean LOS of 1.36 days (95% CI 0.82-1.91, p<0.0001) compared to GPA without renal involvement. GPA with renal involvement hospitalizations had an increase in adjusted total hospital charges of $18,723 compared to GPA without renal involvement (95% CI 9,595-27,852, p<0.0001).

Conclusions: There is no statistically significant difference in inpatient mortality for hospitalizations of GPA with and without renal involvement. However, LOS and total hospital charges in GPA with renal involvement were greater than those without renal involvement. Hence GPA with renal involvement has a greater burden to the healthcare system compared to without renal involvement.

PO1946

Immunological Indexes Both in Renal and Serum Were Associated with Renal and Patient Outcome in Chinese Patients with Myeloperoxidase-ANCA-Associated Glomerulonephritis

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Background: Rapidly progressive glomerulonephritis (RPGN) caused by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are typically characterized by few or no immune deposits in glomerulus which was defined as pauci-immune glomerulonephritis(GN). Immune complex (IC) deposits in glomerulus and abnormal serum immune indexes have also been reported in some studies. Most patients with AAV in China are positive for anti-myeloperoxidase (MPO), which more frequently had renal involvement and developed RPGN. Therefore, it is necessary to assess serum immunological indexes and the IC deposits in renal in MPO-ANCA-associated GN.

Methods: Clinical and histopathologic characteristics of 97 patients who had renal biopsy-proven as necrotizing and crescentic MPO-ANCA-GN from 2002 to 2019 were recruited in this study. Serum immunological indexes (sC3, sC4, sIgA, sIgG, sIgM), immune deposits in the kidney (C3, C4, IgA, IgG, IgM) in immunofluorescence (IF) at diagnosis were retrospectively analyzed.

Results: Patients with low sC3 (≤790 ml/L) and low sC4 (≤100 ml/L) at diagnosis showed poorer renal survival compared to patients with normal value (p=0.003, 0.011). Furthermore, among patients of low sC3 at diagnosis, the cases with persistent low sC3 showed an obviously worse renal survival than those whose sC3 recovered to normal after treatment (p<0.001). There are 41%(40/97) patients showed positive IF findings (≥2+ on a 0 to 4+ scale) for at least one Ig or complement component. in our study. The patients with IC deposits showed higher level of serum creatinine (p=0.01) and lower platelet counts (p=0.009), sC3 level (p=0.013) than patients with pauci-IC deposition at diagnosis. We also found IgG deposits related to worse renal outcome than the negtative cases (p=0.047). What's more, complement C1q deposits displayed significant poorer patient survival than the cases without C1q deposits (p=0.001).

Conclusions: Patients with a persistent low sC3 showed poorer renal prognosis than the patients whose sC3 level return to normal after a period of treatment, which was confirmed that both initial and continuously low sC3 can act as predictive indicators for renal outcome. IgG and complement C1q deposits associated with poorer renal and patient outcome, which can help to judge the prognosis of MPO-ANCA-associated GN to some extent.

PO1947

Rituximab vs. Cyclophosphamide in the Treatment of Anti-GBM Crescentic Glomerulonephritis: An Observational Study

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Background: Anti glomerular basement membrane (GBM) crescentic glomerulonephritis (CsGN) is a rare disease affecting kidneys and/or lungs. At present most of the evidence for its treatment is with use of plasmapheresis (PP), high dose steroids (HDS) and cyclophosphamide (CYC). The use of Rituximab (Rtx) in addition to PP and HDS is only anecdotal. Herein, we are describing our experience with the use of both the regimens.

Methods: A retrospective analysis of all the patients with anti GBM CsGN admitted in our hospital from September 2018 to November 2019 was done. Anti GBM CsGN was diagnosed on the basis of ≥50% crescents on kidney biopsy and immunofluoroscence showing linear IgG deposition along GBM and/or by the presence of anti GBM antibodies.

Results: 11 patients were admitted with anti GBM CsGN, during this period (15 months). Kidney biopsy was done in 10 patients and in one anti GBM GN was diagnosed on the basis of raised anti GBM antibody titres. There were 8 females and three males (age range 37-72 years). The mean serum creatinine was 8.69mg/dl. Out of 11 patients 2 refused for treatment and 2 were lost to follow up. 3 out of 7 patients had diffuse alveolar hemorrhage (DAH) and in all it succeeded renal involvement (one had diagnosis of usual interstitial pneumonia for 1 year). 4 out of 11 patients had concomitant urinary tract infection, 5 out of 7 (71.42%) were ANCA positive, 2 out 11 had type 2 diabetes mellitus, 5 out of 11 were oligoanuric and 7/11 (63.6%) were dialysis requiring at presentation. PP was given on alternate days. Both the patients who refused for treatment died on follow up. Among remaining 7 patients 5 had received PP+HDS + CYC and 2 had received PP+HDS+Rtx. In CYC group 4 (all 4 were dialysis dependent and 3 were oligoanuric) out of 5 patients died whereas in Rtx group both the patients survived (one was dialysis dependent and oligoanuric).

Conclusions: In our study most of the patients presented late to the hospital due to vague symptoms at the onset (mean 30 days) and few had co-existing UTI (this delayed the treatment). 63.6 % were dialysis requiring at presentation and DAH was the most common cause of in-hospital death. Two out the three survivors achieved normal eGFR (one in CYC and one in Rtx arm) whereas third one had no progressive decline in eGFR (Rtx). The use of Rtx along with HDS and PP showed favourable outcomes in our study.

PO1948

Impact of Race on Hospitalization Outcomes for Goodpasture Syndrome in the United States

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Background: Goodpasture's syndrome is a rare and life-threatening autoimmune disease. While Goodpasture's syndrome is well described in Caucasian and Asian populations, its prevalence and outcomes among African American and Hispanic populations are unclear. We conducted this study to assess the impacts of race on hospital outcomes among patients with Goodpasture's syndrome.

Methods: The National Inpatient Sample database was used to identify hospitalized patients with a principal diagnosis of Goodpasture's syndrome from 2003-2014. Goodpasture's syndrome patients were grouped based on their race. The differences in-hospital treatments and outcomes between Caucasian, African American, and Hispanic Goodpasture's syndrome patients were assessed using logistic regression analysis.

Results: 964 patients were hospitalized with a primarily diagnosis of Goodpasture's syndrome. Of these, 786 were included in the analysis: 622 (65%) were Caucasian, 73 (8%) were African American, and 91 (9%) were Hispanic. The need for mechanical ventilation, non-invasive ventilation support, and renal replacement therapy in African Americans and Hispanics were comparable to Caucasians. There was no significant difference in organ failure, sepsis, and in-hospital mortality between African Americans and Caucasians. In contrast, Hispanics had higher in-hospital mortality than Caucasians but similar risk of organ failure and sepsis.

Conclusions: African American and Hispanic populations account for 8% and 9% of hospitalizations for Goodpasture's syndrome, respectively. While there is no significant difference in in-hospital mortality between African Americans and Caucasians, Hispanics with Goodpasture's syndrome carry a higher in-hospital mortality compared to Caucasians.

PO1949

Overlap Syndrome of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis and IgG4-Related Disease: Distinct Clinicopathologic Clues for Precise Diagnosis

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Background: Both antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and IgG4-related disease (IgG4-RD) are multi-system inflammatory disorders. The coexistent of both diseases present the possibility of a new overlap syndrome which leads to different treatment and outcome. In this study, the symptomatic and pathological concurrence of AAV and IgG4-RD is investigated to explore the possibility and clinicopathologic clues to the diagnosis of this overlapped syndrome.

Methods: A case of a 67-year-old man in our hospital who exhibited the characteristics of both AAV and IgG4-RD was presented. The treatment response and outcome of the case were followed up for the next 15 months. Then, a systematic literature review of the overlap syndrome of AAV and IgG4-RD was performed on PUBMED database from 1976 until January 2020.

Results: Mild hematuria with rapid progressive renal failure of the patient was observed while renal biopsy revealed pauci-immune crescentic glomerulonephritis, especially with IgG4-related tubulointerstitial nephritis. Glucocorticoids combined with cyclophosphamide therapy led to partial remission. Literature review of 52 patients met both AAV and IgG4-RD criteria as overlap syndrome and four common clinicopathologic features were identified. First, atypical clinical and laboratory manifestations were characteristics of this entity. Second, positive MPO-ANCA are more common. Third, tissue samples showed overlapping histological patterns when kidneys were involved. Fourth, the combination of glucocorticoids and immunosuppressive therapy was often required and led to a remission within 3 months.

Conclusions: AAV may overlap with IgG4-RD while presenting atypical manifestations. Four common clinicopathologic characteristics could be used as specific clues to the diagnosis of overlap syndrome.

PO1950

Anti-IL-5 Therapy in Eosinophilic Granulomatosis with Polyangiitis (EGPA): An 18-Month Follow-Up Study of a Steroid-Sparing Therapeutic Approach

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Background: EGPA is a small vessel vasculitis with protean renal manifestations including necrotizing glomerulonephritis, eosinophilic interstitial nephritis and obstructive uropathy. In the randomized, placebo-controlled MIRRA trial for relapsing and refractory EGPA, adjuvant therapy with 300mg anti-IL5 mAB Mepolizumab [MEPO], accrued longer times in remission, reduced steroid exposure and reduced relapse rates.

Methods: The aim of our study was to analyze the outcome for EGPA patients who received 100mg s/c of MEPO monthly for 18 months and beyond. This retrospective, descriptive study analyzed 13 patients with EGPA, who received 100mg s/c of MEPO therapy monthly. Time points of assessment included MEPO commencement [M0] and ≧ 18 months [>M18].

Results: This study demonstrates that anti-IL5 therapy serves as a favorable model for steroid minimization in EGPA, with an overall 50% reduction in steroid dosage. Additional reduction in conventional immunosuppressants was also observed in 3 patients. ANCA positive serology normalized in all four patients. Well tolerated, it demonstrated considerable clinical benefit, with 12 patients [92.3%] continuing anti-IL5 therapy beyond 18 months. Renal function was preserved. One patient had MEPO switched to Rituximab to treat both EGPA and new onset rheumatoid arthritis. Three patients were switched to alternative anti-IL5 therapies, benralizumab (x2) and Reslizumab (x1).

Conclusions: The relapsing nature of EGPA places a potential dependency of therapy on steroids, underscoring the importance of targeted pathway specific biologics to minimize steroid exposure, prevent tissue damage and ensure early response to therapy. There was a 50% reduction in steroid dosage in this study, with preserved renal function.

Table 1: EGPA patients receiving anti-IL5 therapy for greater than eighteen months [100mg s/c]

Demographics			**All [n=13]**	
Gender ratio M/F			4M:9F	
ANCA positive/ negative			ANCA: 3MPO, 1 PR3 positive/ 9 ANCA negative	
Age of diagnosis of asthma			35 years [IQR 28.5-40]	
Age of diagnosis of EGPA			47 years [IQR 43.5-53.5]	
Median age			51 years [IQR 47.5- 60.5]	
Response to therapy			**M0 [%]**	**Post M>18 [%]**
Prednisolone dose		N= 11		
	Mean ±SD		20.9 mg ±11.7	10.27 mg ± 9.1
Eosinophil count	$X10^9/L$	N=7		
	Mean ±SD		0.49 mg ±0.254	0.035±0.04
Creatinine		N=8		
	Mean ±SD		60 ± 28.7	66.11±13.33
Continuation of anti-IL5 therapy		N=13		12/13 [92.3%]

	Long term plan > 18 months	N=13 [%]	Current Months	Adjuvant therapy 12M
1	Continue		21	Azathioprine
2	Switched	Benralizumab	32	MMF [+], IVIG [-]
3	Continue		26	
4	Switched	Reslizumab	24	
5	Discontinued	Rituximab	12	
6	Continue		23	
7	Continue		26	*MMF Stopped*
8	Continue		24	MTX [+]
9	Switched	Benralizumab	23	*MMF Stopped*
10	Continue		21	
11	Continue		20	Rituximab
12	Continue		21	*Azathioprine stopped*
13	Continue		21	

PO1951

Pauci-Immune Lupus Nephritis: A Case Report

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Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement, and Lupus nephritis (LN) typically shows immune deposits on biopsy. Pauci-immune LN is a rare entity.

Case Description: A 35 year old female presented with pedal edema, reduced urine output & yellowish discoloration of eyes since 20 days. No vomiting, dyspnea, joint pains, rashes, or hematuria. She had similar episodes in 2011 and 2013 & was given blood transfusion and oral steroids. She is a hypertensive for 10 years and diabetic for 2 years. She had 2 normal vaginal deliveries with no obstetric complications. On examination she had pallor, icterus and generalized edema, blood pressure of 170/80mmHg. Rest of the examination was normal. She had severe anemia, renal failure, positive ANA, dsDNA and direct Coomb's test, with normal complements. There was no evidence of active hemolysis. SLE with Auto immune hemolytic anemia (AIHA) and probable lupus nephritis (LN) was diagnosed. Steroid pulse was started with stabilization of renal function and hemoglobin. Renal biopsy showed necrotising crescentic glomerulonephritis with no endocapillary proliferation. Immunofluorescence did not show any immune deposits. A diagnosis of pauci immune LN was made, and was started on cyclophosphamide. She had partial renal recovery with creatinine of 1.5 mg/dl, no hematuria, no hemolysis.

Discussion: Renal biopsy in SLE patients can reveal varied pathologies like ANCA or lupus vasculitis etc. In our case, renal biopsy was similar to ANCA vasculitis, however systemic features favored SLE. With a diagnosis of SLE, and absence of endocapillary proliferation, a diagnosis of pauci-immune LN was made.

Hemoglobin(g/dl)	4.9
WBC count(cells/mm3)	10400
Platelets(lakh/mm3)	3.3
Urinalysis	3+ protein, 8 RBC, 14 WBC
Creatinine(mg/dl)	4.4
T.Bili(mg/dl)	1.1
Albumin(g/dl)	3.5
LDH(U/l)	191
Reticulocyte count	6%
TSH(mIU/L)	3.7
C3(mg/dl)	103
C4(mg/dl)	23
Anti-dsDNA (IU/ml)	682.7
ANA	53.81
Ultrasound abdomen	Hepatosplenomegaly with cholelithiasis

PO1952

Pulmonary Renal Connection: A Case of ANCA Vasculitis and Atypical Anti-GBM Antibody Associated with Vaping

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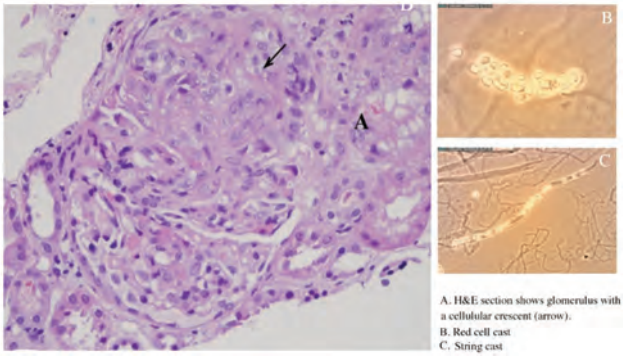
Introduction: The use of e cigarettes and vaping is linked to the development of lung injury (EVALI). We present a case of ANCA (antinuclear cytoplasmic antibody) vasculitis with atypical Anti GBM (glomerular basement membrane) antibody in a patient with EVALI.

Case Description: A 17 year old male with a history of vaping presented with acute respiratory failure requiring mechanical ventilation. CT chest revealed diffuse bilateral consolidation. Evaluation for infection was negative. Nephrology was consulted for acute renal failure. Urine analysis was notable for hematuria and proteinuria. Urine microscopy identified dysmorphic erythrocytes. Renal biopsy showed pauci immune crescentic glomerulonephritis (panel A). ANCA with MPO (myeloperoxidase) specificity and Anti GBM antibody were positive. He was treated with methylprednisolone, therapeutic plasma exchange and oral cyclophosphamide initially and subsequently Rituximab. Four months later his creatinine was 1.2 mg/dL, improved from a peak level of 7.5mg/dL with negative ANCA and Anti GBM titers. Two other patients with vaping associated lung injury admitted to the intensive care unit were noted to have dysmorphic hematuria. Urine microscopy in one was notable for red cell casts (panel B) and numerous string casts (panel C).

Discussion: Anti GBM disease had been associated with alveolar injury from exposure to hydrocarbons or smoking. The presence of the erythrocyte casts and positive anti GBM antibody in patients with vaping associated lung injury raises the possibility of pulmonary and renal injury from a common mechanism. While the pathogenesis of vaping associated renal injury is unclear, examination of the urinary sediment should be performed in all patients presenting with vaping associated lung injury and hematuria.



A. H&E section shows glomerulus with a cellulular crescent (arrow).
B. Red cell cast
C. String cast

PO1953

Sabotaged: Hydralazine-Induced ANCA Glomerulonephritis

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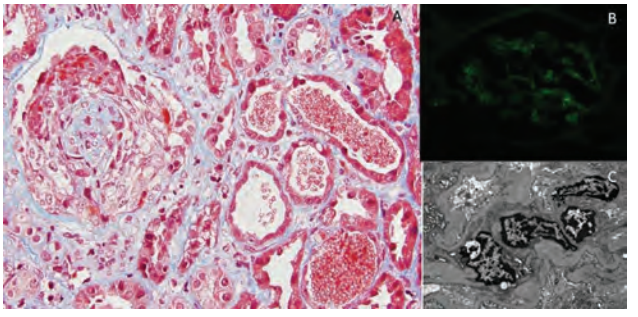
Introduction: While usually well known to cause SLE-like syndrome, hydralazine (HZ) can also be involved in a different clinical scenario with ANCA vasculitis.

Case Description: 77y/o woman with hypertension and COPD presents with 2 days of hemoptysis and hematuria, requiring urgent intubation. CT scan reveals multifocal infiltrates and bronchoscopy shows diffuse alveolar hemorrhage. Labs showed Hb of 6.8 and Cr of 1.9. Dysmorphic RBCs were seen in the urine sediment and proteinuria at 1.2g/g. Given concern for anti-GBM, she received 1g of methylprednisolone and plasma exchange. ANA 1:1280 with MPO-ANCA levels >8.0 U, along with positive anti-histone and SCL-70 antibodies, but with negative anti-GBM and ds-DNA. Kidney biopsy showed pauci-immune crescentic GN with trace staining for IgA, IgM, C3, kappa and lambda. As she had been on HZ, the diagnosis of HZ-induced ANCA-associated vasculitis was made. Offending agent was held and cyclophosphamide was started. After 2 months, kidney function returned to baseline, with resolution of proteinuria and hematuria.

Discussion: In patients with HAV, unusually high titers of MPO are present and can be used to differentiate drug-associated and spontaneous cases. A minority of patients can also present with other positive antibodies, such as ds-DNA, anti-histone, or Scl-70. As HZ can also cause SLE-like pattern of injury, it can be difficult to obtain a diagnosis based on serologies alone; biopsy is essential for diagnosis and prognosis. The treatment of HAV involves not only removing the inciting agent, but also further immunosuppression, as HZ is thought to lead to increased expression of MPO and PR3 breaking neutrophils tolerance and leading to auto-antibody formation. When choosing a treatment strategy, guidelines for spontaneous ANCA should be followed; in this particular case, as she had severe lung involvement, cyclophosphamide was chosen.



(a) Masson thrichrome - Crescent with compression of capilary tuft. Tubules with RBC casts. (b) IF 0 to trace IgG (C) EM Occasional electron dense deposits in mesangium only.

PO1954

Isolated ANCA Renal Arteritis

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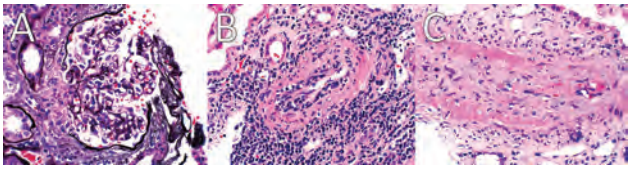
Introduction: Vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) usually causes acute kidney injury (AKI) through crescentic glomerulonephritis (GN). Renal ANCA arteritis without GN is often accompanied by prominent interstitial nephritis (IN). We present a case of AKI due to ANCA renal arteritis without significant GN or IN.

Case Description: An 84-year-old woman with hypertension, chronic kidney disease [baseline creatinine (Cr) 1.6 mg/dL], and prior right nephrectomy for renal cell carcinoma presented with nausea and anorexia. She was admitted the prior month for pyelonephritis and AKI and discharged to a rehab facility. On return, her serum Cr was 4.9. She was readmitted and started on hemodialysis. Urine microscopy was consistent with acute tubular injury (ATI), but also showed non-glomerular hematuria which persisted on several UAs. Urine protein was 2.1 g/g Cr. Both p-ANCA (1:1280) and MPO (>8 AI) were strongly positive. She was given IV corticosteroids and renal biopsy was obtained [Figure]. She was evaluated by rheumatology and felt to have renal-limited disease. She was treated with plasma exchange followed by rituximab, but a week later she opted to stop dialysis and transition to comfort measures and she died 2 days later.

Discussion: Most patients with AKI from ANCA-associated vasculitis will have GN, often crescentic. Extraglomerular features on biopsy of ANCA disease are common and include IN and arteritis/arteriolitis, but often parallel the activity of glomerular disease. Prior case reports of ANCA renal disease without GN have featured prominent IN with or without arteritis/arteriolitis. This case of marked necrotizing arteritis, minimal IN, and absent GN represents a rare phenotype of ANCA renal disease.



Biopsy yielded 31 glomeruli; 7 were globally sclerotic and the rest were without crescents, necrosis, or endocapillary hypercellularity (panel A, silver stain, 400x). IF was negative. Diffuse ATI was seen, with moderate (35%) interstitial fibrosis and mild patchy mononuclear inflammation limited largely to areas of fibrosis. Multiple arteries and few arterioles exhibited fibrinoid necrosis, including focal areas of transmural necrosis and circumferential arteritis (panels B & C, H&E, 400x).

PO1955

Rare Case of Silicosis-Induced Pauci-Immune Glomerulonephritis

Sandheep Venkataraman, Matthew Ray, James F. Dylewski. *University of Colorado, Denver, CO.*

Introduction: Pauci-immune glomerulonephritis(GN) caused by ANCA was first described in 1982. Most cases are idiopathic, however, ANCA vasculitis may induced due to certain exposures. Here we report a case of ANCA vasculitis associated with pulmonary silicosis.

Case Description: A 37-year-old man with no prior history presented with anorexia, weight loss, fatigue, and arthralgias for 6 months. He was employed as a sandblaster, stonecutter, and as a mason. On initial exam he was found to have dactylitis and Raynaud's phenomenon. His presenting creatinine(Cr) was 2.9 mg/dL with urinalysis showing 3+ blood and 1.2 gm proteinuria. Renal ultrasound demonstrated enlarged kidneys bilaterally. Notable serologies were ANA positive 1:1280, p-ANCA positive 1:2560, C3 77 mg/dL, C4 6 mg/dL, and MPO at 78 AU/ml. CT Chest revealed innumerable pulmonary nodules, extensive fibrosis, and mediastinal lymph nodes with eggshell calcifications. Infectious workup was negative. Transbronchial biopsy demonstrated collection of histiocytes containing black pigment without granulomas. Kidney biopsy showed necrotizing crescentic GN, with marked interstitial inflammation and focal intralobular vessel infiltrates. IF and EM was negative, consistent with pauci-immune ANCA vasculitis. Given his history and presentation, he was diagnosed with silica-induced ANCA vasculitis. He was treated with 3 days of IV methylprednisolone, followed by a rapid prednisone taper. He also received IV Rituximab 1 gm on days 0 and 14, plus IV cyclophosphamide 500 mg every 2 weeks for 6 doses starting on day 0. The patient responded well with Cr improving to 1.0 and decreased proteinuria. Unfortunately he relapsed 3 months after last rituximab dose.

Discussion: Silica exposure is most often associated with pulmonary disease but there have been case reports of RPGN associated with it too. The majority of these patients were MPO positive. T-cell dysregulation and endothelial damage from PMNL free radical generation is a proposed mechanism for this disease. Duration and intensity of silica exposure are known risk factors. In addition to pulmonary-renal symptoms, these patients may have systemic manifestations of lupus, rheumatoid arthritis, scleroderma, or dermatomyositis. More research is needed to further understand the management of these patients. This patient represents a rare case of silica-induced ANCA pulmonary-renal vasculitis.

PO1956

ANCA-Negative Small-Vessel Vasculitis with IgG4-Positive Plasma Cell Infiltration: A Case Report and Literature Review

Huipeng Ge, Cuifang Li, Qiongjing Yuan. *Xiangya Hospital Central South University, Changsha, China.*

Introduction: Although the histopathology was critically important for differential diagnosis between AAV and IgG4-RD, overlapping morphologies and clinical manifestations put the clinicians in a dilemma of diagnosis sometimes. Here, we described a case of ANCA negative PICG with IgG4-positive plasma cell infiltration.

Case Description: A 60-year-old male patient presented with cough for 3 months and progressive renal impairment for 8 days. He had elevated serum IgG4 level with absence of anti-neutrophil cytoplasmic antibodies (ANCA). Lung CT as shown in Figure 1. Renal biopsy showed severe tubulointerstitial nephritis (TIN) with extensive infiltration of IgG4-positive plasma cells, suggesting a diagnosis of IgG4-related kidney disease(Figure 2). However, the identification of necrotizing glomeruloneohritis and crescents forming and the absence of storiform fibrosis and obliterative phlebitis led to a diagnosis of ANCA negative renal small-vessel vasculitis. The condition was improved by using corticosteroids and cyclophosphamide at beginning.

Discussion: ANCA negative cannot exclude the diagnosis of AAV. The elevated serum IgG4 and/or abundant IgG4-positive cell infiltration can act as one of the manifestations in AAV. ANCA-negative pauci-immune crescentic glomerulonephritis (PICG) might represent an independent disease entity from ANCA positive PICG. Besides, IgG4-related disease (IgG4-RD) is an exclusive diagnosis and needs to be differentiated from vasculitis and other diseases. It is suggested that ANCA-negative PICG with elevated serum IgG4 and/or abundant IgG4-positive cell need to be further studied.

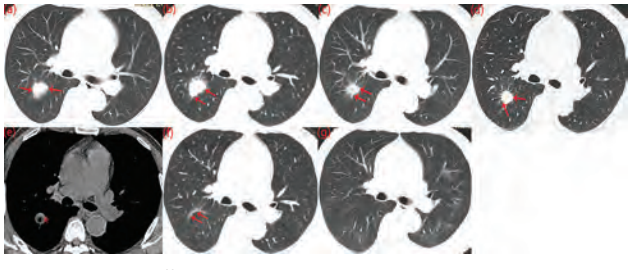


Figure 1. Lung CT in different periods.

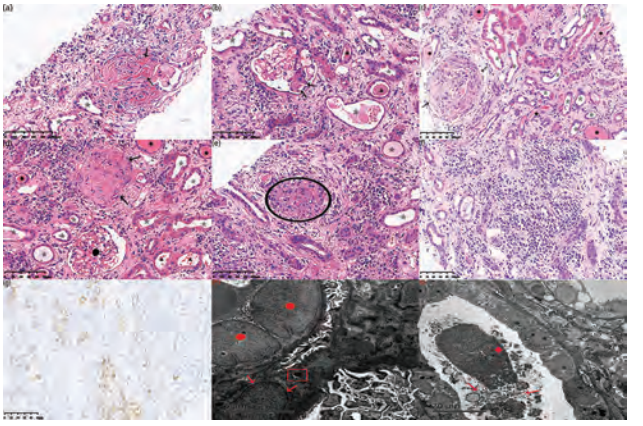


Figure 2. Histological findings of the kidney.

PO1957

Adalimumab-Associated Pauci-Immune Glomerulonephritis: Coincidence or Causation Effect?

Nirav N. Patel, Emma Spangler, Pavan Annamaraju. *Johnston Memorial Hospital, Abingdon, VA.*

Introduction: Adalimumab is a TNF-blocker used in the treatment of hidradenitis suppurutiva (HS). Infections, lupus-like syndrome, and lymphoma are known safety concerns with TNF-blockers. We report a rare case of adalimumab associated pauci-immune crescentric GN (PICGN) in a patient with HS.

Case Description: A 19-yr-old male with a history of HS on adalimumab for 6 months was seen on 4/1/20 with a fever of 103°F, cough & epistaxis for 2 weeks. CT sinuses showed polyps and sinusitis. He was treated with antibiotics for sinusitis. CT chest, nasal PCR for COVID-19, blood, and urine cultures were negative. By hospital day 8, he remained febrile and developed AKI [Creatinine (Cr)1.9 mg/dl; baseline of 0.8 mg/dl]. Physical exam showed chronic scarred skin lesions on the chest and axilla with no signs of infection or rash. Hematuria and microalbuminuria were noted. Ultrasound showed renomegaly. Inflammatory markers were high (CRP 254 mg/L, Ferritin 1059 ng/mL). PR3-ANCA antibody was positive 530 IU/mL. A renal biopsy confirmed PICGN (Fig 1). Bone marrow biopsy showed no evidence of hemophagocytosis. The patient was treated with pulse doses of steroids and rituximab and plasma exchange (peak cr 6.4 mg/dl). On a 3-week follow up creatinine improved to 1.8 mg/dl suggesting a favorable outcome. The patient never required dialysis.

Discussion: AKI, microscopic hematuria, and proteinuria can be seen in a febrile illness. However, epistaxis and renomegaly prompted us to check for ANCA serology. To our knowledge, this is the first case of adalimumab associated PICGN in a patient with HS. Interestingly, our patient is much younger compared to previously reported cases (mean 51.4 years). It is possible that adalimumab may be unrelated to the vasculitis; however, due to a strong temporal association, it was felt to be the culprit agent. Nephrologists must be aware of the renal side effects of this class of drugs.

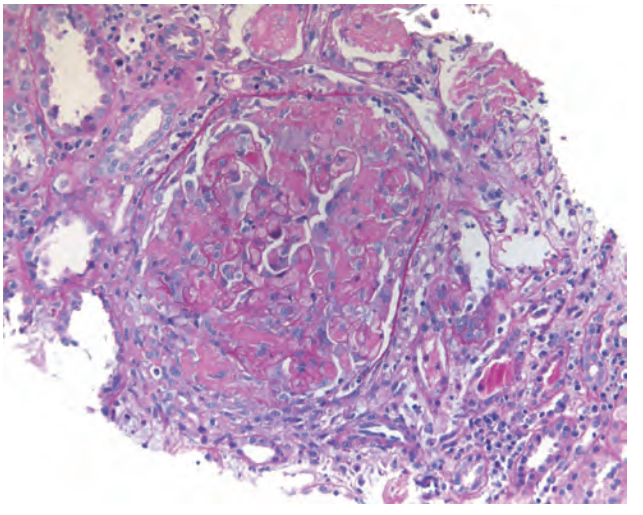


Fig 1. Necrotizing Crescent

PO1958

A Case of C-ANCA Associated Retroperitoneal Fibrosis and Periaortitis

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Introduction: Granulomatosis with Polyangitis (GPA) is a type of small vessel vasculits that has prevalence rate of 25-160 cases per million population, and a incidental rate of 0.4 cases per 100,000 population per year. Clinical features of the disease invlove the respiratory and renal systems. However, large vessels such as the Aorta and retroperitoneal tissue are rarely involved.

Case Description: We present the case of a middle-aged male who presented with an obstructive nephropathy in which abdominal CT revealed a soft tissue mass encompassing the Aorta and Inferior Vena Cava causing obstruction of the Left ureter. Despite ureteric stenting, serum creatinine failed to improve. Furthermore urinanalysis demonstated an active urinary sediment; hemproteinuria. Serum c-ANCA and PR-3 antigen titres were positive. Renal biopsy was performed and confirmed pauci-immune vasculitis. Our patient was induced with pulsed intravenous methylprednisolone and cyclophosphamide and as part of his maintainence treatment received prednisolone and oral cyclophosphamide. On follow up, partial remission has been achieved with his serum creatinine returning to baseline level and proteinuria reduced, though erythrocytes are still evident. Repeat abdominal imaging has revealed a reduction in the size of the soft tissue mass with treatment.

Discussion: Biopsy proven vasculitis has been shown in patients with retroperitoneal fibrosis. Few case reports and series have described this association, inferring a pathogenic role of ANCA in the development of retroperitoneal fibrosis. Moreover it has been suggested that retro peritoneal fibrosis may be an early clinical manifestation of ANCA associated vasculitis. Consequently, ANCA associated vasculitis should be considered in the differential diagnosis of any patient who has Retroperitoneal fibrosis and an active urinary sediment

PO1959

A Rare Case of ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis in an Elderly Woman

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Introduction: Acute kidney injury is usually multifactorial with a broad differential diagnosis. Of those, rapidly progressive glomerulonephritis (RPGN) requires special attention as it represents a true diagnostic and therapeutic emergency that can lead to irreversible kidney failure.

Case Description: A 92-year-old female with a history of Chronic Kidney Disease Stage III, Diabetes Mellitus type II, hypertension, and recurrent deep vein thrombosis sent to the ER for evaluation of rapidly worsening kidney function found on outpatient laboratories for assessment of poor oral intake and fatigue for 2 weeks. On arrival, BP was 133/49mmHg, HR 70bpm, temperature 36.9°C, RR 17 rpm and SO2 of 99%. Mental status was at baseline and physical exam was unremarkable. Laboratory data were remarkable for serum creatinine of 10.55 mg/dl from baseline of 1.8 mg/dl, potassium level of 6 mEq/L and bicarbonate of 17 mEq/L. Urinalysis showed proteinuria (30+), hematuria (344 RBCs/hpf) and leukocyturia (68 WBC/hpf). Urine protein creatinine ratio of 2.4. No acute EKG changes. Renal ultrasound demonstrated increased bilateral echogenicity; otherwise unremarkable. Patient initially treated medically with no improvement requiring hemodialysis. Work up sent with ANCA panel, Anti-GBM, Serum protein electrophoresis, immunofixation, Free Light Chains, complement and Hepatitis panel all negative. Acutely worsening kidney function coupled with active sediment and proteinuria prompted a kidney biopsy which demonstrated pauci-immune crescentic GN. She was started on Methylprednisolone 500mg IV daily for 3 days, followed by prednisone 60mg qd and plasmapheresis every-other-day.

Discussion: PICG is a potentially life-threatening condition leading to renal failure within days or weeks and represents up to 80% of RPGN. The majority of cases (~90%) are ANCA positive and occur in younger patients. Here we present the clinical profile of a rare new diagnosis of ANCA negative PICG in an elderly lady. Renal damage is more severe and kidney survival poorer when compared to ANCA positive crescentic GN. Our patient received RRT throughout hospital stay showing signs of recovery on second week. She was discharged on oral Prednisone 30mg qd and Cyclophosphamide 50mg qd with close follow up.

PO1960

Anti-Glomerular Basement Membrane (GBM) Disease with Atypical Clinical and Histologic Features Precipitated by Parainfluenza

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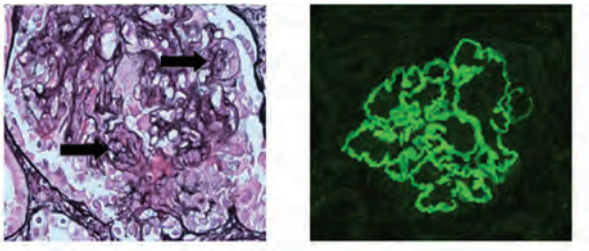
Introduction: Anti-GBM disease typically presents with rapidly progressive glomerulonephritis (RPGN) and linear GBM staining for IgG1 or IgG3. We describe a case of anti-GBM disease with an initially indolent course that progressed to RPGN following parainfluenza infection. Serum anti-GBM antibodies were only mildly elevated and kidney biopsy showed linear GBM staining for IgG4.

Case Description: An otherwise healthy 23-year old male presented with a 2-week history of cough, dyspnea, and hemoptysis. He recently returned from China, where he smoked tobacco heavily. Hematuria and proteinuria were noted during a routine medical exam 2 months prior. Physical exam notable for BP 150/90mmHg, bibasilar chest crackles, and bipedal edema. Investigations: sCr 2.6mg/dL (1.5mg/dL 2 weeks prior); 3+blood and 3+protein by UA; negative/normal C3, C4, ANA, anti-dsDNA, ANCA; viral respiratory PCR positive for parainfluenza; serum anti-GBM 15u/ml (nl <10u/ml). CT Thorax showed bilateral pleural effusions and groundglass nodularity within the right middle and lower lobes. Kidney biopsy showed linear GBM staining for IgG4, wtih glomerular necrosis, crescents, and unusually prominent endocapillary proliferation (Figure). Treatment included diuretics, antibiotics, IV methylprednisolone, oral cyclophosphamide, and 8 plasma exchanges over 11 days. Serum anti-GBM was undetectable after 2 days. He progressed to dialysis-requiring ESRD over the next 6 weeks: a repeat kidney biopsy showed peristent crescentic GN with endocapillary proliferation and strong linear IgG4 staining, despite repeatedly negative serum anti-GBM.

Discussion: This case highlights complexities in the pathogenesis and diagnosis of anti-GBM disease. RPGN was likely triggered by parainfluenza infection, a rarely described association. Low anti-GBM antibody levels were likely explained by the poor sensitivity of ELISA to detect IgG4. Finally, prominent endocapillary proliferation is characteristic of "atypical anti-GBM disease", yet serum anti-GBM was positive in this case.



Left: Light microscopy (methenamine silver stain) showing areas of endocapillary proliferation (arrows). Right: IF microscopy showing linear IgG4 deposition along the GBM.

PO1961

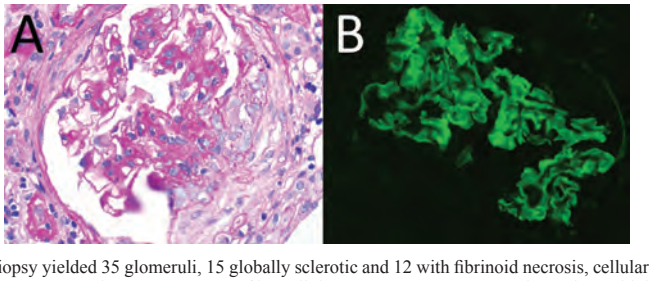
Seronegative Anti-GBM: A Spectrum of Disease

Alisa Illescas,[1] Michael B. Kuperman,[2] Sara Combs,[1] J Pedro Teixeira.[1] *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]Arkana Laboratories, Little Rock, AR.*

Introduction: Glomerulonephritis (GN) due to anti-GBM disease is usually associated with detectable antibodies against the NC1 domain of the type IV collagen alpha-3 chain [NC1-α3(IV)], but a subset of seronegative atypical disease has been described with no lung involvement, non-crescentic GN on biopsy, and indolent course. We present a case of anti-GBM disease that is neither typical nor atypical.

Case Description: A 56-year-old woman with hypertension and obesity underwent renal biopsy after routine labs showed rise in creatinine (Cr) above baseline of 1.5 mg/dL 6 months prior and hemoproteinuria on UA. The results [Figure] prompted transfer to our center. On admit, she noted mild chronic dyspnea but denied cough or hemoptysis. She had mild hypertension (146/80) and trace edema. Cr had risen to 4.5, urine protein was 3.4 g/g Cr, and chest x-ray was clear. She was started on IV corticosteroids and plasma exchange (PLEX). Anti-GBM IgG [multiplex bead assay, ARUP], drawn prior to PLEX, was negative (4 AU/mL, upper limit normal 19). She was treated with IV cyclophosphamide and 7 PLEX sessions over 2 weeks and her Cr stabilized at 3.5. She avoided dialysis and was discharged on prednisone with plans to continue monthly cyclophosphamide.

Discussion: Our patient exhibited an intermediate phenotype of anti-GBM disease with crescentic GN, subacute Cr rise, no lung involvement, and negative serology. Modern assays for anti-GBM antibody have a sensitivity of 94-100%. However, negative serology is also seen in rare cases of anti-GBM GN due to antibodies against epitopes of the GBM other than NC1-α3(IV). Our case illustrates that a negative anti-GBM antibody does not exclude anti-GBM disease which is ultimately a pathologic diagnosis. It also suggests a spectrum exists between classic and atypical anti-GBM disease, but favorable outcome is possible regardless with biopsy-directed therapy.



Biopsy yielded 35 glomeruli, 15 globally sclerotic and 12 with fibrinoid necrosis, cellular crescents (panel A, PAS, 600x), or fibrocellular crescents. RBC casts and 50% interstitial fibrosis were seen. IF showed linear GBM staining with λ (3+), IgG1 (3+), and IgG4 (3+, panel B, 400x).

PO1962

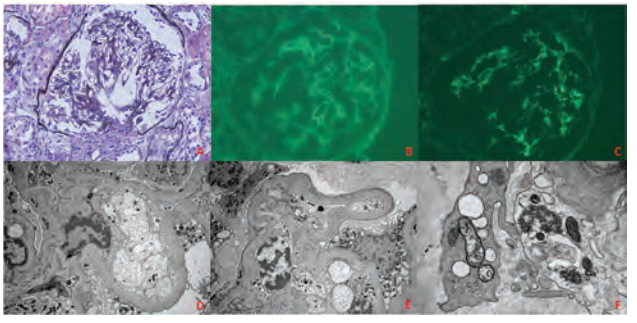
A Case of Lupus Podocytopathy (LP) with Focal Segmental Glomerulosclerosis (FSGS): Is It Time to Add LP to the Next Revision of the Classification of Lupus Nephritis?

Hasan Zahid, Jeremy Carlson, Muhammad usama shah Hamdani, Chintan V. Shah. *University of Florida Health, Gainesville, FL.*

Introduction: Lupus podocytopathy is not included in the commonly used International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of Lupus Nephritis (LN). It has been reported in literature for the last 20 years. LP can have pathologic transition with variable outcomes. We describe a case of LP with FSGS in a young male patient with subsequent relapse.

Case Description: 25 year old male with past history of lupus without nephritis and chronic immune mediated thrombocytopenia presented with generalized fatigue. Physical exam revealed diffuse rash and vital signs were within normal limits. Relevant laboratory findings included platelet count of 21000/microliter, acute kidney injury with creatinine (Cr) of 1.6 mg/dl (baseline Cr of 0.8 to 1.1 mg/dl), spot urine protein creatinine ratio of 4.3 g, 24 hour urine protein of 4.1 g, low C3 and C4, hemoglobin of 9.6 g/dl and WBC count of 3.6/microliter. Serology was positive for ANA, dsDNA and SSA indicating active lupus flare. Left kidney biopsy showed mild mesangial expansion, no endocapillary proliferation and subtotal (>80%) podocyte foot process effacement. No subendothelial or subepithelial deposits were seen. He was treated with pulse dose steroids followed by oral steroids and serum Cr came back to baseline. Subsequently he was treated with mycophenolate mofetil 2 g/day. At 2 weeks, proteinuria came down to 1.8 g/day and by 12 weeks he achieved remission. However at 6 months, he had urine protein of 8.8 g in 24 hours with increase in Cr to 2.4 from 1.6, suggesting relapse.

Discussion: The presence of minimal or no capillary wall immune deposits with or without mesangial proliferation and effacement of podocyte foot processes in the setting of nephrotic range proteinuria is collectively termed as LP. LP must be considered in patients with lupus presenting with NS (Nephrotic Syndrome). It is cardinal that we consider adding this distinct entity in the classification of lupus nephritis.



PO1963

Minimal Change Disease in Systemic Lupus Erythematosus: An Infrequent Variant

Ehsun Naeem, Paul S. Kellerman, Saima Mansuri. *Beaumont Health, Royal Oak, MI.*

Introduction: Lupus Nephritis (LN) is thought to complicate the disease course of almost half of all patients diagnosed with Systemic Lupus Erythematosus (SLE). While nephrotic syndrome (NS) in these patients is usually due to type IV/V Lupus Nephritis (LN), it may in rare instances occur secondary to minimal change disease (MCD), a phenomenon known as Lupus Podocytopathy (LP). We report a case of a young female with LP with concomitant Acute Tubular Necrosis (ATN)

Case Description: 40 year old female, known case of SLE (not on maintenance immunosuppression) and Hypertension presented with bright red blood per rectum and dyspnea for 2 weeks. Review of systems was pertinent for generalized swelling and facial rash. On initial assessment, she was hypertensive and physical exam revealed facial swelling, discoid rashes and 2+ lower Extremity edema bilaterally. Workup revealed Normocytic Anemia, Acute Kidney injury, Hyperkalemia and Metabolic Acidosis. Urine studies showed nephrotic-range proteinuria and hematuria but were negative for casts. Free K/L ratio was high at 2.32 and C3 levels low at 42 mg/dL. Ultrasound guided kidney biopsy showed mild thickening of GBM and dilated tubules with diminished brush borders in the absence of crescentic changes. Electron Microscopy noted diffuse fusion of foot processes, along with rare intramembranous deposits. Immunofluorescence revealed a full house staining pattern within the Mesangium and the patient was diagnosed with Lupus Podocytopathy with concurrent LN Type I. Substantial reduction in proteinuria was noted with a brief course of Prednisone

Discussion: Our patient with SLE presented with NS and AKI, features typical of membranous/proliferative LN. Interestingly, her biopsy findings provided little evidence of endocapillary proliferation or sub-epithelial IC deposits and were more consistent with MCD, suggestive of Lupus podocytopathy. LP is rare to the extent that it does not form part of the official WHO classification for LN and has only been described a handful of times in prior literature, mostly in the form of case reports. However, given its prognostic implications, LP remains an important consideration in the evaluation of NS in SLE patients. While patients with Type IV/V LN require aggressive immunosuppressive therapy, patients with LP frequently respond well to steroids alone and have a much slower progression of disease

PO1964

Olinciguat Protects Renal Function and Podocytes in In Vivo and In Vitro Models of Podocytopathies

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Background: The nitric oxide (NO) receptor soluble guanylate cyclase (sGC) is a signal-transduction enzyme producing the secondary messenger cGMP. Impaired NO-sGC-cGMP signaling is associated with renal dysfunction. sGC stimulators, small molecules that enhance NO-mediated cGMP signaling, improve renal function in animal models of cardiorenal injury.

Methods: We studied the reno-protective effects of olinciguat, a clinical-stage sGC stimulator, by studying *in vitro* and *in vivo* models of glomerular injury.

Results: In an acute focal segmental glomerulosclerosis (FSGS) model of glomerular injury induced by nephrotoxic serum (NTS), treatment with olinciguat attenuated proteinuria and kidney pathology when compared to vehicle-treated mice. Additionally, olinciguat treatment prevented NTS-induced mislocalization of the slit diaphragm proteins synaptopodin and nephrin. Ultrastructural analysis by transmission electron microscopy revealed that podocyte foot process morphology was preserved in mice treated with olinciguat. To further assess the protective effect of sGC stimulation on podocytes, human podocytes injured by exposure to protamine-sulfate (PS) were treated with olinciguat. Olinciguat treatment restored PS-induced damage of podocyte actin cytoskeleton organization and the localization of podocyte cell membrane proteins. In the genetic MRL/MpJ-Fas^{lpr}/J mouse model of systemic lupus erythematosus (SLE), disease progression, assessed by increased proteinuria, was less pronounced in mice treated with the positive control cyclophosphamide or with olinciguat than in vehicle-treated mice. Fewer kidney lesions (interstitial infiltrates, tubular atrophy, tubular epithelium vacuolation, tubular and interstitial lesions, and glomerular lesions) were observed in mice treated with cyclophosphamide or olinciguat than in vehicle-treated mice. In contrast to cyclophosphamide, olinciguat treatment did not result in leukopenia, reduction in spleen weight, or lower anti-dsDNA antibody in serum, suggesting that olinciguat did not impact the auto-immune aspect of SLE.

Conclusions: In summary, olinciguat, an orally bioavailable sGC stimulator, exhibits significant reno-protective effects in nonclinical models and warrants further evaluation for the treatment of FSGS, other podocytopathies, or nephropathies associated with diseases such as sickle cell disease.

Funding: Commercial Support - Cyclerion

PO1965

Urinary Rac1, a Novel Predictive Biomarker, Is Elevated in FSGS and Diabetic Nephropathy Patients and Reduced by TRPC5 Inhibition with GFB-887 in a Rat FSGS Model

Yossi Dagon, Hari Raghu, Tingting Ge, Liron Walsh, John F. Reilly. *Goldfinch Bio Inc, Cambridge, MA.*

Background: Activation of Ras-related C3 botulinum toxin substrate 1 (Rac1) plays a key role in podocyte injury and dysfunction in focal segmental glomerular sclerosis (FSGS) and diabetic nephropathy (DN). In diseased podocytes, Rac1 activation is mediated by calcium influx through the transient receptor potential canonical 5 (TRPC5) ion channel. GFB-887 is a sub-type selective, small molecule inhibitor of TRPC5 that reduces albuminuria in deoxycorticosterone acetate (DOCA)-salt and ZDSD rat models of FSGS and DN, respectively. Here, we aimed to develop a urinary biomarker to assess podocyte Rac1 activity in kidney disease and in response to GFB-887 treatment.

Methods: Using a sandwich ELISA, we measured Rac1 concentrations in supernatants from cultured human iPSC-derived podocytes, in urine from DOCA-salt rats following treatment with GFB-887, and in urine from healthy volunteers, FSGS, DN and Alport patients.

Results: Rac1 was detected in extracellular vesicles (EV) isolated from podocyte culture supernatant and rat and human urine. GFB-887 treatment lowered urinary Rac1 concentrations in normal and DOCA-salt rats, and the decreased Rac1 was associated with decreased albuminuria in the DOCA-salt rats. Urinary Rac1 concentrations were markedly elevated in FSGS and DN but not in Alport patients.

Conclusions: The TRPC5 inhibitor, GFB-887, targets the TRPC5-Rac1 pathway and suppresses urinary Rac1 associated with its therapeutic action in a rat model of FSGS. Urinary Rac1 concentrations are markedly higher in FSGS and DN compared to healthy subjects, but not elevated in Alport. GFB-887 is efficacious in rodent models of FSGS and DN, but not of Alport, suggesting that elevated urinary Rac1 is predictive of response. Together, these data support the potential for clinical utilization of urinary Rac1 as a pharmacodynamic and predictive biomarker for GFB-887 treatment in FSGS and DN. GFB-887 is currently being studied in TRACTION™, a Phase 2 clinical trial in FSGS and DN in which baseline and on-treatment urinary Rac1 measurements will support further development of the biomarker.

Funding: Commercial Support - Goldfinch Bio Inc

PO1966

A Novel In Vivo Approach to Capture the Podocyte Foot Process Proteome

Lori L. O'Brien, Gary F. Gerlach. *University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Podocytes are an extraordinary cell of the kidney filtration system with their tentacle-like foot processes flowing out from each cell body and interdigitating with neighboring processes. Proper kidney function relies on these cells and the complex architecture created by the interdigitating processes. They are the most critical component of the glomerular filter. Podocytes are injured and their integrity is compromised in the majority of kidney diseases leading to progressive proteinuria. However, we know little about the full complement of proteins localized to the foot process and how they change with disease.

Methods: We have developed a novel genetic mouse model capable of generating a spatially restricted, real-time, in vivo proteome. Recently, proximity labeling techniques have been developed to provide snapshots of spatially localized proteomes. The BioID method utilizes a promiscuous bacterial biotin ligase flexibly linked to a target protein of interest to biotinylate proteins within the vicinity. We have adapted this approach to identify the podocyte foot process proteome. Using podocin as a handle, we have modified the *Nphs2* (podocin) locus to link the mutated, promiscuous BirA biotin ligase to podocin (*Nphs2*^{BioID}). A flexible, 13x linker allows for a generous proximity around podocin, thereby capturing the broad proteome of the podocyte foot process.

Results: We have obtained viable *Nphs2*$^{BioID/+}$ animals. Utilizing immunstaining, we have confirmed the proper expression and localization of the podocin-BioID. The HA-tagged BirA ligase appended to podocin colocalized with podocin and other foot process proteins. To test it's functionally, we injected biotin dialy for 7 days. This produced an increase of biotinylated proteins in *Nphs2*$^{BioID/+}$ podocytes versus wild type biotin injected controls or uninjected *Nphs2*$^{BioID/+}$ mice. We have affinity purified the biotinylated proteins from glomerular isolations and are currently performing proteomic analyses.

Conclusions: We have generated the first of it's kind in vivo mouse model to specifically identify the spatially localized proteome of the podocyte foot process. Our proteomics results will provide unprecedented insights into the make-up of this highly specialized and critical structure.

Funding: NIDDK Support, Other NIH Support - Vanderbilt O'Brien Kidney Center

PO1967

Soluble RARRES1 Induces Apoptosis of Podocytes to Promote Progression of Kidney Disease

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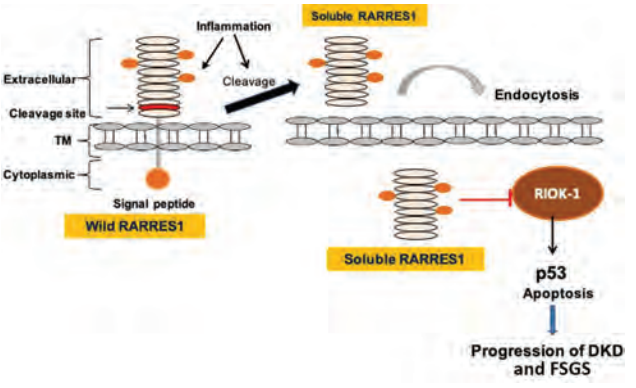
Background: Podocyte loss is a major event leading to the progression of focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy (DN). Here, we found that retinoic acid receptor responder protein 1 (RARRES1) contributes to the podocyte loss in FSGS and DN.

Methods: We determined the role of RARRES1 in human and mouse with FSGS and DN. We investigated the mechanisms of RARRES1 in cultured human podocytes.

Results: The expression of RARRES1 increased in the glomeruli of patients with FSGS and DN and correlated with the eGFR. Single-cell RNA-sequencing of the kidney showed that RARRES1 expressed highly in podocytes. Immunostaining confirmed that podocyte expression of RARRES1 increased in patients with DN and FSGS as compared to MCD. RARRES1 expression was strongly induced by TNF-α in cultured human podocytes. RNA-sequencing of podocytes with RARRES1 overexpression revealed genes enriched in apoptosis. RARRES1 was cleaved into a soluble RARRES1 and the cleavage site was mapped at the aa70. Overexpression of wild RARRES1 or adding soluble RARRES1 in cultured human podocytes induced apoptosis, while overexpression of RARRES1 cleavage mutant lost the apoptotic effect. Further, we showed that soluble RARRES1 underwent endocytosis to interact with intracellular RIOK1, leading to the activation of p53 and apoptosis in podocytes. In vivo, podocyte-specific overexpression of RARRES1 resulted in marked glomerular injury and albuminuria in mice, while the overexpression of RARRES1 cleavage mutant had no renal phenotype. Finally, knockdown of RARRES1 in podocytes ameliorated kidney injury in mice with adriamycin-induced nephropathy.

Conclusions: we demonstrate a new role and mechanism of RARRES1 in regulation of podocyte apoptosis in glomerular disease, as summarized in the Figure: TNFα induces expression of RARRES1, which is cleaved, then undergoes endocytosis to interact with intracellular RIOK1, leading to the activation of p53 and apoptosis. High RARRES1 expression promotes the progression of FSGS and DKD.

Funding: Government Support - Non-U.S.



PO1968

The Glomerulus-on-a-Chip as a System to Unravel Novel Membrane Attack Complex (MAC)-Independent Role of Complement in Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide due to the deposition of anti-podocyte-antibodies against in the glomerular subepithelial space. While complement deposition is thought to play a crucial pathogenic role, the exact effector mechanism of complement in MN is unclear due to the lack of in vitro and in vivo systems that recapitulate human disease. We have developed a novel glomerulus-on-a-chip system (GOAC) using human primary podocytes and human glomerular endothelial cells (GEC) in combination with OrganoPlates and assessed the functional response to human MN serum and the role of MAC deposition and C3a/C3aR1 signaling in MN pathogenesis.

Methods: Glomerular chips were cultured with serum from anti-PLA2R+ MN patients or healthy individuals. Functional response was assessed by albumin permeability assay to evaluate selective-permeability. Role of MAC and C3a/C3aR1 signaling pathway in glomerular filtration barrier damage was assessed by immunofluorescence and functional analysis while mechanisms of action were explored by PCR arrays, Western Blotting and immunostaining. Results were confirmed in vitro using podocytes on which C3aR1 was silenced and in vivo using a C3aR1 KO mice model.

Results: Following exposure to sera from MN patients, we have confirmed deposition of human IgG on podocytes and formation of MAC complex, accompanied by albumin leakage. GOAC supplemented with C3aR1 antagonists as well as GOAC using podocytes in which C3aR1 was silenced were able to prevent glomerular filtration damage on the GOAC as confirmed by rescue of permselectivity efficiency, while inhibition of MAC formation by protein S (an inhibitor of MAC formation) did not significantly reduce GOAC permeability.

Conclusions: We have successfully developed a glomerulus-on-a-chip system that closely mimics the GFB structure and provides a powerful tool for studying renal regenerative and disease mechanisms in proteinuric diseases. Using this model, w showed that C3a/C3aR signaling plays a dominant role in complement-mediated MN pathogenesis.

Funding: Private Foundation Support

PO1969

Dach1 Is Essential for Maintaining Normal Podocytes

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Background: Dach1 is a transcription factor, determining cell fates in various organs. Dach1 polymorphism has been reported to be associated with nephrotic syndrome and chronic kidney diseases. We previously found that Dach1 was highly expressed in normal podocytes and rapidly disappeared after induction of podocyte injury, similarly to WT1. We, therefore, aimed to elucidate the function of Dach1 in normal podocytes *in vivo.*

Methods: Podocyte-specific *Dach1*-knockout (KO) mice were generated by mating *Dach1*-flox mice with *Nphs1*-Cre or *Nphs2*-CreERT2 mice. Podocyte injury was evaluated by urinalysis (SDS-PAGE) and histology. In addition, we analyzed primary cultured podocytes of Dach1 overexpressing knock-in transgenic (KI) mice (n=9), in which Dach1 is expressed under the control of Rosa26 promoter.

Results: Although the efficiency of Cre-mediated recombination was not high, all of the congenital *Dach1*-KO mice (n=20, more than 4 weeks old) presented abnormal albuminuria. Seven out of the 11 (63%) mice histologically analyzed showed focal segmental glomerulosclerosis. Injured podocytes lacked Dach1 staining, whereas intact podocytes retained Dach1. When Dach1 KO was induced in adult mice, the mice showed abnormal albuminuria within two weeks. Immunostaining revealed that podocytes lacking Dach1 causes leakage of albumin, while retaining WT1 protein. Since endogenous Dach1

expression in podocytes is very high compared with transgenic expression of Dach1 driven by the Rosa26 promoter, we analyzed primary cultured podocytes, in which endogenous Dach1 was downregulated. *Dach1* mRNA was 3.8-fold higher (p=0.0007) in *Dach1*-KI podocytes than in control podocytes. We previously found that *Dpp4* is one of the candidate target genes of Dach1 by knockdown experiments. *Dpp4* mRNA in *Dach1*-KI podocytes was found to be increased (1.5-fold, p=0.0022).

Conclusions: These results indicate that Dach1 is important in maintaining normal podocyte integrity, and *Dach1* gene deficiency induces podocyte injury.

PO1970

Dysregulated Dynein-Mediated Vesicle Trafficking Is a New Mechanism of FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is a deteriorating kidney disease with poor prognosis. The lack of understanding of its mechanism has hindered the development of treatment. Mutations in INF2 cause FSGS characterized by a podocytopathy with mistrafficked slit diaphragm (SD) protein critical for the integrity of the glomerular filtration barrier (GFB). This feature has been found in FSGS of other etiologies, making INF2 related podocytopathy a good model to dissect the disturbed vesicle trafficking in podocytopathies prone to FSGS. By yeast two hybridization screening we identified the interaction of INF2 with Dynll1, a dynein component. We hypothesize that INF2 regulates dynein mediated vesicle trafficking, which shuttles endocytosed protein to proteolytic system. This interaction could be disrupted by pathogenic mutations in INF2, suggesting dysregulation of dynein mediated trafficking is an underlying mechanism of the disease.

Methods: The INF2-Dynll1 interaction was confirmed by yeast mating and CO-IP. The dysregulated dynein mediated trafficking of nephrin was investigated in cultured podocytes by fluorescent based and surface biotinylation based assays, and time-lapse imaging in vitro; and was also demonstrated in the puromycin aminoglycoside induced nephropathy (PAN) of INF2 transgenic mice with knockin (KI) of R218Q, a pathogenic mutant that disrupts INF2/Dynll1 interaction.

Results: 1. We demonstrated that INF2 limited dynein mediated retrograde trafficking of nephrin by binding to and sequestering Dynll1, a component essential for the integrity of dynein. 2. R218Q KI podocytes illustrated an impaired recycling of nephrin with enhanced recruitment of dynein components, which could be rescued by targeting dynein transport pathway using Ciliobrevin D (Dynein inhibitor), dominant negative Dynactin 1, siRNA for Dynll1 or overexpression of wildtype INF2 (to sequester Dynll1). 3. PAN of R218Q KI mice was characterized by increased recruitment of Dynll1 to nephrin, correlated to increased ubiquitination and decreased surface nephrin, suggesting an enhanced dynein trafficking pathway underlies the impaired functional trafficking of nephrin, disintegrity of SDs and malfunction of the GFB.

Conclusions: Recognition of the dysregulated dynein mediated trafficking of SD protein has enlightened a new understanding and therapeutic targets for INF2 related podocytopathy and FSGS.

Funding: NIDDK Support

PO1971

Podocyte Cell Cycle Activation During CKD Progression

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Background: Podocytes, quiescent cells, seem not capable of regeneration to compensate for their loss during CKD progression. Their only adaptive response to loss is through hypertrophy, allowing the remaining podocytes to effectively cover the filtration surface. This adaptive response is associated with signs of cell cycle activation, but podocytes do not divide successfully: they detach from the basal membrane and are lost in urine. How the cell cycle phases modulate this "mitotic catastrophe" is not known. To study the cell cycle in CKD, we used an Alport Syndrome (AS) mouse model characterized by podocyte loss, combined with the FUCCI technology which allow the identification of the cell cycle phases using fluorescent reporters: red for G1/S, green for S/G2/M, no color for G0.

Methods: We established a mouse model where FUCCI proteins are under the control of *NPHS2* gene (podocytes specific) and crossed these mice with AS mice to generate AS-POD-FUCCI mice. Using flow cytometry, we isolated and evaluated podocyte number in different cell cycle phases in WT (male and female) and AS-POD-FUCCI mice (hemizygote males; heterozygote, Ht females) and perform proteomics in G1 and G0 podocytes. In vitro studies were performed in primary podocytes damaged with puromycin.

Results: In WT mice (males and females), as expected, 98.1% of podocytes were quiescent (G0). In AS mice, podocyte number in G0 decrease over time: at 2months (mild proteinuria) 89% are in G0, at 6months (end-stage kidney disease) 59% are in G0 while the percentage of podocytes in G1 increased from 7.6% at 2 months to 33% at 6 months. Podocytes also increased their cellular size (hypertrophy) along disease progression. In 6monts AS Ht females (mild proteinuria), only 15% of podocytes are in G1. PAN damage induced podocytes to switch from G0 to G1 phase, and rapamycin (a cell cycle regulator) rescue damage by maintaining cells in G0. Proteomics data showed important differences of cell cycle regulators (cyclins and CKDs, mTor, integrin signaling) between G0 and G1 of WT and AS mice.

Conclusions: We demonstrated that podocytes enter their cell cycle (in male and female) with an increase of cells in G1 (associated with proteinuria) as the disease worsens. Regulating cell cycle may be pivotal in developing novel therapies to prevent podocyte loss.

Funding: Private Foundation Support

PO1972

Sphingomyelin Phosphodiesterase Acid-like 3B (SMPDL3b) Affects Podocyte Lipid Metabolism and Lipid Droplets Formation

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Background: Lipid droplets (LD) play an important role in many biological processes and LD size and number have been linked to several diseases such type 2 diabetes, heart disease, and non-alcoholic fatty liver disease. LD are mainly composed of triglycerides and cholesterol. We previously demonstrated that the accumulation of LDs occurs in glomeruli of experimental models of diabetic kidney disease (DKD), focal segmental glomerulosclerosis (FSGS) and Alport syndrome, and that lipid accumulation in podocytes is one of the factors contributing to disease progression and may be linked to glomerular TNF expression. We furthermore demonstrated that glomerular expression of sphingomyelinase phosphodiesterase like 3b (SMPDL3b), a glycosylphosphatidylinositol (GPI) anchored protein primarily localized at plasma membrane (PM), affects the function of podocytes in FSGS and diabetic kidney disease (DKD). With this study, we aimed at exploring the role of SMPDL3b in fatty acid uptake and in the formation of LDs ultimately contributing to podocyte damage

Methods: Fatty acid uptake Assay, Lipid droplets isolation, Western blotting, Mass spectrometry, Lipolysis, TNF IV injections.

Results: We demonstrate that decreased SMPDL3b expression (siSMPDL3b) in podocytes is associated with increased FATP5 protein expression, fatty acid uptake and an increased number of LDs. The number of LDs was decreased in podocytes with increased SMPDL3b expression (SMPDL3b OE). Similarly, TAGs and CE contents were increased in siSMPDL3b when compared to control podocytes. Finally, we demonstrate for the first time that SMPDL3b is present in isolated LDs suggesting a possible role for SMPDL3b in the formation of LDs and/or in lipolysis. *In vivo*, podocyte specific induction of SMPDL3b is sufficient to protect from TNF induced podocyte injury.

Conclusions: Our results identify a new role of SMPDL3b in the uptake of fatty acids, the accumulation of TAGs, CEs and the formation of LDs. Further experiments to understand the exact mechanism by which SMPDL3b expression contributes to the progression of podocyte damage in FSGS are underway.

Funding: NIDDK Support

PO1973

RNA Sequencing and ATAC-Seq Reveal Gene Profiles in Injured Podocytes in Mice, and Podocyte-Specific Hypoxia Inducible Factor 2α Deletion Protects from Adriamycin-Induced Podocyte Injury

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Background: Roles for hypoxia-inducible factor (HIF) in kidney diseases have been controversial. Upregulating HIF expression is beneficial in protecting kidney from acute injury, while we and others showed that HIF aggravates chronic fibrosis. In podocytes, deletion of VEGFR caused progressive glomerular damage, prevented by overexpression of hypoxia inducible factor 2α. Here, using podocyte-specific HIF-2α deletion mice, we tested effects of HIF-2a deletion on gene profiles in injured podocytes.

Methods: HIF-1$\alpha^{f/f}$ or HIF-2$\alpha^{f/f}$ mice were crossed with either NPHS1 or 2-Cre mice. HIF-2$\alpha^{f/f\ or\ WT}$; NPHS1/2-Cre mice were further crossed with Z/EG mice that express GFP only in cells where Cre is active. At 8 weeks old, the mice were given Adriamycin (12 mg/kg BW, i.v.). Two weeks later, kidneys, urine and blood were harvested. Creatinine and albumin levels in urine and serum, and blood urine urea levels in serum were measured with ELISA kits. Podocytes were isolated from HIF-2$\alpha^{f/f\ or\ WT}$; NPHS2-Cre; Z/EG mice by flor sorting, and RNAseq and ATACseq were performed.

Results: HIF-2$\alpha^{f/f}$; NPHS2-Cre showed preservation of foot processes and kidney functions, and significantly less proteinuria compared to the WT littermates after being subjected to Adriamycin, while HIF-1$\alpha^{f/f}$; NPHS2-Cre mice developed a similar degree of proteinuria to that of WT. HIF-1 or 2$^{f/f}$; NPHS1-Cre mice did not show any protective effect. HIF-1 or 2$\alpha^{f/f}$; NPHS1-Cre; Z/EG mice showed little GFP expression in podocytes, suggesting that weak penetrance of NPHS1-Cre led to minimal functional effects. This group was therefore not further evaluated. Podocytes isolated from HIF-2$\alpha^{f/f\ or\ WT}$; NPHS2-Cre; Z/EG were subjected to RNAseq and ATACseq. In RNAseq, Ndufa12 [NADH:ubiquinone oxidoreductase subunit A12] was most significantly upregulated in podocytes subjected to ADR, while Slc22a30 [solute carrier family 22, member 30], Slc7a13 [solute carrier family 7, (cationic amino acid transporter, y+ system) member 13] and Pzp [PZP, alpha-2-macroglobulin like] were most significantly downregulated. Correlation with ATAC-seq results are being processed.

Conclusions: HIF-2α deletion in podocytes protects podocyte from acute adriamycin injury. Novel genes associated with podocyte injury were discovered by RNAseq and ATACseq of podocytes.

Funding: NIDDK Support

PO1974

Shroom3-FYN Regulates Podometrics via LKB1-AMPK Signaling

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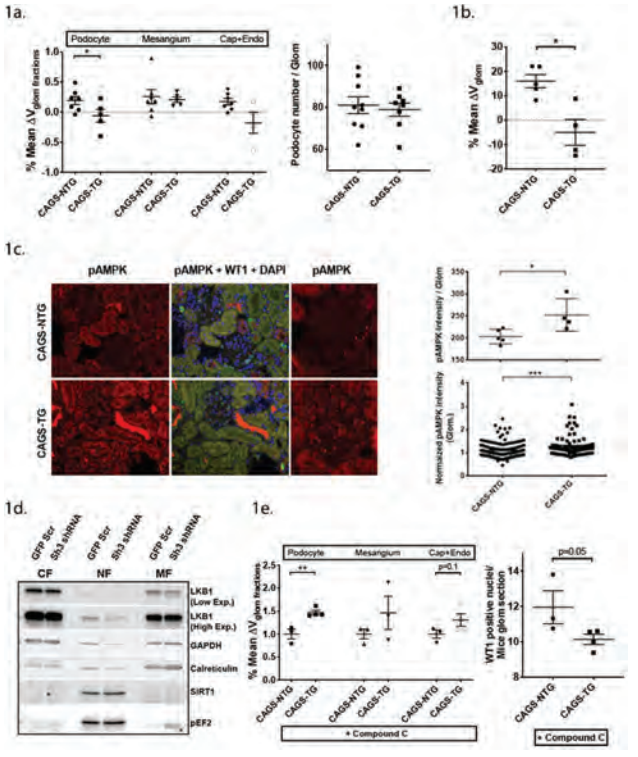
Background: Previously, we showed Shroom3–FYN interaction regulated podocyte cytoskeleton via FYN activation. Intriguingly, global Shroom3 knockdown mice (CAGS-TG/Shr3 Kd) displayed reduction in glomerular volume-V_{glom}, podocyte & endothelial fraction of V_{glom} without podocytopenia [**1a**]

Methods: To examine mechanism of podometrics regulation by Shr3, we used Shr3 & FYN Kd human podocytes (hPodo) to study cell protein content & growth regulatory pathways; performed unilateral nephrectomy examining V_{glom} hypertrophy in remnant kidneys

Results: At day-7, CAGS-TG mice showed restricted V_{glom} hypertrophy with reduced expansion of PodoV_{glom} vs NTGs [**1b**]. We observed reduced hPodo volume (FSC), Protein:DNA ratios (n=5; P<0.01) & inhibited ribosomal biogenesis (18S RNA) *in vitro* & *in vivo* suggesting reduced protein synthesis and FYN to be downstream of Shr3 in regulating hPodo size. Notably, we observed increased AMPK activation, increased p-EF2 & autophagy (high p-ULK1 and LC3II levels) downstream of AMPK *in vitro*/*in vivo* by immunoblot (IB) & immunofluorescence (IF)[**1c**] suggesting negative regulation of protein synthesis. Next, we examined LKB1 localization (AMPK-kinase) by IB after subcellular fractionation & IF in Shr3/FYN Kd hPodo identifying increased LKB1 Cytosolic:Nuclear ratio, explaining AMPK activation due to increased cytosolic pool of active LKB1 [**1d**]. Finally, we used an AMPK inhibitor, Compound C in CAGS-TG mice and observed reversal of podometric changes-V_{glom} & V_{glom} fractions, induction of podocytopenia with AMPK-inhibition [**1e**]

Conclusions: Here, we show Shroom3-FYN interaction regulating podometrics via AMPK-signaling in podocytes. The protective morphometric effects have implications to disease models with podocyte/nephron loss requiring obligate V_{glom}/Podocyte hypertrophy

Funding: NIDDK Support



PO1975

The Role of Opioid Receptor Signaling in Podocytes and Renal Damage in Dahl Salt-Sensitive Rats

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Background: The rise in opioid use underscores the urgent need to better understand the direct and indirect effects of opioids on renal function, especially in patients with chronic kidney disease (CKD) or hypertension. The extensive use of opioids is strongly correlated with poor cardiovascular outcomes. We hypothesize that stimulation of opioid receptors (ORs) elevates intracellular calcium level in podocytes leading to kidney damage and progression of hypertension.

Methods: Freshly isolated glomeruli from Dahl salt-sensitive (SS) rats, human kidneys and immortalized human podocytes were used to elucidate the contribution of specific ORs to podocyte calcium flux. Calcium response in the podocytes was analyzed via ratiometric confocal fluorescent microscopy. For chronic studies Dahl SS rats were on a 0.4% (LS) or 8% (HS) NaCl diets for 14 days with or without a daily *intravenous* bolus infusion of BRL52537, a potent and selective kappa-OR agonist.

Results: Stimulation of kappa-ORs, but not mu-ORs or delta-ORs, mediated calcium influx in podocytes through activation of TRPC6 channels in rat and human kidney. The effect of BRL52537 was completely abolished when we used the 0 mM calcium media or when SAR7334 (a TRPC6 channel inhibitor) was applied. Triggering the kappa-OR/TRPC6 pathway induced podocyte cell shape changes via actin cytoskeleton remodeling. *In vivo* studies revealed that SS rats chronically treated with BRL52537 exhibited augmented blood pressure (MAP was 179 ± 15 mmHg vs. 151 ± 11 mmHg), nephrinuria, albuminuria, and elevation in podocyte calcium in BRL52537 treated Dahl SS rats.

Conclusions: Stimulation of kappa-OR modulates calcium influx in podocyte via TRPC6 channels. The opiate-induced increase in the calcium flux in podocytes is expected to contribute to podocytopathy, proteinuria, kidney injury and progression of salt-induced hypertension. These findings are important to advance our knowledge of the pathogenesis of the development of CKD and hypertension in the context of pain management.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute grant R35 HL135749 to A.S., Veterans Affairs Support, Private Foundation Support

PO1976

Knockout of the Neonatal Fc Receptor (FcRn) Alters Lysosomal Function in Podocytes

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Background: FcRn is a trafficking protein that diverts monomeric IgG from the lysosome but sorts multimeric IgG and immune complexes (ICs) to the lysosome for processing. FcRn is required in dendritic cells to traffic ICs to the lysosome for proteolytic processing and presentation on MHC II. Podocytes express FcRn and previous work had proposed that podocytes can act as antigen presenting cells. Here we show that cultured podocytes are weak antigen presenting cells (APCs) and that knockout (KO) of FcRn in podocytes does not alter podocyte response to an immune stimulus but does result in significant downregulation of lysosomal function.

Methods: Cultured wild type (WT) and FcRn KO podocytes were treated with interferon gamma (IFNg) to simulate proinflammatory conditions. MHC II and costimulatory marker expression was assessed by flow cytometry. Antigen presentation was evaluated by examining T cell response when WT or FcRn KO podocytes were treated with ICs and used as APCs. Lysosomal size and cellular location in WT and FcRn KO podocytes were examined using confocal microscopy. WT or FcRn KO podocytes were treated with ICs and colocalization of lysosomes and ICs was quantitated. RNA-seq was used to examine lysosomal pathways.

Results: Both WT and FcRn KO podocytes upregulated MHC II after treatment with IFNg but there was no difference in expression levels between WT and KO. There was no change in CD80 expression between WT and KO after treatment with IFNg. CD86 and ICOSL expression levels in WT and FcRn KO were minimal at baseline and after treatment with IFNg. When used as APCs, WT podocytes induced a very modest amount of IL-2 production by T cells (a marker of T cell activation) whereas KO podocytes induced none. After treatment with ICs, lysosomes in WT podocytes were significantly larger and were also clustered around the nucleus, indicating lysosomal activation. In contrast, after IC treatment lysosomes in the KO were smaller and more peripherally located. Treatment with ICs also resulted in significantly greater colocalization between lysosomes and ICs in WT versus FcRn KO podocytes, demonstrating that ICs were not directed to the lysosome in the KO. RNA-seq showed significant downregulation of lysosomal pathways in KO podocytes compared to WT after treatment with ICs.

Conclusions: FcRn KO in podocytes alters lysosomal trafficking and function.

Funding: NIDDK Support

PO1977

Apolipoprotein M as a Biomarker of Glomerular Lipotoxicity in Nephrotic Syndrome

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Background: Dysregulation of intrarenal metabolic pathways involved in cholesterol efflux is implicated in lipid-induced podocyte injury in glomerular diseases. Among several genes that are involved in cholesterol efflux, we recently reported a significant downregulation of glomerular apolipoprotein M (APOM) expression in patients with FSGS. HDL-associated APOM facilitates reverse cholesterol transport and is the carrier for the bioactive sphingolipid sphingosine-1-phosphate (S1P). Mutations in S1P lyase, the enzyme responsible for S1P degradation, cause a familial form of FSGS. We hypothesize that glomerular APOM deficiency is a surrogate biomarker for lipid-induced kidney injury in NS.

Methods: Patients with FSGS, MN, and MCD enrolled in NEPTUNE, a multi-center observational cohort study of children and adults with NS, who had uPCR >1 g/g at baseline were selected for analysis. RNA expression data were obtained from the

glomerular compartment isolated from kidney biopsies and compared with living kidney donor controls. Plasma and urinary APOM levels were measured by ELISA using baseline samples. Linear regression analysis was used to correlate glomerular APOM expression with plasma and urinary levels of APOM and to correlate glomerular APOM expression and plasma and urinary APOM levels with eGFR at baseline.

Results: Among 84 patients, 68% were male, mean age was 40 years, mean baseline eGFR was 80.6 mL/min/1.73m^2, and mean uPCR was 4.9 g/g. Glomerular APOM expression was decreased in patients with NS compared to healthy controls ($p < 0.001$), irrespective of histologic diagnosis. APOM expression was positively correlated with plasma but not urinary APOM levels in the NS cohort ($R^2 = 0.089$, $p = 0.003$) and in the FSGS subgroup ($R^2 = 0.189$, $p = 0.0218$). Decreased APOM expression ($p = 0.005$) and decreased plasma APOM ($p = 0.031$) were associated with a lower eGFR at baseline in the NS cohort. After adjustment for age, sex, and race, each unit decrease in APOM expression was associated with a 9.83 mL/min/1.73m^2 (95% CI, 3.72 to 15.93, $p = 0.002$) lower eGFR at baseline.

Conclusions: Glomerular APOM deficiency and decreased plasma APOM levels were associated with decreased kidney function at baseline in the NS cohort. These findings identify APOM as a potential biomarker of lipid-induced kidney injury in NS.

Funding: NIDDK Support

PO1978

The Sensitivity of Podocytes to ATP In Vivo Is Distinctly Lower than the Sensitivity of Glomerular Endothelial and Proximal Tubular Cells

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Background: ATP signaling is involved in a plethora of pathways, involving damage signaling. Cell culture models as well as experiments on isolated glomeruli indicate that podocytes respond to ATP with a calcium transient. To date a direct effect of ATP on podocyte calcium levels *in vivo* has not been demonstrated.

Methods: In this study mice expressing GCaMP3 in podocytes (Pod:cre), proximal tubular cells (Pax8:cre) or endothelial cells (Tie2:cre) underwent multiphoton *in vivo* imaging of the kidney. Mice were anaesthetized, an arterial catheter was placed into the right carotid artery or the aorta and the left kidney was exteriorized. The vasculature was labelled with a 70-kDa dextrane. Different doses of ATP were injected as a bolus via the catheter and dose-dependent calcium transients were monitored.

Results: Our data indicates that even doses of 5 mg/kg ATP did not induce calcium transients in podocytes when injected via a carotid artery catheter, while robust activation of calcium signaling was induced in endothelial and proximal tubular cells with 0.5 mg/kg ATP. Further increasing the ATP dose by injection via an abdominal aortic catheter resulted in a calcium transient in podocytes.

Conclusions: In contrast to endothelial cells and proximal tubular cells, podocytes show a low sensitivity to ATP-mediated calcium signaling. We therefore hypothesize, that the low sensitivity ATP of podocytes is a protection mechanism to avoid calcium signals from filtered ATP.

Funding: Government Support - Non-U.S.

PO1979

Cytomegalovirus Viremia-Associated Collapsing FSGS in an Immunosuppressed Systemic Lupus Erythematosus Patient

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Introduction: Maintaining a broad differential in evaluating AKI in SLE patients with a history of lupus nephritis (LN) is important. We describe a patient with SLE and AKI progressing to dialysis dependence due to collapsing FSGS in the setting of CMV infection.

Case Description: A 23 yo African American F with a history of LN class IV + V (maintained on MMF 1g BID) and APLS presented with one week history of nausea, vomiting and diarrhea. Admission labs were notable for a Cr of 10.5 mg/dl (baseline Cr 0.7), pancytopenia, with albumin of 1.7 mg/dl. Spot urine protein to creatinine ratio was >27 g/g. Serologies showed low C3 and C4, positive ANA, LDH 1437 and negative HIV test. Patient became anuric and required hemodialysis. Stress dose steroids were administered for presumed RPGN from LN. Renal biopsy on hospital day 8 demonstrated collapsing FSGS with 100% podocyte foot process effacement without significant IFTA and 4/9 globally sclerotic glomeruli. Testing revealed CMV viremia with viral load of >700,000 IU/mL. MMF was held. Ganciclovir was initiated with a subsequent decrease in viral load and sufficient renal recovery to stop hemodialysis. Patient was discharged off MMF on oral valganciclovir with a steroid taper. Three months after discharge, patient's viral load was undetectable and renal function had returned to baseline.

Discussion: Our patient with SLE had an atypical presentation. The appearance of significant proteinuria and severe AKI led to initial empiric treatment for LN. Rarely, collapsing FSGS has been described as the primary lesion in lupus podocytopathies. The high CMV viral load and robust response to antiviral therapy argue that the lesion was mediated by CMV infection rather than SLE. The development of collapsing FSGS is commonly due to a "second hit" on a high risk APOL1 genetic background, in our case from elevated interferon levels in the setting of CMV viremia. APOL1 has been implicated in collapsing FSGS due to CMV viremia in African American DDRT recipients, demonstrating the role of genetic testing in African American patients. Our case demonstrates an infectious trigger, rather than autoimmune cause of renal failure in an immunosuppressed patient with SLE.

PO1980

Transcriptional Reprogramming by WT1 Mediates a Repair Response During Podocyte Injury in Mice and Human Kidney Organoids

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Background: We previously identified WT1 as one of the most upstream transcription factors regulating gene expression in podocytes, binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. Here, we focus on understanding WT1 transcriptional mechanism in response to injury.

Methods: We used Adriamycin (ADR)-induced podocyte injury as a model for human Focal Segmental Glomerulosclerosis in mice and human kidney organoids, and a conditional *Wt1* inactivated mouse model to decipher the transcriptional mechanism through which WT1 regulates podocyte gene expression during injury, using transcriptomic approaches.

Results: After injury, we observed a transient increased expression of podocyte genes in mice and human kidney organoids. Transcriptomics analyses of podocytes isolated from *mTmG-Nphs2cre* mice during the course of injury revealed a transient increase in the expression of crucial podocyte genes, including *Nphs2, Synpo* and many others, reflecting a reparative response during the early stages of injury. ChIP-seq analyses demonstrated that WT1 binds nearly 50% of known genes in podocytes, and the vast majority of genes whose expression changes during the response to injury. We identified *de novo* binding of WT1 that were only bound during the course of injury, and the expression of novel WT1 target genes. It appears that WT1 increases gene expression during injury through both the acquisition of novel binding sites, and increasing its binding intensity at sites bound in uninjured podocytes. Additionally, motifs predicting binding of other podocyte-specific transcription factors were highly enriched at sites where WT1 binding increased after injury. Since the DNA binding of transcription factors is modulated by chromatin accessibility, we used FACS-isolated podocytes to study epigenetic reprogramming. Both ADR-mediated podocyte injury or inducible podocyte specific inactivation of *Wt1* resulted in the conversion of active to repressive histone marks at WT1-bound sites.

Conclusions: These results demonstrate that target gene binding of WT1 is highly dynamic in response to injury. WT1 directs the epigenetic regulation of gene expression, maintaining active chromatin marks at bound genes, that change to repressive marks in the absence of WT1.

Funding: NIDDK Support

PO1981

Atypical Caspase 3-Dependent Death Process in Podocytes

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Background: Apoptosis of podocytes has been widely reported in many *in vitro* studies, but definitive apoptosis has been rarely documented *in vivo* podocytes. To elucidate this discrepancy, we analyzed dying process in podocytes *in vitro* and *in vivo*.

Methods: Primary mouse podocytes were transiently transfected with hCD25 and EGFP expression plasmids and treated with a hCD25-targeting immunotoxin, LMB2 (1nM). 24 hours later, EGFP, cleaved-caspase 3 (cCasp3) and TUNEL staining were imaged. In *in vivo* experiments, podocyte injury was induced by injecting LMB2 into NEP25 mice, which express hCD25 in podocytes. In some experiments, NEP25 mice carrying another transgene expressing EGFP in podocytes were used.

Results: In *in vitro* studies, administration of LMB2 caused leakage of co-introduced EGFP in 56.8±13.6% of hCD25-transfected cells, incorporation of propidium iodide in 13.6±2.5%, activation of caspase 3 in 19.6±2.6% and TUNEL staining in 4.5±1.3%. However, LDH activity in the culture medium did not significantly increase. These phenomena were not observed in cells without hCD25 or without LMB2. Ac-DEVD-CHO (10μM), a caspase-3 inhibitor, attenuated the leakage of EGFP by 38.2%, while inhibitors for caspase-1, necroptosis or autophagy did not. These indicate that LMB2 induced typical caspase-3 dependent apoptosis in podocytes *in vitro*. In *in vivo* studies, injection of LMB2 (25ng/g BW) frequently induced leakage of EGFP from podocytes. In separate six NEP25 mice, 7 days after injection of LMB2 (1.25ng/gBW), 41.8±5.1% of glomeruli were found to contain cCasp3-positive cells, but no TUNEL-positive cell was observed. The urinary sediments contained podocalyxin-positive podocytes (2.5±0.3/μl). Among these, 39.1±3.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. To evaluate the effect of glomerular filtration, three NEP25 mice were similarly injected with LMB2 and subjected to UUO 1 day before sacrifice. Detaching podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: These collectively indicate that podocytes dying dependently on caspase 3 are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. Glomerular filtration facilitates detachment of dying podocytes.

PO1982

Systematic In Silico Exploration of the Kidney Rho-GTPase System Regulation in CKD

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Background: It has become evident that dysregulation of the RhoGTPase system would result in rearrangement of the actin cytoskeleton in the podocyte with resulting foot process effacement, a hallmark for glomerular diseases. To build further understanding how this disbalance in the RhoGTPase system occurs in CKD, we performed a systematic mining of kidney transcriptomics data to generate a full-picture view and insights on complex interplay between the members of the large family of RhoGTPases and their regulatory proteins, the Guanine Nucleotide Exchange Factors (GEFs) and the GTPase-activating proteins (GAPs).

Methods: A comprehensive list of 143 genes was compiled including the members of the three gene families according to HUGO Gene Nomenclature Committee (HGNC). Publicly available human transcriptomics data from healthy and CKD kidneys (microarray and RNA-seq, bulk-tissue and single-cell) were used for interrogation of gene expression patterns, including presence of detectable expression, its abundance, cell type specificity, modulation in disease, and co-expression structure. WGCNA and Cytoscape were used to correspondingly generate and visualize the gene co-expression network.

Results: All but one (142/143) genes were detectable in the human kidney, with 121 having robust levels >1TPM. The majority of genes were broadly expressed across the different tissues outside the kidney, however expression of several GEF and GAP members showed specific kidney enrichment. A number of GEFs and GAPs were modulated in CKD patient kidneys as compared to controls, predominantly with tendency for up-regulation and negative correlation with renal function, reflecting modulation in potentially pathophysiological or compensatory disease mechanisms. Hierarchical clustering of pairwise correlation values and WGCNA module analyses identified clusters of similarly expressed genes that may implicate functional similarities.

Conclusions: To our knowledge, this is the first systematic evaluation of the RhoGTPases, GEFs and GAPs kidney expression in the CKD context. Elucidation of the molecular interplay provides systems-level understanding and mechanistic insights that can lead to new biological hypotheses and therapeutic targets.

Funding: Commercial Support - Both authors are AstraZeneca employees

PO1983

Hepatocyte Growth Factor-Induced Activation of NEPHRIN and NEPH1 Serves as a Novel Mechanism for Recovery of Podocytes from Injury

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Background: Podocytes (podo.) and their slit diaphragm(SD) are critical components of glomerular filtration barrier, whose dysfunction leads to ESRD (end stage renal disease). Treating ESRD remains a global challenge due to our poor understanding of the mechanisms that participate in recovery of podo. from injury. Glomerular injuries commonly induce podo. cell death and loss of SD, which is a modified tight junction and is constructed through a trans-interaction between the extracellular domains of NEPHRIN and NEPH1 that maintain its structural integrity. Here, we present a novel concept showing that apart from structural organization, NEPHRIN and NEPH1 constitute a receptor-based function, and can be activated in a ligand-induced fashion.

Methods: Proteomics, SPR, Immunofloroscence

Results: The ability of NEPHRIN and NEPH1 to interact with tyrosine phosphatase SHP-2 in a phosphorylation (phos.) dependent manner prompted us to investigate whether ligands that induce PTPN11 stimulation also induced activation of NEPHRIN and NEPH1. Ligands screening identified HGF as a prominent inducer of both NEPHRIN and NEPH1 phos. To further establish HGF as a ligand, we used baculovirus system to generate purified NEPHRIN and NEPH1 proteins and confirmed not only a direct interaction between HGF and the extracellular domains of NEPHRIN and NEPH1, but also, the ligand-induced phos. of these proteins. In addition to their ligand-induced activation, we demonstrate that SHP-2 can directly dephos. these proteins, thus presenting for the first time activation and deactivation mechanism for these proteins. Since HGF has a protective role in podo. and NEPHRIN and NEPH1 phos. participates in actin cytoskeletal reorganization, we hypothesize that HGF-induced activation of these proteins is critical for recovery of podo. from injury. We demonstrate that while HGF treatment repaired cultured podo. or nephrocytes in Drosophila that were injured by protamine sulphate, addition of inhibitory NEPHRIN or NEPH1 peptides that bind HGF, significantly attenuated this recovery.

Conclusions: We provide compelling evidence for the first time that HGF is a novel ligand and can stimulate signaling of slit diaphragm proteins NEPHRIN and NEPH1 in podocytes

Funding: NIDDK Support

PO1984

Bag3 as a Potential Mechanoprotector in Podocytes

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Background: Podocyte loss is a hallmark of glomerular diseases leading to glomerulosclerosis and progresssion of kidney disease. Sitting on the outside of the glomerular tuft podocytes have to withstand extensive mechanical stress due to perfusion and filtration. Hyperfiltration und hyperperfusion e.g. in disease states cause podocyte detachment when overwhelming their mechonoprotective capacity, which start a vicious cycle of mounting strain on the remaining podocytes. Bag3 is an important mechanoprotector in many mechanical strained tissues and by inducing chaperone-assisted autophagy (CASA) maintains the proteostasis of e.g. Filamin and Synaptopodin – indispensable for podocyte biology. Additionally Bag3 insufficiency renders susceptibility to diabetic nephropathy in a mouse model. These findings point toward Bag3 as a candidate for mechanical stress protection in podocytes.

Methods: Using immunofluorescence, super-resolution-microscopy and mass-spectrometry we examined glomeruli and podocytes for Bag3/CASA expression and characterized the CASA-complex composition in podocytes by immunoprecipitation. The influence of mechanical clues was examined by stiff matrices and cyclic stretch. The role of Bag3 in vivo is being evaluated in different mouse lines (Bag3.P209L mutation, a conditional knockout, fusion-protein).

Results: In the glomerulus the Bag3 and the entire CASA-complex is enriched in podocytes in mass-spectrometry. Bag3 staining localizes to the slit diaphragm protein nephrin in superresolution microscopy. Importantly the co-chaperone Bag3 shows interaction with essential actin-cytoskeleton regulators like RhoA, Arpc2 and Dynamin2 in co-immunoprecipitation. The expression of Bag3 and the CASA-complex in podocytes is regulated by mechanical clues. Knockdown of the Bag3 homologue starvin in drosophila nephrocytes displays a mild filtration disturbance. The dominant-negative Bag3.P209L mutation causes a mild proteinuria in a whole-body overexpression mouse line.

Conclusions: The data further emphasize the role of Bag3 and chaperone-assisted-selective-autophagy in podocyte mechanoprotection and maintenance of podocyte cytoskeleton architecture. Currently undergoing characterization of podocyte specific Bag3 mouse lines and the use of disease models will further help to understand the role of Bag3 at the kidney filtration barrier.

Funding: Government Support - Non-U.S.

PO1985

Knockout of the Neonatal Fc Receptor in Podocytes Ameliorates Nephritis by Reducing Glomerular Apoptosis

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Background: There are few targeted treatments for immune mediated kidney diseases which can result in progressive renal failure. Podocytes express the neonatal Fc receptor (FcRn), a trafficking protein that sorts immune complexes (ICs) to the lysosome. In dendritic cells FcRn mediated trafficking of ICs to the lysosome is required for antigen processing and presentation on MHC II. We have found that podocyte specific knockout (KO) of FcRn ameliorates nephrotoxic serum (NTS) nephritis but that this protection occurs via a non-immune mediated mechanism. Here we show that KO of FcRn in podocytes results in a significant reduction in apoptosis both in vitro and in vivo after an immune challenge

Methods: Wild type (WT) and FcRn KO podocytes were cultured in the presence or absence of ICs. The intrinsic and extrinsic apoptotic pathways were assayed by Western blot and ELISA. RNA-seq was performed to evaluate changes in apoptotic pathways. NTS nephritis was induced in control and podocyte specific FcRn KO (podFcRn KO) mice. Glomerulosclerosis and crescent formation were quantitated on PAS sections. Flow cytometry was used to measure renal CD4+, CD8+ or FoxP3+ T cells. Glomerular apoptosis was assayed using the TUNEL assay.

Results: In vitro, after treatment with ICs, FcRn KO podocytes expressed significantly less caspase-3 and caspase-9 (intrinsic pathway caspases) and caspase-3 activity was significantly decreased in KO podocytes compared to WT. There was no difference in caspase-8 expression (a marker of extrinsic apoptosis) between WT and KO podocytes. RNA-seq analysis demonstrated significant downregulation of intrinsic apoptotic pathways in FcRn KO podocytes compared to WT. In vivo, after induction of nephrotoxic serum nephritis, there was no change in renal CD4+, CD8+ or FoxP3+ T cells in podFcRn KO mice compared to controls but podFcRn KO mice had significantly less glomerulosclerosis and crescent formation. Podocyte-specific KO of FcRn also resulted in a significant reduction in the number of apoptotic cells within the glomerulus.

Conclusions: KO of FcRn reduces apoptosis via the intrinsic pathway in cultured podocytes after an immune challenge and ameliorates immune-mediated nephritis in vivo by reducing glomerular apoptosis.

Funding: NIDDK Support

PO1986

The African APOL1 E150 SNP and Cell Surface Expression Are Required for Kidney Risk-Variant (G1/G2)-Mediated Cytotoxicity in Podocytes

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Background: Apolipoprotein L1 (APOL1) variants G1 and G2 protect against trypanosome infection, but homozygosity greatly increases the risk of chronic kidney diseases, purportedly by acting as surface cation channels in kidney podocytes. "Wild type" APOL1-G0 exhibits various single nucleotide polymorphisms (SNPs), most commonly haplotype E150K, M228I and R255K ("KIK", where the Reference Sequence is "EMR"), whereas G1 and G2 are only found in a single African haplotype background ("EIK"), also seen in some G0 Africans. Lannon *et al* (*Kidney Int.* **96**: 1303) recently documented that differential cytotoxicity of APOL1 G1 and G2 variants versus G0 in HEK-293 cells depended on the haplotype. However, HEK-293 cells are unusually sensitive to APOL1, and podocytes are a more relevant cell type. Furthermore, only the small fraction of APOL1 that is transported to the cell surface (from its major expression site in the ER) is responsible for cytotoxicity and cell surface levels were not shown in that study. Since APOL1 residue 150 can differ in G0 Africans, we focused on comparing the cytotoxicities of E150 vs K150 SNPs in podocytes expressing equal surface levels of APOL1.

Methods: We generated podocytes stably expressing APOL1 G0, G1 or G2 under a doxycycline-inducible promoter and compared the effect of the African E150 (EIK) vs K150 (KIK) SNPs on cytotoxicity (by the Cyto-Tox Glo™ assay). Surface and total APOL1 were measured by FACS and Western blotting at increasing doxycycline levels. Brefeldin A was used to prevent APOL1 transport to the cell surface.

Results: Cell surface APOL1 levels increased in a doxycycline dose-dependent manner, but only the E150 G1 and G2 variants caused toxicity to podocytes as compared to E150 G0 at equal surface expression levels; K150 G0, G1 and G2 were not toxic. E150 G1 and G2 cytotoxicity was dose-dependent and required exit of APOL1 from the ER.

Conclusions: Using a physiologically relevant podocyte cell line, we confirmed that the African haplotype (EIK) is required for APOL1 G1 and G2 to exert cytotoxicity. Non-natural KIK versions were not toxic. Additionally, APOL1 G0 was not toxic in either the KIK or EIK background. Furthermore, African (E150) G1 and G2 cytotoxicity required ER exit, supporting the surface cation channel hypothesis. Our data thus suggest two potential therapeutic avenues for APOL1 nephropathies.

Funding: Commercial Support - Genentech,Roche

PO1987

Glomerular Heterogeneity and Modulation of miR-93: The Role of Extracellular Vesicles

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Background: Modulation of miRNA in podocytes and glomerular endothelial cells (GEC) has been associated with development of renal diseases. miR-93 is a potent regulator of pathways responsible for glomerular damage, like VEGF, TGFb and Msk2. We have evidence that miR-93 is altered in the glomeruli of mice with X-linked Alport syndrome (AS), carrying the Col4a5 mutation, and in glomeruli of AS patients. Here, we investigated the role of miR-93 in mesangial cells, podocytes and GEC from WT and AS mice. We also used extracellular vesicles (hEVs) derived from human amniotic fluid stem cells (hAFSC) to assess their disease modifying activity in vitro and in vivo by regulation of miR-93.

Methods: miR-93 expression was evaluated by qRT-PCR in mesangial cells, podocytes and GEC sorted from glomeruli of male and female WT (C57BL6/J), and homozygous and heterozygous AS (Col4a5-/-) mice at different stages of disease (2m, 3.5m and 5.5m) and in biopsies of AS patients. Modulation of miR-93 by hEVs was evaluated in vitro and EV therapeutic effect was evaluated in vivo by RNA-seq and survival.

Results: miR-93 expression is different between male and female mice along disease progression. In AS males miR-93 level was significantly lower in GEC, but not in podocytes or mesangial cells vs WT cells. miR-93 expression was downregulated also in AS patients. Expression of WT1 in puromycin aminonucleoside damaged podocytes, and expression of fibronectin and VEGF in damaged GEC was restored by miR-93 hEV cargo transfer. In vivo, hEVs showed therapeutic effect by ameliorating the level of proteinuria and increasing life span. Transcriptomic analysis showed that WT male and female present differences in respiratory and metabolic pathways, extracellular matrix and cell adhesion molecules. AS males injected with hEVs showed improved gene modulations in metabolic function and in the development of vasculature, angiogenesis and fibrosis pathways, important miR-93 targets.

Conclusions: Gender specific variation in miR-93 expression in glomerular cells might indicate important differences in response to injury in progressive disease. hEVs demonstrate great potential to restore lost miR-93 expression and its targets, thus presenting a targeted approach for treatment of CKD.

Funding: NIDDK Support

PO1988

GDC-0879 Rescues Lipid Peroxidation and Podocyte Dysfunction in Coenzyme Q-Deficient Kidney Disease

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Background: Mutations affecting mitochondrial coenzyme Q (CoQ) biosynthesis lead to kidney failure due to selective loss of essential cells of the kidney filter called podocytes. Curiously, neighboring tubular epithelial cells are spared early in disease, despite their higher mitochondrial content. We therefore sought to illuminate new, cell-specific roles for CoQ, independent of its role in the electron transport chain (ETC).

Methods: Here we use CoQ deficiency caused by a monogenic disorder due to *PDSS2* mutations as a model system with which to investigate the cell-specific mechanisms of disease. The resolution afforded by single nucleus RNA sequencing revealed podocyte-specific disease pathways in homozygous *kd/kd* (kidney disease) mice, the result of a spontaneous missense mutation in *Pdss2* (V117M, *Pdss2*$^{kd/kd}$). We combine single nucleus transcriptomics with *in vitro* metabolomics and transcriptomics analyses to better understand the metabolic perturbations within this disease.

Results: Single nucleus RNA sequencing from kidneys of *Pdss2*$^{kd/kd}$ mice, characterized by nephrotic syndrome and CoQ deficiency in all cells, identified a podocyte-specific perturbation of the Braf/Mapk pathway. Treatment with GDC-0879, a Braf/Mapk-targeting compound ameliorated kidney disease in *Pdss2*$^{kd/kd}$ mice. *In vitro,* mechanistic studies in Pdss2-depleted podocytes revealed a previously unknown perturbation in PUFA metabolism leading to lipid peroxidation. Aberrant PUFA metabolism was confirmed *in vivo,* where the abundance of Gpx4, an enzyme that protects cells from lipid peroxidation, was elevated in disease and restored after treatment with GDC-0879. We demonstrate broader human disease relevance of these findings by uncovering patterns of Gpx4 and Braf/Mapk pathway gene expression in tissue from patients with several kidney diseases.

Conclusions: Our studies reveal ETC-independent roles for CoQ in podocyte injury and point to Braf/Mapk as a conserved, podocyte-specific pathway for the treatment of kidney diseases.

Funding: NIDDK Support

PO1989

Noncanonical PAR-1 Signalling Leads to Profibrotic Effects in Podocytes in Response to Steroid-Resistant Nephrotic Syndrome Disease Plasma

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Background: Post-transplant recurrence of steroid-resistant nephrotic syndrome (SRNS) is thought to be due to the presence of an unknown "circulating factor", the identity of which has so far remained elusive. Our previous works suggest a role for protease-activated receptor-1 (PAR-1) involving an unknown circulating protease leading to increased podocyte motility. We have now further elaborated the signalling pathways downstream of PAR-1, which suggests pro-fibrotic activation in podocytes.

Methods: Conditionally immortalised human podocytes (ciPods) were treated with PAR-1 agonist peptide or post-transplant SRNS relapse and paired-remission plasma with or without PAR-1 antagonists, RWJ 56110, SCH 79797, Vorapaxar, and FR171113. ciPods were also treated with TGF-β1 or SRNS plasma along with SB-43152, an effective TGF- β1 receptor inhibitor. A new 3D co-culture glomerular spheroid model was used to study both signalling pathways and podocyte loss.

Results: We found that PAR-1 agonist and patient relapse disease plasma, but not paired remission plasma significantly induced the phosphorylation of VASP, JNK, and proteins involved in pro-fibrotic pathways. These changes were inhibited by co-incubation of ciPods with certain PAR-1 inhibitors, but not by TGFb1 inhibitor. These four PAR-1 inhibitors demonstrate distinct antagonistic properties and among 4 inhibitors, only FR17113 was effective in inhibiting effects of relapse plasma, suggesting a non-canonical agonism of PAR-1 by disease plasma. The phosphorylation of VASP and JNK on a 3D spheroid model corroborates the finding from a 2D ciPods model. Functionally, the circulating factor enhanced podocyte motility and podocyte loss.

Conclusions: We propose that the SRNS circulating factor acts as a pro-fibrotic effector that can activate PAR-1 leading to increased podocyte injury. A greater understanding of these signalling pathways will lead to the identification of novel therapeutic targets for this disease.

Funding: Government Support - Non-U.S.

PO1990

TRPC6 Is a Key Mediator of a PAR-1 Activation Pathway in Podocytes That Is Responsible for FSGS

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Background: There is good evidence for the role of a circulating factor in the pathogenesis of idiopathic nephrotic syndrome (iNS). We have previously presented our work hypothesising the role of circulating plasma proteases. An active form of the protease activated receptor, PAR-1 expressed in the podocytes of SV129 mice (PAR-1_{Active}) led to proteinuria, sclerosis and death at 42 days. It was found that the signalling

response to PAR-1 agonist treatment of podocytes *in vitro* was also present in the kidney IHC sections from the PAR-1_{Active} mouse, and in human podocytes treated with post-transplant recurrence plasma. This response includes the phosphorylation of VASP, JNK and Paxillin. We hypothesised that the downstream response to PAR-1 signalling involves activation of TRPC6.

Methods: Conditionally immortalised human WT podocytes and TRPC6 KO mouse podocytes were treated with a PAR-1 agonist (15 μM PAR-3931-PI Peptides International). The PAR-1_{Active} mouse was crossed with a TRPC6 KO on a C57 Bl6 background to develop the *NPHS2* Cre PAR-1_{Active} TRPC6 KO mouse. Biopsy tissue was obtained via the UK Nephrotic Syndrome Study, NephroS, housed within the UK Renal Rare Disease Registry, RaDaR.

Results: We present data confirming activation of the same signalling pathways *in vitro* in podocytes treated with a PAR-1 agonist, and *in vivo* in our *NPHS2* Cre PAR-1_{Active} mouse. Then *in vivo* in human nephropathy biopsies pVASP and pJNK signalling was significantly higher in FSGS and Minimal Change Disease biopsies when compared to IgA nephropathy biopsies. TRPC6 is a calcium channel that can be found at the slit diaphragm and can signal to the actin cytoskeleton. TRPC6 Knock Out (T6KO) podocytes showed an altered response to PAR-1 agonist treatment. There was no phosphorylation of VASP and only brief phosphorylation of JNK and no phosphorylation of Paxillin. When we crossed a T6KO mouse with our *NPHS2* Cre PAR-1 Active mouse we saw significantly increased survival from a median of 40 days in the *NPHS2* Cre PAR-1 Active mouse to 60 days when TRPC6 is knocked out.

Conclusions: We have identified a common signalling response to PAR-1 activation in podocytes *in vitro* and *in vivo*, including in human disease. We identified TRPC6 as being a key player in the response, suggesting a unique role of this ion channel in mediating circulating factor disease, and a direct therapeutic target.

PO1991

A Novel Insulin Sensitizer Targeting Nuclear Receptor PPARγ Provides Beneficial Effects in a Glomerular Disease Model

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Background: Thiazolidinediones (TZDs) are nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) agonists traditionally used to treat type II diabetes due to their insulin-sensitizing effects. These have recently been demonstrated to be beneficial in protecting podocytes and reducing proteinuria in glomerular disease. Since these FDA-approved drugs are associated with adverse effects such as weight gain, edema, bone loss and increased risk for heart failure and bladder cancer, we hypothesized that disparate beneficial vs. adverse molecular activities of PPARγ can be modulated. We determined if GQ-16, a novel insulin sensitizer and a partial PPARγ agonist, which de-phosphorylates PPARγ at Ser273 like other TZDs, provides therapeutic advantage in glomerular disease.

Methods: The studies were approved by the Institutional Animal Care and Use Committee at Nationwide Children's Hospital. Proteinuria was induced in male Wistar rats by single intravenous puromycin amino-nucleoside (PAN) injection, while the control group received saline. PAN-injected rats received sham vehicle, pioglitazone (Pio) or GQ-16 by oral gavage daily (n = 7/group). The rats were weighed daily, and urine samples were collected and analyzed for proteinuria. Plasma with sodium citrate and corn trypsin inhibitor was collected from the inferior vena cava. Endogenous thrombin potential was determined by thrombin generation assay.

Results: PAN induced robust proteinuria (P=0.009) on Day 11 and Pio reduced PAN-induced proteinuria significantly with 63.3% mean reduction (P=0.038). Interestingly, GQ-16 reduced proteinuria even further by 81.2% (P=0.008), and these were comparable to healthy control levels (ns, P=0.66). Furthermore, proteinuria reduction correlated with correction of disease associated hyper-coagulopathy. GQ-16 improved PAN-induced hyper-coagulopathy as measured by improved endogenous thrombin potential and peak thrombin. No significant differences in body weights were observed in treatment vs. PAN groups.

Conclusions: GQ-16, a novel insulin sensitizer and partial PPARγ agonist, shows better efficacy profile in an experimental glomerular disease model than Pio, a traditional TZD with full PPARγ agonistic activity.

Funding: Private Foundation Support

PO1992

Tropomyosin Isoforms Play a Role in Healthy and Injured Kidney Podocytes

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Background: The podocytopathies are a group of glomerular diseases that affect the kidney's ability to filter the blood, and often lead to kidney failure. Healthy podocytes cover the glomerular capillaries with thousands of extensions called foot processes that interdigitate with one another and maintain their elaborate cell shape by tightly regulating their actin cytoskeleton. Podocytes respond to insults in a typical fashion by undergoing foot process effacement (FPE), a dramatic shift in podocyte morphology and the disappearance of the intricate foot processes. Tropomyosins (Tpms) are coiled-coil dimers that form co-polymers along actin filaments and change the filaments' biophysical properties. Over 40 different Tpm isoforms have been identified as the gene products of 4 *Tpm* genes: *Tpm1, 2, 3* & *4*. Various Tpm isoforms target to different locations inside cells and change the type of actin cables assembled in those locations. We hypothesize that podocyte shape is controlled by a specific set of Tpm isoforms that regulate actin cytoskeletal dynamics. Changing the tropomyosin isoforms after injury might be linked to changing podocyte shape and the FPE phenomenon.

Methods: To test our hypothesis, we used RT-PCR and RNAseq (Illumina and PacBio) to identify the whole array of Tpm isoforms that are enriched in podocyte and in isolated healthy glomeruli. Using different mouse models for podocyte injury (i.e., *Cd2ap* KO, *Lamb2* KO, *Col4a3* KO & Adriamycin-nephropathy (AdrN)), we identified a change in Tpm isoforms in the glomeruli isolated from these mice.

Results: RNAseq results from WT glomeruli show a different pattern of Tpm expression than the injured glomeruli counterparts, with the most significant changes occurring in Tpm 1.7 & Tpm 3.4. PacBio data also showed an interesting novel Tpm-related gene product only in injured glomeruli. We isolated RNA from WT and AdrN glomeruli and compared them to primary podocytes taken from podocyte-specific translating-ribosome-affinity-purification ("TRAP") mice. This system allowed us to purify podocyte mRNA for RNAseq, away from that in other glomerular cell types. Comparing the isolated RNA from WT-TRAP & AdrN-TRAP mice, we are able to identify the podocyte-specific Tpm isoforms that are associated with injury.

Conclusions: This study suggests roles for tropomyosin isoform changes in regulating podocyte shape in health and injury conditions.

Funding: Private Foundation Support

PO1993

IRE1α Is Essential for Podocyte Proteostasis and Mitochondrial Health

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Background: Glomerular epithelial cell (GEC)/podocyte proteostasis is disrupted in glomerular diseases. To maintain proteostasis, the endoplasmic reticulum (ER) orchestrates the unfolded protein response (UPR), which includes upregulation of chaperones and clearance of misfolded proteins via autophagy. Inositol requiring enzyme-1α (IRE1α) resides in the ER membrane and is a transducer of the UPR. This study characterizes the mechanisms by which IRE1α regulates proteostasis in GECs.

Methods: Mice with podocyte-specific deletion of IRE1α (IRE1α KO) were produced by breeding IRE1α flox/flox mice with mice expressing podocin-Cre recombinase. Nephrosis was induced with a single injection of adriamycin (ADR). GECs were cultured from glomeruli of IRE1α flox/flox mice and IRE1α was deleted by transduction of Cre recombinase. Cellular oxygen consumption rate (OCR) was quantified using the Seahorse mitochondrial stress test. Mitochondria were visualized using MitoTracker Red CMXRos or MitoTracker Green FM.

Results: Podocyte-specific IRE1α KO mice had greater ADR-induced albuminuria compared to control littermates. ADR increased expression of ER chaperones in glomeruli of control mice, but this upregulation was impaired in IRE1α KO mice. Autophagy induction was blunted in ADR-treated IRE1α KO animals, evidenced by reduced LC3-II and increased p62 levels, compared to treated controls. Electron microscopy showed prominent swelling of the ER and mitochondrial injury in podocytes of ADR-treated IRE1α KO mice. In cultured GECs incubated with tunicamycin (TM), deletion of IRE1α or chemical inhibition of the IRE1α RNase with 4μ8C attenuated upregulation of ER chaperones and LC3 lipidation compared to control. LC3 transcription and total LC3 protein levels were also reduced in TM-treated IRE1α KO GECs. Compared to control, IRE1α KO GECs showed decreased maximal and ATP-linked OCR. Mitochondrial membrane potential was lower in IRE1α KO GECs than in control, while total mitochondrial mass was similar in both groups. Inhibition of IRE1α signaling increased ER stress-induced apoptosis.

Conclusions: Stress-induced chaperone production, autophagy and mitochondrial health are compromised by deletion of IRE1α. The IRE1α pathway is cytoprotective in glomerular disease associated with podocyte injury and ER stress.

Funding: Government Support - Non-U.S.

PO1994

Studying the Pathogenesis of Congenital Nephrotic Syndrome Using NPHS2 Mutant Kidney Organoids

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Background: Nephrotic syndrome (NS) is one of the most common forms of renal disease in children. NPHS2 mutations are the most common cause of congenital NS with missense NPHS2 mutations reported to result in misfolding and mistrafficking of the encoded slit-diaphragm protein, Podocin. Such studies overexpressed mutant protein in immortalised podocyte and non-podocyte cell lines, which may not reflect the *in vivo* consequences of the mutant protein. Here we generated NPHS2 mutant iPSC-derived kidney organoids as a model to dissect the pathogenic process.

Methods: We have simultaneously reprogrammed and CRISPR/Cas9 gene edited a control human fibroblast line, generating 3 iPSC lines containing mutations of the endogenous NPHS2 locus as well as a control wild type (WT) line. These include the sequence variants c274G>T, c353C>T and c503G>A leading to the protein changes G92C, P118L and R168H respectively. Control and mutant lines were used to generate

kidney organoids containing all nephron segments. Podocin localisation was assessed using immunofluorescence together with known markers of subcellular compartments.

Results: Podocin protein was evident in the glomeruli of all organoids, however all mutant lines revealed a marked reduction of the Podocin protein. While the G92C mutant protein co-localised with Nephrin at the plasma membrane, the R168H mutant protein displayed a punctate perinuclear staining suggesting of Golgi retention, together with peripheral co-localisation with the early endosome marker EEA1. Interestingly, the R168H mutant was previously predicted to mislocalise in the endoplasmic reticulum (ER). The P118L mutant was previously predicted to accumulate in the ER and present a transmembrane localisation in cell lines. This mutant protein was observed both in ER and cytosol in kidney organoids. Finally, all 3 mutants displayed significantly more apoptotic podocytes as evidenced by an increased cleaved-Caspase3 staining in glomeruli compared to the control WT line.

Conclusions: Discrepancies between mutant protein localisations in previous reports and our kidney organoids highlight the need for a more appropriate model to study the pathobiology of NPHS2 mutations. These organoids will allow us to explore approaches to rescue individual Podocin defects, ultimately guiding the development of therapeutic strategies for such patients.

Funding: Government Support - Non-U.S.

PO1995

OASIS in Podocytes Promoted Tubular Injury by Suppressing PRKCI Expression

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Background: Old astrocyte specifically induced substance (OASIS), a transcription factor, plays important roles in physiological and pathophysiological processes, such as bone formation. Previously, we found that OASIS is expressed in podocytes in murine kidney. However, the pathophysiological roles of OASIS in podocytes remains unknown. The aim of this study is to investigate the functional roles of OASIS in podocytes in the development of kidney diseases.

Methods: The expression of OASIS protein was investigated in glomeruli of murine kidney and cultured mouse podocytes cell line after lipopolysaccharide (LPS) treatment. To examine the roles of OASIS in podocytes on kidney injury, podocyte-specific OASIS knockout (OASIS CKO) mice were established and subjected to LPS. Twenty-four hours after LPS treatment, serum creatinine and urinary albumin ratio were measured. Podocytes injury was assessed by electron microscope analysis and tubular injury was analyzed by PAS staining and by measuring LCN2 mRNA expression. To explore the secretory molecules downstream of OASIS, DNA microarray analysis was performed using podocytes with lentiviral overexpression of OASIS. In order to examine the effects of the downstream molecule of OASIS on proximal tubule cells, HK-2 cells were cultured.

Results: LPS treatment increased OASIS expression in glomeruli of murine kidney and in cultured podocytes. Podocyte-specific *OASIS* deletion suppressed LPS-increased serum creatinine (sCr) level (sCr (mg/dL): control-LPS; 1.01±0.27, OASIS CKO-LPS; 0.76±0.16, n=8-10, $p<0.05$), but did not influence albuminuria and podocyte injury. Surprisingly, on the other hand, OASIS CKO mice were protected from LPS-mediated tubular injury. DNA microarray analysis using OASIS-overexpressed podocytes revealed that PRKCI was negatively regulated by OASIS in podocytes. Finally, we found that recombinant PRKCI suppressed LPS-induced LCN2 mRNA expression in HK-2 cells in a dose-dependent manner.

Conclusions: Suppression of OASIS in podocytes attenuated LPS-induced tubular injury in part by increased PRKCI secretion. Targeting OASIS-PRKCI signaling in podocytes could be of therapeutic value in kidney diseases.

PO1996

The Renal Risk Variants of Apolipoprotein L-1 Lead to an Influx of Sodium and Calcium That Drive Cytotoxicity

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Background: Apolipoprotein L-1 (APOL1) is an innate immunity gene that protects against protozoan parasites. Recently evolved variants, G1 and G2, provide increased immunity against African trypanosomes while increasing the risk of chronic kidney disease. There is little consensus on how these renal risk variants (RRVs) lead to cell death or kidney disease, or which pathways to target for drug development. As APOL1 kills trypanosomes by forming cation channels, and because many of the pathways associated with the RRVs are linked to pore-forming toxins, we hypothesize that a similar mechanism is involved in kidney disease. In this study, we performed a series of experiments to delineate the events leading up to RRV-mediated cell death.

Methods: Stable cell lines were generated to express the RRVs and non-toxic G0 variant of APOL1. We also generated constructs using the retention using selective hooks system (RUSH) to control the trafficking of APOL1. Live-cell fluorescent microscopy was performed to measure the influx of cations Ca^{2+} and Na^{+} with GCaMP6f and FliCR sensors (membrane voltage), respectively. Confocal imaging was performed to test APOL1 localization. Ion reduction experiments were performed to test the effect of each ion on cell death. Finally, planar lipid bilayers were used to test for APOL1 channel selectivity.

Results: We discovered that in addition to K^{+} and Na^{+}, the APOL1 channel is permeable to Ca^{2+}. The RRVs led to an influx of Ca^{2+} and Na^{+} that preceded cell swelling and lysis by several hours. These events required RRV trafficking out of the ER and to the plasma membrane, where they localized prior to cation flux. Reduction of Ca^{2+} and Na^{+} in the media inhibited RRV-mediated cell death. We also found that the previously reported high K^{+} media protects against the RRVs due to a lack of Na^{+}.

Conclusions: We report that the earliest event in RRV-mediated cytotoxicity is localization to the plasma membrane, followed by cation flux driven by Ca^{2+} and Na^{+}. Because many of the proposed models of RRV cytotoxicity and kidney disease can be activated by pore-forming toxins, we propose that the cytotoxic cation channels at the cell surface are the upstream even that links them together. Our data suggests that targeting RRV channel activity represents a promising avenue for drug development.

PO1997

Cloning of an IgG Autoantibody Specific for Phospholipase A2 Receptor (PLA2R) Using IgG-Producing Cells from a Patient with Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is a common autoimmune kidney disease, in which 70% of patients exhibit circulating autoantibodies to one or more conformational epitopes in PLA2R. Anti-B cell therapies have proved effective to decrease autoantibody production and limit further development of the glomerular subepithelial immune deposits of PLA2R and IgG. However, better characterization of anti-PLA2R autoantibodies is needed.

Methods: We used Epstein-Barr virus (EBV)-immortalized B cells isolated from peripheral blood from an anti-PLA2R seropositive MN patient to develop a protocol for the cloning and expression of recombinant IgG (rIgG) specific for PLA2R. A C-terminally His-tagged fragment consisting of the first 5 domains of human PLA2R was expressed in Expi293 system and affinity purified. B cells were enriched by incubation with biotin labeled reagents (recombinant PLA2R or IgG-specific antibody) and streptavidin-conjugated magnetic beads. A FITC-conjugated N-terminal PLA2R peptide was used to isolate B cells with antigen-specific B-cell receptor (membrane IgG) by FACS. Variable segments of IgG heavy (VH) and light (VL) chains were cloned through a single-cell workflow that allowed expression of rIgG for follow-up screening using an in-house ELISA to assess IgG binding to human PLA2R. Sera from anti-PLA2R seropositive MN patients and healthy controls served as positive and negative controls, respectively.

Results: Starting with $1x10^{8}$ EBV-immortalized cells, we first isolated $3.6x10^{5}$ cells with membrane IgG specifically reactive with non-reduced PLA2R. This subpopulation was next stained with FITC-conjugated PLA2R peptide and the corresponding VH and VL of IgG were cloned using our single-cell workflow. We expressed the cloned VH and VL as rIgG in Expi293 system. ELISA confirmed that the rIgG bound PLA2R.

Conclusions: This is the first report of cloning a PLA2R-specific IgG autoantibody from a patient with MN. These approaches can be used for further characterization of the molecular mechanisms of autoimmunity and epitope spreading in MN.

Funding: NIDDK Support

PO1998

Pharmacologic Blockade of the Natriuretic Peptide Clearance Receptor Ameliorates Glomerular Disease in an Animal Model of FSGS

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Background: Glomerular podocytes play a key role in glomerular disease processes. Accumulating evidence suggests that cGMP signaling has podocyte protective effects in kidney diseases (J Am Soc Nephrol 28: 260, 2017). cGMP is produced by nitric oxide and by natriuretic peptides (NPs). NPs are the predominant source of cGMP generation in podocytes. NPs stimulate cGMP production by binding to NP receptors (NPRs). NPRA and NPRB stimulate cGMP generation. In contrast, NPRC binds and degrades NPs. Podocytes express all three NPRs (NPRA, NPRB, and NPRC). We hypothesized that blockade of NPRC would enhance local NP levels, promote cGMP signaling in podocytes and attenuate glomerular injury.

Methods: We blocked clearance of NPs by NPRC using the pharmacologic agent ANP (4-23), which specifically binds NPRC without binding NPRA or NPRB. For the experiments, we used a mouse transgenic (TG) model of focal segmental glomerulosclerosis (FSGS) created in our laboratory (J Clin Invest 125:1913, 2015). These TG mice express a constitutively active Gq α-subunit specifically in podocytes. In these animals, treatment with a single dose of the podocyte toxin puromycin aminonucleoside (PAN) causes robust albuminuria in TG mice, but only mild disease in non-TG animals.

Results: PAN induced heavy proteinuria in vehicle-treated TG mice at day 14 (1426 ± 425 [day 14] vs. 49 ± 19 [baseline] ug/mg creatinine; $P = 0.0002$). The increase in albuminuria at day 14 was significantly reduced by treatment with ANP(4-23) (1426 ± 425 [vehicle] vs. 383 ± 157 [ANP(4-23)] ug/mg creatinine; $P = 0.003$). Treatment with ANP(4-23) also tended to reduce the number of mice with glomerular injury (83% [vehicle] vs 54% [ANP(4-23)]; P = NS). Systolic BP was similar in mice receiving ANP(4-23) and in the vehicle treated group (129 ± 3 [vehicle] vs. 127 ± 3 [ANP(4-23)] mm Hg; P = NS). Urinary cGMP excretion tended to be higher in ANP(4-23) treated mice (6.7 ± 1.0 ng/mg creatinine) compared to mice treated with vehicle (4.9 ± 1.0 ng/mg creatinine), but this difference was not statistically significant.

Conclusions: These data suggest that: 1. Pharmacologic blockade NPRC may be a useful strategy for treating proteinuric kidney diseases, and 2. Treatment outcomes might be improved by optimizing blockade of the NPRC to more effectively inhibit clearance of NPs from the circulation.

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PO1999

Mitochondrial Damage in FSGS due to ANLN Mutation

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Background: We previously identified *ANLN R431C* as a cause of focal segmental glomerulosclerosis (FSGS). In addition to defects in actin bundling, targeted evaluation of this variant in cultured human podocytes identified disruption of AKT/mTOR signaling as a cause of ER stress and reduced podocyte viability. Creation of the orthologous *R431C* point mutation in mice confirmed the increased podocyte ER stress and identified mitochondrial damage as another possible feature of disease. To gain an unbiased view of the molecular mechanisms driving *ANLN R431C* induced disease, we used transcriptomic analysis and automated live cell imaging to interrogate cultured human podocytes.

Methods: Conditionally immortalized human podocytes overexpressing wildtype *ANLN* or the *R431C* variant were evaluated by mRNA-Seq and smRNA-Seq analysis to identify differentially expressed genes and microRNAs, as well as the molecular pathways involved. Potential therapeutic strategies were examined by evaluating cultured podocyte cellular and organelle-specific viability using automated live cell imaging.

Results: The top differentially expressed genes encode molecules that interact with previously identified pathological mechanisms including F-actin bundling (*SYNPO2L*) and AKT/ mTOR signaling (*CAVIN3, KIT*), with mTOR signaling identified as a pathway likely to be affected by *ANLN R431C*. A common feature of the top differentially expressed gene and microRNA candidates is the potential to regulate mitochondrial viability. When evaluated for changes in mitochondrial membrane potential, *ANLN R431C* podocytes displayed increased susceptibility to mitochondrial damage that could be rescued by treatment with AKT/mTOR pathway inhibitors. Additionally, compounds targeting improved mitochondrial viability through increased bioenergetic function (AP39), reduced oxidative stress (MitoQ, MitoTEMPO) and prevention of pore opening (Olesoxime) could all rescue the increased susceptibility to apoptosis *in ANLN R431C* podocytes.

Conclusions: Unbiased transcriptomic analysis confirmed that *ANLN R431C* disrupts AKT/mTOR signaling and actin cytoskeletal dynamics, resulting in increased ER stress and mitochondrial damage that reduce podocyte viability. Targeting various aspects of mitochondrial regulation may present viable alternative treatment strategies for FSGS due to defects in *ANLN* gene.

PO2000

Prothrombin Modulates Podocyte Health and Function During Glomerular Proteinuria

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Background: Ongoing podocyte injury is a known critical determinant of glomerular disease progression. Recent research suggests thrombin exacerbates *in vitro* podocyte injury, however, pharmacologic manipulation may cause both on- and off-target effects. Thus, the purpose of this study was to directly examine the effects of thrombin on glomerular proteinuria by manipulating its zymogen precursor, prothrombin (**PT**). We hypothesized that circulating PT would directly modulate both podocyte function and *in situ* survival in a rat model of nephrotic syndrome.

Methods: Puromycin aminonucleoside (PAN)-induced proteinuria was treated with: 1) PT antisense oligonucleotide to induce hypoprothrombinemia (LoPT), 2) Serial i.v. PT infusions to sustain hyperprothrombinemia (HiPT), or 3) sham (PAN only) controls (Con; n=12/group). Morning spot urine and citrated plasma were collected at day 10 post-PAN. Plasma PT activity was measured by chromogenic kit. Glomeruli were isolated from the kidney, dissociated into single-cell suspension and analyzed by flow cytometry following immunofluorescent antibody and TUNEL staining.

Results: Circulating plasma PT levels (**Figure A**) modulated proteinuria (**B**) such that it was significantly decreased in LoPT and increased in HiPT, compared to Con. LoPT also decreased *in situ* podocyte death (**C**), while HiPT increased *in situ* podocyte death, and resulted in fewer podocytes per glomerulus (**D**).

Conclusions: In conclusion, prothrombin modulates podocyte function (proteinuria) and survival (death and numbers) in the PAN model of glomerular proteinuria. Future studies should work to determine the prothrombinase mechanism that enables thrombin formation and signaling in the glomerulus and evaluate its potential as a novel therapeutic target to slow glomerular disease progression toward chronic kidney disease.

Funding: NIDDK Support

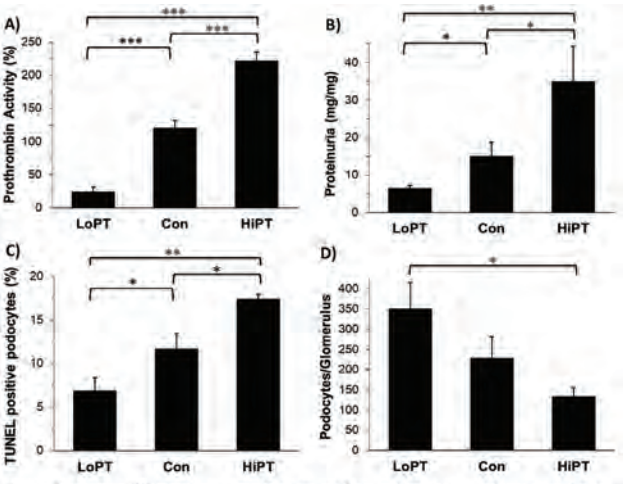

Figure: Prothrombin (PT) modulates podocyte health and function during glomerular proteinuria. Graphs depicting mean ± SE of **A)** plasma PT activity, **B)** proteinuria, **C)** TUNEL positive podocytes, and **D)** count of podocytes per glomerulus, in rats with glomerular proteinuria treated with i) an antisense oligonucleotide to knockdown circulating PT (**LoPT**), ii) serial PT i.v. infusions to induce hyperprothrombinemia (**HiPT**), or iii) sham (**Con**) (n=12/group). *; P<0.05, **; P<0.01, ***;P<0.001.

PO2001

Exosomal Long Non-Coding RNA-G21551 as a Potential Predictive Biomarker for Segmental Sclerosis Change in IgA Nephropathy

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Background: Segmental sclerosis (S) is an independent pathological predictor for renal progression in IgAN patients, and is closely related to proteinuria. However, there is less invasive biomarker for pathological S change. We investigate the difference in expression profiles of exosomal long non-coding-RNAs (lncRNAs) in plasma from IgAN patients compared with their healthy first-degree relatives, then explore the possible lncRNA associated with S.

Methods: To isolate exosomes from the plasma of both IgAN patients and their healthy first-degree relatives. High-throughput RNA sequencing and real-time quantitative polymerase chain reaction (qRT-PCR) was used to validate lncRNA expression profiles. Target lncRNAs were selected by bioinformatics analysis. The relationship between target lncRNA and S was analyzed by Spearman correlation. ROC curve evaluated the area under curve (AUC) of the target lncRNA for diagnosis S and its predictive sensitivity and specificity.

Results: 18 pairs of IgAN patients and their healthy first-degree relatives were enrolled in this study. The mean age was 29.71±6.06 years and urinary protein was 1.00±0.63 (g/24h) in these IgAN patients. LncRNA-G21551 was significantly down-regulated in IgAN patients. The predicted target genes of lncRNA-G21551 are FCGRs, which encode family of Fc gamma receptors (FcγRs). S was observed in 12 IgAN patients (66.7%) and was positively correlated with lncRNA-G21551 relative expression (r=0.545, *P*=0.019), but had no correlation with proteinuria, blood pressure, mesangial hypercellularity(M), endocapillary proliferation(E), tubulointerstitial fibrosis (T) and crescent(C). The relative expression (fold change) of lncRNA-G21551 was significantly higher in S1 group than in S0 group (11.26(9.79,20.38) *vs* 7.04(1.39,11.00), P=0.025). The AUC of lncRNA-G21551 to predict S change was 0.81(95% confidence interval, 0.62~1.00) with a sensitivity of 83.3% and a specificity of 83.3% when a cutoff value of 9.58 was used for lncRNA-G21551 relative expression (Fold change). In addition, patients with higher lncRNA-G21551 relative expression had more severe podocyte injury.

Conclusions: Exosomal lncRNA-G21551 was down-regulated in IgAN patients, but positively correlated with S change. Exosomal lncRNA-G21551 may be a potential independent predictor for S lesion in IgAN patients.

PO2002

Analysis of the Relationship Between Proteasome and Autophagy in Podocytes Using Podocyte-Specific Proteasome Impairment Mice

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Background: Ubiquitin-proteasome system and autophagy-lysosome system are major intracellular protein degradation mechanism. The relationship of these systems in podocyte has not well been understood.

Methods: In this study, we generated podocyte-specific proteasome impaired mice (Rpt3pdKO) by deletion of Rpt3, which is essential for construction of 26S proteasome, using Cre-loxP system. Albuminuria and number of sclerotic glomeruli increased in the Rpt3pdKO mice compared with Rpt3control mice. Oxidative stress and podocytes apoptosis were related to podocyte injury. To evaluated autophagic activity, LC3 dots

in podocytes were evaluated after administration of chloroquine, inhibitor of autophagic flux. In vitro experiment, cultured podocytes were treated with bortezomib (BTZ), proteasome inhibitor, which lead to podocyte apoptosis. The expression of LC3 was evaluated in podocytes after administration of bortezomib in the presence of E64d/pepstatinA, inhibitor of autophagic flux.

Results: In vivo, after administration of chloroquine, LC3 dots decreased in podocytes of Rpt3pdKO mice compared with Rpt3control mice. In vitro, the expression of LC3 decreased and the accumulation of p62 increased in cultured podocytes after treatment of BTZ in the presence of E64d/pepstatinA. These results indicated autophagic activity was suppressed in podocytes with proteasome impairment. pULK1, which is a down stream of mTOR signal, was phosphorylated in podocytes with proteasome impairment, suggested that suppression of autophagic activity was associated with mTOR activation. Pre-treatment of rapamycin, inhibitor of mTOR, ameliorated podocyte apoptosis induced by BTZ in vitro. In vivo, the number of sclerotic glomeruli decreased in Rpt3pdKO mice with rapamycin administration compared with in Rpt3pdKO mice without rapamycin administration.

Conclusions: Impairment of proteasome suppressed autophagic activity associated with mTOR activation in podocytes. Activation of autophagy have the protective effect on podocyte injury due to proteasome impairment.

PO2003

Functionally Resolving *WT1* Variants of Uncertain Significance in Nephrotic Syndrome

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Background: Patients with Mendelian forms of nephrotic syndrome (NS) are likely to progress to end stage kidney disease. Because of the increased availability and promise to guide clinical decision, genetic screening among affected patients is proliferating. However, accurate attribution of pathogenicity to rare variants found during genetic screening remains challenging. *WT1* is the second most common gene causing Mendelian NS. Therefore, this project aims to develop a model system to test the transcriptional activity of *WT1* variants, as a first step towards high-throughput functional analysis to comprehensively classify variants in this key NS gene.

Methods: Wild-type and several bona fide pathogenic *WT1* variants were tested for transcriptional activity in a standard dual-luciferase assay. Several cell lines including HeLa, HEK293, and HK2, were co-transfected with variant or wild-type *WT1* and an *NPHS1* promoter luciferase vector. Furthermore, potential *WT1* target genes specific to HEK293 cells were identified by analyzing differential gene expression in RNA-Seq data of *WT1* over-expressing HEK293 cells, in order to identify additional *WT1*-responsive promoters for use as *WT1* activity reporters.

Results: Overexpression of wild-type *WT1* in HeLa cells and HEK cells increased expression of luciferase under the *NPHS1* promoter by ~2-fold relative to truncated *WT1*. The luciferase activity of bona fide pathogenic WT1 variants was also significantly lower than the wild-type *WT1* and bona fide benign *WT1* variants ($P<0.05$). Overexpression of wild-type *WT1* in HEK293 resulted in upregulation (log2 fold change>0.4, adjusted $p<0.05$) of *IGF1R*, *EGFR*, *TGFB2*. These candidates are being developed as *WT1*-responsive reporters.

Conclusions: Previous reports suggested *NPHS1* promoter reporters as a model system to investigate mutant *WT1* function. However, the transcriptional effect of *WT1* was subtle and may be cell specific. Future work to establish a robust *WT1* reporter is ongoing using cloned *IGF1R*, *EGFR*, *TGFB2* promoters.

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PO2004

Sources of Variability in Podocyte Foot Process Width Measurements and Approaches to Mitigation

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Background: Podocyte foot process (FP) morphometry is used in the research setting to quantify podocyte injury and has the potential to be leveraged for diagnostic use. However, the impact of pre-analytic and analytic variables on these measurements are not well understood. We sought to identify these sources of variability and develop a robust method for podocyte foot process width (FPW) measurement within various kidney diseases.

Methods: We examined the impact of operator bias and sample size on FPW measurement in electron micrographs from nephrectomies (Nx) and podocytopathy (Px) cases, including primary focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD), and other glomerular lesions effecting the podocyte. FPW was measured for each individual FP between the midpoints of flanking filtration slits and the geometric mean of these measurements was reported by image. We found that identification of filtration slits was subjective, but interoperator variability was mitigated through use of standardized morphologic criteria, operator training, adjudication of ambiguous features, and a mapping process that eliminated duplicate measurements in adjacent images. These methods reduced interoperator variability in FPW, averaged by image, from 12% to 7%.

Results: Preliminary analysis suggests that, in addition to the expected larger FPW mean in MCD cases vs. Nx cases, there is also larger FPW *variability* in MCD cases. Related analysis shows ~125 FPW measurements within each of 2 glomeruli (~250 total) in a Nx case has the same precision as ~100 FPW measurements in each of 10 glomeruli (~1,000 total) in a MCD case. We also found that intraglomerular variability among 3 glomeruli in each of 2 cases (1 Nx, 1 MCD) ranged from 29% to 46% (Geometric CV), whereas interglomerular variability within these cases ranged from 0.5% to 6.3%, signifying that number and selection of FP within glomeruli is more impactful than number and selection of glomeruli within a specimen.

Conclusions: Our results suggest that careful measurement standardization and sampling improves validity of FPW measurements as a supplement to other diagnostic approaches or for assessment of podocyte injury in the course of treatment.

Funding: Commercial Support - Pfizer, Inc.

PO2005

Glomerular Transcriptomic Analysis of Glucocorticoid- and Pioglitazone-Treated Nephrotic Syndrome

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Background: Nephrotic Syndrome (NS) is among the most common glomerular diseases in children. Glucocorticoids (GC) are the primary treatment for NS, but 15-20% of children have or develop steroid resistant NS, creating an unmet need for novel treatments. Thiazolidinediones (TZDs) such as pioglitazone (Pio) have been reported to slow diabetic nephropathy progression, and to reduce proteinuria in animal models of NS. Since both GC and Pio act via binding to nuclear receptors we hypothesized that the reported similar degrees of proteinuria reduction by GC and Pio are driven via common molecular pathways.

Methods: We performed transcriptome analyses on glomeruli isolated from GC- and Pio-treated rats 11 days after induction of NS with PAN (n=4/group).

Results: Principal component analyses revealed distinct transcriptional profiles between control vs. PAN-treated rats, with 319 and 126 differentially up- and down-regulated genes in PAN respectively, which were largely reversed by both GC and Pio. Ingenuity pathway analyses (IPA) combined with drug-target interaction network analyses and gene set enrichment analyses identified 29 glomerular genes that were commonly regulated by GC, Pio, and their respective nuclear receptors (NR3C1 and PPARγ). Gene ontology annotation revealed these 29 genes to be involved in: ECM modification, plasma membrane dynamics, DNA damage/repair, transcription factor binding, lipid metabolism, and cytoskeletal organization. Gene segregation into their cells of origin using reported glomerular single cell transcriptomes revealed most dysregulation and restoration of gene expression within podocytes, with moderate changes within mesangial cells and minimal changes within endothelial cells. IPA-based disease and toxicity algorithms developed from these cell-specific data also revealed enhanced cytoskeletal organization and improved cell viability after both GC and Pio vs. PAN.

Conclusions: GC and Pio treatment reduced proteinuria similarly in NS, but by inducing alterations in both distinct and overlapping glomerular gene-sets. Notably, informatics analyses of overlapping genes identified ECM proteins, as potential novel targets for future therapies for NS, distinct from current immunosuppressive approaches.

Funding: NIDDK Support

PO2006

Novel Podocyte Protective Compounds Identified Using Ultra-Miniaturized High-Content Screening (HCS) Assays

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Background: Podocytes are specialized epithelial cells which are part of the filtration barrier in the kidney. Podocyte dysfunction is part of kidney pathology hallmarked by proteinuria. Using a high-content imaging based assay, we have shown that podocytes can be used to identify novel therapeutic compounds.

Methods: Differentiated mouse podocytes were seeded on collagen-I coated multi-well plates. After 10-14 days of differentiation, cells were exposed to puromycin aminonucleoside (PAN, podocyte injury inducing agent), with compounds from the screening library or newly identified targets, or DMSO as control, for 48 hours. After, cells were fixed with 4% paraformaldehyde and permeabilized with 0.1% Triton X-100. Cells were labeled with cytoplasmic stain HCS CellMask Green, and actin fibers were detected by using labelled phalloidin. Cell images were taken with using Opera High-Content Screening (HCS) System. Columbus software was used to quantify morphology properties such as roundness, as well as the overall F-actin signal. We utilized commercial libraries containing >50k unique compounds to identify podocyte protective hits.

Results: Using PAN as a podocyte damaging agent, we noticed marked reduction in F-actin fiber numbers and intensity, and increased roundness in podocytes. Screening of a library of chemical compounds identified >25 hits which had favorable profiles.

Conclusions: Using our optimized podocytes high-throughput screening assay in 1536-well plates, we have identified a number of highly novel compounds. Further validation on smaller well formats reproduced these findings. In vitro and in vivo mechanistic studies provide new insights about podocyte pathways that can be therapeutically targeted.

Funding: NIDDK Support

PO2007

The Role for FNBP1L in Podocytes

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Background: Podocytes exhibit a complex cellular morphology characterized by the formation of foot processes. The normal structure of podocytes depends on their unique cytoskeleton, of which actin microfilaments are one component. Nucleation of actin monomers is the rate limiting step in actin polymerization. There are two distinct nucleators for actin nucleation in podocytes, Arp2/3 complex and formins, which mediate branch and linear actin filament formations, respectively. Our previous study identified hundreds of genes expressed in every single podocyte, which were potential podocyte essential genes. Of them, FNBP1L is known to be involved in Arp2/3 complex and formins activity in nucleation, supporting FNBP1L's essentiality for podocytes. Here, we test this hypothesis.

Methods: Cultured podocytes were used for this study. FNBP1L was knocked down by siRNA, and immumostaining, immunoblotting, qPCR, wound healing assay, co-immunoprecipitation were performed to test FNBP1L essentiality and mechanism.

Results: FNBP1L was specifically expressed in podocytes in glomeruli, and its expression was decreased in purimycin aminonucleasides-treated in podocytes. When FNBP1L was knocked down, we found that the expression of WT1, SYNPO and CD2AP was decreased; that the migratory capability was impaired; that F-actin stress fibers were reduced and disorganized; and that focal adhesion number was decreased while their size increased as shown by p-FAK staining. Mechanistically, FNBP1L regulated Arp2/3 complex and INF2 (a formin) actin nucleation activities. Co-IP and IF showed that FNBP1L colocalized and interacted with CDC42 and N-WASP to facilitate interaction of N-WASP with Arp2/3 complex, thereby increasing the activity of Arp2/3 complex in actin nucleation. FNBP1L also interacted with INF2 and affected its localization in cytoplasm and its actin nucleation. Consistently, the reduction of FNBP1L impaired the interaction between N-WASP and Arp2/3 complex and mis-localized INF2 in the cytoplasm.

Conclusions: FNBP1L may regulate branched and linear actin filament polymerization by regulating Arp2/3 complex and INF2 actin nucleation activities in podocytes, thereby maintaining podocyte normal structure and function. Reduction of FNBP1L expression is involved in podocyte injury and targeting FNBP1L may represent a novel therapeutic approach for podocytopathies.

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PO2008

Role of ATE1 in Radiation-Induced Nephrotoxicity

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Background: Arginylation increases actin polymerization and supports cellular morphology. However, the effect of radiation therapy (RT) on arginylation is not known. This study investigated the impact of RT on arginyltransferase 1 (ATE1) and its role in podocyte morphology and kidney function

Methods: Human podocytes were irradiated with 4 Gy, and preceded by rituximab mAb (100 μg/ml) or IgG (100 μg/ml) treatment, 30 min before RT. Additionally, 6-8-week-old C57BL/6 male and female mice were submitted to either (i) 1x14Gy bilateral kidney-only RT (ii) lethal-dose total body irradiation (TBI 10.5Gy) and rescued by strain-donor hematopoietic stem cell transplantation (HSCT) or (iii) left untreated (sham-RT control). Functional, histopathological, and biochemical changes were studied at baseline and 10 weeks post RT

Results: In podocytes, RT (4Gy) produced time-dependent downregulation of ezrin (30%) and ATE1 (50%) and a significant increase in apoptosis at 4h ($p=0.001$). Rituximab pretreatment protected from ezrin relocalization and ATE1 downregulation, and podocyte apoptosis. In C57BL/6 mice, RT significantly decreased glomerular surface area and increased mesangial expansion scores in 14Gy and TBI animals compared to controls ($p<0.01$). Similarly, both RT schedules resulted in significant increases in renal fibrosis ($p<0.01$), serum BUN ($p<0.01$), and serum creatinine levels ($p<0.01$). Western blot analysis showed downregulation of ATE1 in the kidney cortex: 67.7±9.6% (14Gy); 69.3±13.3% (TBI) compared to control. Similarly, IHC data showed a decrease in ATE1 expression in glomeruli after 14Gy (50%) and TBI (70%) compared to control. Podocyte number (WT1) in kidney cortex, also decreased significantly after both RT treatments. TEM showed that both RT schedules resulted in significant increases in GBM thickness when compared to control ($p<0.001$). Foot process width also increased significantly in 14Gy and TBI animals compared to controls ($p<0.001$)

Conclusions: Our study demonstrates that rituximab pretreatment protects from ATE1 downregulation and confers radioprotective effects in cultured podocytes. ATE1 may be an important therapeutic target for radiation-induced kidney injuries in HSCT patients

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PO2009

Podocyte Infolding Glomerulopathy: New Disease or Pattern of Injury?

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Introduction: Occasional podocyte infolding is reported in membranous nephropathy, but global and diffuse infolding is rare. Whether this is a new disease entity or a pattern of podocyte injury may influence therapy.

Case Description: 52 year-old-male with hypertension developed lower extremity edema, pleuritic chest pain and dyspnea. CT chest showed bilateral pulmonary emboli. Creatinine was 0.92 mg/dL, cholesterol 239 mg/dL, albumin 3.2 g/dL, urine protein:Cr ratio 32,647 mg/gCr. Renal biopsy showed immune complex deposition in a membranous pattern, and subepithelial deposits with targetoid microvesicular substructures, suggesting a podocyte infolding glomerulopathy (PIG) [Fig.1 Electron microscopy showing PIG]. Immune deposits were dominantly reactive for IgG4, and also for other IgG subclasses, C3, IgM, and kappa and lambda light chains. Deposits were reactive for PLA2R. Serum PLA2R antibody and other serologies were negative. He was anticoagulated and treated for 6 months with the modified Ponticelli protocol. Creatinine remains normal, but hypoalbuminemia and proteinuria (190mg – 1.2g) persist 8 months after starting treatment.

Discussion: In 1985, Dales and Wallace [1] described massive deposits of spherular organelles in the subepithelial space of glomerular capillary walls in a patient with membranous nephropathy. In 2008, Joh et al [2] studied 25 Japanese patients with microspheres and microtubular structures associated with podocyte infolding, coining the term "podocyte infolding glomerulopathy." Rare cases are reported in India, Latin America, and Europe. It is unclear whether PIG is a subtype of membranous nephropathy or a distinct glomerular lesion. Identification of PIG associated with vesicoureteral reflux, myeloma, and autoimmune diseases, and the absence of immune complexes in many biopsies, suggest a distinct type of podocyte injury. Ultimately, the pathophysiology of PIG is not understood. Response to therapy and prognosis are not well-described. This patient was treated with the modified Ponticelli protocol, given findings of membranous nephropathy, with a reduction in proteinuria but not full remission. This may represent a partial response to therapy or may imply that podocyte infolding glomerulopathy is a separate disease entity not responsive to immunosuppression.

PO2010

CKD Remodels Skeletal Muscle Metabolism Toward Carbohydrate Oxidation

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Background: Skeletal muscle health progressively declines from chronic kidney disease (CKD). To test the hypothesis that exercise mitigates abnormal muscle metabolism in CKD, we utilized high-resolution mitochondrial respiration and metabolomics techniques for indices of skeletal muscle carbohydrate and fat metabolism in a progressive CKD rat model.

Methods: *Animals-* 1) Cy/+ (CKD) rats, 2) CKD + wheel running, and 3) normal littermates (NL) (N=12/gr). Running wheel was accessible 24 hr/day 25-35 weeks of age; moderate to severe CKD, respectively. Extensor digitorum longus (EDL) and soleus were harvested at sacrifice. Mitochondrial respiratory subunit complexes were quantified by Western blot. *Mitochondrial respiration:* Measured in the presence of multiple substrates (Oxygraph-2k, Oroboros). *Metabolomics:* Targeted mass spectrometry (MS) and nuclear magnetic resonance (NMR) were performed.

Results: In the EDL, protein content of Complex 1 was reduced, but pyruvate-stimulated respiration increased with CKD wheel running. Metabolomic analysis (MS) of the EDL supported this, as wheel running lowered long-chain fatty acids (C14-18; $p<0.05$). In the soleus, Complex 1 content decreased and pyruvate-stimulated respiration increased in both CKD and CKD running compared to NL ($p<0.05$). Soleus MS demonstrated lower long-chain fatty acids (C14-18; $p<0.05$). Serum NMR demonstrated increased pyruvate and reduced lactate concentrations suggesting greater re-direction of pyruvate to mitochondrial oxidative phosphorylation. Carnitine levels were low in serum and muscle, suggesting impaired transport of fatty acids to the mitochondria.

Conclusions: These intriguing results indicate CKD impairs skeletal muscle mitochondrial oxidative capacity despite increased pyruvate oxidation. In addition, metabolomics data suggests impaired fatty acid oxidation that worsened with wheel running due to low carnitine levels. These results suggest dual alterations in response to mild exercise in CKD: 1- impaired fatty acid oxidation from deficient carnitine; 2- enhanced pyruvate oxidation consistent with lower lactate production. These cellular metabolic reprogramming events suggests that skeletal muscle may shift away from fatty acid metabolism towards carbohydrates which may explain why patients with CKD do not experience the usual benefit of exercise.

Funding: NIDDK Support

PO2011

Podocyte-Derived Testican 2 Promotes In Vitro Glomerular Angiogenesis

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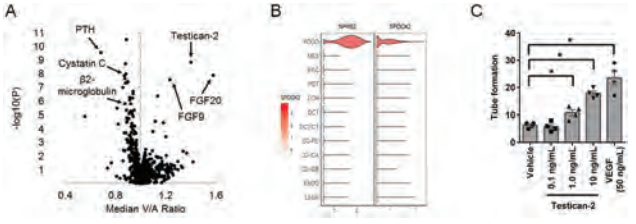
Background: In addition to their fundamental role in clearance, the kidneys release select molecules into the circulation, but whether any of these anabolic functions provides insight on kidney function is unknown.

Methods: Using aptamer-based proteomics, we characterized arterial (A) to renal venous (V) gradients for >1,300 proteins in 22 human individuals who underwent invasive sampling. To localize testican-2, immunohistochemistry, immunofluorescence, immunogold electron microscopy and single cell RNA sequencing in human kidney tissue were used. Functional effects of testican-2 were tested on cultured primary human glomerular endothelial cells (HGEC).

Results: Although most of the proteins that changed significantly decreased from A to V, consistent with renal clearance, several were found to increase, the most significant of which was testican-2 (V/A = 1.40, $P = 1.5 \times 10^{-9}$). Imaging and single cell RNA sequencing demonstrated testican-2 expression in human podocytes. Testican-2 promoted angiogenesis and migration in cultured HGEC, but not proliferation. Further, testican-2 upregulated MMP-2/MMP-9 activity in the culture media of HGEC.

Conclusions: Testican-2 is a circulating protein that is synthesized in the human podocyte. Testican-2 promotes angiogenesis in cultured HGEC, which may be mediated by upregulating MMP-2/MMP-9 activity and increased endothelial cell migration.

Funding: NIDDK Support



(**A**) Volcano plot showing median V/A ratio for all 1317 proteins detected by aptamer in 22 individuals, with *P* values plotted on the y axis. (**B**) Violin plot demonstrating podocyte-specific *SPOCK2* expression (encodes testican-2), with *NPHS2* as positive control. (**C**) Tube formation of primary HGECs treated with vehicle, testican-2, or VEGF.

PO2012

Mitochondrial Quality Control Mechanisms in Renal Cortex During the Normoalbuminuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the normoalbuminuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria. Because accumulation of damaged mitochondria can contribute to renal dysfunction, we aimed to determine if oxidative stress in DM triggers 1) mitochondrial fission or fusion, 2) increased fatty acid metabolism, and/or 3) mitophagy as quality control mechanisms.

Methods: Rats receiving i.p. injection of streptozotocin (STZ, 65 mg/kg) or vehicle (Sham) were either left untreated or treated with telmisartan (TLM, an angiotensin receptor blocker; 10 mg/kg/d). Two weeks later, blood glucose levels (BG), blood pressure (BP), glomerular filtration rate, and urinary excretion of albumin and *N*-acetyl-β-D-glucosaminidase (NAG) were measured. The oxidative stress marker, 3-nitrotyrosine (3-NT), was detected by HPLC. Fission-, fusion-, and mitophagy-related proteins were quantified by Western blot. Levels of acylcarnitine, which transports fatty acids into mitochondria for β-oxidation, were calculated as the difference between total and free carnitine levels measured by the enzymatic cycling method using commercial kits.

Results: TZ rats displayed hyperglycemia and hyperfiltration that were unaffected by TLM. BP, albumin excretion, and NAG excretion were similar in all groups. Renal cortical 3-NT levels were increased in STZ rats, a change that was prevented by TLM (STZ+TLM). Renal cortical acylcarnitine levels in STZ rats were more than double those of Sham rats ($P<0.05$) and were further elevated in STZ+TLM rats ($P<0.05$ vs STZ alone). Renal cortex from STZ rats displayed TLM-sensitive increases in the mitophagy-related proteins LC3-II and PINK1 (all $P<0.05$). Renal cortical Drp1 levels were 3-fold higher in STZ than in Sham, with STZ+TLM rats exhibiting intermediate levels of this fission marker. Levels of the fusion marker Mfn2, and mitophagy-related proteins BNIP3 (dimer) and p62 did not differ among groups.

Conclusions: During the normoalbuminuric stage of DM, renal cortical mitochondria undergo increased fatty metabolism, as well as enhanced fission and mitophagy that are blunted by TLM in association with its antioxidant effect and, thus, are likely quality control mechanisms triggered by oxidative damage.

PO2013

Indoxyl Sulfate Modulates Expression of Myosin Heavy Chain Isoforms and induces Sarcopenic Phenotype in Mouse

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Background: In patients with chronic kidney disease, sarcopenia is frequently associated with decreased renal function and correlates with increased morbidity and mortality. However, the molecular mechanism to underlie uremic sarcopenia is not fully elucidated yet. We hypothesized that the accumulation of uremic toxin might have a direct negative effect on skeletal muscle, and investigated the mechanism of indoxyl sulfate (IS) induced toxicity on mouse skeletal muscle.

Methods: We conducted the vivo experiments using C57BL/6j mice. After unilateral nephrectomy, vehicle (PBS) or high dose IS was intraperitoneally administered daily for 1 week, and evaluated exercise tolerance (treadmill fatigue test and four limbs grip test), skeletal muscle wet weight, cross-sectional area, and protein levels of myosin heavy chain isoforms characterizing fast/slow twitch muscle fibers (fluorescent immunostaining and western blot, respectively), and the expression of muscle atrophy related genes (quantitative-PCR).

Results: In mice treated with IS, exercise tolerance was deteriorated and gastrocnemius muscle wet weight were decreased compared to the control group. Intriguingly, IS administration also reduced a cross-sectional area of fast twitch myofiber and protein levels of fast twitch myosin heavy chain. Also, IS treatment tended to up-regulated mRNA expression of muscle atrophy related genes (*Atrogin-1* and *Myostatin*) of the gastrocnemius muscle tissue.

Conclusions: IS induces direct sarcopenic effect on mouse skeletal muscle and predominantly decreases on fast-twitch muscle fibers. In the future, we will further investigate the molecular mechanism of uremic toxin induced sarcopenia.

PO2014

Lnc-Gm43360 Regulates TCMK-1 Senescence by the miR-141/Sirt1 Pathway

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Background: Aging is a complex process, which will lead to the gradual decline of physiological functions of all organ systems. The kidney, which is a metabolically active organ, is extremely susceptible to aging, but the mechanism of kidney aging is not clear. Long-chain non-coding RNA (lncRNA) is an non-coding RNA consisting of 200 nucleotides, which play an important role in kidney fibrosis and diabetic nephropathy, but there is no study on kidney senescence.

Methods: Dectection of lnc-Gm43360 expression by qRT-PCR. Transfection with lnc-Gm43360 siRNA and overexpressed plasmid to measure the miR-141 and Sirt1 expression by qRT-PCR, and the p53, p21 and p16 expression by western blot, and SA-β-gal expression. Transfection with miR-141 mimic and inhibitor to measure Sirt1 expression by qRT-PCR, and p53, p21 and p16 expression by western blot, and and SA-β-gal expression.

Results: Lnc-Gm43360 expression in 24-month-mouse lower than 3-month-mouse kidney tissue. The reduction of lnc-Gm43360 expression significantly increases miR-141 expression, decrease Sirt1 expression on both the mRNA and protein level, and induces the SA-β-gal expression. miR-141 mimic and inhibitor decrease and increase Sirt1 expression. lnc-Gm43360 negatively regulates miR-141 expression and positive negatively regulate Sirt1 expression at both the mRNA and protein level. The function of lnc-Gm43360 in regulating Sirt1 expression depends on modulating miR-141 expression.

Conclusions: Lnc-Gm43360 can induce TCMK-1 senescence by miR-141/Sirt1 pathway.

PO2015

Modified Lipoproteins Modulate Renal Lymphatic Vessel Vasodynamics via NKCC1 on Lymphatic Endothelial Cells

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Background: In addition to its pivotal role in chloride transporting epithelia, the sodium–potassium–chloride cotransporter 1 (NKCC1) is increasingly recognized as a key modulator of vascular tone. We previously documented NKCC1 expression in renal lymphatic endothelial cells (LECs) of rats and cultured human LECs. *Ex vivo* we showed that blocking NKCC1 by furosemide caused a dose-dependent dilation in renal lymphatic vessels, decreased amplitude, and decreased frequency of spontaneous contractions. Since lymphatic vessels clear interstitial lipids and kidney injury increases lipid peroxidation products including isolevuglandins (IsoLG) which modify lipoproteins (apoAI), we examined if IsoLG-modified apoAI can affect renal lymphatic vessel contractility through NKCC1.

Methods: Puromycin nephrotoxicity (PAN) was induced in Sprague Dawley rats, while non-injected rats served as controls (Cont). Renal lymphatic vessels were isolated and mounted in a perfusion chamber to assess vasoactivity. The effects of apoAI or IsoLG-apoAI on the NKCC1 signaling pathway were assessed in LECs.

Results: PAN rats had significantly higher renal lymph flow which contained significantly more IsoLG vs Cont. *Ex vivo* studies showed renal collecting lymphatic vessels from PAN were more dilated vs Cont. Immunostaining revealed NKCC1 expression on LECs that was more prominent in PAN renal lymphatic vessels vs Cont.

LECs (prox-1 positive cells) isolated from PAN kidneys also had more NKCC1 gene expression than cells from Cont. In LECs, IsoLG-apoAI increased NKCC1 expression vs apoAI. Similarly, WNK1, OxSR1 and SPAK, upstream activators of NKCC1, were significantly increased in LECs exposed to IsoLG-apoAI vs unmodified apoAI, which was accompanied by increased eNOS expression. *Ex vivo* renal collecting lymphatic vessels significantly increased diameter, amplitude, and frequency of spontaneous contractions when exposed to IsoLG-apoAI vs with apoAI.

Conclusions: IsoLG-apoAI change renal lymphatic vessel vasodynamics through the WNK1-OxSR1/SPAK-NKCC1 pathway on LECs which we propose is a novel target to improve lymphatic vessel function in kidney disease.

Funding: NIDDK Support

PO2016

Progranulin Deficiency Exacerbates High-Fat Diet-Induced Inflammation in Kidney

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Background: Progranulin (PGRN) has been reported to bind to tumor necrosis factor (TNF) receptor (TNFR) and inhibit TNFα signals. Conversely, PGRN is a 'bad' adipokine that can contribute to insulin resistance in some metabolic diseases. We evaluated the effect of augmentation of TNFα signals by PGRN deficiency on the progression of kidney injury in high-fat diet-induced obesity model mice.

Methods: Eight-week-old PGRN knockout (KO) mice and their wild-type (WT) mice were fed a standard diet or high-fat diet (HFD) for 12 weeks. Mouse proximal tubule (mProx24) cells knocked down with PGRN siRNA were treated with TNFα stimulation.

Results: The body weight and albuminuria were significantly increased in WT-HFD group compared with WT-standard diet (SD) group. The body weight of KO-HFD group was significantly decreased compared with WT-HFD group. However, albuminuria and the expression of renal inflammatory markers including TNFα in KO-HFD group were increased than those in WT-HFD group. On the other hand, the WT-HFD mice showed vacuolization in the proximal tubule, but KO-HFD mice did not. Immunohistochemical analysis showed that vacuolar membranes were clearly positive for a lysosomal marker, LAMP-1, suggesting impairment in lysosomal function. The expression of megalin which plays a critical role in the reabsorption of protein in proximal tubules was found to be decreased in KO mice compared with WT mice, and also reduced in mProx stimulated with TNFα.

Conclusions: PGRN deficient exacerbated renal inflammation caused by high-fat diet, while the results also showed improvement in tubular vacuolation. Anti-inflammatory treatment with PGRN for kidney diseases should be considered based on the opposing function of PGRN.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO2017

Diet Has a Stronger Impact on the Gut Microbiota Than Kidney Function in Rats with Moderate CKD

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Background: Diet and CKD have been shown to alter the gut microbiota. However, whether diet or kidney function plays a stronger role in the gut microbiota in moderate CKD is not well established. We assessed the effects of two diets on the gut microbiota in rats with moderate CKD.

Methods: Cy/+ rats (CKD) and normal littermates (NL) consumed an autoclaved grain-based diet containing 0.7% phosphorus (0.3% phytate-bound) and 3.5% crude fiber from birth. At 17-wk-old, half of the animals were maintained on the same diet (Grain) and the other half switched to a semi-purified casein-based diet containing 0.7% phosphorus (0% phytate-bound, 0.6% phosphate additives) and 5% non-fermentable cellulose (Casein) until 28-wk-old (n=8-10 rats/group). DNA was extracted from cecal and fecal samples collected at euthanasia, the V4 region of the 16S rRNA gene was sequenced via Illumina MiSeq, and data were analyzed using QIIME2 and LEfSe.

Results: Intestinal microbial a-diversity, or diversity within a sample, was significantly greater in rats fed the grain diet compared to casein diet regardless of kidney function. Diet and kidney function both had significant impacts on microbial β-diversity (diversity between samples), but diet explained a larger portion of the observed variability (27%) than kidney function (11.5%). Consumption of the grain-based diet increased many genera with short-chain fatty acid (SCFA) producing capacity, including *Bifidobacterium, Ruminococcus, Roseburia,* and *Prevotella* than the casein diet. Whereas the casein diet drove greater *Bacteroides* abundance that can metabolize tryptophan to indoles, which may exacerbate the formation of uremic toxins. Notably, the casein diet led to a greater abundance of *Bilophila* in NL rats and greater *Allistipes* in CKD. Both of these taxa have been suggested to drive the pathogenesis of inflammatory bowel disease. Additionally, CKD rats fed the casein diet had a higher relative abundance of *Akkermansia,* which has been shown to be greater in fiber-free or low fiber interventions, as it may degrade the mucus layer.

Conclusions: In rats with moderate CKD, diet had a stronger effect on diversity and gut microbial taxonomic differences than kidney function. Particularly, those fed the grain-based diet had higher bacterial genera known to produce SCFA.

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PO2018

Effect of High Fiber or Probiotics-Enriched Diets on Kidney Injury in Mice Model of Bilateral Ischemia Reperfusion

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Background: Changes in dietary intake have a significant effect on the incidence and development of chronic kidney disease (CKD). The progressive decline in kidney function during CKD can lead to increased systemic chronic inflammation and worsening of kidney injury. Fibers and probiotics are used by gastrointestinal bacteria to produce metabolites with anti-inflammatory activities. The objective of our study was to investigate the role of fiber and probiotics in ameliorating kidney injury using bilateral ischemia reperfusion (IR) surgery as a CKD model in mice.

Methods: Thirty-six C57BL/6J wild type, male mice were purchased from the Jackson Laboratory (Bar Harbor, ME, USA). After co-housing for a week, they were then isolated and randomly assigned to a diet: normal chow (C; control), high fiber (HF; modified AIN-93G with increased Hi-Maize Corn), and probiotics (P; AIN-93G with added *Bifidobacteria* spp.). After 14 days, mice underwent sham surgery (5 per group) or IR surgery (7 per group) and then resumed assigned diet for 28 days. Blood and fecal samples were collected both before surgery and after surgery. Mice were euthanized after 42 days to collect kidneys, small intestine, colon, fecal, and blood samples. Measurements of plasma creatinine, markers of kidney injury, and tissue staining were performed. Fecal samples were further processed to assess diversity of gut microbiota. Two-way ANOVA with Tukey's multiple comparisons was used for statistical analysis.

Results: On each diet, the IR increased serum creatinine compared to sham ($p<0.005$), confirming kidney injury. Transcripts of kidney injury markers, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM1), were also higher with IR in all groups ($p<0.05$). However, NGAL and KIM1 were lower in HF and P compared to C, respectively ($p<0.005$). The histology sections in control group appeared to be more fibrotic compared to the other two groups. The sequencing of 16s rRNA gene was completed and is currently being used to assess the composition and diversity of gut microbiota in each group.

Conclusions: Supplementation with fiber or probiotics may reduce kidney injury after ischemia. Additional studies to identify specific changes in metabolites driving this protection are needed.

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PO2019

Nutritional Status and Oral Nutritional Supplement (ONS) Use Among Patients with Non-Dialysis CKD in British Columbia (BC)

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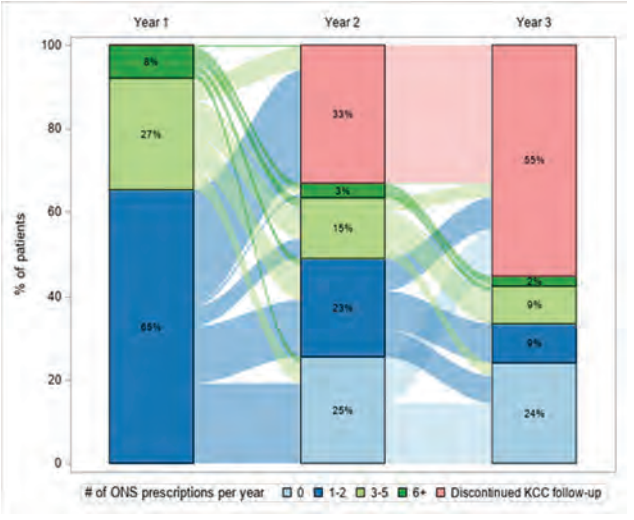
Background: Malnutrition and protein-energy wasting are complications of advanced CKD that are associated with increased risk of mortality and morbidity. In BC, a government-funded Nutritional Supplement Policy stewarded by renal dietitians guides ONS prescription for CKD patients who meet weight or nutrient intake criteria.

Methods: We conducted a retrospective study of CKD-ND patients who entered multidisciplinary CKD clinics in BC during 2013-2018 (N=15859). We used Wilcoxon signed-rank test to compare baseline nutrition/inflammation parameters among patients with any ONS prescription within 1 year of clinic entry and those not prescribed ONS. Longitudinal ONS prescription patterns over 3 years were described in the 2013-2015 entry cohort (N=7611).

Results: 1389 patients (9%) were eligible for and prescribed ONS, with variation between health regions. Patients taking ONS had lower eGFR, BMI, bicarbonate, hemoglobin, and greater age, ferritin, phosphate, PTH, neutrophil-to-lymphocyte ratio compared to those who did not receive ONS ($p<0.0001$ for all comparisons). Overall ONS use during the first 3 years of follow-up remained stable, with 40% new ONS users and 60% previous ONS users during year 2 and 3 of follow-up. For patients prescribed ONS within the 1st year of clinic entry, 65% had 1-2 ONS prescriptions/year, and among those continuing follow-up in year 2, 38% discontinued ONS, 35% had 1-2 ONS prescriptions/year, and 27% had 3+ ONS prescriptions/year (Figure).

Conclusions: This is the first Canadian study to describe ONS use among CKD-ND, which provides an estmate of incidence of undernutrition, as defined by dietitian assessment and corroborated by nutritional lab parameters. Among patients prescribed ONS, the majority have infrequent ONS use, while another subset has regular ONS use longitudinally.

Funding: Government Support - Non-U.S.



PO2020

Dietary Fat Intake and Mortality Across Kidney Function in a Nationally Representative Cohort

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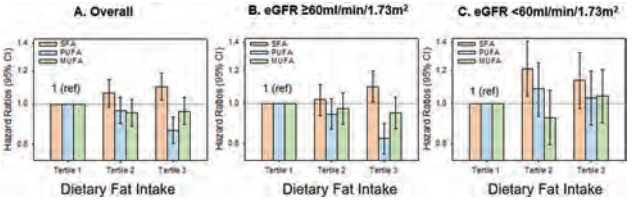
Background: In the general population, lower dietary intake of saturated fatty acids (SFA) and higher intake of polyunsaturated fatty acids (PUFA) are associated with greater survival. However, the optimal amount and type of dietary fat intake in patients with kidney disease is unknown. We assessed the relationship between dietary fat intake and mortality in a cohort of US adults with and without kidney disease.

Methods: We examined the association between dietary intake of fat subtypes (SFA, PUFA, monounsaturated fatty acids [MUFA]) ascertained by 24-hour dietary recall with mortality in continuous NHANES adult participants (1999-2014) stratified by absence vs. presence of kidney dysfunction (eGFRs ≥60 vs. <60ml/min/1.72m^2, respectively). Dietary fat intake was estimated as a proportion (%) of total energy intake, and associations with all-cause mortality were estimated using adjusted Cox models.

Results: Among 37,155 participants who met eligibility criteria, 7% (N=2,677) had kidney dysfunction. In participants with normal kidney function, those with the highest tertile of SFA intake had higher death risk (ref: lowest tertile) (HRs [95%CI] 1.10 [1.01,1.19]), whereas those with the highest tertile of PUFA intake had better survival (HR [95%CI] 0.82 [0.76, 0.90]). In participants with kidney dysfunction, those in the second and third highest tertiles of SFA intake had significantly higher mortality risk and trended towards higher mortality, respectively: HRs (95%CIs) 1.21 (1.04, 1.41) and 1.13 (0.97, 1.32), respectively; however, PUFA was not associated with survival. In participants with and without kidney dysfunction, MUFA intake was not associated with mortality.

Conclusions: Higher dietary SFA intake was associated with a higher mortality in US adults with and without kidney dysfunction, whereas higher PUFA intake was associated with greater survival in those with preserved kidney function only. Further studies are needed to elucidate mechanisms behind the association of dietary fat intake with mortality.



PO2021

Predictors of Healthy Behavior Engagement in CKD

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Background: Guidelines for chronic kidney disease (CKD) management recommend healthy behaviors to mitigate disease progression, but behavior engagement is low. Identifying predictors of behavior engagement could inform strategies to increase healthy behaviors.

Methods: Using data from the Chronic Renal Insufficiency Cohort Study, potential predictors of behavior engagement included demographics, clinical and psychosocial factors, and behaviors at baseline. We dichotomized behaviors (recommended vs. not): smoking (no vs. current), body mass index (BMI <18.5 or ≥30 kg/m^2), physical activity (≥150 vs <150 minutes/week), diet (score of ≥2 vs 0-1), and hemoglobin A1c (<7 vs ≥7) if diabetes. Relationships between predictors and behaviors at 2 years were estimated by multivariable adjusted logistic regression models.

Results: Among 5,209 participants at baseline, mean age was 60 years, mean eGFR was 48 ml/min/ml^2, and 51% had diabetes. In multivariable analyses, baseline behaviors were most strongly associated with behaviors at 2 years (**Table**). Higher SF-12 physical component scores, which relate to better physical function and pain control, associated with recommended behaviors at 2 years. In models that did not adjust for baseline behaviors, no smoking was associated with older age, female sex, and non-White race, but the other behavior associations were not notably changed.

Conclusions: Interventions to increase healthy behavior engagement should be implemented and tested to evaluate whether they improve physical function and pain control, and possibly mitigate CKD progression.

Funding: NIDDK Support

Associations with Recommended Behaviors at 2 years. ORs and 95% CI reported.

Predictors^	Diet score 2-4 (vs 0-1)	BMI 18.5 to <30 kg/m^2 (vs <18.5 or ≥30 kg/m^2)	Physical Activity ≥150 minutes/week (vs <150)	Non-smoking (vs. current smoking)	Hemoglobin A1c <7 (vs. ≥7)
Age (per 10 years)	1.16 (1.00-1.34)	1.07 (0.92-1.25)	1.07 (0.97-1.19)	1.05 (0.81-1.36)	1.21 (1.02-1.43)
Non-Hispanic Black (vs Non-Hispanic White)	1.65 (1.26-2.15)	0.71 (0.54-0.94)	0.96 (0.81-1.14)	0.85 (0.55-1.31)	1.01 (0.78-1.31)
Medicaid (vs no-insurance)	1.08 (0.64-1.82)	1.10 (0.60-2.04)	0.69 (0.47-1.02)	0.39 (0.17-0.90)	1.52 (0.86-2.68)
Medicare (vs no insurance)	0.67 (0.41-1.10)	1.21 (0.68-2.16)	0.70 (0.48-1.00)	0.77 (0.34-1.75)	1.94 (1.13-3.33)
High school or higher (vs less than high school)	0.99 (0.68-1.42)	0.93 (0.64-1.37)	1.35 (1.05-1.74)	1.23 (0.73-2.10)	0.79 (0.56-1.08)
Diabetes (vs. no diabetes)	0.68 (0.52-0.89)	0.67 (0.51-0.88)	0.86 (0.73-1.03)	1.25 (0.81-1.93)	---
CKD stage 4-5 (vs stage 1-2)	0.83 (0.52-1.33)	1.57 (0.96-1.02)	0.80 (0.58-1.10)	0.96 (0.44-2.09)	3.10 (1.94-4.94)
SF-12 Mental Component Summary (per SD)	1.03 (0.88-1.20)	1.19 (1.02-1.40)	1.00 (0.90-1.10)	1.33 (1.05-1.68)	0.95 (0.82-1.09)
SF-12 Physical Component Summary (per SD)	1.06 (0.92-1.21)	1.29 (1.12-1.48)	1.16 (1.06-1.28)	1.30 (1.04-1.63)	1.03 (0.91-1.17)
Adequate health literacy (vs inadequate)*	0.69 (0.48-0.99)	0.86 (0.59-1.25)	1.12 (0.87-1.43)	0.85 (0.48-1.52)	0.99 (0.73-1.36)
Recommended behavior of interest at baseline (vs not recommended)	2.76 (2.20-3.46)	75.88 (60.50-95.17)	3.89 (3.37-4.49)	228.30 (154.42-337.53)	5.52 (4.44-6.85)

Models adjusted for age, sex, race/ethnicity, education, health insurance, diabetes, Charlson comorbidity index, total medications, CKD stage (1-2, 3, 4-5), duration of CKD awareness, Mini-mental status exam score, SF-12 mental component summary score, SF-12 physical component summary score, Beck's depressive index, health literacy, and baseline behavior of interest.

*Adequate determined by score of >22 on the Short Test of Functional Health Literacy.

^Predictors not significantly associated: sex, Comorbidity index, total medications, CKD stage 3, duration of CKD awareness, MMSE score, Beck's depressive index.

PO2022

Impact of Participation in Food Assistance Programs Among NHANES Dialysis Patients from 2001-2016

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Background: Food insecurity and malnutrition are recognized risk factors for poor outcomes and mortality among end-stage renal disease (ESRD) patients on dialysis. However, little is known about the effect(s) of participation in food assistance programs such as Supplemental Nutrition Assistance Program (SNAP) on outcomes among dialysis patients.

Methods: This study is a cross-sectional analysis of dialysis patients in the National Health and Nutrition Examination Survey (NHANES) cohorts from 2001-2016. Food assistance program participation was self-reported as part of the NHANES interview. Differences in baseline characteristics were determined through null hypothesis testing. Logistic and linear regressions were used to examine the association between food assistance program participation and outcomes including hospitalizations and albumin as

a marker of nutrition status. The analyses were adjusted for demographics, BMI, diabetes, hypertension, and hyperlipidemia.

Results: A total of 156 dialysis patients were analyzed across all NHANES cohorts. Dialysis patients receiving food assistance were more likely to be younger, female, and obese ($p<0.05$). Food assistance participants had significantly larger household size, but lower income and lower levels of post-secondary education ($p<0.05$). These patients also reported significantly higher daily sugar intake. Dialysis patients receiving food assistance were significantly more likely to report very low food security and less likely to report full food security. Specifically, they reported more concerns regarding food running out, food not lasting, and not being able to afford balanced meals. Approximately 30% of dialysis patients report food insecurity but do not participate in food assistance programs. When adjusted to be representative of the non-institutionalized U.S. population, there was a non-significant trend towards increased hospitalization among dialysis patients on food assistance programs (OR 1.73 [95% CI: 0.42-7.12]). There was a non-significant negative correlation between food assistance program participation and serum.

Conclusions: Food assistance programs are not widely used among dialysis patients, even when patients report food insecurity. Food assistance program participation among dialysis patients did not significantly impact hospitalizations and serum albumin.

PO2023

Trends in the Prevalence of Food Insecurity Across Racial-Ethnic Groups with CKD: An Analysis of NHANES 2003-2016

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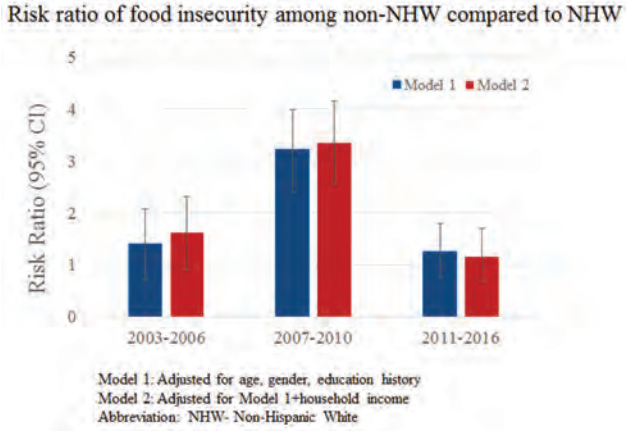
Background: Food insecurity has been associated with CKD and its progression. Trends in food insecurity among adults with CKD have not been well characterized in the US population, particularly across racial/ethnic groups.

Methods: Data from NHANES from 2003-2016 were used to estimate the prevalence of food insecurity among individuals with CKD (defined by albuminuria or eGFR 15-59 ml/min/1.73 m^2), overall and by racial/ethnic group. We included individuals aged≥20 years and with a household income≤400% of the federal poverty level (n=3180). Food insecurity was defined as ≥3 yes responses on the 18-item questionnaire. Racial/ethnic groups were defined as non-Hispanic white (NHW) and non-NHW. Survey years were collapsed into time periods 2003-2006, 2007-2010, and 2011-2016. Prevalence rates were estimated after standardization to the 2010 age population distribution from the US Census. Log binomial regression model was used to estimate adjusted risk ratios (RR) for the association of food insecurity and racial/ethnic groups.

Results: Overall prevalence of food insecurity in adults with CKD was 19.9%. During the period, the age-standardized prevalence rate of food insecurity increased from 5.7% to 32.8% among NHW and from 23.2% to 35.8% among non-NHW (p-trend=0.001). After adjusting for age, sex, education level, and annual household income, non-NHW had a significantly higher prevalence of food insecurity compared to NHW in 2007-2010 but not in 2003-2006 or 2011-2016 (Figure).

Conclusions: From 2003 to 2016, food insecurity among both NHW and non-NHW increased, with the highest RR among non-NHW compared to NHW during 2007-2010. One potential explanation may be the US economic recession during that period. Targeted interventions such as medically tailored meals for individuals with CKD and poverty may be evaluated for their impact on reducing healthcare utilization and costs and in reversing the increasing trend in food insecurity.

Funding: Other U.S. Government Support



PO2024

Approach to Nutritional Protein Intake in Hemodialysis Patients with Hyperphosphatemia: Associations with Mortality in the DOPPS

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Background: Pts undergoing hemodialysis (HD) have poorer nutritional status than the general population, and worse nutritional status is associated with poor outcomes. Hyperphosphatemia is common in HD pts due to abnormal mineral and bone metabolism. Nephrologists manage hyperphosphatemia by prescribing phosphate binders and/or promoting dietary protein restriction; the latter may, however, adversely affect nutritional status. We address the hypothesis that, even in the presence of hyperphosphatemia, liberalizing dietary protein leads to better outcomes.

Methods: The analysis includes 11,628 HD pts in 12 countries in DOPPS phase 4 (2009-11), from 254 facilities where the medical director reported facility practices. The primary exposure variable was response to the following question: "For pts with s. albumin 3.0 g/dL and phosphate 6.0 mg/dL, do you typically recommend to (A) increase or (B) not change/decrease dietary protein intake?" The primary outcome was all-cause mortality, analyzed by Cox regression. Linear regression was used to model associations between the exposure and intermediate nutrition markers. Models were adjusted for country, case-mix, and lab values.

Results: In the case scenario, 91% of medical directors in N. America recommended to increase protein intake compared to 58% in Europe (range=36-83% in 7 countries) and 56% in Japan. Advice to increase dietary protein intake was associated with 0.33 mg/dL higher s. creatinine levels (95% CI: 0.08-0.57) while clinically meaningful associations were not observed for s. albumin and phosphorus. Advice to increase dietary protein intake was weakly associated with lower mortality-HR (95% CI)=0.89 (0.77-1.03). The association with survival was stronger in pts with age 70+ yrs and for those without diabetes (p=0.08 and 0.20 for interaction).

Conclusions: In this large international cohort study, the medical director's preference to recommend increase in dietary protein intake for HD pts with low albumin and high phosphorus levels was most common in N. America and associated with higher s. creatinine levels and potentially lower all-cause mortality. Further research into the possible benefits of protein intake liberalization for HD pts, even in the presence of hyperphosphatemia, is warranted.

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PO2025

Dietary Acid Load Is Associated with the Risk of Mortality and Kidney Replacement Therapy in Diabetic CKD Patients but Not in Non-Diabetics

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Background: Dietary acid load (DAL) may be related to CKD progression but results are still conflicting. In addition, no studies have evaluated the association of DAL with mortality in CKD. The aim of this study was to evaluate two estimates of DAL, PRAL (potential renal acid load) and NEAP (net-endogenous acid production), in relation to events of mortality and kidney replacement therapy (KRT) in CKD.

Methods: Baseline clinical and dietary data (food frequency questionnaire) from the PROGREDIR Cohort (n=454), a CKD cohort based on Sao Paulo, Brazil, composed predominantly of older people with CKD G3 and G4 was used in this analysis. PRAL and NEAP were computed using previously validated formulas, and those with missing values were excluded (n=11). Events of death (n=190) and KRT (n=62) were ascertained after a median follow-up time of 6 years. Uni and multivariable Cox proportional hazards and Competitive Risk models were computed.

Results: Mean age was 68 ± 12 y, mean eGFR was 38 ± 15 mL/min/1.73m^2, 63% were male and 56% were diabetic. Mean intake of PRAL and NEAP were 4.1 ± 18.5 and 51.9 ± 17.4 mEq/d, respectively. Initially, neither PRAL nor NEAP were associated with mortality or KRT. However, after stratification for diabetes, both estimates were positively related to the risk of KRT and death in diabetics only, even after adjustments (Table). Competing risk analysis were consistent with the Cox findings. By entering interaction terms between diabetes and DAL estimates, which were significant, both PRAL and NEAP showed an inverse association with the risk of clinical events.

Conclusions: Our results suggest the existence of a relevant interaction between PRAL/NEAP and diabetes: whereas DAL estimates were associated with mortality and KRT in diabetics, this association was not observed in non-diabetics.

Funding: Government Support - Non-U.S.

	DEATH		KRT	
	HR (95% CI)	p	HR (95% CI)	p
All participants (n = 443)				
PRAL	0.999 (0.992 to 1.007)	0.89	1.009 (0.995 to 1.023)	0.23
NEAP	0.998 (0.990 to 1.007)	0.71	1.008 (0.995 to 1.022)	0.24
Diabetes only (n = 250)				
PRAL	1.008 (0.997 to 1.019)	0.15	1.026 (1.006 to 1.045)	0.01
adj.*	1.016 (1.001 to 1.032)	0.04	1.027 (1.000 to 1.054)	0.05
NEAP	1.010 (0.999 to 1.021)	0.07	1.026 (1.008 to 1.045)	0.005
adj.*	1.019 (1.005 to 1.033)	0.01	1.025 (1.001 to 1.050)	0.04

*Adjusted for age, sex, eGFR, bicarbonate, and energy and protein intakes.

PO2026

Mediterranean Diet and the Risk of CKD: A Systematic Review and Meta-Analysis

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Background: Mediterranean diet has been shown to be associated with lower risk for cardiovascular disease. However, its association with chronic kidney disease (CKD) remains inconclusive as the results were not consistent among population-based studies. Thus, this study aims to assess the association between Mediterranean diet adherence and CKD prevention.

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched from database inception to March 2020 without language restrictions. We included studies describing the risk for CKD in community-dwelling subjects > 18 years of age. CKD was defined by eGFR < 60 mL/min/1.73m^2. Mediterranean diet adherence was assessed by standardized food frequency questionnaires. Meta-analysis and meta-regression analysis were used to evaluate the risk of CKD and the association between clinical factors and incidence of CKD, respectively.

Results: Of 168 citations, a total of ten (n = 19,151) and five studies (n = 9,099) were included in the systematic review and meta-analysis, respectively. Only studies adopting Mediterranean Diet Scale (MDS) were included in the meta-analysis. The mean score was 4.0 ± 0.1 points. The mean age was 53.1 ± 8.2 years. The mean eGFR was 77.3 ± 29.6 mL/min/1.73m^2. The average total daily energy intake was 1,989.4 ± 258.0 kilocalories per day. Up to 50.4% were male, 7.1% were black, and 14.9% had a history of diabetes mellitus. With the mean follow-up duration of 11.5 ± 9.5 years, the pooled adjusted odds ratio (OR) for CKD was 0.897 (95% CI, 0.865-0.930; I^2 26.5%). By excluding kidney transplant patients, the pooled adjusted OR for CKD was 0.901 (95% CI, 0.868-0.935; I^2 9.4%). Both findings remained significant on sensitivity analysis. No publication bias was detected. The incidence of CKD was 0.028 events per person-year (95% CI, 0.012-0.044). From meta-regression analysis, male sex was associated with higher incidence of CKD in an adjusted model. There was no significant association between age, black race, eGFR, and total daily energy intake vs. CKD incidence.

Conclusions: Adherence to Mediterranean diet by a 1-point increment of MDS was associated with 10% lower risk of CKD. However, this only applies to healthy individual without a history of pre-existing CKD, whether Mediterranean diet slows CKD progression is to be discovered.

PO2027

Attitudes Toward Plant-Based Eating (PBE), Self-Reported Habits, and Relationship to BMI and Blood Pressure in a Population of Inner-City CKD/ESKD Patients

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Background: The benefits of a PBE dietary pattern are well described, yet there is scarcity in the literature on the attitudes of CKD/ESKD patients regarding PBE as well as their self-reported habits.

Methods: A face-to-face survey was conducted in a random convenience sample patients from CKD clinic (15), Transplant clinic (12), and the Dialysis Unit (4). Pts were asked to answer questions assessing their attitudes and understanding of PBE using a 5-point Likert scale, and to rate their daily vegetable intake. There was no difference noted in answers among the clinics so all data were analyzed together. All comparisons are by t-test unless noted.

Results: Mean age was 54.7±1.7 yrs. There were 16 (53%) men and 14 (47%) women with 25 Black (81%). 12 people (40%) had an income < $20K, with 10 (33%) between $20K and 40K. 10 (33%) were employed. 64.5% (20) were interested in learning more about PBE; 35% had never heard of it. 22(71%) reported consuming animal protein 1-3x/d or more. 20 (57%) reported consuming plant-based foods less <1/d or never. Pts who did not eat plant-based foods had a higher BMI than those who consumed plants (30.9±1.86, p<0.05), and higher systolic and diastolic BP (144.3±5.9 vs 126±5.2, p<0.05 and 77.9±3.5 vs 66.3±4.1, p=0.019). 46.4% thought it would be difficult to find things to eat at restaurants, 51.7% thought it would be difficult to buy food or groceries on a budget; 46.4% thought they could not get all the protein they need from plant-based foods without eating animal meat or products; 40.7% thought it would be hard to get all the vitamins and nutrients but 63.1% thought it would be easy to find recipes that taste good if they followed PBE.

Conclusions: In our population: 1. The majority of pts were interested in learning about PBE but ate few to no vegetables on a daily basis. 2. Possible obstacles to introducing PBE in this populations are misconceptions including the difficulty of affording food, getting enough protein and finding something to eat when eating out, believed by almost half of those surveyed. 3. Intensive educational programs targeted towards our population should be developed as pts who ate more vegetables had lower BMI and both systolic and diastolic BP and in general PBE has been shown beneficial for pts with CKD/ESKD.

PO2028

Higher Estimation of Dietary Phosphorus Content with More Plant-Based Protein in Hemodialysis Patients Across Race/Ethnicity Using 3-Day Food Records with Interviews

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Background: Dietary phosphorus (P) restrictions are commonly recommended based on the estimated phosphorus (P) content of foods, not accounting for P type or its absorbability. Whereas plant-based diets have important benefits, they are traditionally not recommended to dialysis patients given perceived higher P content in plant vs. animal-based proteins, although P is less absorbable in plant foods. We examined dietary differences across race/ethnicity in a group of hemodialysis (HD) patients from several dialysis centers in Southern California.

Methods: The self-administered 3-day diet diary with face-to-face *interview* was conducted by a trained dietitian among 80 in-center HD patients, and the data were entered into a diet software (Nutrition Data System for Research), and dietary components of the individuals and subgroups were obtained.

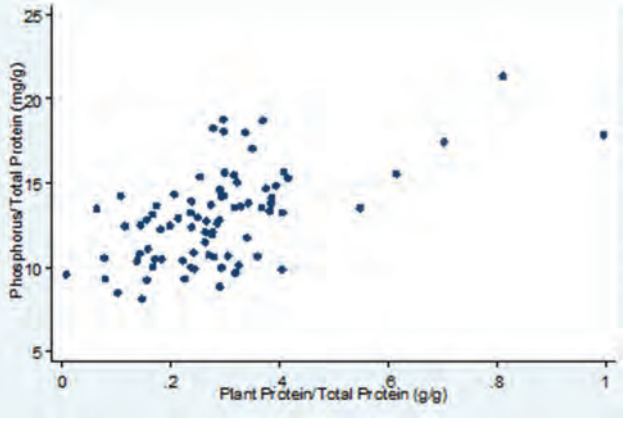
Results: Patients were 57±15 years and included 25% Blacks, 36% Hispanics and 18% non-Hispanic Whites. Table shows dietary data across race/ethnicity. [table] Figure shows the association of the phosphorus-to-protein ratio with the percentage of plant protein, correlation coefficient r was 0.58 (p<0.001) for all including 0.28, 0.61 and 0.38 for Blacks, Hispanics and Whites, respectively.[figure]

Conclusions: Whereas estimated dietary potassium was not substantially different across race/ethnicity or different plant- vs. animal based protein proportions, dietary phosphorus content analyses may not account for varying phosphorus bioavailability across sources, which may lead to incorrect assumptions that higher plant-based protein for dialysis patients is associated with more phosphorus burden.

Funding: NIDDK Support

Analyses of 3-day diet diary across race/ethnicity

	P to protein ratio, mg/g	Plant to total protein, %	P, mg/1000Cal	Potassium, mg/1000Cal
Blacks	11.6±2.0	23%	595±107	1,034±249
Hispanics	13.4±2.6	27%	614±137	1,059±235
Whites	12.9±2.1	31%	600±127	1,025±220



PO2029

Benefits of Home-Delivered, Low-Sodium Meals in Hemodialysis Patients

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Background: Patients undergoing maintenance hemodialysis (HD) therapy are routinely counseled to reduce dietary sodium intake to reduce sodium retention, volume overload (VO), and hypertension. Unfortunately, low-sodium trials in HD are sparse and mostly indicate that dietary education and behavioral counseling alone are ineffective in reducing sodium intake. The purpose of this study is to determine if 4-weeks of a low-sodium home delivered meals intervention will reduce interdialytic weight gain (IDWG) and subsequent VO and hypertension in patients undergoing HD when compared to 4-weeks of a usual diet.

Methods: We recruited 20 subjects (55±12 years, BMI 40.7±16.6 kg/m^2, 45% male, 65% AA, 70% DM, 50% CVD) from a HD clinic in central IL. Participants followed a usual-control diet for the first 4-weeks. PurFoods, LLC prepared and shipped 3 low-sodium kidney meals (<700 mg sodium, potassium, and phosphorus each) per day to patients in the following 4-weeks. We collected monthly IDWG, bioelectrical impedance, standardized blood pressure, 3 days (HD, non-HD, and weekend day) of dietary recalls, and blood at baseline (0M), after a usual diet (1M), and post-intervention meals (2M).

Results: Home-meal delivery significantly reduced both dietary sodium intake, IDWG, systolic blood pressure (SBP), and diastolic blood pressure (DBP) (Table). These changes were accompanied by reductions in total body water (TBW) and calculated VO (Table). These changes were mostly driven by reductions at 2M, except for a significant increase in IDWG from 0M to 1M ($p < 0.05$).

Conclusions: Low-sodium home-meal delivery appears to be an effective method to reduce dietary sodium intake, IDWG, BP, and VO in HD patients. It will be important determine if these changes can be sustained long-term with additional counseling and in larger sample sizes. The long-term benefits and cost-effectiveness of this approach also needs to be evaluated.

Funding: Commercial Support - Renal Research Institute

Changes in Volume-Related Parameters

Variable (mean ± SD)	0M	1M	2M	P-value
Dietary sodium, mg	3603 ± 1341	3640 ± 1358	1890 ± 360	< 0.01
IDWG, kg	2.9 ± 1.2	3.2 ± 1.1	2.4 ± 1.1	< 0.01
TBW, L	56.5 ± 15.3	58.3 ± 13.5	54.3 ± 11.8	< 0.05
VO, L	2.9 ± 4.9	2.9 ± 5.1	1.9 ± 4.6	< 0.05
SBP, mmHg	161 ± 18	161 ± 24	143 ± 18	< 0.01
DBP, mmHg	91 ± 13	88 ± 11	82 ± 14	< 0.01

PO2030

Performance of GLIM for Nutritional Assessment of Hemodialysis Patients: Comparison with Subjective Global Assessment (SGA) and Malnutrition-Inflammation Score (MIS)

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Background: There is a need for methods to identify and monitor malnutrition in maintenance hemodialysis (MHD) patients (pts). We assessed GLIM (Global Leadership Initiative on Malnutrition) and evaluated agreement and survival prediction of GLIM vs. SGA and MIS in MHD pts.

Methods: We investigated two cohorts, MHD_{Italy} (121 adult pts from Italy; 67±16y, 65% men, BMI 25±5 kg/m^2) and MHD_{Brazil} (169 elderly (age>60 y) pts from Brazil; 71±7y, 66% men, BMI 25±4 kg/m^2), followed for 40 (27; 46) and 17 (12; 31) months (median and 25th; 65th), respectively. GLIM comprises: 1. *Screening* and 2. *Confirming malnutrition by phenotypic and etiologic criteria*. For 1., presence of >1 criteria from protein energy wasting definition was used. Pts at risk were re-tested with GLIM's phenotypic criteria: non-volitional weight loss or low BMI (<20 kg/m^2 if <70y, or <22 kg/m^2 if <70y) and reduced muscle mass (MAMC<90%). As dialysis is a catabolic procedure, all pts were positive for the etiologic criteria. For SGA and MIS, a score ≤5 and ≧8 was considered for malnutrition, respectively.

Results: Malnutrition was present in 38.8% by GLIM, 25.6% by SGA and 29.7% by MIS in the MHD_{Italy} cohort, and in 47.9% by GLIM, 59.8% by SGA and 49.7% by MIS in the MHD_{Brazil} cohort. Cohen's kappa coefficient (κ) showed only "fair" agreement between GLIM and SGA and MIS respectively (Table). Cox regression analysis adjusted for gender and age showed that in the MHD_{Italy} cohort, only pts malnourished by MIS had higher risk for mortality (HR= 2.42; 95% CI 1.28 to 4.59; P=0.007) while in the MHD_{Brazil} cohort, pts malnourished by GLIM (HR= 2.09; 95% CI 1.13 to 3.86; P=0.02), SGA (HR= 1.96; 95% CI 1.01 to 3.79; P=0.04) and MIS (HR= 2.24; 95% CI 1.20 to 4.16; P=0.01) had higher risk for mortality.

Conclusions: In MHD pts, GLIM showed low agreement with SGA and MIS, raising question on its validity and usefulness in renal care. Only malnutrition by MIS predicted mortality risk in MHD_{Italy} cohort, but in the MHD_{Brazil} cohort, malnutrition by all three methods predicted higher mortality risk.

Agreement vs. GLIM	MHDItaly	MHDBrazil
GLIM x SGA, κ (P)	0.26 (0.003)	0.22 (0.003)
GLIM x MIS, κ (P)	0.33 (< 0.001)	0.25 (0.001)

PO2031

Dietary Fiber Intake, Cardiovascular Risk Factors, and Kidney Function: A Mediation Analysis

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Background: Higher fiber intake may be associated with higher eGFR but the mechanisms underlying this association are poorly understood. Considering that higher fiber intake is linked to improved cardiovascular (CV) risk factors, we hypothesize that the effect of fiber intake on eGFR could be mediated by these CV factors.

Methods: CARTaGENE is a population survey of healthy adults. We used multiple linear regression to study the association between fiber intake and eGFR while adjusting for confounding factors, including age, sex, diabetes, hypertension, dyslipidemia, body mass index [BMI], smoking, prior CV disease, physical activity and caloric intake. We assessed whether CV risk factors lie in the causal pathway between fiber intake and eGFR through mediation analyses.

Results: We included 9,854 of the CARTaGENE participants with a completed food questionnaire (mean age: 53 years, 56% males). The main comorbidities were hypertension (25%), diabetes (8%) and cardiovascular disease (7%). The median daily fiber intake was 17.2g (IQR 10.7-23.7) and the mean eGFR was 87.3 ±14.6 mL/min/1.73 m^2. After adjustment for the above factors, fiber intake was associated with higher eGFR and serum HDL levels, and lower BMI, glycated hemoglobin and triglyceride levels (Table). Other risk factors were found to be non-significant. The mediation analysis demonstrated that only 10% of the effect of fiber intake on eGFR was mediated through BMI and triglyceride levels.

Conclusions: Higher dietary fiber intake is associated with higher eGFR and better control of certain cardiovascular risk factors. While the association between fiber intake and kidney function may be marginally mediated by healthy weight and triglyceride levels, further studies are needed to understand the mechanisms underlying this association.

Association between dietary fiber intake and clinical variables.

	β coefficient† (95% CI)	p
eGFR	0.08 mL/min/1.73m2 (0.03, 0.13)	0.02
Body mass index	-0.06 kg/m2 (-0.08, -0.04)	0.001
HDL levels	0.002 mg/dL (0.001, 0.003)	0.02
Triglyceride levels	-0.01mmol/L (-0.01, -0.001)	0.001
Glycated hemoglobin	-0.002% (-0.005, -0.001)	0.03

† Adjusted for the variables included in the table and age, sex, smoking, caloric intake, physical activity, hypertension, history of cardiovascular disease.

CI, confidence interval.

PO2032

Interplay Between Dietary Phosphorus and Protein Intake with Mortality in a Prospective Hemodialysis Cohort

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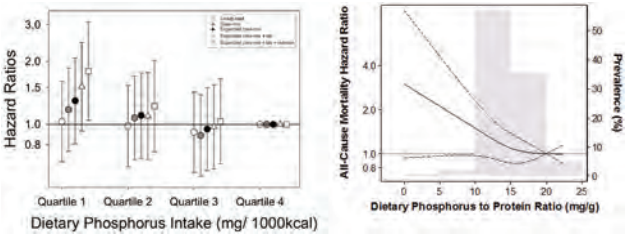
Background: Current dietary recommendations for dialysis patients suggest that high phosphorus (P) diets may be associated with negative outcomes such as increased serum P and death. However, caution must be practiced to ensure dietary P intake is not compromised at the expense of dietary protein intake. We hypothesized that higher concentrations of dietary P intake is associated with higher mortality among a diverse cohort of hemodialysis (HD) patients.

Methods: Among 415 patients from the prospective multi-center Malnutrition, Diet, and Racial Disparities in Kidney Disease Study, we conducted standardized collection of dietary and dialysis treatment characteristics every six months starting in 2011. We examined the association of quartiles of dietary P scaled to 1000 kcal (mg/kcal), as measured by food frequency questionnaires, with all-cause mortality using Cox models adjusted for expanded case-mix+laboratory+nutrition covariates. To model the association between continuous daily dietary P intake scaled to protein (mg/g) and mortality, we conducted analyses in which dietary P/protein intake was examined as a restricted cubic spline.

Results: In baseline analyses, patients in the lowest quartile of dietary P scaled to 1000 kcal had increased mortality risk compared to those in the highest quartile: adjusted HR (95%CI) 1.80 (1.05, 3.09). In analyses examining the association between continuous dietary P/protein (mg/g) intake and mortality using a cubic spline, we observed that there was a monotonic decrease in death risk with higher dietary P/protein intake.

Conclusions: Contrary to current practice, we found that lower intakes of dietary P scaled to protein and caloric intake were each associated with higher mortality risk. National nutrient databases indicate that foods with lower vs. higher P/protein ratios tend to be from animal proteins vs. plant proteins and dairy. Further studies are needed to clarify the relationship between sources of dietary P intake and mortality in HD patients.

Funding: NIDDK Support



PO2033

Protein Supplements and Proteinuria: A Case-Control Study in Military Candidates

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Background: Man has long wanted to improve both image and physical performance using supplements some of which include proteins. Low protein diets are recommended by guidelines to attenuate the progression of chronic kidney disease. In healthy individuals, however, protein intake does not seem a risk factor. This study addressed whether protein supplements could cause proteinuria in a healthy population.

Methods: We performed a case-control study at the Military Hospital of Oporto including 1541 military academy candidates who had urinalysis in 2017. Among them, 102 (6.6%) had proteinuria (dipstick test ≥+/+++) and these were compared to a random sample of 106 non-proteinuric candidates. Telephone interviews collected data on comorbidities, exercise, smoke, alcohol habits, drugs, supplements, height and weight. Protein supplements were accessed as risk factors for proteinuria using the Pearson Qui-square test.

Results: Answers were obtained from 49 cases and 52 controls. Of these 101 candidates, 88 were males, had a median age of 19 and mean body mass index of 24.1±2.4kg/m2. Most (97%) exercised for a mean weekly time of 6±3.7h: 40% practiced only resistance training; the rest both resistance and strength. Half used supplements at some point in time and 32 were current users. All used protein powder, mainly whey protein. Additional supplements (mostly amino acids) were used by 13. The weekly powder dose ranged from 3 to 14 scoops (20-30g/scoop). No significant association was found between the use of protein supplements and proteinuria (p=0.51). Similarly, no difference was found in creatinine, urea or other laboratory parameters. Supplements were significantly used more by those who practiced strength, as compared with resistance-training subjects.

Conclusions: One third of Portuguese military candidates used protein supplements. Increased use was noted in strength training most likely due to peer pressure. Proteinuria was found in 6.6%, similar to screenings in other healthy populations. No relation was found between protein supplements and proteinuria which could mean that the kidneys of healthy individuals are capable of dealing with a higher metabolic strain after increasing protein loads. However we acknowledge that proteinuria as a marker of disease has limitations and that the cumulative exposure and longtime impact of protein supplements was not considered and may be relevant.

PO2034

Continuous Intradialytic Amino Acid Infusion from the Start of Dialysis Is Better to Avoid Catabolism Under the High-Volume Pre-Dilution Online Hemodiafiltration

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Background: Amino acid infusion during dialysis is useful for improving nutritional status (Clin Nephrol 3:234,1975). Usually, amino acid is infused 60 to 90 minutes before the end of dialysis, but it is reported that continuous administration from the start of dialysis is better (Kidney Int 21: 500, 1982). Moreover, these effects are unclear in the high-volume pre-dilution on-line HDF (HVPO-HDF). The optimal administration method of amino acid infusion under the HVPO-HDF was analyzed.

Methods: The subjects were 10 patients receiving HVPO-HDF (7 males, 4 diabetics, mean age: 77.2±5.5 years). We compared the pre- and post-dialysis plasma amino acids levels and the total amino acids amount in the waste fluid when the amino acids infusion was performed from the start of dialysis (Group A) and from 1 hour before the end of dialysis (Group B). The treatment time is 4 hours. The mean blood flow rate was 200 mL/min. The dialysate flow rate was 600 mL/min. The replacement fluid flow rate was 400 mL/min and total replacement fluid volume was 90. Hemodiafilter MFX-21Meco (Nipro, Ltd) was used.

Results: In pre-dialysis plasma levels of total amino acid (TAA), Group A and Group B showed the same level (2472±267 nmol/mL and 2623±319 nmol/mL, respectively). In the essential amino acid (EAA) and non-essential amino acid (NEAA), similar results were obtained (827±145 nmol/mL and 847±99 nmol/mL of EAA, 1644±216 nmol/mL and 1120±193 nmol/mL of NEAA, respectively). Moreover, the losses of amino acids were also same (9008±113 mg and 8886±1204 mg of TAA, 4966±579 mg and 4544±453 mg of EAA, 4042±644 mg and 4342±862 mg of NEAA, respectively). However, in Group A, post-dialysis plasma levels of amino acids were significantly lower than in Group B (2066±370 nmol/mL and 3826±636 nmol/mL of TAA, 946±193 nmol/mL and 2249±439 nmol/mL of EAA, 1120±193 nmol/mL and 1577±260 nmol/mL of NEAA, respectively. $p < 0.01$).

Conclusions: The result of high post-dialysis plasma levels despite the same loss of amino acids suggests more catabolism from muscle to blood in Group B. The continuous intradialytic amino acid infusion from the start of dialysis is better to avoid catabolism under HVPO-HDF.

PO2035

Association of Low-Density Lipoprotein Cholesterol with Time to ESRD Across CKD Stages in 2 Million US Veterans

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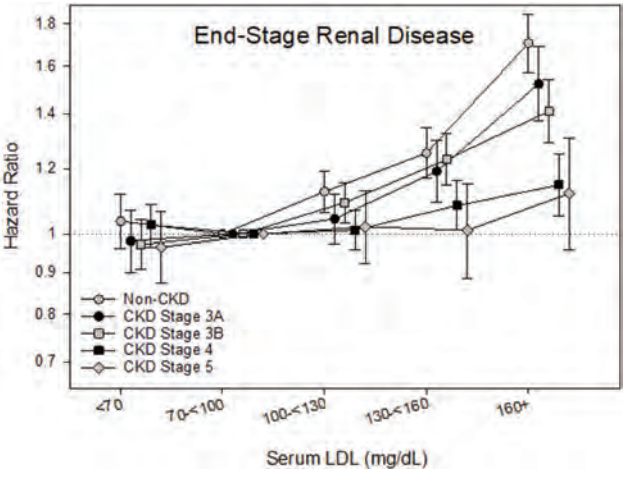
Background: Prior studies have noted that abnormal triglyceride (TG) and high-density lipoprotein cholesterol (HDL) are predictors for chronic kidney disease (CKD) outcomes. However, it remains unclear whether similar patterns are observed for low-density lipoprotein cholesterol (LDL). Therefore, we sought to investigate the relationship of LDL with time to end-stage renal disease (ESRD) risk across CKD stages.

Methods: The cohort comprised 1,961,854 US veterans with a serum LDL between 2004-2006 and were not on ESRD. Patients were followed until ESRD, death, loss to follow up or Dec 2014, whichever occured first. We used a Cox model to examine the association of LDL and time to ESRD stratified by baseline CKD stages. The model adjustment include demographics, comorbid conditions, smoking status, prescription of statins and non-statins, body mass index, albumin, HDL, and TG.

Results: Patients were an average age of 64±14 years, and included 5% females, 14% African- Americans, 19% diabetics, 32% statin-users, and 44% current smokers. The median [IQR] of serum LDL level and eGFR at baseline were 103[81,128] mg/dL and 75[60,91] mL/min/1.73m^2, respectively. Higher LDL (>100 mg/dL) was associated with incrementally higher ESRD risk across all CKD stages compared to the reference (LDL 70-<100 mg/dL). Notably, LDL≥ 160 mg/dL were associated with the highest risks of ESRD, and this association gradually diminished across progressive CKD stages. Low LDL (<70 mg/dL) was associated with null risk of ESRD across all CKD stages.

Conclusions: Higher serum LDL was associated with higher risk of ESRD across all CKD stage in the US veterans. However the strength of this relationship attenuated with worsening CKD. Future studies with considerations for competing death events, time varying covariates and the impact of lipid modifying therapies are warranted.

Funding: Veterans Affairs Support



PO2036

Association of Low-Density Lipoprotein Cholesterol with Urine Albumin-to-Creatinine Ratio Slope Across Baseline Albuminuria Strata

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Background: Change in urine albumin to creatinine ratio (UACR) is considered as a marker of kidney disease progression. Prior studies showed abnormal lipid levels may predict the progression of renal function decline; however, associations of low-density lipoprotein cholesterol (LDL) with UACR change is unclear. Therefore, we sought to investigate the association of LDL and UACR slope across albuminuria stages.

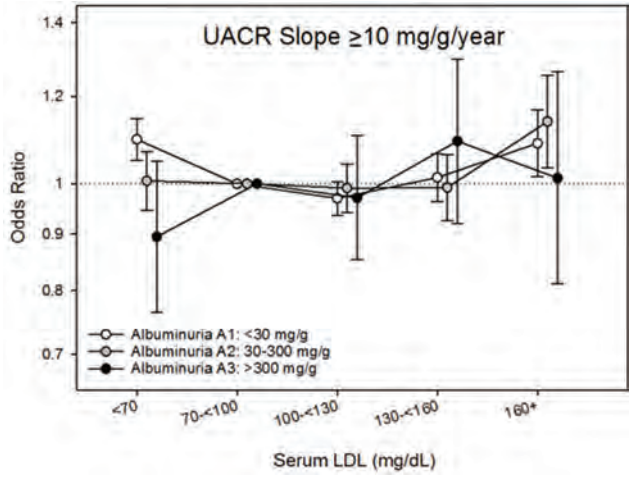
Methods: We analyzed 175,392 US veterans who received care between 2004 and 2006, with available serum LDL and albuminuria (UACR) data. All UACR measurements until the end of follow-up (2014) were used to ascertain UACR slopes using mixed effects modeling. The relationships between LDL with faster UACR slope (≥10 mg/g/year) stratified by baseline albuminuria stage (A1-A3) were estimated using logistic models adjusted for baseline demographics, comorbidities, prescription of statins and non-statins, BMI, albumin, HDL, triglycerides, eGFR, and UACR.

Results: Cohort mean age was 65±11 and included 3% females, 14% African-Americans, and 87% diabetics. The median [IQR] of serum LDL level and eGFR were 97 [75,119] mg/dL and 73 [58,88] mL/min/1.73m^2, respectively. There was a U-shaped association between LDL and odds of faster UACR slope among A1 patients. A similar

yet attenuated relationship was observed among A2 patients. Odds of faster UACR slope was higher only in patients with LDL ≥160 mg/dL and with index UACR≤300 mg/g. For A3 patients, there was no association between LDL level and UACR slope.

Conclusions: Among patients with baseline UACR <300 mg/g, both low and very high LDL were associated with higher odds of having fast UACR change. Yet, among those with higher albuminuria, the relationship with LDL and UACR change was null. More studies are needed to delve into the mechanism between LDL and CKD progression in order to further manage patients kidney health.

Funding: Veterans Affairs Support



PO2037

Lipidomic Markers for Cognitive Impairment in Maintenance Hemodialysis Patients

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Background: Cognitive impairment (CI) was relatively common in maintenance hemodialysis patients. The pathophysiology of CI in this particular population was not well understood. Whether the classic lipid components that affect cognitive outcome in general population have similar effect in dialysis patients is not clear. In this study, we tried to get a better understanding of the pathogenesis CI in hemodialysis patients by lipidomic analysis and find potential lipids markers to predict cognitive decline.

Methods: From July 2013 to July 2019, we followed up the cognitive evaluation results of the hemodialysis patients in our dialysis center. The cognitive function was evaluation by the MMSE and MoCA at baseline and follow-up period. Plasma and hemocytes of enrolled patients were collected at baseline. Lipidomic analyses were performed on an Exion LC-system coupled with a QTRAP 6500 PLUS system (Sciex). Principal component analysis and orthogonal project to late structures discriminant analysis, and t-test were used to analyze the differences in patients in cognitive decline group and cognitive retained group.

Results: At the baseline, plasma from 21 patients and hemocytes from 65 patients were collected for lipidomic analyses. 539 lipids were detected in plasma and 237 lipids were detected in hemocytes. In individuals with plasma lipids files data, 10/21 suffered MMSE scores decrement and 16 /21 showed MoCA decrement. In patients with hemocytes lipids files date, 29/65 of them suffered MMSE scores decrement and 43/65 showed MoCA decrement. Compared with retained MMSE scores group, decreased MMSE scores group presented higher level of plasma PA 32:1, PA 38:5, CE-17:1, and lower level of plasma DAG 40:6(18:0/22:6), PE 36:4(18:1/18:3). There was no significant difference in erythrocytes lipids between the two groups. Compared with retained MoCA scores group, decreased MoCA scores group presented higher level of plasma LacCer d18:1/18:0, LPE 18:2, GM3 d18:1/20:1, PE 36:3(18:1/18:2), LPE 18:1, lower level of plasma PI 38:5(18:0/20:5), and higher level of erythrocytes GM3 d18:0/20:0 (Fold change >1.5 or <1/1.5, P value <0.05).

Conclusions: The pathogenesis of CI in dialysis patients may closely relate with vascular injury. Lipid analysis may contribute to a new approach to predict the risk of cognitive decline in hemodialysis patients.

PO2038

The Combination of Malnutrition Inflammation and Limitations in Functional Status Is Associated with a Very High Risk of Mortality in Hemodialysis Patients: Results from the DOPPS

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Background: The malnutrition-inflammation-complex (MIC) is a risk factor for mortality and lower quality of life in hemodialysis (HD) patients. The identification of MIC and its risk factors, which include the limited ability to perform functional status (FS), is key to improve the patient experience on HD. Our study investigates the association of MIC and FS combinations with mortality in HD patients

Methods: We analyzed data from a cohort of 5465 HD patients from Australia, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, and United Kingdom, enrolled in the Dialysis Outcomes and Practice Patterns Study phases 4 (2009-2011) and 5 (2012-2015). MIC syndrome was defined as low serum albumin (<3.8 g/dL) and high serum C-reactive protein (>3mg/L in Japan; >10 mg/L elsewhere). Poor functional status was defined as the sum of scores from the self-reported limitations in the Katz Index of Independence in Activities of Daily Living (0 to 5) and the Lawton-Brody Instrumental Activities of Daily Living Scale (score ranges from 0 to 8) less than 11. We investigated the association between combinations of MIC (+/-) and FS (low/high) with death, using Cox proportional hazards models adjusted for possible confounders including patient demographics, comorbidity history, catheter use, serum creatinine, phosphorus levels, WBC count, hemoglobin level, and time on dialysis therapy.

Results: The prevalence of different combinations were: MIC-/High FS 57%, MIC-/Low FS 24%, MIC+/High FS 9%, and MIC+/Low FS 10%. Patients with MIC-/high FS were younger, better nourished, and had lower prevalence of comorbidities. Compared to the reference group, the hazard ratios [HR (95% CI)] for all-cause mortality were 1.56 (1.24-1.98) for MIC-/ low FS, 1.75 (1.32-2.32) for MIC+/ high FS, and 2.97 (2.31-3.82) for MIC+/ low FS groups. The adjusted HRs for infection-related mortality were 1.57 (0.91, 2.71) for MIC-/low FS, 1.67 (0.84, 3.31) for MIC+/High FS, and 5.45 (3.15, 9.45) for MIC+/low FS groups.

Conclusions: The combination of MIC and low FS is a strong predictor of mortality, and infectious mortality in particular, in HD patients. Identification of patients with MIC and FS.

PO2039

High-Amylose Resistant Starch (RS) Cookies Supplementation Does Not Decrease Trimethylamine N-Oxide (TMAO) Plasma Level in Hemodialysis (HD) Patients

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Background: TMAO is generated from dietary nutrients by the gut bacteriome and it is associated with cardiovascular mortality in HD patients. Thus, to reduce its generation, nutritional strategies have been proposed. The aim of this study was to analyze the TMAO levels and potential changes in TMA-associated bacterial taxa in HD patients after RS supplementation.

Methods: This is a randomized, double-blind, placebo-controlled trial with HD patients that were allocated to RS or placebo group to receive alternately 9 cookies/d (dialysis days) and 1 sachet/d (non-dialysis days) containing 16g/d of RS (Hi-Maize 260, Ingredion®) or manioc flour as the placebo, during 4 weeks. Plasma TMAO, choline, and betaine levels were measured with LC-MS/MS. Fecal bacteriome composition was evaluated by high-throughput sequencing of 16S ribosomal RNA gene V1–V3 region, followed by a search for TMA-associated taxa.

Results: Thirty-one participants finished the study, 15 in RS group (53.3% ♀; 56.0±7.5 yrs; 50.0±36.5 months on HD and BMI 26.1±5.0 kg/m²) and 16 in the placebo group (31.2% ♀; 53.5±11.4 yrs; 44.3±26.4 months on HD and BMI 26.6±5.2 kg/m²). After four weeks of supplementation no significant changes in TMAO, choline and betaine plasma levels were observed (Table 1). Notably, after the RS supplementation, TMA-producing bacterial taxa such as *Ruminococcus* torques group [(0.026 (0.023 - 0.04) vs. 0.017 (0.017 - 0.02), p=0.06)] and *Streptococcus* had decreased the relative abundance, while *Prevotellaceae family and Enterococcus* increased their relative abundance in placebo group. However, the differences did not reach statistical significance. Additionally, the relative abundance of TMA-producing bacterial taxa was low in both groups.

Conclusions: RS supplementation did not influence TMAO plasma levels nor fecal taxa potentially linked to TMAO in HD patients, suggesting that RS did not modify the composition of gut bacteriome that convert its precursors into TMAO.

Funding: Government Support - Non-U.S.

Effects of RS supplementation or placebo on plasma TMAO, choline and betaine levels

	RS group (n=13)		p values	Placebo group (n=12)		p values
	Before	After		Before	After	
TMAO (ng/μl)	4.1 (3.0 - 8.2)	4.4 (2.6 - 6.3)	0.89	3.3 (2.5 - 5.2)	4.6 (3.1 - 5.6)	0.49
Choline (ng/μl)	12.3 (10.8 - 13.6)	12.5 (10.2 - 14.3)	0.97	10.8 (9.95 - 13.9)	11.2 (9.7 - 19.9)	0.21
Betaine (ng/μl)	5.0 (3.4 - 7.1)	5.7 (3.2 - 7.3)	0.99	5.2 (3.9 - 7.2)	5.6 (4.2 - 6.1)	0.57

PO2040

Public Health Effects of Sterilized, Used Hemodialyzers for Water Purification in Rural Ghana

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Background: Consumption of contaminated water is a risk factor for infectious diarrhea and according to estimates of the World Health Organization remains the most often reported cause of death in children and the elderly. Our organization "Easy Water for Everyone (EWfE)" uses a membrane filtration device with repurposed hemodialyzers and has achieved remarkable public health effects (Raimann for EWfE, SciRep 2020). Here we report the impact our project had on the incidence of diarrhea in two villages in rural Ghana.

Methods: This prospective study was conducted with approval from Ghana Health Services and involved the quantification of self-reported diarrhea 4 months before and after implementation of a membrane filtration device in a school and a primary healthcare center. Using a mixed-effects generalized linear model, the odds of developing diarrhea in presence of the membrane filtration device were estimated. We additionally tested the association of age on the estimate, and conducted a subset analyses in those younger than 15 years old. Analyses were conducted in R version 4.0 and odds ratios (OR) reported as OR (95%CI).

Results: We studied 927 villagers (55% female, 43% <15 yrs and 13% > 50yrs) and the incidence rate of diarrhea was 0.30 per subject month per village-month before and 0.26 after implementation of the device. We found a statistically significant association between the device and incidence of diarrhea [OR 0.79 (0.67 to 0.95)] with significantly higher odds of diarrhea in the younger [OR 1.32 (1.07 to 1.63)] and the elderly [OR 1.45 (1.06 to 1.99)].

Conclusions: Our study supports provision of clean drinking water as means to prevent diarrhea and its possible adverse sequelae such as acute kidney injury (AKI). Additionally, we conclude the youngest and the eldest in the population are at highest risk of diarrhea.

PO2041

Development and Validation of a Multifrequency Bioimpedance Spectroscopy Equation to Predict Appendicular Skeletal Muscle Mass in Hemodialysis Patients

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Background: Sarcopenia is prevalent and associated with poor outcomes in patients with chronic kidney disease (CKD). Although bioimpedance analysis is accepted by major consensus statements as an alternative for muscle mass assessment, it can be affected by hydration status in CKD patients. The Body Composition Monitor (BCM), a multifrequency bioimpedance spectroscopy device, has been widely used to assess body composition and dry weight in hemodialysis patients because it can distinguish normally hydrated lean tissues from overly hydrated tissues. Therefore, our study aimed to develop and validate an equation for obtaining appendicular skeletal muscle mass (ASM) from BCM using dual-energy X-ray absorptiometry (DXA) as the reference among hemodialysis patients.

Methods: A total of 322 consecutive body composition measurements with BCM and DXA in 263 hemodialysis patients were randomly divided at a ratio of 2:1 into development and validation groups. Stepwise multiple regression modeling was applied to develop the ASM prediction equation. Tests for agreement included mean differences and Bland-Altman plots. We evaluated the model as a diagnostic tool for sarcopenia using cutoffs of ASM defined by the Asian Working Group for Sarcopenia (AWGS). We further explored the association between ASM predicted by the BCM equation and all-cause mortality in two independent cohorts: one with 326 stage 3–5 CKD patients and one with 629 hemodialysis patients.

Results: BCM yielded the following equation: ASM (kg) = –1.838 + 0.395 × total body water (L) + 0.105 × body weight (kg) + 1.231 × male sex – 0.026 × age (years) (R^2 = 0.914, standard error of estimate = 1.35 kg). In the validation group, Bland-Altman reliability analysis showed no significant bias of 0.098 kg and limits of agreement ± 2.440 kg. Using the AWGS criteria, the model was found to have a sensitivity of 94.1%, a specificity of 98.8%, a positive predictive value of 84.2%, and a negative predictive value of 99.6% for the diagnosis of sarcopenia. Low ASM predicted by the BCM equation was associated with significantly worse overall survival among CKD patients but not hemodialysis patients.

Conclusions: The new BCM equation provides a feasible and valid option for assessing ASM in hemodialysis patients. Its utility in clinical practice requires further research.

Funding: Private Foundation Support

PO2042

Indoxyl Sulfate Reduces the Inducibility of NLRP3 Inflammasome in Hemodialysis Patients

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Background: The NLRP3 inflammasome is a cellular component of innate immunity responsible for the maturation of interleukin-1β (IL-1β). Studies have shown that the basal activity of the NLRP3 inflammasome is increased in the immune cells of hemodialysis (HD) patients, but the inducibility of the NLRP3 inflammasome upon canonical stimulation has not been studied.

Methods: Peripheral blood mononuclear cells (PBMCs) isolated from 13 HD patients and 18 volunteers without a history of chronic kidney disease (CKD) were treated with a combination of lipopolysaccharide (LPS) and nigericin to induce NLRP3 inflammasome activation. Likewise, THP-1 monocytic cell-derived macrophages, with or without indoxyl sulfate (IS) pretreatment, underwent the canonical NLRP3 inflammasome stimulus as well. The activity of the inflammasome was determined by immunoblot analysis.

Results: Despite the high plasma levels of IL-1β in HD patients, caspase-1 and IL-1β in the PBMCs of HD patients remained predominantly immature and were not secreted in response to the canonical stimulus. Further investigations showed that while IS treatment alone facilitated the secretion of IL-1β from THP-1-derived macrophages, IS pretreatment reduced the inducibility of NLRP3 inflammaosme in response to LPS and nigericin, characterized by the low mature rate of caspase-1. The PBMCs derived from the HD patients and the macrophages exposed to IS both had low expression levels of NLRP3 inflammasome components, suggesting insufficient supplies of inflammasome machinery.

Conclusions: The low stimulation response of the NLRP3 inflammasome attributed to indoxyl sulfate probably constitutes a breach of the immune defense system, which may explain the high infection risk in HD patients.

Funding: Clinical Revenue Support

PO2043

Prevalence and Risk Factors of High-Altitude Hyperuricemia in the Bai Ethnic Group

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Background: The Bai ethnic group is one of the 55 minorities in the People's Republic of China. Hyperuricemia is not rare among this ethnic partly due to the chronic exposure to high altitude. However, the prevalence of hyperuricemia in the Bai ethnic group remains unclear.

Methods: We collected retrospectively the demographic characteristics and laboratory measurements of 1393 Bai ethnic adults undergoing annual medical examination during Jan 2019 to Dec 2019 in the People's Hospital of Jianchuan County (average altitude 2300m), Yunnan Province. We investigated the prevalence of hyperuricemia as well as its clinical features and risk factors.

Results: Of the 1393 participants enrolled in the study, the prevalence of hyperuricemia was 24.8%, and the prevalence was significantly higher in male gender (33.2% in men vs. 11.0% in women, P<0.001). The prevalence of hyperuricemia increased from 19.2% among participants aged 30-40 years to 30.1% among participants aged 50 years and older. Also, the prevalence elevated from 17.2% among participants with normal body mass index (BMI) to 35.5% among those who were overweighed/obese. Interestingly, we found a positive correlation between hemoglobin level (Hb) and serum uric acid (β=2.19, P<0.01). Logistic regression analysis revealed main risk factors for hyperuricemia in the Bai ethnic group included age, sex, BMI, systolic blood pressure (SBP) and Hb.

Conclusions: Hyperuricemia is common in the Bai ethnic group. Besides traditional risk factors such as age, sex and BMI, polycythemia secondary to chronic exposure to high altitude may also contribute to the hyperuricemia.

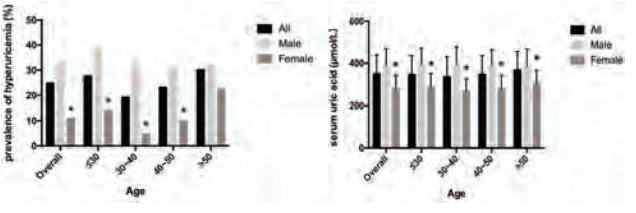

Fig 1 Prevalence of hyperuricemia and serum uric acid level in different age group (Left: Prevalence of hyperuricemia, Right: serum uric acid level). *P<0.001

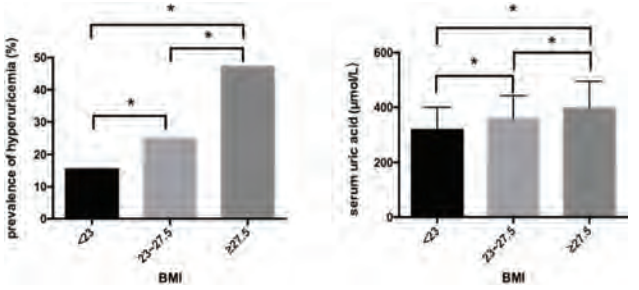

Fig 2 Prevalence of hyperuricemia and serum uric acid level in different BMI group (Left: Prevalence of hyperuricemia, Right: serum uric acid level). *P<0.001

PO2044

Changes in the Gut Microbiota After a Controlled Feeding Study in Individuals with CKD and Healthy Controls

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Background: Diet has been shown to alter the gut microbiota composition and function. However, controlled diet studies assessing the gut microbiota in CKD patients are limited. We assessed the differences in the gut microbiota composition before and after a week of controlled meals in patients with moderate-to-advanced CKD and healthy adults.

Methods: In a secondary analysis, we studied patients with CKD (n=7, eGFR 29-55mL/min/1.73m^2) vs. controls (n=7) matched for sex, age, and race. Participants ate a diet controlled for macronutrients (protein 0.8g/kg/d), fiber (25g/d), P (1500mg/d), Ca (1400mg/d), K (3500mg/d), and Na (2400mg/d) for 1 week. Fecal samples were obtained before and after the dietary intervention. Fecal DNA was extracted and used to amplify the V4 region of the 16S rRNA gene. Sequencing was performed via Illumina MiSeq platform and analyzed using QIIME2 and LEfSe.

Results: Fecal microbial diversity did not differ between patients with CKD or matched controls and was not affected due to the dietary intervention. At baseline, control individuals had a higher relative abundance of *Blautia* and an unclassified genus within Coriobacteriaceae, while CKD patients had a higher relative abundance of *Lachnobacterium.* After receiving a week of controlled meals, CKD patients had a higher relative abundance of *Anaerofustis* and *Clostridium*, while controls had a higher relative abundance of *Parabacteroides* and *Sutterella.* Comparing data before and after dietary treatment within groups, CKD individuals had a lower relative abundance of *Lachnobacterium* and higher *Bacteroides* and *Holdemania*. Meanwhile, healthy controls had a lower relative abundance of unclassified Mogibacteriaceae, and a higher relative abundance of *Bacteroides, Phascolarctobacterium, Parabacteroides*, and *Sutterella.*

Conclusions: While there were no major changes in microbial diversity, healthy controls and CKD patients responded differently to a week of controlled meals.

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PO2045

Mitochondrial Dysfunction and Uremic Toxins from Gut Microbiota in CKD Patients: Is There a Link?

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Background: Dysbiosis in patients with chronic kidney disease (CKD) is associated with increased production of uremic toxins, such as indoxyl sulfate (IS), p-cresyl sulfate (p-CS) and indole-3-acetic acid (IAA), which are linked to oxidative stress and may be related to mitochondrial dysfunction with alterations in peroxisome proliferator activated gamma receptor coactivator 1 alpha (PGC-1α), respiratory nuclear factor 1 (NRF-1) and mitochondrial transcription factor (TFAM). The aim of this study was to verify possible associations between metabolites produced by gut microbiota and genes related to mitochondrial function (PGC-1α, NRF-1, TFAM) in CKD patients.

Methods: This was a cross-sectional, observational study, involving 46 patients with CKD: 20 patients on hemodialysis (HD) (12 men, 44.2 ± 8.9 years) and 26 non-dialysis patients (8 men, 57.6 ± 6.2 years, GFR 25.0 ± 13.0mL/min), selected by non-probabilistic sampling of convenience. Plasma levels of IS, p-CS and IAA were assessed by high-performance liquid chromatography (HPLC). The analysis of the gene expression of PGC1-α, NRF-1 and TFAM were performed by real time Polymerase Chain Reaction (RT-PCR) in peripheral blood mononuclear cells (PBMCs). For statistical analysis, software R, version 3.5.0 (R Core Team, Vienna, Austria) was used and the results were expressed as mean ± standard deviation, with a significance level of p <0.05.

Results: As expected, the levels of uremic toxins were higher in HD patients than in non-dialysis patients [IS: 31.1 ± 14.3 mg/L vs 2.9 ± 1.7 mg/L (p <0.001); p-CS: 53.4 ± 34.6 mg/L vs 14.6 ± 10.8 mg/L (p <0.001); IAA: 2560.1 ± 1379.6 ug/L vs 1050.4 ± 984.8 ug/L)]. There was no significant difference in the mitochondrial parameters TFAM and PGC1a between the groups of patients. In the HD group was observed a positive linear correlation between TFAM and NRF1 (r = 0.978, p <0.001); as well as between PGC1a and NRF1 (r = 0.8, p = 0.006). However, in both groups there was no correlation between mitochondrial genes and uremic toxins.

Conclusions: The uremic toxins levels were significantly higher in HD patients; however, we did not find any correlations with the parameters of mitochondrial function analyzed.

Funding: Government Support - Non-U.S.

PO2046

Dysbiosis of Gut Microbiota in Adult Idiopathic Membranous Nephropathy with Nephrotic Syndrome

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Background: Gut bacterial microbiota is altered in patients with chronic kidney disease (CKD) and those on dialysis. However, it is not yet clear what bacterial composition changes occur in patients with idiopathic nephrotic syndrome. We present in this report the changes in gut bacterial microbiota in idiopathic nephrotic syndrome patients with membranous nephropathy.

Methods: A total of 158 individuals were recruited for this study. Of these, 80 were CKD3–5 stage patients without nephrotic syndrome, 48 patients had idiopathic nephrotic syndrome and pathological diagnosis of membranous nephropathy, and 30 were age- and sex-matched healthy controls. The gut microbiome composition was analyzed using a 16S ribosomal RNA gene-based sequencing protocol.

Results: The results indicate that the nephrotic syndrome (NS) patients had a significantly different alpha and beta diversity compared with the CKD3–5 group and healthy controls (p < 0.01). At the phylum level, the NS patients showed increased *Fusobacteria* and *Proteobacteria* but reduced *Firmicutes* when compared with the healthy controls. At the genus level, *Megamonas*, *Megasphaera*, *Akkermansia*, and the butyrate-producing bacteria *Lachnospira*, *Roseburia*, and *Fusobacterium* were more abundant in the controls (LDA score > 3) than the CKD3–5 and NS patients. Compared with the healthy controls, we found that *Parabacteroides* was increased in CKD3–5 and NS patients. In addition, *Oscillospira* and *Ruminococcus* were more abundant in CKD patients than in the other two groups (LDA score > 3). At the genus level, ten bacterial taxa were more prevalent in the healthy controls. *Providencia* and *Myroides* were more prevalent in NS patients.

Conclusions: Our findings highlight that, NS patients had a significantly different alpha and beta diversity and decreased gut microbiota-derived short-chain fatty acids, such as butyrate. However, large-scale prospective studies should be performed to identify the cause and effect factors of these changes in the microbiota in NS patients.

Funding: Government Support - Non-U.S.

PO2047

The Alter of Gut Microbiota in Dialysis Patients and Its Influence on the Prognosis for ESRD Patients

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Background: Previous studies have found that alteration in gut microbiota occurred in end-stage renal disease (ESRD) patients with or without dialysis, and are associated with complications such as inflammation and cardiovascular events. However, it has not been clarified whether gut microbiota are influenced by dialysis intervention in ESRD patients.

Methods: The fecal samples of 73 ESRD patients were collected, including 33 pre-dialysis ESRD patients, 19 peritoneal dialysis (PD) patients, and 21 hemodialysis (HD) patients; 19 healthy fecal samples were also collected as control in this study. The 16S rRNA sequencing and the bioinformatics was used to analyze the the composition and function of gut microbiota. The clinical outcomes of the patients were tracked from April 2017 to the end of May 2020.

Results: Compared with the pre-dialysis patients, Bacteroidetes decreased significantly in HD patients. At the genus level, a total of 14 genera showed differences between patients before and after dialysis. Pre-dialysis patients have a increased abundance of Parabacteroides, Prevetolla and Oscillospira, and the decreased abundance of Lachnospira, Klebsiella, Akkermansia and Roseburia. HD could repair the abnormal changes of these flora in pre-dialysis patients. We could not found any bacteria defference between PD and pre-dialysis patients in phylum and genus level. The PICRUSt analysis showed that PD and HD could change the signal transduction and metabolic pathways of ESRD patients. It was found that Bacteroides and SMB53 were associated with the occurrence of cardiovascular events. Blautia, Faecalibacterium, and Veillonella were associated with peritonitis in PD patients.

Conclusions: Our results suggested that compared with healthy control, the composition and function of gut microbiota of pre-dialysis patients were changed, HD could restored the relative abundance of beneficial bacteria and reduced some potential pathogenic bacteria. Some gut microbiota were associated with prognosis in all of ESRD patients and peritonitis in PD patients.

PO2048

Effect of Intradialytic Oral Nutritional Supplementation with and Without Exercise on the Skeletal Muscle Quantity and Quality of Adult Hemodialysis Patients

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Background: The muscle mass (MM) is one of the major tissues affected by the chronic kidney disease. Patients undergoing chronic hemodialysis (HD) have loss of MM due to many factors. Intradialytic oral nutritional supplementation (ONS) and exercise (EX) have been shown to improve the amount and quality of MM and physical function (PF). We evaluate the effect of the ONS with and without exercise during the HD sessions for 6 months in the quality and quantity of MM in adult HD patients.

Methods: Patients were randomized in two different groups: 1) ONS and 2) EX + ONS. Patient's realized 30 minutes of aerobic EX using static bicycles and 30 minutes of resistance EX using Theraband Bands. Quantity and quality of MM were measured with anthropometrics and computed tomography (CT). PF was measured by short physical performance battery (SPPB), six-minute walk test (6 MWT) and handgrip strenght (HGS)). According to the data distribution Student t test or Mann-Whitney test were used to analyze the data.

Results: Twenty-three patients conclude the study. Both groups improves their weight (*ONS*: baseline, 53 ± 5.4kg; final, 54.3 ± 4.9kg; p = 0.020 and *ONS + EX*: baseline, 57.2 ± 9.2kg; final: 59 ± 9.2kg; p = 0.001) and the AMC (*ONS*: baseline, 227 ± 20mm; final; 241 ± 19mm; p = 0.040 and *ONS + EX*, baseline: 235 ± 27mm, final: 250 ± 31; p = 0.047). In the ONS group we observed decreases in the 6MWT; baseline: 417 ± 53.9m, final: 405 ± 52m; p= 0.016 and improvements in the SPPB; baseline:10.8 ± 1.3, final: 11.2 ± 1.4, p= 0.005) with no change in the intramuscular lipid infiltration (baseline: 53.5 ± 5.8UH, final: 53.5 ± 3.9UH; p= N.S.). The EX group had improvements in the 6MWT, HGS and in the SPPB (baseline: 383 ± 58m, final: 425 ± 46m; p= 0.000; baseline: 22.6 ± 8.8kg, final: 24.8 ± 8kg, p= 0.000 and baseline: 10.2 ± 1.1, final: 10.8 ± 1.4, p= 0.801, respectively) with decreases in the intramuscular lipid infiltration (baseline: 53.1 ± 4.5HU, final: 55 ± 3.8HU; p= 0.093).

Conclusions: Exercise training for 6 months improves the MM composition of HD patients measured by CT and this was reflected with the improvements in the PF tests and no changes were observed in MM composition in the ONS group.

Funding: Private Foundation Support

PO2049

Muscle Mitochondrial Function and Physical Performance Are Associated with Branched-Chain Amino Acid Levels in Patients with CKD

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Background: Muscle mitochondrial function and physical performance are impaired in patients with chronic kidney disease (CKD). Previous studies suggest that decreased branched-chain amino acids (BCAA) levels are associated with muscle catabolism in patients with CKD. We hypothesized that BCAA is lower in patients with CKD and associated with mitochondrial function and physical performance, critical components of protein-energy wasting observed in patients with CKD.

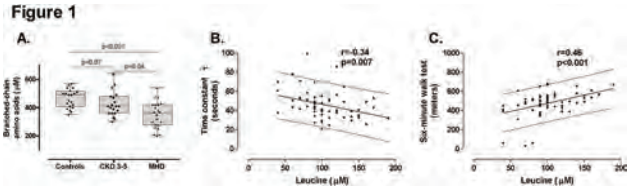
Methods: In a cross-sectional study, we evaluated 63 participants [20 with CKD stage 3-5, 20 with CKD stage 5 on maintenance hemodialysis (MHD), and 20 controls with no history of CKD]. Mitochondrial function was evaluated using ^{31} phosphours magnetic resonance spectroscopy to evaluate the phosphocreatine (PCr) recovery after exercise. A longer PCR recovery results in a greater time constant tau (τ), which indicates worsening mitochondrial function. Physical performance was measure using the six-minute walk test. BCAA levels were measured in plasma samples using nuclear magnetic resonance. Linear regression analysis was used to evaluate association and adjusting by age, race, sex, and body mass index (BMI).

Results: Groups were similar in terms of gender, BMI, and history of diabetes and hypertension. Patients on MHD were younger than patients with CKD stage 3-4 (47.7±11.7 vs. 63.6±9.0) but had similar age compared to controls (46.9±9.5). BCAA levels were lower in patients with CKD and patients on MHD compared to controls (**Figure 1A**). Lower levels of BCAA, particularly leucine, were associated with worse mitochondrial function (higher time constant τ, **Figure 1B**) and lower physical performance (**Figure 1C**) in unadjusted and adjusted linear regression.

Conclusions: CKD is associated with lower levels of BCAA. Furthermore, low levels of BCAA are associated with impaired mitochondrial function and poor physical performance. Future studies should evaluate the effect of BCAA supplementation in mitochondrial function and physical performance in patients with CKD.

Funding: NIDDK Support, Veterans Affairs Support

Figure 1



PO2050

High Prevalence of Sleep Disordered Breathing and Its Association with Renal Function in Patients with CKD: A Cross-Sectional Study

Kanji Ota, Yosuke Nakayama, Tomofumi Moriyama, Yusuke Kaida, Kei Fukami. *Division of Nephrology, Department of Medicine, Kurume University, Kurume, Japan.*

Background: Sleep disordered breathing (SBD) is known as a novel risk factor for cardiovascular disease, and one of five adults suffer from SBD in general population. In non-dialysis chronic kidney disease (CKD) and hemodialysis (HD) patients, a high prevalence of SBD has been reported due to the excess accumulation of extracellular fluid. However, precise prevalence and associated factors of SBD in patients with peritoneal dialysis (PD) has not been known. This cross-sectional study aimed to investigate the prevalence and determinant factors associated with SBD in patients with CKD.

Methods: This was a single-center retrospective cohort study recruited 334 patients with CKD stages 1-3a, 3b-5, HD, and PD enrolled from 2018 to 2020. All patients were hospitalized and received our CKD educational program, and did not have sleep complaints. The diagnosis and assessment of the severity of SBD were evaluated using PULSOX-Me300 and SAS2100 systems. The 3% oxygen desaturation index and SpO_2 were measured during sleep. SBD was defined as 3% oxygen desaturation index (ODI)>15.0 and SpO_2<92% in this study.

Results: Proportion of the patients with CKD1-3a, CKD3b-5, HD, and PD were 28%, 53%, 11%, and 8%, respectively. 31% of the patients were diagnosed with SBD in all CKD patients. In a generalized linear model, 3% ODI>15.0 and SpO_2<92% were significantly correlated with apnea hypopnea index ($p<0.05$, $r=0.87$ and $p<0.05$, $r=-0.45$, respectively). Further, it became clear that the proportion of 3%ODI>15 and SpO_2<92% was significantly higher in PD patients (50%) than in other CKD patients. Furthermore, 3% ODI was significantly correlated with BMI and HDL cholesterol levels in PD patients ($p<0.05$, $r=0.67$ and $p<0.05$, $r=-0.54$, respectively).

Conclusions: We reported for the first time that the prevalence of SBD was very high and that the severity of SBD was significantly associated with BMI in patients with PD. These findings suggest that the extracellular fluid overload and excess glucose exposure due to PD fluid might accelerate SBD in patients with PD. Further clinical studies are needed to determine whether PD-associated SBD might influence the development of cardiovascular disease in CKD patients.

PO2051

Effects of Resistant Starch (RS) Type 2 Cookies on Gut Microbiota Profile in Hemodialysis (HD) Patients

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Background: Dysbiosis is recognized as a new cardiovascular risk factor in HD patients. In this context, nutritional strategies as the use of high amylose RS have been proposed to modulate the gut microbiota in HD patients. The aim of the present study was to evaluated the effects of RS supplementation on gut microbiota modulation in HD patients.

Methods: This double-blind, placebo-controlled clinical trial evaluated HD patients randomized in two groups, RS or placebo. They received 9 cookies/day (16g of RS - Hi-Maize 260, Ingredion®), in the HD days and 1 sachet/day in non-HD days for 4 weeks. The placebo group received manioc flour. Fecal bacteriome composition and diversity were evaluated by high-throughput sequencing of 16S rRNA gene.

Results: Twenty patients concluded the study: 10 in the RS group (3 ♂, 53.2 ± 12.3 yrs, BMI, 24.6 ± 3.9 Kg/m²) and 10 in the placebo group (8 ♂, 55.1 ± 11.1 yrs, BMI, 25.6 ± 4.9 Kg/m²). Microbial diversity (Shannon index) and richness (ACE) were similar in both groups at baseline. RS supplementation increased mainly the relative abundance of the genus *Ruminococcus 2* and maintained genus *Blautia*, while the placebo group decreased both of these genera, as showed in the Fig 1. After RS supplementation the beta diversity (PCA) changed, increasing the short-chain fatty acid producers, which are related to benefits effects.

Conclusions: The RS supplementation was able to change the gut microbiota in HD patients. Linking these results with our previous studies, which RS was able to reduce the inflammatory and oxidative stress markers and uremic toxins plasma levels in HD patients, we suggest that RS can be a good nutritional strategy to modulate the gut microbiota in HD patients.

Funding: Government Support - Non-U.S.

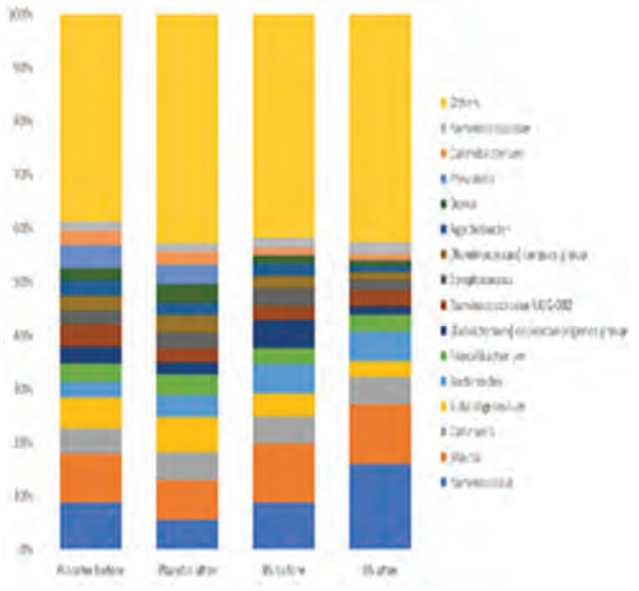


Fig.1: Relative abundance at genus level from RS and Placebo group.

PO2052

Gut Dysbiosis and Mortality in Hemodialysis Patients

Ting-yun Lin. *Taipei Tzu Chi Hospital, Taipei, Taiwan.*

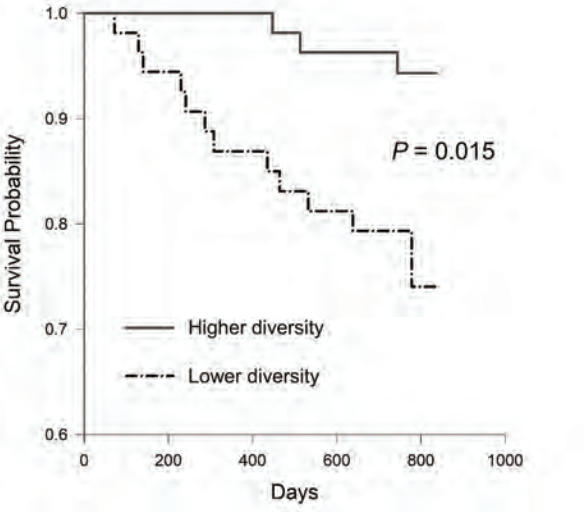
Background: Persistent inflammation plays a pathogenic role in CKD-associated protein-energy wasting, cardiovascular disease, and mortality. Gut dysbiosis, characterized by decreased microbial diversity, promotes inflammation. The gut microbiota is markedly altered in patients with ESKD. Therefore, we aimed to determine the relationship between gut dysbiosis and mortality in an ESKD cohort.

Methods: In an observational study, we examined the associations between microbial diversity and mortality in ESKD patients undergoing maintenance hemodialysis (*n*=109) using Cox proportional hazards models. The gut microbiota was assessed by 16S rRNA sequencing. Microbial diversity was calculated using the Simpson index. Participants were stratified into higher- (above the median) and lower-diversity (below the median) groups and were followed up for a median of 2.1 years. Next, in a matched case-control study, we compared the microbial composition between nonsurvivors and survivors.

Results: Kaplan-Meier analyses revealed a significant association between higher diversity and a lower risk of death (*P*=0.015). After adjustment for patient characteristics and comorbidities, the risk of death among patients with higher diversity was 74% lower than that among patients with lower diversity (hazard ratio, 0.26; 95% CI, 0.07 to 0.95). Nonsurvivors and survivors were matched 1:4 for age and sex. We observed significantly lower values of microbial diversity and higher levels of proinflammatory cytokines (IL-6 and TNF-α) among nonsurvivors (*n*=14) than survivors (*n*=56). Notably, the relative abundance of *Succinivibrio* and *Anaerostipes*, two short-chain fatty acid-producing bacteria, was reduced in nonsurvivors compared with survivors.

Conclusions: A unique gut microbial composition is associated with an increased risk of mortality in patients with ESKD and may be used to identify subjects with a poor prognosis. Our findings need to be validated in a larger independent cohort.

Funding: Private Foundation Support



Kaplan–Meier analysis curves. Hemodialysis patients were stratified by the median of the Simpson index to assess the unadjusted risks for all-cause mortality.

PO2053

Insulin Resistance and Pancreatic Beta-Cell Function in Calcium Kidney Stone Formers

Olive W. Tang,[1] Kevin Mitchell,[2] Jie Tang.[2] *[1]Johns Hopkins Medicine, Baltimore, MD; [2]Alpert Medical School of Brown University, Providence, RI.*

Background: Diabetes mellitus is common among individuals with kidney stones; however, the risk factors associated with glucose dysregulation in this population is unclear.

Methods: We characterized the independent associations between vitamin D, urinary measures of dietary intake (sodium, magnesium), and urinary ammonia and citrate with homeostasis model assessment of β-cell (HOMA-B) and insulin resistance (HOMA-IR) in prevalent calcium kidney stone formers without diabetes mellitus recruited from Lifespan Kidney Stone Clinic (N = 96). We used linear regression with adjustment for demographics, body mass index, hypertension, hyperlipidemia, parathyroid hormone, and serum uric acid.

Results: The study population had a mean age of 53 years, 48% were male, and 83% were Caucasian. The mean 25-hydroxy-vitamin D (25D) was 30 ng/ml, 1,25-dihydroxy-vitmain D (1,25D) was 55 pg/ml, 24-hour urine sodium was 145 mmol, urine ammonia was 30 mEq, urine citrate was 590 mg, and urine magnesium was 102 mg. Mean HOMA-B was 172.1, and mean HOMA-IR was 5.4. Urine sodium was negatively associated with HOMA-B, but not HOMA-IR. Urine ammonia was positively associated with HOMA-IR, but not HOMA-B. Urine citrate was positively associated with both HOMA-B and HOMA-IR (**Table**).

Conclusions: In our cohort of calcium kidney stone formers, high salt intake and low urine citrate were associated with worse beta-cell function. High urine ammonia and citrate were associated with increased insulin resistance.

Funding: Clinical Revenue Support

Table. Association (β [95% confidence interval]) of risk factors with HOMA-IR and HOMA-B in prevalent calcium kidney stone formers from the Lifespan Kidney Stone Clinic, N = 96

Risk Factor	HOMA-B	HOMA-IR
25-hydroxy-vitamin D, per ng/mL	-1.1 (-3.1, 0.9)	-0.1 (-0.2, 0.1)
1,25-dihydroxy-vitmain D, per pg/mL	-0.5 (-2.3, 1.2)	-0.0 (-0,1, 0.1)
Urinary sodium, per mmol	-0.7 (-1.1, -0.3)**	-0.0 (-0.0, 0.0)
Urinary ammonia, per 10 mEq	-0.4 (-22.8, 22.1)	1.2 (0.1, 2.4)*
Urinary citrate, per 10 mg	0.9 (0.1, 1.7)*	0.1 (0.0, 0.1)**
Urinary magnesium, per mg	-0.2 (-0.8, 0.5)	0.0 (-0.0, 0.1)

* p < 0.05
** p < 0.01

PO2054

Time to Hyperkalemia Recurrence in 1 Year Among 103,155 US Veterans

Jui-Ting Hsiung,[1] Rubeen K. Israni,[2] Cachet Wenziger,[1] Nipun Atreja,[2] Connie Ha,[2] Deborah A. Anzalone,[2] Kamyar Kalantar-Zadeh,[1] Elani Streja.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]AstraZeneca, Wilminton, DE.*

Background: Elevated serum potassium (sK) is commonly asymptomatic, but in a subset of patients, hyperkalemia (HK) is associated with worse outcomes and frequent recurrence. Whether the initial HK event was captured during a hospitalization may be associated with time to recurrence. Further characterizing time to recurrence in inpatient (INPT) and outpatient (OPT) settings may improve HK monitoring and treatment.

Methods: Among 3,958,837 US veterans that had a sK between 2004-2006, there were 589,019 that had an index HK event (sK >5.0 mEq/L) during this period where we could ascertain INPT/OPT status. We then identified patients who had a recurrent HK event 7-365 days after the index HK and had at least one normal sK ≤5.0 mEq/L in between events. We examined time to recurrence in 30-day intervals according to whether the index sK was INPT or OPT. Patients who's INPT/OPT status at HK recurrence could not be ascertained were excluded.

Results: HK recurrence over one year occurred in 103,155/589,019 (17.5%) patients, or 17,215/51,262 (34%) and 85,940/537,757 (16%) of patients with index INPT and OPT events, respectively. The 103,155 patients with HK recurrence had a mean patient age of 68±11 years, consisted of 98% males, 14% African Americans, 56% diabetics, and 60% with estimated glomerular filtration rate <60 mL/min/1.73m^2. In patients with HK recurrence, 50% (n=51,675) developed this event 6 months after the initial HK (table). Among patients who had an OPT index HK, 56% developed recurrence 6 months after index HK event. However, 51% of the patients who had an INPT index HK event developed recurrence within 60 days of the index HK.

Conclusions: A significant proportion of VA patients with HK developed another HK event within one year. Hospitalized patients with HK developed recurrence faster than patients in the OPT setting despite requiring 7 days between HK events and normalization of sK between events. This could be due to the fact that hospitalized patients are usually sicker or they were monitored more closely by the healthcare providers, therefore it is easier to catch HK recurrence in INPTs than OPTs.

Funding: Commercial Support - Astrazenenca

Days from index date to HK recurrence	Total Cohort, n (%)	Index HK: Inpatient, n (%)	Index HK: Outpatient, n (%)
0-30	10,651 (10)	6,072 (35)	4,579 (5)
31-60	8,803 (9)	2,701 (16)	6,102 (7)
61-90	7,859 (7)	1,615 (9)	6,244 (7)
91-180	24,167 (23)	3,184 (19)	20,983 (24)
181-365	51,675 (50)	3,643 (21)	48,032 (56)

PO2055

Primary Care and Annual Wellness Visits Before and After Dialysis Initiation

Virginia Wang,[1,2] Lindsay Zepel,[1] Clarissa J. Diamantidis,[1] Valerie A. Smith,[1,2] Sarah H. Scholle,[3] Matthew L. Maciejewski.[2,1] *[1]Duke Univ, Durham, NC; [2]Durham VAHCS, Durham, NC; [3]NCQA, Washington, DC.*

Background: Demands of dialysis regimens may pose challenges for patients to receive care for the management of non-renal conditions. Dialysis initiation may affect primary care provider (PCP) engagement and timely preventive care. Provided mostly by PCPs, AWVs provide a unique opportunity outside of routine evaluation and management visits to reassess health risks and functional limitations, update care plans, screen for depression, and better coordinate care. AWVs may be particularly useful for older adults undergoing dialysis who usually have other chronic, non-renal needs that commonly require ongoing monitoring and management. This study examined variation and patient factors associated with having PCP care and receipt of AWVs before and after initiating dialysis.

Methods: We used de-identified data from the OptumLabs® Data Warehouse to conduct a cohort study of Medicare Advantage (MA) enrollees initiating dialysis in 2014-2017. We used logistic regression to examine whether MA enrollees had an outpatient visit with a PCP in the year after dialysis initiation and whether they received an AWV, adjusting for demographic characteristics, dialysis modality, comorbidity, and pre-dialysis care by a PCP or nephrologist.

Results: One year after dialysis initiation, 93.3% of MA enrollees had an outpatient PCP visit. They were more likely to see a PCP if they had seen a nephrologist (OR=1.60, 95% CI: 1.01-2.52) or a PCP (OR=15.65, 95% CI: 9.26-26.46) prior to initiation. They were less likely to see a PCP if they had lower comorbidity burden (Charlson score 0-5 vs 6-9: odds ratio (OR)=0.59, 95% CI: 0.37-0.95). Of MA enrollees initiating dialysis, 24.4% had an AWV. Hispanic MA enrollees were less likely (OR=0.57, 95% CI: 0.39-0.84) to have an AWV compared to White MA enrollees. Peritoneal dialysis patients (OR=1.54, 95% CI: 1.07-2.23) or those with an AWV in the year before dialysis (OR=4.96, 95% CI: 3.88-6.34) were more likely to have an AWV.

Conclusions: While nearly all MA enrollees saw a PCP in the year after dialysis initiation, few had an AWV in this pivotal year. Since most MA enrollees who initiated dialysis continue to see primary care providers, there is opportunity to increase access to AWVs for these complex patients, through patient education and awareness of the value of AWVs and by encouraging providers to offer AWVs.

Funding: Other U.S. Government Support

PO2056

Workplace Outreach Program Facilitates Referral into Physician Care and Diagnosis of CKD

Olga A. Iakoubova, Carmen H. Tong, Charles M. Rowland, Andre Arellano, Lance A. Bare, Maren S. Fragala, James J. Devlin, Charles E. Birse. *Quest Diagnostics Nichols Institute, San Juan Capistrano, CA.*

Background: Chronic kidney disease (CKD) is often unrecognized and undertreated. Timely diagnosis can improve disease management and slow CKD progression. We asked whether a workplace outreach program facilitates CKD diagnosis and improves management of CKD.

Methods: An annual workplace health assessment that included eGFR testing was offered to employees. Those with confirmed CKD by repeat eGFR <60 mL/min/1.73 m^2 or by albumin to creatinine ratio test were eligible to participate in a CKD outreach program. A study coordinator made up to 3 phone calls in an effort to contact each eligible employee, to provide an explanation of CKD risk and to offer a physician consultation to discuss test results and referral into care. Those who accepted the phone call (participation group) were compared to those who were not reached by phone (control group). Using logistic regression models that adjusted for prevalent CKD, we analyzed claims data to estimate the effect of outreach participation on nephrologist visits, physician visits, and new CKD diagnoses 5 months after the outreach. Changes in eGFR levels were evaluated at the following annual health assessment.

Results: Of the 398 eligible employees, 156 participated in the outreach program; the remaining 242 served as the control group. CKD risk factor profiles at baseline were similar between participants and controls. Participants had 3-fold greater odds of visiting nephrologists, 60% greater odds of visiting physicians and 80% greater odds of being diagnosed with CKD, compared with the controls. Participants had 40% lower odds of an annual eGFR decline >5 ml/min/1.73 m^2 compared with controls (Table). One participant initiated kidney dialysis, compared with none in the control group.

Conclusions: A workforce CKD outreach program facilitates diagnosis of CKD and improves disease management including referral to a nephrologist.

Funding: Commercial Support - Quest Diagnostics supports annual health assessments and the CKD outreach program for employees and their spouses. It also provided funds for the analysis presented in the abstract

Effect of the CKD Outreach Program on Disease Management

Outcome	Adjusted Odds Ratio	95% CI	P value
Nephrologist visits	3.0	1.38 - 6.77	0.006
Physician visits	1.61	1.07 - 2.42	0.023
Newly diagnosed CKD	1.83	1.05 - 3.10	0.034
Annual eGFR decline >5 ml/min/1.73 m2	0.59	0.32-1.09	0.095

PO2057

A Pilot Randomized Clinical Trial to Embed Technology-Enabled Group-Based Exercise Programming in the Clinic: The Exercise Is Medicine in Chronic Kidney Disease Trial

Susan Ziolkowski,[1] Shuchi Anand,[1] Ahad A. Bootwala,[2] Jianheng Li,[2] Nhat M. Pham,[1] Jason Cobb,[2] Felipe Lobelo.[2] *[1]Stanford University School of Medicine, PALO ALTO, CA; [2]Emory University School of Medicine, Atlanta, GA.*

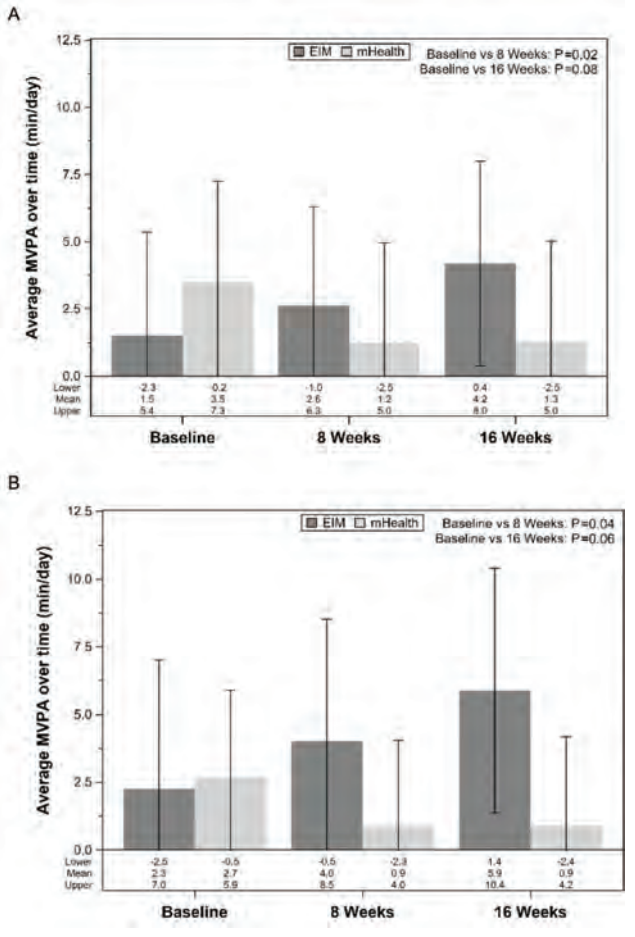
Background: Physical activity (PA) is associated with improvement of cardiovascular health, transplant outcomes, and survival in CKD. We evaluated the feasibility and effectiveness of integrating referral from nephrology clinics to a technology-enabled and/or group-based exercise program.

Methods: We conducted a pilot trial to test the ACSM Exercise is Medicine (EIM) framework in persons with eGFR <45 not on dialysis in San Jose, CA and Atlanta, GA. Participants were randomized to 1. mobile health (mHealth) group: wearable PA trackers + counseling, or 2. EIM group: mHealth + twice weekly small group exercise sessions. Physical and mental health assessments were done at baseline, 8, and 16 wks. Multilevel mixed models evaluated group differences.

Results: Of 56 participants, 86% belonged to a racial/ethnic minority. In intention-to-treat analyses, the EIM group increased moderate-vigorous PA compared to the mHealth group (time x intervention p=0.02) at 8 wks, no differences were observed between group daily step count. In as-treated analyses, daily step count, distance covered, light and moderate-vigorous PA improved in the EIM group and declined in the mHealth group at 8 wks (p ≤0.05) but group differences faded at 16 wks. No differences in physical function or mental health were found.

Conclusions: We successfully integrated recruitment, assessment, and group-based fitness interventions into clinical settings servicing minority patients with advanced CKD. Despite poor baseline measures, improvements in PA were observed in the EIM group, particularly in persons who participated in exercise sessions.

Funding: Private Foundation Support



Intention to treat (A) and as-treated (B) analyses: change moderate to vigorous physical activity (MVPA) in EIM vs mHealth

PO2058

Effect of Exercise on Quality of Life and Functional Capacity in Patients with CKD

Varun kumar Bandi,[1] Haneesha Kolli,[2] Sreelakshmi Nimmagadda,[2] Sandhya Komatla.[2] *[1]Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & RF, Gannavaram, India; [2]Kommareddy Venkata Sadasiva Rao Siddhartha College of Pharmaceutical Sciences, Vijayawada, India.*

Background: Chronic kidney disease patients have lower activity levels when compared to normal population, compounded by sedentary lifestyle and is associated with increased mortality, which might reduce with exercise

Methods: Patients with chronic kidney disease were evaluated for 12 weeks of supervised exercise program. The subjects were divided into 2 groups: Group I (CKD stage 3-5) and Group II (CKD on maintenance hemodialysis). Serum hemoglobin (Hb), calcium (Ca), phosphorous (Pi), and albumin (Alb) were done at baseline and at 12 weeks. Symptom burden was assessed using Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) and Leicester Uremic Symptom (LUS) Scale, Quality of life using SF-36 questionnaire, functional capacity using Duke Activity Status Index, Physical activity using Godin-Shephard Leisure time Exercise Questionnaire and Nutritional status using modified Subjective Global Assessment at baseline and at 12 weeks. Subjects in Group I were advised aerobic and resistance exercises at home, with once in 3 weeks hospital visit. Subjects in Group II underwent aerobic and resistance exercise in the pre-dialytic and intra-dialytic period during every dialysis visit

Results: Group I included 28 patients, while group II had 30 patients. At baseline, Hb and Albumin were significantly different between groups, while other parameters and scores were similar. At baseline, SF-36 and FACIT-F significantly correlated positively with Hb, Alb, Ca and Pi, while SGA correlated significantly with Alb, Ca & Pi. At end of study, in group I there was a non- significant increase in SF-36 (p=0.41), and DUKES (p=0.17), with a non-significant decrease in LUS (p=0.36), FACIT-F (p=0.83) and SGA (p=0.1136), while in group II there was a significant increase in SF-36 (p<0.001), with non-significant increase in Dukes (p=0.75), and a significant decrease in LUSS (p<0.001), SGA (p<0.05) and FACIT-F (p<0.001)

Conclusions: Exercise increased the quality of life and decreased symptom burden but there was an increase in fatigue perception in patients on dialysis. However, LUSS reduced with reduced FACIT-F which could mean decrease in symptom burden but persistence of fatigue. In patients not on dialysis there was no significant increase in quality of life or decrease in symptom burden.

PO2059

The Effect of Caloric Restriction and Aerobic Exercise on Serum FGF-23 in Patients with Moderate to Severe CKD

Elvis A. Akwo,[1] Thomas G. Stewart,[1] Cassianne Robinson-Cohen,[1] Adriana Hung,[1] Jonathan Himmelfarb,[2] Katherine R. Tuttle,[2] Talat Alp Ikizler.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of Washington Department of Medicine, Seattle, WA.*

Background: Chronic kidney disease (CKD) is associated with elevated serum fibroblast growth factor 23 (FGF23) which correlates with increased cardiovascular risk. Prior data suggest serum FGF23 is also associated with increased adiposity. We tested the hypothesis that an intervention involving caloric restriction and aerobic exercise to reduce body weight would reduce serum FGF23 in patients with moderate to severe CKD.

Methods: We performed a secondary analysis of data from a 2X2 factorial randomized trial enrolling 103 participants randomized to receive combined caloric restriction and aerobic exercise, caloric restriction alone, aerobic exercise alone, or usual care. Enrollees were persons with a median estimated glomerular filtration rate (eGFR) of 40.5 ml/min/1.73m^2 (IQR: 30.3, 56.2). Measurements of Serum FGF23 (using C-terminal ELISA assay) and serum phosphate were obtained at baseline and month 4. Changes in serum FGF23 between baseline and month 4 across intervention arms were examined using analysis of covariance with robust standard errors.

Results: After adjustment for baseline differences, serum FGF23 levels fell by 20.6% [95%CI: 0.4, 36.7, p = 0.047] more in the combined intervention arm compared to usual care. Further adjustment for baseline serum phosphate attenuated the relative difference in serum FGF23 decline between the combined intervention arm and usual care [percent change = -18.6, 95% CI: -35.3, 2.9; p = 0.10]. Caloric restriction or exercise alone did not demonstrate significantly greater decline in serum FGF23 compared to usual care. The median values of change in serum phosphate between baseline and month 4 among participants in the combined intervention and diet-only arms were -0.15 and 0.05 mg/dl whereas the exercise and usual care arms experienced no change in serum phosphate. Neither intervention arm showed a significantly greater percent change in serum phosphate from baseline to month 4 compared to usual care.

Conclusions: A combined 4-month calorie restriction and aerobic exercise intervention led to significant reductions in serum FGF23. The magnitude of serum FGF23 reduction appeared to be influenced in part by baseline serum phosphate levels while the latter remained relatively unchanged at the end of the trial.

Funding: Other NIH Support - R01HL070938 from National Heart, Lung, and Blood Institute

PO2060

Changes in Body Composition, Muscle Strength, and Fat Distribution Following Renal Transplantation

Susan Ziolkowski,[1] Simin Goral,[2] Jin Long,[4] Joshua F. Baker,[2] Justine Shults,[6] Babette Zemel,[3] Peter P. Reese,[2] Francis P. Wilson,[5] Mary B. Leonard.[1] *[1]Stanford University School of Medicine, Stanford, CA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]Lucile Salter Packard Children's Hospital at Stanford General Pediatrics, Palo Alto, CA; [5]Yale University School of Medicine, New Haven, CT; [6]University of Pennsylvania, Philadelphia, PA.*

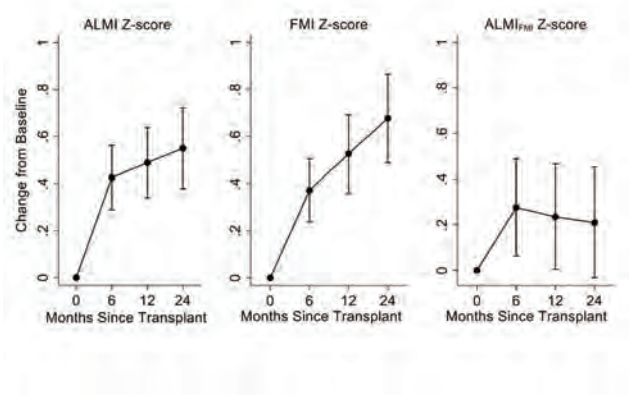
Background: The impact of renal transplantation on body composition and muscle quality has not been established. Low muscle mass relative to fat mass (relative sarcopenia) has been associated with mortality and disability but has not been examined following transplantation.

Methods: DXA measures of fat mass index (FMI) and appendicular lean mass index (ALMI; representing muscle mass), CT measures of muscle density (low density represents increased intramuscular adipose tissue), and leg muscle strength were assessed in 60 transplant recipients (ages 20-60 years) at transplantation, and 6, 12, and 24 months after transplantation. ALMI relative to FMI (ALM_{FMI}) is an established index of relative sarcopenia. Measures were expressed as age, sex, and race-specific Z-scores and compared with 327 healthy controls.

Results: At transplantation, ALMI, $ALMI_{FMI}$, muscle strength and muscle density Z-scores were lower vs. controls (all p≤0.001). Transplant recipients received glucocorticoids throughout. The prevalence of obesity increased from 18 to 45%. Although ALMI increased following transplantation (p<0.001) and was comparable to controls from 6 months onward, gains were outpaced by increases in FMI, resulting in persistent $ALMI_{FMI}$ deficits (mean Z-score -0.31 at 24 months, p=0.02 vs controls). Fat gains were disproportionately visceral in distribution (p<0.05). Muscle strength improved but remained low compared with controls independent of ALMI (p<0.05). Exercise increased in the early months following transplantation (p<0.05) but remained lower than controls (p=0.02).

Conclusions: The two-year interval following renal transplantation was characterized by gains in muscle mass and strength that were outpaced by gains in fat mass resulting in persistent relative sarcopenia.

Funding: NIDDK Support



Change in Body Composition Z-scores from baseline after Transplantation

PO2061

Home-Based Aerobic Exercise and Resistance Training in Pre-Dialysis Patients with Advanced CKD: A Randomized Controlled Trial

Kiyotaka Uchiyama, Keika Adachi, Shu Wakino, Hiroshi Itoh. *Keio University School of Medicine, Shinjuku-ku, Japan.*

Background: Muscle wasting, a common and progressive condition in patients with uremia, is associated with increased risk for morbidity, lower health-related quality of life (HRQOL), and mortality. But, the potential effects of aerobic and resistance training in predialysis patients with advanced chronic kidney disease (CKD) have not been fully elucidated. This randomized controlled trial with a parallel-group design investigated the effects of a home-based exercise program on physical functioning and HRQOL in patients with stage 4 CKD.

Methods: A total of 46 patients (median age, 73 years; 33 males; estimated glomerular filtration rate, 23.2 ± 4.7 ml/min/1.73 m^2) were randomly assigned to exercise (n = 23) and control (n = 23) groups. The exercise group performed aerobic exercise thrice weekly and resistance training twice weekly at home for 24 weeks. The control group received no specific intervention. Primary outcomes were distance in incremental shuttle walking test (ISWT) and HRQOL assessed by the Kidney Disease Quality of Life-Short Form questionnaire. Secondary outcomes were kidney function assessed by combined urea and creatinine clearance, urinary biomarkers, and anthropometric/biochemical parameters associated with CKD.

Results: ISWT distance was significantly improved in the exercise group than in the control group (34.5 ± 50.5 vs. −21.9 ± 48.2 m; P < 0.001). The intervention increased several HRQOL subscales including symptoms/problems, quality of interaction, sleep, kidney disease component summary, and mental health. Although the change in combined urea and creatinine clearance was not significantly different between the groups (P = 0.69), natural log-transformed (ln) urinary excretion of liver-type fatty acid-binding protein, ln serum C-reactive protein, and acylcarnitine/free carnitine ratio were significantly decreased in the exercise group compared to the control group (P = 0.02, 0.005, and 0.03, respectively). No adverse events associated with the intervention were reported.

Conclusions: The 24-week home-based exercise program improved aerobic capacity and HRQOL with possible beneficial effects on kidney function and CKD-related parameters, in patients with stage 4 CKD. The present trial demonstrated the multifaceted efficacy of home-based training on predialysis patients with advanced-stage CKD.

PO2062

Association of Self-Reported and Objective Measures of Physical Activity with Leg Muscle Mitochondrial Oxidative Capacity in CKD

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Background: Chronic kidney disease (CKD) is associated with skeletal muscle dysfunction leading to lower muscle mitochondrial oxidative capacity and decreased physical performance. However, the influence of physical activity (PA) on muscle mitochondrial function remains unknown.

Methods: We included participants from the CKD Mitochondrial Energetics and Dysfunction (CKD-MEND) study. Muscle mitochondrial oxidative capacity (ATPmax) in the leg muscle was measured using in vivo ^{31}Phosphorus Magnetic Resonance Spectroscopy. We measured self-reported PA using the adjusted Human Activity Profile (HAP) score and objective PA using an Actigraph accelerometer. Linear regressions were used to test associations between CKD status and ATPmax adjusting for confounders.

Results: We included 36 participants with CKD (mean eGR=38) and 19 controls. Mean age was 61±13 years, 51% male, and 25% had diabetes. Diabetes and CKD were independently associated with lower ATPmax (-0.12 mM/s, p<.01 and -0.19 mM/s, p<.01, respectively). Accelerometry counts per minute (r=.58, p<.01) was more strongly correlated with ATPmax than HAP scores (r=.46, p<.01) with no interaction by CKD status (p=.9). Accelerometry counts explained 43% of the difference in ATPmax between CKD and controls and HAP scores 15% after adjustment.

Conclusions: Objective PA was more strongly associated with ATPmax and explained more of the differences in ATPmax between CKD and controls than self-reported PA. Further studies should demonstrate if exercise interventions can improve muscle ATPmax in CKD.

Funding: NIDDK Support, Private Foundation Support

Figure 1. Association of ATPmax with log-transformed accelerometry counts

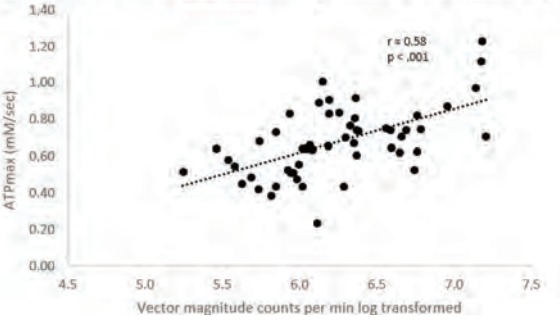
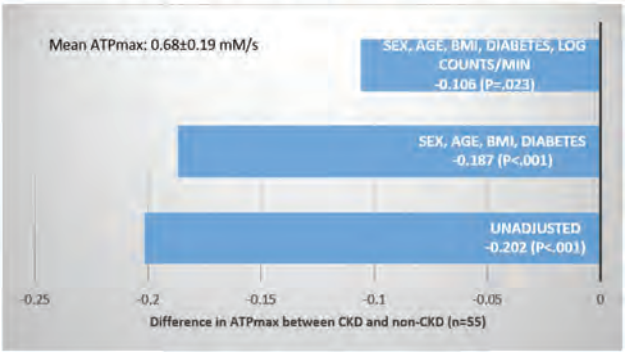


Figure 2. Linear regression models of the association of CKD with ATPmax



PO2063

Serum and Skeletal Muscle Acylcarnitines And Physical Function in CKD Stage 5-5D

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Background: Sarcopenia is highly prevalent among those with advanced CKD. The metabolite signature of skeletal muscle in patients with CKD is poorly studied. We hypothesized that skeletal muscle metabolites would be different between serum and muscle in those with CKD 5-5D as compared to healthy adults.

Methods: *Subjects:* 34 subjects participated; 17 with CKD (10 CKD-5, 7 CKD 5D) undergoing renal transplant and 17 healthy donors. All had blood drawn and transversus abdominus muscle biopsy during surgery. *Physical Function tests done the week before were:* Sit to stand (STS), 6 minute walk test (6MW), 4m gait speed (fast and usual). *Metabolomics:* Targeted mass spectrometry (MS) was performed on serum and muscle using the Biocrates Absolute IDQ. Differences were tested between those with and without CKD.

Results: There were no differences in age, height, weight or BMI between CKD and healthy subjects. *Physical Function:* The CKD group had poorer performance for the STS(13 vs 19), 6MW(434 vs 589m), fastest gait speed(1.62 vs 2.00 m/s) and usual gait speed(1.18 vs 1.34m/s), all p<0.05. *Metabolomics:* The heatmap depicted two distinct signatures in both serum and skeletal muscle between CKD and donors. Serum demonstrated 59 significantly different metabolites, especially in fatty acid metabolism with increases in short and medium chain acylcarnitines C4-C12, and nine hydroxylated and dicarboxylated acylcarnitines in CKD (p<0.05). Lower 6MWT distance was independently associated with levels of C10-14 even after adjusting for CKD status and age in multivariate regression analyses. Skeletal muscle demonstrated significant differences in 42 metabolites, with consistently higher acylcarnitine levels in recipients, including short chain (i.e. C4.1, C5.1, C6.1), long chain and dicarboxyls.

Conclusions: Our data demonstrates patients undergoing renal transplant have increased acylcarnitine levels in serum and muscle that are independently associated with poor physical performance. These results suggest impaired b-oxidation of fatty acid metabolism that affects physical function. Understanding these pathways will allow targeted therapeutics to improve the disabling sarcopenia observed in patients with CKD.

Funding: NIDDK Support

PO2064

Metabolic Acidosis and Muscle Metabolic Health Are Important Determinants of Fatigue in Persons with CKD

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Background: Chronic kidney disease (CKD) is associated with a high prevalence of physical frailty, reduced physical function and fatigue, contributing to increased morbidity, mortality risk, and poor quality of life. Impaired muscle mitochondrial oxidative capacity (ATPmax) underlies poor physical endurance in persons with CKD. Metabolic acidosis may mediate effects of CKD on ATPmax. Little is known about the relevance of metabolic acidosis and ATPmax on patient-reported fatigue in CKD.

Methods: We performed a cross-sectional analysis of 58 participants (39 CKD and 19 non-CKD) from the CKD Muscle Mitochondrial ENergetics and Dysfunction (MEND). *Muscle metabolic health* of the tibialis anterior leg muscle was measured from the time course of phosphocreatine after exercise using ^{31}Phosphorus Magnetic Resonance Spectroscopy. *Fatigue* was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale. *Metabolic acidosis* (MA) was determined from serum bicarbonate (< 22 mmol/L). Linear regression was used to test associations adjusting for age, sex, body mass index (BMI), and diabetes.

Results: The cohort included 48% female and 29% diabetes with a mean age of 61±12 years and a mean BMI of 28±5. The mean eGFR was 39±19ml/min per 1.73m^2 in CKD and 98±15 in non-CKD. The mean ATPmax was 0.672±0.185mM/sec and mean FACIT-F score was 40±11.5. CKD was associated with increased fatigue (mean difference: 7.6, 95% CI [1.8, 13.5], p<.05) compared to non-CKD after adjustment. Of those with CKD each 1 SD (standard deviation) greater ATPmax was associated with a 5.4-point (95% CI [1.03, 9.7], p=.017) reduction in fatigue after adjustment. Further adjustment for MA attenuated the estimated association by 38% (3.3 points, 95% CI [-1.1, 7.7], p=.134). Of those with CKD, participants with MA (n=18) had a 10. points greater fatigue (95% CI [1.8,18.1], p=.018) after adjustment compared to those without MA (n=21).

Conclusions: ATPmax is directly associated with fatigue. MA might play an important role in the association of muscle metabolic health with fatigue in CKD. Further research is needed to examine the impact of treating MA on improvement in muscle metabolic health, fatigue and quality of life in CKD.

Funding: NIDDK Support, Other NIH Support - Dialysis Clinics Incorporated

PO2065

Blood Pressure in Young Adults with CKD and Associations with Cardiovascular Events and CKD Progression

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Background: Young adults (age 18-40yrs) with CKD are a poorly studied subset of CKD patients. Blood-pressure management for young adults with CKD relies on extrapolating findings from studies conducted in older adults or children. Our objective was to perform an observational study exclusively in young adults with CKD to test the association between BP and adverse outcomes.

Methods: Participants aged 21-40yrs of age enrolled in the Chronic Renal Insufficiency Cohort Study were included (n=317). Exposures included baseline systolic BP (SBP) category, <120, 120-120, ≥130, and per +10 higher baseline SBP. Outcomes included cardiovascular (CV) events, including heart failure, myocardial infarction, stroke, or all-cause death, and CKD progression, defined as 50% eGFR decline or ESRD. We used cox-proportional hazard models to test association between baseline SBP with outcomes. Adjusted models included age, race, eGFR, diabetes, with prevalent CV disease for CV event models and urine albumin to creatinine ratio for CKD progression.

Results: As seen in **Figure 1**, incidence rates for HF, death, CV events, and CKD progression were greater at higher SBP categories. In adjusted models, a baseline SBP >130 was significantly associated with CV events (HR: 3.32, 95% CI: 1.53-7.20) and CKD progression (HR: 1.63, 95%CI: 1.02-2.59) compared with SBP<120. Every +10 in SBP was significantly associated with CKD progression (HR: 1.13, 95%CI: 1.02-1.26) in adjusted models.

Conclusions: There is a graded association of higher SBP with greater risk of CV events and CKD progression in young adults with CKD. Among those with SBP>130, 5.8% per year had a CV event and risk was 3-fold higher compared with SBP<120; and 20.7% per year had CKD progression and risk was nearly 2-fold higher. These data suggest that higher SBP is an important risk factor for adverse outcomes in young adults with CKD.

Funding: NIDDK Support

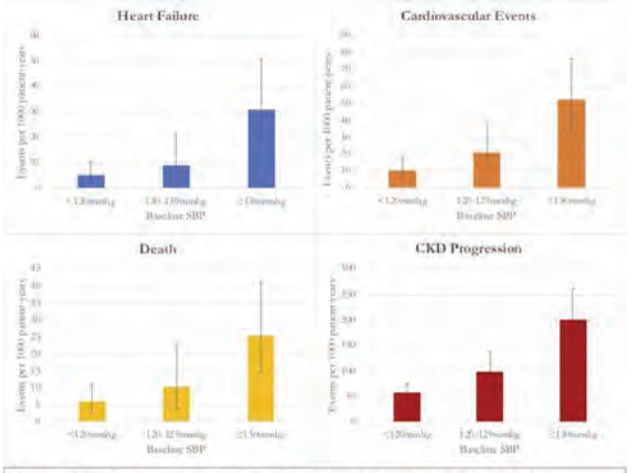

Figure 1: Incidence rates for HF, cardiovascular events, death, and CKD progression across baseline SBP categories for young adults with CKD enrolled in the CRIC study (n=317). Error bars represent 95% CI.

PO2066

Angiotensin Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Use Among Hypertensive US Adults by Albuminuria Status, 2013-2018

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Background: Since 2003, U.S. hypertension (HTN) guidelines have recommended angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy for urine albumin/creatinine ratio (UACR) ≥300 mg/g. Our objective was to assess the prevalence of ACEi/ARB use for UACR ≥300 mg/g among adults with HTN and to examine the association between UACR and ACEi/ARB use.

Methods: We studied adults with HTN in the National Health and Nutrition Examination Surveys 2013-2018. Respondents were classified as having HTN if they had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, were currently using anti-hypertensive medications, or reported being told by a clinician they had HTN. ACEi/ARB use was assessed by review of medication containers by study staff. Modified Poisson regression was used to estimate crude and adjusted prevalence ratios (PR) for the association between ACEi/ARB use and UACR; adjustment was for age, sex, race/ethnicity, diabetes, systolic blood pressure (continuous), chronic kidney disease stage, and having a reported routine site for healthcare.

Results: Among 7,377 adults with HTN, 83.4% had UACR 0-29 mg/g, 13.5% had UACR 30-299 mg/g, and 3.2% had UACR ≥300 mg/g. ACEi/ARB use was 43%, 54%, and 48% in UACR categories 0-29, 30-299, and ≥300 mg/g, respectively. This represents approximately 1.5 million adults with UACR ≥300 mg/g who are not receiving ACEi/ARB therapy. Adjusted ACEi/ARB use was minimally associated with UACR ≥30 mg/g (PR = 1.09, 95% CI 1.03-1.17 for UACR 30-299 mg/g; PR = 0.96; 95% CI 0.83-1.10 for UACR ≥300 mg/g; reference = UACR <30 mg/g).

Conclusions: Nationally representative data indicate a large gap in guideline-concordant ACEi/ARB use among adults with HTN and UACR ≥300 mg/g. Improving uptake of ACEi/ARB therapy presents a substantial opportunity for prevention of cardiovascular disease and kidney disease progression for adults with HTN.

Funding: NIDDK Support

PO2067

Increased Residual Cardiovascular Risk in US Veterans with Moderately Elevated Baseline Triglycerides, Well-Controlled LDL Cholesterol Levels on Statins, and Decreased Renal Function

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Background: Recent studies have suggested a causal role for elevated triglycerides (TG) in incident cardiovascular (CV) events. Using a large cohort of U.S. veterans with statin-controlled LDL-C levels (40-100mg/dL), we explored whether increased residual CV risk existed in patients with elevated baseline TG levels versus those with normal TG levels in the subset who had reduced eGFR (<60 ml/min).

Methods: We identified veterans receiving a statin but not a TG-lowering agent from the VA Corporate Data Warehouse, a database of the VA electronic health record,

from 2010-2015. We compared CV event rates (nonfatal MI, stroke, unstable angina, or coronary revascularization) between the elevated TG (150-499 mg/dL) and normal TG (<150 mg/dL) groups. We calculated crude event rates, rate ratios, and 95% CI for both groups, and adjusted event rate ratios for age, sex, baseline blood pressure, glomerular filtration rate, and weight.

Results: We included 152,266 veterans (predominantly male and white) in the analysis cohort of whom 43,670 (29%) had elevated TG levels. These subjects were younger and had higher BMIs. Table 1 details the crude and adjusted CV event rates. The overall crude and adjusted CV event rate ratios were 1.28 (95% CI 1.23,1.33) and 1.12 (95% CI 1.07, 1.16), respectively.

Conclusions: In this large cohort of veterans, those with elevated TG levels and moderately decreased renal function showed a significant increase in CV events despite well-controlled LDL-C on statins compared to veterans whose baseline TG was in a normal range.

Funding: Commercial Support - Amarin Corp

Crude prevalence, crude and adjusted rate ratios of cardiovascular outcomes

	Elevated TG (n=43,670)	Normal TG (n=108,596)	Unadjusted Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)
Composite CV outcome	3,977 (9.1%)	1,129 (2.6%)	1.28 (1.23, 1.33)	1.12 (1.07, 1.16)
Individual CV outcomes				
Non-fatal MI	2,459 (5.6%)	4,656 (4.3%)	1.29 (1.23, 1.35)	1.13 (1.08, 1.19)
Non-fatal stroke	924 (2.1%)	4,656 (4.3%)	1.15 (1.06, 1.24)	1.04 (0.96, 1.12)
Coronary revascularization	428 (1.0%)	623 (0.6%)	1.67 (1.48, 1.89)	1.27 (1.12, 1.44)
Unstable angina	1,129 (2.6%)	1,891 (1.7%)	1.46 (1.35, 1.57)	1.24 (1.15, 1.34)

Rate ratio for each outcome based on generalized linear model with Poisson errors. Composite CV outcome was the 1st occurrence of all individual CV endpoints. Analysis based on 150,151 subjects with complete data.

PO2068

Deep Learning Analysis of Derived Cardiac Function Metrics for the Detection of CKD and Subsequent Outcome Prediction in Community-Dwelling Individuals

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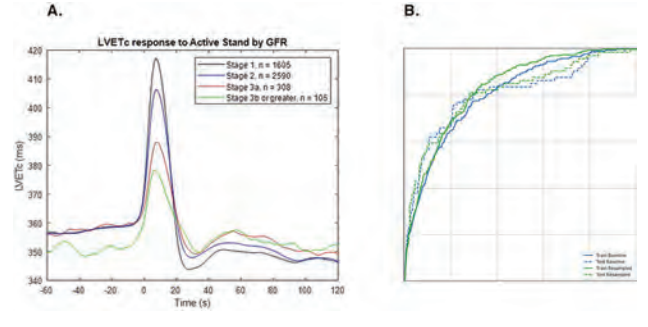
Background: Whether subtle abnormalities in cardiac function exist in community dwelling individuals and can be used to agnostically discern those with reduced kidney function and incident adverse outcomes over follow up is unknown.

Methods: The Irish Longitudinal Study on Ageing (TILDA) is a prospective nationally representative cohort study based on random sampling of the community-dwelling general population aged ≥ 50 years in Ireland. Wave 1 was performed between June 2009-June 2011. Participants underwent a detailed health assessment including blood tests, and an active stand test using the Finometer, which measures continuous blood pressure and heart rate for 10 mins while supine at rest, then throughout the standing test and for 2 mins thereafter. Cardiac function metrics are derived : left ventricular ejection time (LVET), cardiac output, and total peripheral resistance. CKD-EPI equation was used for eGFR. We analysed repeated measures data at 10 second intervals over the entire observation period using sequential neural networks with the categorical outcomes of coincident CKD, and incident mortality. Follow up was approximately 10 yrs. Python v 3.77 and TensorFlow v2.0.0 were used for the analysis.

Results: N=4388 TILDA participants were included, N=2013 were male, mean age was 62 (8) yrs, 647 had CKD. 178 died over follow up. **Figure 1. A** demonstrates profiles in LVET by eGFR category and **B** an ROC curve output from the Neural Network model predicting conincident CKD AUC = 0.81(resampled model: which included an input layer, 2 hidden layers and an output layer based on cardiac metrics, age and sex). AUC for mortality was 0.75 (resampled model).

Conclusions: Deep Learning analysis of repeated measures of derived cardiac function metrics discerned community dwelling individuals with CKD and subsequent outcomes. This method has potential for population level risk dsicrimination.



PO2069

Risk of Mortality, ESKD, and Hospitalization Among Medicare Beneficiaries with Pulmonary Hypertension and CKD

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Background: Pulmonary hypertension (PH) is highly prevalent among patients with non-dialysis dependent CKD (~20%). We studied the risks of mortality, ESKD, cardiovascular (CV) and non-CV hospitalizations among those diagnosed with both PH and CKD.

Methods: Patients with PH (based on 2 claims within 2 years) were identified from a Medicare 5% sample (1995-2016). For each PH patient we randomly selected 5 patients diagnosed with the same CKD stage as the PH patient but without a PH diagnosis. We used Cox proportional hazards models to assess the association between PH and mortality, adjusting for age, sex, race, and comorbidities. We considered death as a competing event in Fine-Gray models to assess the association between PH and ESKD.

Results: We studied 41,478 patients with PH and CKD and 207,390 CKD stage-matched patients without diagnosed PH. Over 59% of the study population were >80 years, 12% were African American, 47% had diagnosed diabetes and 46% had COPD. The presence of diagnosed PH (vs. no PH diagnosis) was associated with increased risk of mortality, ESKD, and CV and non-CV hospitalizations at 1-, 3-, and 5-year follow-up (Table 1). Diabetes modified these associations with higher risk of all outcomes noted among those without diabetes.

Conclusions: Among older Medicare beneficiaries diagnosed with CKD, the presence of PH increased risk of mortality, ESKD, and hospitalization. Mechanistic understanding of these associations, especially the increased risk of ESKD, requires additional study.

Funding: NIDDK Support

Table 1. Associations of PH with mortality, ESKD, and cardiovascular and non-CV hospitalization in those with PH and CKD

Outcome		Unadjusted HR (95% CI)	Multivariable adjusted HR (95% CI)
Mortality	1-year	3.24 (3.17, 3.31)	2.35(2.29, 2.41)
	3-year	2.71(2.67, 2.75)	1.98 (1.94, 2.01)
	5-year	2.54(2.50, 2.58)	1.87 (1.84, 1.90)
ESKD	1-year	2.73 (2.57, 2.90)	2.49 (2.33, 2.67)
	3-year	1.82 (1.74, 1.91)	1.70 (1.61, 1.79)
	5-year	1.59 (1.52, 1.66)	1.54 (1.47, 1.62)
		Unadjusted RR (95% CI)	Multivariable adjusted RR (95% CI)
Cardiovascular hospitalization	1-year	7.97 (7.82, 8.13)	5.92 (5.80, 6.05)
	3-year	6.72 (6.60, 6.83)	4.77(4.68, 4.85)
	5-year	6.39 (6.28, 6.49)	4.48 (4.40, 4.56)
Non-CV hospitalization	1-year	3.83 (3.77, 3.89)	2.98 (2.93, 3.03)
	3-year	3.36 (3.31, 3.40)	2.54 (2.51, 2.58)
	5-year	3.20 (3.15, 3.24)	2.41 (2.38, 2.45)

PO2070

A Marginal Structural Model to Estimate Causal Effect of Time-Dependent Anemia Status on Renal and Cardiovascular Outcomes Among Community-Dwelling Japanese Subjects at Beginning of Impaired Renal Function

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Background: We investigated whether anemia increases the risk of renal and cardiovascular (CV) outcomes considering the changes of anemic status over time, using a marginal structural model.

Methods: We retrospectively analyzed data from a Japanese database (JMDC) consists of annual health checkup data linked to medical and pharmacy claims for over 3 million of beneficiaries. Subjects with consequent eGFR values of ≥60 and then <60 mL/min/1.73 m^2 within 2 years and during the period between 2008 and 2019 were included. The first date where the eGFR value became <60 was defined as the index date. Patients without serum creatinine (SCr) record within 38 months from the index date were excluded. Anemia status (yes/no) was defined by the age-sex specific hemoglobin value according to the Japanese guidelines. Renal outcomes (composite of ≥30% eGFR decline over 3 years, eGFR <15 ml/min/1.73m^2, SCr doubling, initiation of chronic dialysis and kidney transplantation), CV outcomes (myocardial infarction, stroke, unstable angina and heart failure) and mortality was assessed. In order to incorporate dynamic change of anemia status and covariates during the follow-up, a time-dependent standardized inverse probability weight at time x was estimated based on propensity score to either be—or not be—anemia at time x. Weighted survival probability and weighted hazard ratio were estimated.

Results: 32,870 subjects were enrolled in the study cohort (median age 52, 73% male) and 4.2% of subjects had anemia at the baseline. Anemia treatment was rarely provided even in the anemia group (3.9%). During the average of 4.1-year of follow-up period, 210 renal outcomes and 1039 CV outcomes occurred. In 91% of the cases with the renal outcomes, eGFR decline occurred first. The weighted hazard ratios (95% confidence intervals) for renal outcomes, CV outcomes and mortality were 2.6 (1.7-3.8), 1.6 (1.2-2.2), and 2.8 (1.8-4.3), respectively.

Conclusions: Anemia was an independent risk for eGFR decline, CV events and mortality in these Japanese community-dwelling subjects at the very beginning of renal impairment, considering the time-dependent nature of anemia status.

Funding: Commercial Support - Astellas Pharma, Inc

PO2071

Estimation of Sodium Consumption by Novel Formulas Derived from 12-Hour Urine Collection

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Background: 24-hour urine sodium excretion is the gold standard for estimating sodium intake. Several equations have been used to estimate 24-hour urine sodium excretion from spot urine samples. However, a validated formula for predicting 24-hour urine sodium excretion from 12-hour urine collection has not been established. This study aims to establish novel equations for predicting 24-hour urine sodium excretion from 12-hour urine collection and to also validate spot urine equations for predicting 24-hour urine sodium excretion.

Methods: 209 adults were recruited from hospital personnel. Participants were asked to perform a 12-hour daytime, nighttime, and a random spot urine collection in 1 day. Pearson correlation was used to compare measured 24-hour sodium excretion to the estimated values from three different methods. A multivariate linear regression analysis was performed to create novel equations. Bland-Altman method was used to estimate bias and agreement between the equations.

Results: The mean 24-hour urine sodium excretion was 4,055±1,712 mg/day (male 4,307±1,694 and female 3,882±1,710 mg/day, P=0.078). The 24-hour urine sodium excretion in non-healthcare workers was higher than in healthcare workers (4,442±1,865 and 3,617±1,406 mg/day respectively, P<0.001). Estimated urine sodium excretion from 3 different equations using spot urine samples showed moderate correlation with actual 24-hour urine sodium excretion (r=0.54, P<0.001 for Kawasaki; r=0.57, P<0.001 for Tanaka; r=0.60, P<0.001 for INTERSALT). Novel equations for predicting 24-hour urine sodium excretion was then developed using variables derived from 12-hour daytime urine collection, 12-hour nighttime urine collection, and random spot urine samples which showed strong correlation with actual measured values; r=0.88, P<0.001, r=0.83, P<0.001, r=0.67, P<0.001 respectively. Bland-Altman plots indicated good agreement between predicted values and actual 24-hour urine sodium excretion using the new equations, with biases for 12-hour daytime urine collection of -0.28 mmol/day (95%CI: -5.09 to 4.53), for 12-hour nighttime urine collection of 0.85 mmol/day (95%CI: -4.86 to 6.56), and for random spot urine sample of 0.90 mmol/day (95%CI: -6.66 to 8.45).

Conclusions: Newly derived equations from 12-hour daytime urine collection and 12-hour nighttime urine collection can accurately predict 24-hour urine sodium excretion.

Funding: Government Support - Non-U.S.

PO2072

Serum Magnesium, Blood Pressure, and Risk of Hypertension: Insights from the Chronic Renal Insufficiency Cohort (CRIC) Study

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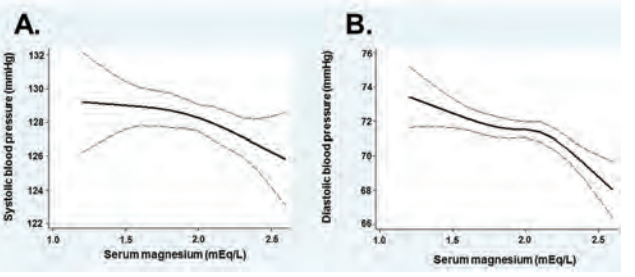
Background: Magnesium (Mg) has been implicated in regulation of blood pressure (BP). Abnormalities in serum Mg (sMg) are common in CKD and ESRD due to decreased intestinal absorption, impaired renal handling and diuretics use. Studies assessing the association of sMg and BP are scarce, and the association of sMg with the risk of developing hypertension (HTN) is unknown.

Methods: We analyzed data from 3,866 participants from CRIC. Adjusted linear regression models assessed the association of sMg with SBP and DBP at baseline and adjusted smoothing splines were fit. Adjusted logistic regression models explored the association of baseline sMg with baseline HTN (CRIC-defined HTN: SBP ≥140 or DBP ≥90 or anti-HTN drug use; AHA-defined HTN: SBP ≥130 or DBP ≥80 or anti-HTN drug use) and sub optimally controlled blood pressure (SBP ≥120 or DBP ≥80). Adjusted cox-proportional hazard models stratified by clinical site explored the association of baseline sMg with incident HTN. All models were adjusted for demographics, CV comorbidities, eGFR, proteinuria, serum albumin, FGF-23, calcium, phosphate, total PTH, Na, K, urine Na, and urine K.

Results: Median sMg was 2.0 mEq/L (25th-75th percentile 1.9 to 2.1 mEq/L). Higher sMg at baseline was associated with lower SBP (-2.63 mmHg, 95% CI-5.01 to -0.25, per 1 mEq/L) and lower DBP (-2.75 mmHg, 95% CI -4.16 to -1.34, per 1 mEq/L) (Fig 1A, 1B). Higher sMg was associated with a lower risk of AHA-defined HTN at baseline (aOR 0.25, 95% CI 0.12-0.55, per 1 mEq/L), a lower risk of sub optimally controlled BP (aOR 0.22, 95% CI 0.10-0.53, per 1 mEq/L) but not with a higher risk of CRIC-defined HTN (aOR 0.77, 95% CI 0.50-1.20, per 1 mEq/L). In time-to-event analyses, higher baseline sMg was associated with a numerically lower risk of incident CRIC-defined HTN (aHR 0.68, 95% CI 0.40-1.13, per 1 mEq/L).

Conclusions: Higher sMg is associated with lower SBP, lower DBP and a nominally lower risk of incident HTN. Monitoring and optimal control of sMg should be considered in patients with CKD for improved BP control.



PO2073

Cardiac Structure and Function and Long-Term Risk of ESKD in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study

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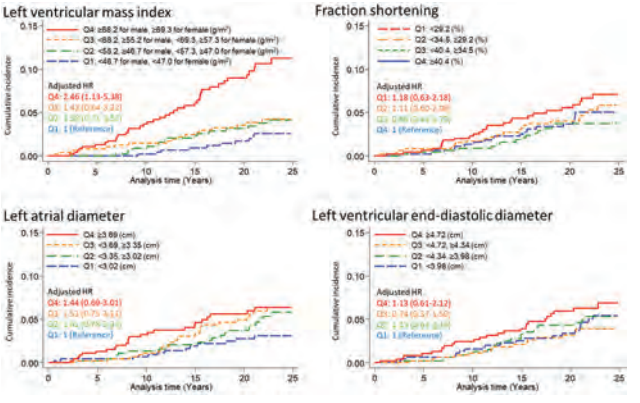
Background: Cardiovascular disease and end-stage kidney disease (ESKD) disproportionally affect African Americans. Whether cardiac structure and function is associated with the risk of ESKD in this population is not well-characterized.

Methods: In 1,929 African American ARIC participants who underwent echocardiography between 1993-1995 (mean age 58.5 [SD 5.6] years, 36% male), we explored the association of left ventricular mass index (LVMI), fraction shortening (FS), left atrial diameter (LAD), and LV end-diastolic diameter (LVEDD) with the subsequent risk of ESKD using Kaplan-Meier method and multivariable Cox models.

Results: During a median follow-up of 22.3 years, 82 participants developed ESKD (incidence rate, 3.0 per 1,000 person-years). The cumulative incidence of ESKD was highest in the top quartile (bottom quartile for FS) of all echo parameters (Figure), although the risk separation was most evident for LVMI. The association of LVMI with ESKD remained significant even after accounting for potential confounders like blood pressure and clinical history of cardiovascular disease (HR, 2.46 [1.13-5.38] in the top vs. bottom quartile). FS, LAD, or LVEDD were not independently associated with ESKD.

Conclusions: Among African Americans, higher LVMI was robustly and independently associated with the risk of ESKD. Our findings support the importance of LVMI or its pathophysiology in CKD progression in African Americans.



PO2074

Myeloperoxidase and the Risk of Atrial Fibrillation in the Chronic Renal Insufficiency Cohort (CRIC) Study

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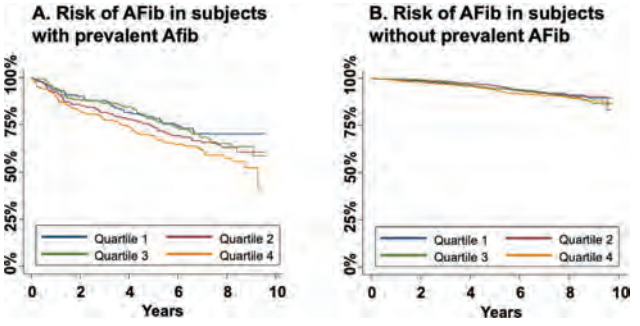
Background: Myeloperoxidase (MPO) catalyzes the formation of reactive oxygen intermediates and is associated with adverse CV outcomes and progression of chronic kidney disease (CKD). We wished to determine the association of MPO with hospitalization for atrial fibrillation (AFib) in patients with baseline CKD.

Methods: We evaluated 3,872 participants with MPO measured at baseline in the CRIC Study, a large prospective multicenter cohort of non-dialysis dependent CKD. The association of MPO with hospitalization due to AFib was evaluated through adjusted Cox proportional hazard models in all study participants, and separately in subjects with and without AFib at baseline. Models were adjusted for age, sex, race, DM, SBP, coronary artery disease, CHF, eGFR (CKD-EPI), proteinuria, ACEi- ARB, beta-blocker and diuretic use.

Results: Mean age was 57.5 years, 55.2% were male and 40.4% were black. In the overall population, MPO was associated with a 15% higher risk of AFib hospitalization (aHR 1.15, 95% CI 1.05-1.27, per 1 SD log transformed MPO). The association of MPO with future Afib hospitalization was predominantly noted in those with a prior history of AFib (n=650; P-interaction<0.01), such that there was a 16% higher risk in those with baseline AFib (aHR 1.16, 95% CI 1.01-1.34, per 1 SD log transformed MPO) (Fig 1A), while there was no significant association for those without baseline Afib (aHR 1.11, 95% CI 0.97-1.28, per 1 SD log transformed MPO) (Fig 1B).

Conclusions: In patients with CKD, higher MPO was associated with an increased risk of hospitalization due to AFib, which appeared to be restricted to those with a prior AFib diagnosis. Whether therapies targeting MPO activity and oxidative stress in this population reduce AFib hospitalizations remains to be tested.



PO2075

The Association Between Pre-Donation Hypertension and Early Post-Donation Systolic Blood Pressure Among Older Living Kidney Donors

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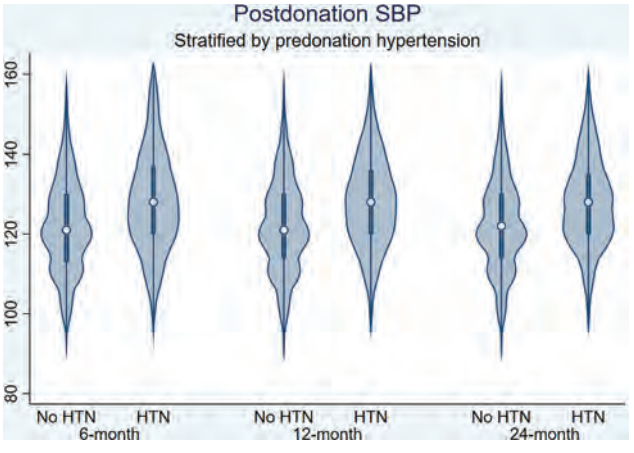
Background: One mechanism underlying predonation hypertension in older (age≥50) living kidney donors is a reduced number of nephrons. The 50% nephron mass reduction associated with donor nephrectomy may exacerbate predonation, controlled hypertension. In light of evolving hypertension guidelines, we aimed to study systolic blood pressure (BP) trajectory in older donors with- vs. without hypertension.

Methods: We conducted a national registry study of 11,969 older living kidney donors from 2010-2018. We modeled the association between predonation hypertension and postdonation systolic BP using a mixed linear model with donor-level random intercept adjusting for age, sex, race, predonation systolic BP, BMI, and year of donation. We modeled odds of having 6-month postdonation systolic BP >130 mmHg and >140 mmHg using multivariable logistic regression.

Results: 1,161 of 11,969 older donors (9.7%) had hypertension. Median (IQR) predonation systolic BP was 130 mmHg (122-140) among donors with hypertension vs. 124 mmHg (115-132) among those without (p<0.001). After adjustment for baseline characteristics including predonation systokic BP, hypertension was associated with a $_{1.8}2.4_{3.0}$ mmHg increase in postdonation systolic BP (p<0.001). Hypertension was associated with 39% higher odds of having 6-month postdonation systolic BP >130 mmHg (aOR=$_{1.20}1.39_{1.61}$, p<0.001) and 50% higher odds of having 6-month postdonation systolic BP >140 mmHg (aOR=$_{1.25}1.50_{1.82}$, p<0.001).

Conclusions: Predonation hypertension was associated with higher risk of uncontrolled 6-month postdonation systolic BP among older donors, even after adjusting for predonation systolic BP. Our findings call for programs to monitor postdonation systolic BP in donors with hypertension to ensure adequate BP control following nephrectomy.

Funding: NIDDK Support



Postdonation Systolic BP Trajectories in Older Donors with vs. without Predonation Hypertension

PO2076

Temporal Trends of the Burden of CKD Among Hospitalized Aortic Stenosis Patients in the Province of Quebec, Canada

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Background: Aortic stenosis (AS) is associated with valvular calcifications which are highly prevalent in chronic kidney disease (CKD). The aim of this study was to describe the temporal trends of comorbid CKD status in patients hospitalized for AS and evaluate the impact of these two conditions on 1-year mortality in the province of Quebec, between 2000 and 2017.

Methods: Using the Quebec Integrated Chronic Disease Surveillance System, we identified patients ≥ 20 years with incident AS using ICD-9 and ICD-10 codes, in the hospital discharge database. We then combined hospital discharges and physician billing claims databases to identify patients with comorbid CKD status in the two years prior to the AS diagnosis. Three subgroups of CKD status were considered: 1) non-CKD, 2) pre-dialysis and 3) dialysis. To allow comparison over time, direct adjustment using age distribution of the 2016-2017 AS population was used for proportion, 1-year all-cause and cardiovascular mortality.

Results: We included 108,780 patients with incident AS (Women: 51.8%; mean age (±SD): 76.4 ±11.7; non-CKD: 74.2% (n=80,768); pre-dialysis: 24.6% (n=26,809); dialysis: 1.1% (n=1,203). During the study period, the age-adjusted proportion of AS patients with non-CKD comorbid status decreased by 14% (80.7% [95% CI 77.6-84.0] to 69.6% [95% CI 67.2-71.9]). Inversely, the age-adjusted proportion of AS patients with pre-dialysis and dialysis comorbid status increased by 58% (18.5% [95% CI 16.9-20.2] to 29.3% [95% CI 27.8-30.9]) and 46% (0.76% [95% CI 0.5-1.1] to 1.1% [95% CI 0.8-1.4]), respectively. Age-adjusted 1-year all-cause and cardiovascular mortality decreased over time but remained higher in patients with comorbid CKD. In 2015-2016, age-adjusted relative risk (RR) of 1-year all-cause mortality was significantly higher in pre-dialysis (RR=1.56 [95% CI 1.44, 1.69]) and dialysis (RR=2.04 [95% CI 1.62-2.61]) compared to non-CKD patients. Age-adjusted RR of 1-year cardiovascular mortality was also significantly higher in pre-dialysis (RR=1.83 [95% CI 1.66-2.03]) and dialysis (RR=2.28 [95% CI 1.68-3.09]) compared to non-CKD patients.

Conclusions: Proportion of patients with incident AS and comorbid CKD increased from 2000 to 2017. One-year all-cause and cardiovascular mortality improved over time but remained higher in AS patients with comorbid CKD.

PO2077

Troponin Level in Relation to Angiographic Coronary Artery Disease in CKD Patients

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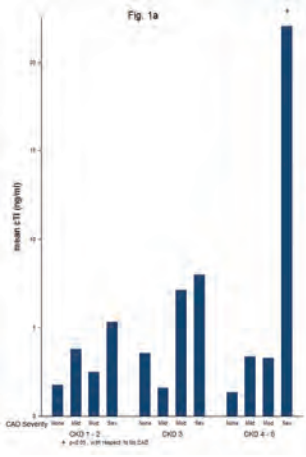
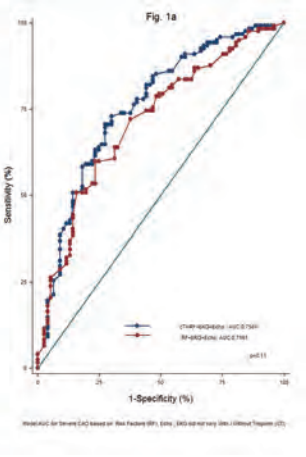
Background: An association between cardiac troponin I (cTI) in the diagnosis of angiographic coronary artery disease(CAD) is unclear in the CKD population. We evaluated the association between cTI to findings of angiographic significant CAD in CKD patients with traditional risk factors.

Methods: Data was collected from left cardiac catheterizations (LCHs) performed between 2006 -2017 at Jacobi Medical Center. CAD outcomes were defined as:none, mild(<50% stenosis), moderate(50-69% stenosis), severe (≥70% stenosis of any major epicardial artery). ROC characteristics of cTI as biomarker for severe CAD was performed in patients with CKD stages 3-5. C-Statistic/AUC were used to compare pretest probabilities for severe CAD based on CAD risk factors (age, race, HTN, HLD, DM, smoking), abnormalities on ECHO and ECG, cTI level, and CKD stage.

Results: 798 LHCs were included. Fig1a shows that cTI level is only significantly higher in severe CAD as compared to no CAD among CKD 1-2 patients. ROC showed cTI >0.3ng/mL displayed peak sensitivity (59%), specificity (62%). Multivariate analysis for predictors of severe CAD among 223 CKD patients was stratified by cTI >0.3 and cTI <0.3. Among cTI <0.3 subgroup, age >65(OR 4.6, 95% CI 1.55-13.9, p=0.006), segmental wall motion abnormalities(OR 6.46; 95% CI 1.49-27.9, p=0.012) and eGFR<30(OR 2.92; 95% CI 0.94-9.00; p=0.06) were associated with severe CAD. Among cTI>0.3 subgroup, none of the clinical factors were significantly associated with severe CAD. Fig1b shows that the addition of dichotomized cTI > or < 0.3 to CAD risk factors did not significantly change the AUC value.

Conclusions: cTI levels are not associated with different levels of CAD in patients with eGFR <=60. The addition of cTI>0.3 does not alter the predictive value of severe CAD when other cardiac risk factors are considered. It will be important to study if the change in cTI during a cardiac event would be more predictive in the CKD population.





PO2078

Pediatric vs. Adult Ambulatory Blood Pressure Monitoring (ABPM) Criteria for the Diagnosis of Hypertension (HTN) and Detection of Left Ventricular Hypertrophy (LVH) in Adolescents

Kumail Merchant,[1] Paras P. Shah,[2] Pamela Singer,[1] Laura J. Castellanos,[1] Christine B. Sethna.[1,2] *[1]Cohen Children's Medical Center, Queens, NY; [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

Background: Normative values for clinic blood pressure (BP) measurements in adolescents were recently updated to align with adult HTN guidelines (CPG 2017). However, the most widely accepted pediatric normative values used to diagnose HTN by ABPM criteria have not been updated. The objective of this study was to compare pediatric ABPM criteria (pHTN) vs. adult ABPM criteria (aHTN) for the diagnosis of HTN and detection of LVH in adolescents.

Methods: ABPM and ECHO reports from adolescents age 13-21 years performed from 2015-2019 at a single center were analyzed. The concordance of HTN diagnosis based on pHTN (AHA 2014) was compared to aHTN from ACC/AHA 2017 (overall BP ≥125/75mmHg, wake BP ≥130/80mmHg, sleep BP ≥110/65mmHg) using Cohen's kappa statistic. Logistic regression adjusted for body mass index (BMI) z-score and receiver operating curves (ROC) were used to compare the ability of pHTN vs. aHTN to predict LVH (left ventricular mass index [LVMI] >95th%ile reference values and LVMI >51g/m$^{2.7}$).

Results: Of 306 adolescents (15.9±1.86 years, 73.5% male), 140 (45.8%) had HTN based on pHTN compared to 228 (74.5%) based on aHTN. There was poor agreement in the diagnosis of HTN between pHTN and aHTN (59.3%, N=137, kappa 0.41). 1.0% (N=3) had HTN by pHTN only while 29.7% (N=91) had HTN by aHTN only. Although a higher prevalence of LVH was captured by aHTN only, 9 (5.6%) adolescents who had LVH >95th%ile did not have HTN by either criteria. In logistic regression, adjusted for BMI z-score, there were no significant differences between pHTN and aHTN in the detection of LVH >95th%ile (OR 1.24, CI: 0.66-2.31, p=0.51) or >51g/m$^{2.7}$ (OR 1.06, CI: 0.47-2.40, p=0.89). ROCs for pHTN were not significant for detecting LVH >95th%ile (0.50, p=0.91) or >51g/m$^{2.7}$ (0.55, p=0.45). However, the ROC for aHTN was significant for detecting LVH >95th%ile (0.59, p=0.045) but not >51g/m$^{2.7}$ (0.63, p=0.07).

Conclusions: There is poor concordance between pHTN and aHTN for the diagnosis of HTN in adolescents. aHTN appears to better predict LVH than pHTN, although neither criteria diagnosed all patients who had LVH. A consideration to align the ABPM criteria for the diagnosis of HTN in adolescents with adult guidelines is warranted.

PO2079

Effect of Psychiatric Diagnosis and Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) Use on BP Using 24-Hour Ambulatory Blood Pressure Monitoring (ABPM)

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Background: Hypertension (HTN) and psychiatric disorders frequently co-exist. Psychiatric conditions and their treatment by SSRIs/SNRIs affect serotonin & norepinephrine and may cause variation in blood pressure (BP). There is limited data to assess this variation by using ABPM.

Methods: Subjects who underwent psychiatric evaluation & ABPM within six month of each other between 1/2012 to 12/2017 were identified. Demographics, co-morbidities, medications, ABPM, lab data were retrospectively collected. Subjects were divided into group–subjects with no psychiatric diagnosis & no psychiatric medicine(Group 1), subjects with psychiatric diagnosis & on SSRIs/SNRIs(Group 2) and subjects with psychiatric diagnosis & on no medication(Group 3). BP systolic & diastolic levels(daytime, nighttime) were compared between groups controlling for age, sex, race, HTN, DM and smoking. Single and multivariable linear regression models were used to analyze group differences.

Results: Total of 475 subjects met inclusion criteria–Group 1=135, Group2=232, and Group3=108. First, Group 1 was compared with Group 2 for daytime systolic & diastolic, nighttime systolic & diastolic BP. In multivariable analysis adjusted for age, sex, race, HTN, DM, and smoking, subjects in Group 2 had higher nighttime systolic BP(122.7vs110.5 mm;β 8.36; 95%CI 4.21,12.51;P<0.0001) and nighttime diastolic BP(68.2vs63.4 mm;β 4.6;CI1.92,7.29;P=0.001). To determine whether higher nighttime systolic & diastolic BP in Group 2 were due to psychiatric diagnosis or effect of SSRIs/SNRIs, we compared ABPM between Group1 & Group3. In adjusted model, there was no statistically significant difference between Group 1 & 3 for daytime or nighttime systolic or diastolic BP suggesting higher nighttime BP in Group 2 was associated with SSRIs/SNRIs use.

Conclusions: In this single center retrospective study, use of SSRIs/SNRIs was associated with significantly higher nocturnal systolic & diastolic BP among subjects with psychiatric diagnosis using SSRIs/SNRIs. This may be due to ongoing sympathetic activation during sleep with serotonin & norepinephrine with SRRIs/SNRIs use. Further prospective studies using ABPM are needed to determine the risk of nocturnal hypertension with SSRIs/SNRIs use that could adversely impact cardiovascular outcomes.

PO2080

Obesity-Related Renal Damage in Adolescent Women: Body Surface Area Matters

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Background: Obesity is a potentially modifiable risk factor for the development and progression of kidney disease, both in adults and children. We aim to assess the prevalence of early signs of kidney dysfunction among overweight and obese adolescents by examining routine labs including creatinine for hyperfiltration and albuminuria.

Methods: De-identified electronic health record (EHR) data were extracted for female adolescents aged 12-21 years, who received health care services from 1/1/2011 to 12/31/2015 in NYC from 12 academic health centers and community health centers that are part of PCORnet NYC Clinical Data Research Network (NYC-CDRN). Data were analyzed using SAS (v 3.2.5) on 60,549 unique subjects. Patient characteristics overall and by subgroups were examined using standard summary statistics. BMI groups were coded according to NHANES as underweight, normal weight, overweight or obese. Multiple linear regression analyses will control for covariates.

Results: Mean creatinine values were similar between normal weight, overweight and obese BMI groups, yet after calculating eGFR and adjusting for BSA, significant and alarming differences appeared. Obese adolescent women had significantly higher eGFR, estimated by CKD-EPI and the Schwartz formula according to age, compared to normal weight subjects. Only subjects in the obese group (BMI>30) exhibited hyperfiltration (eGFR>135 ml/min). Mean systolic and diastolic blood pressure across the four BMI groups increased linearly with a statistically significant trend (p<0.0001), even though means were within normal limits.

Conclusions: Obese adolescent women present with significant alteration in kidney function that without intervention will lead to ESRD, and adverse outcomes associated with the deleterious effects of adiposity. Awareness should be raised to consider body size when estimating GFR in adolescents.

Funding: Other NIH Support - This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through The Rockefeller University, Grant # UL1 TR001866, The Sackler Center for Biomedicine at The Rockefeller University, The Sackler Institute for Nutritional Science at the New York Academy of Sciences, and the Patient-Centered Outcomes Research Institute (PCORI) PCORnet Contract # CDRN-1306-03961., Private Foundation Support

PO2081

Urinary Magnesium Predicts Risk of Cardiovascular Disease in Pre-Dialysis CKD Patients

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Background: 24h Urinary magnesium concentration (24h UMg), an indicator of intestinal magnesium absorption, may provide a better insight in the connection of CKD progression.

Methods: We examined 3179 participants aged 18 to 74 years pre-dialysis patients in the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) study. We performed a time-to-event analysis of the data using Kaplan-Meier Survival model, Cox proportional hazard and competing risks Fine and Gray sub-distribution hazard models.

Results: During the median follow-up of 4.19 (IQR 3.432-5.09) years, lower incidence rate of ESRD events was observed with increases in 24h UMg (Figure 1). Higher incidence rate of CVD events was seen with increase in 24 h UMg (Figure 2). After adjustment for demographic and traditional ESRD risk factors, 24h UMg was strongly associated with risk of CVD (HR of 1.509 [95% CI 1.031-2.208])(Table 1).

Conclusions: 24h UMg risk variants display a modest association with CVD in pre-dialysis CKD patients.

Funding: Government Support - Non-U.S.

Table 1 Association of 24h UMg with CVD events among pre-dialysis CKD patients

UMg ratio	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Total CKD patients (n= 3179)		
<3.05	1.00 (Ref)	1.00 (Ref)
≥3.05	1.466(1.027, 2.093)	1.509(1.031,2.208)
p for trend	0.035**	0.034**

** Statistically significant at 0.05.

Model1 Age, gender

Model2 Age, gender, CVD, HBP, DM, drinking, smoking, UA, HCO3-, TC, LDL, eGFR, BMI, ACR, iPTH, HGB, sP, sMg, sCa, sK, sNa, UNa, UK

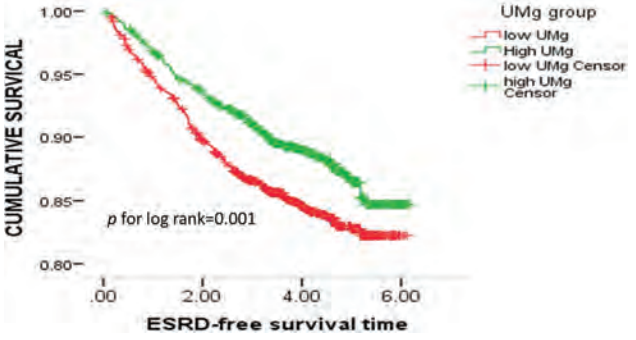

Figure 1. Kaplan-Meier curve for ESRD events according to binary of 24h UMg

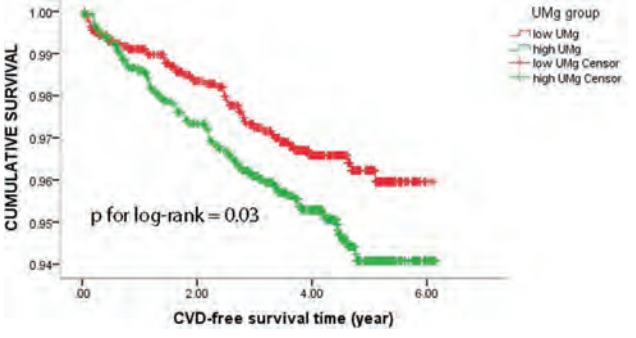

Figure 2. Kaplan-Meier curve for CVD events according to binary of 24h UMg

PO2082

Non-Dipping and Left Ventricular Hypertrophy Among Adolescents with White Coat Hypertension

Paras P. Shah,[1,2] Kumail Merchant,[2] Pamela Singer,[2] Laura J. Castellanos,[2] Christine B. Sethna.[2,1] *[1]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [2]Cohen Children's Medical Center, Queens, NY.*

Background: Recent literature suggests that white-coat hypertension (WCH) may not be a benign phenomenon. In adults, WCH has been associated with increased cardiovascular disease (CVD) risk. Additionally, non-dipping has been independently linked to left ventricular hypertrophy (LVH) and CVD. However, the prevalence and prognostic impact of non-dipping in WCH in the pediatric population remains unclear. The objective was to determine the prevalence of non-dipping in adolescents with WCH and to examine the association of dipper status with left ventricular mass index (LVMI) and LVH.

Methods: Ambulatory blood pressure monitoring (ABPM) and echocardiogram (ECHO) reports from adolescents age 13-21 years performed from 2015-2019 at a single center were analyzed. WCH was defined as office blood pressure (BP) >95th%tile and mean ABPM <95th%tile (AHA 2014). Those with hypertension or pre-hypertension were excluded. Non-dipper status was defined as <10% drop in nocturnal BP. Non-dippers with an increase in nocturnal BP were classified as reverse dippers. T test and chi-square were used to compare LVMI and LVH (defined by LVMI >95th%ile reference values and LVMI >51g/m$^{2.7}$) by dipper status. Linear/logistic regression adjusted for age, sex and body mass index (BMI) z-score were used to determine the association of non-dipping with LVMI and LVH.

Results: Of 49 adolescents (15.7±1.7 years, 84% male), 17 (34.7%) were identified as non-dippers. Of the non-dippers, 4 (23.5%) exhibited reverse dipping. Of those with LVMI >95th%ile, 3 (33.3%) were non-dippers and 3 (23.1%) were dippers (p=0.68), and the only individual (11.1%) with LVMI >51g/m$^{2.7}$, was a non-dipper (p=0.24). There was no significant difference in LVMI between dippers and non-dippers (35.9±8.8 vs. 34.2±6.8 g/m^2, p=0.63). There were no significant associations between dipper status (reference dipper) and LVMI (β 0.67, CI: -7.92-9.26, p=0.87) or LVH by LVMI >95th%ile (OR 0.72, CI: 0.08-6.74, p=0.78) in adjusted regression models.

Conclusions: Although non-dipping is not associated with LVMI or LVH in adolescents with WCH, the fair prevalence (34.7%) of non-dipping among this population is of note. Given adult studies demonstrating the progression of non-dipping to poor CVD outcomes, these potentially high-risk patients should be monitored closely.

PO2083

Left Atrial Strain Measurements Are Associated with Cardiovascular Outcomes in Patients with ESRD

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Background: Left atrial (LA) strain is a marker of diastolic dysfunction, heart failure and atrial fibrillation that has been validated in populations without chronic kidney disease. There are few studies of LA strain in patients with end-stage renal disease (ESRD), among whom cardiovascular (CV) mortality is high and there are no accepted methods of CV risk stratification. We sought to examine associations of LA reservoir strain with CV hospitalization and mortality in a cohort of patients with ESRD on dialysis, and to investigate prognostic utility of strain measurements for CV outcomes.

Methods: 190 ambulatory participants with ESRD on dialysis in the Cardiac, Endothelial Function and Arterial Stiffness in ESRD (CERES) study underwent 2D echocardiography at one study visit. The composite outcome, CV hospitalization or death, was adjudicated over a median of 2 years. Hospitalizations attributed to missing dialysis were not counted as events. LA and left ventricular (LV) structure and function were captured by a single technician, and de-identified images were read by a single reader using GE EchoPac software. Associations of LA reservoir strain with the composite outcome were analyzed with cox survival analyses, adjusting for age, gender, comorbidities, and systolic blood pressure.

Results: Mean age was 56 years, 1/3 were women, and the median time since dialysis initiation was 3.5 years. 45% were diabetic and 14% had a history of heart failure. Participants were relatively euvolemic, based on well-controlled blood pressure and weight. Mean (SD) LA volume index was 40ml/m^2(±12), mean LA reservoir strain was 24%(±6.9). There were 61 events: 40 hospitalizations and 21 deaths. In the adjusted model, HR (95%CI) per SD LA volume index was 1.4(1.04, 1.9); LA reservoir strain HR(95%CI) per SD was 0.67(0.47, 0.94). A risk model including age, LA reservoir strain and LV global longitudinal strain had a c-statistic(95%CI) of 0.72(0.63, 0.81) for the composite outcome.

Conclusions: Our results suggest that LA strain is independently associated with CV hospitalizations and death among patients with ESRD on dialysis. Strain measurements have the potential to contribute to CV risk stratification in this population. Larger studies are necessary to validate our findings.

Funding: NIDDK Support

PO2084

Under Diagnosis of Pediatric Hypertension

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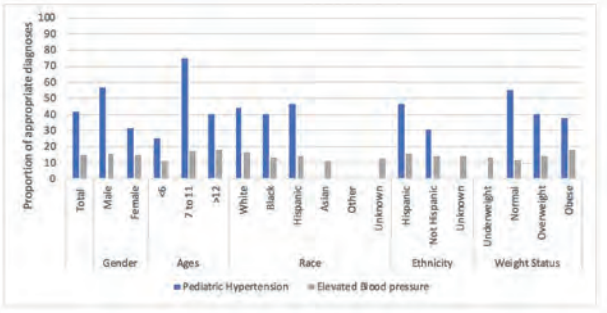
Background: Pediatric hypertension is associated with target organ damage in children and cardiovascular morbidity in adults. Therefore, prompt diagnosis and treatment are critical. Application of clinical practice guidelines is inconsistent.

Methods: Using electronic health record data (from 8 community centers), we evaluated the proportion of children (3-18 years) with elevated blood pressures (≥90th percentile) who were appropriately diagnosed as either hypertension or elevated blood pressure over 1 year (2016-17), and provided guideline directed follow-up; by age, sex, race/ethnicity and weight.

Results: The sample included 6233 children with elevated blood pressure, 15% were appropriately diagnosed. These children were more likely to be older, white, and obese. 55 children met criteria for hypertension with 23 being appropriately diagnosed, there was no difference by patient characteristics. Of children with blood pressure ≥95th percentile, 13% had follow-up within 1 month; they were more likely to be older, female, of Hispanic ethnicity or 'other' race. Of children with blood pressure ≥90th percentile, 41% had follow-up within 6 months, and were more likely to be older, of either white, Hispanic, Asian race or Hispanic ethnicity.

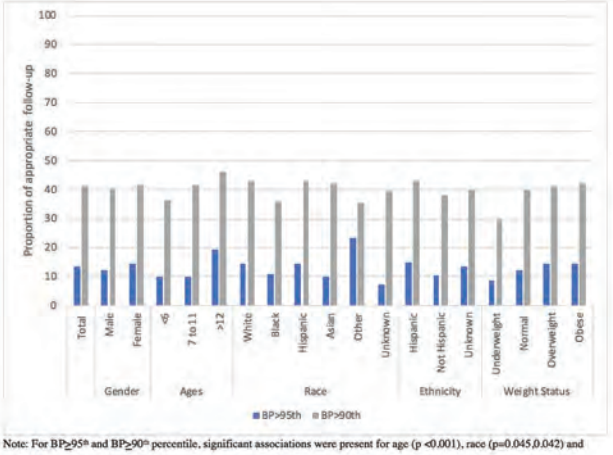
Conclusions: We found persistent underdiagnosis of pediatric hypertension and elevated blood pressure as well as disparities in the diagnosis of elevated blood pressure and guideline-directed follow-up among diverse children in a community setting. New strategies are needed to improve compliance with guidelines.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute of the National Institutes of Health; National Institute on Drug Abuse



Note: For elevated blood pressure, significant associations present for age (p<0.001), race (p=0.03) and weight status (p<0.001).

Proportion of children who are appropriately diagnosed



Note: For BP≥95th and BP≥90th percentile, significant associations were present for age (p <0.001), race (p=0.045,0.042) and ethnicity (p=0.006,0.036).

Proportion of children with appropriate follow-up

PO2085

Associations of Blood Pressure Variability with Cardiovascular Events, Death, and ESKD in Patients with CKD

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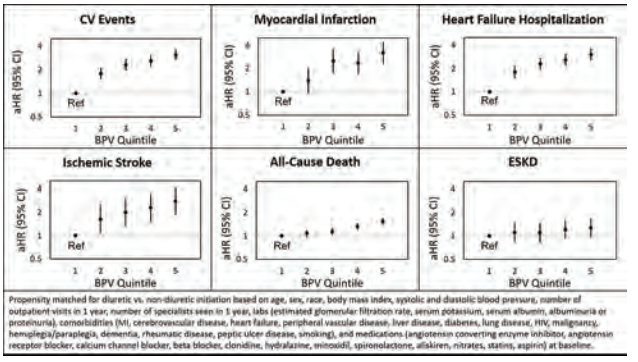
Background: Visit-to-visit blood pressure variability (BPV) is associated with cardiovascular (CV) events in individuals with chronic kidney disease (CKD) stages 3-5. We examined the associations of BPV with CV events, death, and end-stage kidney disease (ESKD) among veterans with CKD stages 1-5 and hypertension, and if treatment with a thiazide or loop diuretic modified these associations.

Methods: In a matched cohort study, patients seen between 2010-2016 with non-dialysis CKD and hypertension on single-agent therapy with a non-diuretic were propensity matched 1:1 for initiation of a loop or thiazide diuretic *vs.* other antihypertensive class as their second agent. BPV, defined as the coefficient of variation of outpatient systolic blood pressure over 6 months after prescription of the second antihypertensive, was divided into quintiles. Cox proportional hazards regression measured associations of BPV with time to CV events (first among myocardial infarction [MI], hospitalization for heart failure, or ischemic stroke), each component of the primary outcome, all-cause death, and ESKD.

Results: We included 31,394 new users of diuretics and 31,394 patients initiating other agents. Over a median (IQR) follow up time of 939 (404-1,606) days, there were 7,326 CV events, 16,567 deaths, and 2,029 ESKD events. Higher BPV was associated with composite CV events (**Figure**). Diuretic exposure attenuated these associations at the fourth and fifth quintiles of BPV (interaction *P*=.03 at the 4th and .04 at the 5th quintile). BPV was also associated with MI, heart failure, stroke, and death, but not with ESKD (**Figure**). Diuretic treatment did not modify these associations.

Conclusions: BPV was associated with CV events and all-cause death but not ESKD in patients with CKD and hypertension. Diuretic use attenuated the association of BPV with CV events at the highest quintiles of BPV. Future studies should test whether diuretics improve CV outcomes in those with high BPV.

Funding: Private Foundation Support



Propensity matched for diuretic vs. non-diuretic initiation based on age, sex, race, body mass index, systolic and diastolic blood pressure, number of outpatient visits in 1 year, number of specialists seen in 1 year, labs (estimated glomerular filtration rate, serum potassium, serum albumin, albuminuria or proteinuria), comorbidities (MI, cerebrovascular disease, heart failure, peripheral vascular disease, liver disease, diabetes, lung disease, HIV, malignancy, hemiplegia/paraplegia, dementia, rheumatic disease, peptic ulcer disease, smoking), and medications (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, beta blocker, clonidine, hydralazine, minoxidil, spironolactone, aliskiren, nitrates, statins, aspirin) at baseline.

PO2086

Importance of Continuous Blood Pressure Monitoring in CKD

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Background: A strong relationship exists between CKD and high blood pressure (BP), tight BP control is essential for delaying CKD progression and improving cardiovascular outcome. Automated blood pressure monitoring (ABPM) is associated with hypertension-related target-organ damage and cardiovascular outcomes compared with office-based BP in general population.

Methods: We performed a prospective study in CKD. Heart ultrasound and ABPM were performed at inclusion. Normative values for ABPM were defined according to AHA recommendation from 2019. Medical data were recorded for at least one year or until death. The aim was to analyze the correlation between ABPM and left ventricular (LV) changes and cardiovascular outcome.

Results: We included 339 pts (171F, mean age 60.1±14): 15.9% stage 1/2, 31.8% stage 3, 19.7% stage 4. 66 were in HD, 24 in PD. Prevalence of increased BP readings was higher in advanced CKD- 21.5% in stage 1/2, 56.7% in stage 5. Mean diastolic load was higher in LV hypertrophy (35.6±29 *vs* 19.7±19.6 mmHg, p<0.05). We found a negative correlation between mean arterial pressure (MAP) and GFR (r=-0.457, p<0.05). MAP was higher in PD compared to HD (109.1 ± 17.6 *vs* 98.9±9.3 mmHg, p=0.01). Serum albumin had a weak negative correlation (r=-0.245, p=0.01) and fibrinogen a weak positive correlation (r=0.266, p=0.02) with mean systolic BP, and mean LDL-cholesterol (as an indirect marker of malnutrition) was lower in non-dipper (95.4±35.4 vs. 130.5±27.2 mg/dl, p<0.05), suggesting a negative influence on BP control of malnutrition and inflammation. 225 (72.8%) were non-dipper, with 56 being extreme non-dipper. Anemia (OR 4.5, p=0.001) and C-reactive protein >10 mg/l (OR 3.7, p<0.001) induced a higher risk of non-dipper profile. We had 78 cardiovascular deaths (23.0%). Independent predictive factors for cardiovascular death were male gender, calcium x phosphate>55 mg^2/dl^2 and extreme non-dipper.

Conclusions: This study demonstrates an increased prevalence of high BP readings and non-dipper profile especially in advanced CKD. Malnutrition and inflammation were associated with non-dipper pattern and extreme non-dipper was an independent risk factor for cardiovascular death. ABPM monitoring may be useful in optimizing BP control and improving cardiovascular outcome in CKD.

PO2087

Ambulatory Blood Pressure Monitoring Patterns in Children and Adolescents with Lupus Nephritis

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Background: Hypertension (HTN) is often underdiagnosed and undertreated. Masked HTN can reach 49% in chronic kidney disease (CKD) in children. The prevalence of HTN in systemic lupus erythematosus (SLE) varies from 30 to 77%. A small study demonstrated that children with SLE are prone to have blunted dipping. Nocturnal HTN and blunted dipping are independent predictors for all-cause cardio-vascular morbidity/mortality, independent of 24-hr systolic blood pressure (BP) levels.

Methods: Patients (<21 years) with lupus nephritis (LN) were enrolled. Clinical, laboratory, ambulatory blood pressure monitor (ABPM) and echo were reviewed. Max dose of steroids was 20 mg (1 patient). Variables included age, gender, ethnicity, CKD stage, BMI, MMF level, complement levels, dsDNA, proteinuria.

Results: Of the 10 patients (8 F, 2 M), 8 were Hispanic, 2 African American, 9 had CKD stage 1, 1 had CKD stage 2, and mean age was 16.2 y (11-20y). Class III LN was in 4 patients, class IV and V – in 3 patients each. BP during the previous 3 visits were normal in 8 patients and 6 patients were on BP medications. Based on ABPM data, 3 of 6 treated patients had uncontrolled HTN. Of the 4 patients without BP treatment 2 had pre-HTN. Blunted dipping was seen in 6 patients. Echo was done for 5 patients with ABPM

abnormalities. Left ventricular mass index (LVMI), relative wall thickness (RWT) and ejection fraction were normal. Left ventricle was dilated in 1 patient. Obesity, dsDNA, MMF level, proteinuria, use of steroids and antihypertensives did not differ significantly between the patients with and without BP abnormalities.

Conclusions: Masked HTN and blunted nocturnal dipping is common in adolescents with SLE and can be missed if ABPM is not applied in clinical practice. Additional studies are required to find risk factors and management strategy.

Patient	Obesity	LN class	Urine protein creatinine ratio, g/g	Prednisone, mg daily	Office BP	BP medications	ABPM	Blunted dipping	LVMI, g/m2.7	RWT
1	-	4	0.2	15	Normal	-	Normal	+		
2	+	3	1.8	0	Normal	-	Normal	+	47	0.28
3	+	4	0.3	0	Normal	+	Controlled HTN	-		
4	+	3	0.1	7.5	Normal	+	Controlled HTN	-		
5	-	5	0.1	10	Normal	+	Controlled HTN	+	37	0.32
6	-	5	0.1	0	Normal	-	Pre-HTN	-		
7	-	3	0.1	0	Normal	-	Pre-HTN	+	29	0.37
8	+	3	0.1	5	Normal	+	Uncontrolled HTN	-	33	0.38
9	-	5	0.4	20	HTN	+	Uncontrolled HTN	+		
10	-	4	0.8	0	HTN	+	Uncontrolled HTN	+	31	0.33

PO2088

Hypertension with Target Organ Damage and Discrepancy Between Ambulatory Blood Pressure Monitoring and Exercise Blood Pressure Results: A Pediatric Case Series

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Introduction: The prevalence of hypertension is increasing worldwide in the Pediatric population. Ambulatory blood pressure monitoring (ABPM) is recommended by the American Academy of Pediatrics (AAP) for the screening and management of pediatric hypertension. ABPM has been shown to correlate with target organ damage and provides a more reliable assessment of blood pressure (BP) control compared to clinic BP. Exercise stress testing (EST) is not recommend by the AAP for the evaluation of hypertension although anecdotally, it is used frequently by pediatric cardiologists. Despite this, reports in adults show an association between exaggerated exercise systolic blood pressure (EESP) and cardiovascular mortality and morbidity, masked hypertension, and target organ damage. We report 2 pediatric patients with hypertension and evidence of target organ damage, but with a discrepancy between their ABPM and EST BP results.

Case Description: See table below.

Discussion: We describe 2 adolescent cases of hypertension diagnosed by clinic BP and target organ damage but not confirmed by ABPM. Both patients had EST done as part of their evaluation because they were first seen by cardiologists at the study center who frequently employ EST as part of evaluation for hypertension. The cut-off value of 180mmHg for EESP was employed in this report as a previous study had identified 181 mmHg as the most discriminatory systolic BP threshold for predicting hypertension at follow-up. The discrepant results between the ABPM and EST BP in our patients with target organ damage may indicate that multiple diagnostic tools may be required to confirm the diagnosis of hypertension. Both tests could be viewed as complimentary as ABPM is not recommended during exercise which is a part of everyday life. Furthermore, a normal ABPM may not exclude a diagnosis of hypertension in patients with elevated clinic BP and target organ damage. Further studies are needed to confirm these findings in a larger population, and to better understand how these 2 tests may perhaps be used adjunctively to diagnose hypertension.

Case Description

Cases	Age/Sex/Race	Clinical presentation	Weight/Height/BMI/Clinic BP	Cardiology Work-up	Renal Work-up	Treatment and Outcome
1	16y/Male/Hispanic	Elevated BP	86kg/173.7cm/ 28.5kg/m2/96th percentile)/131/81mmHg	EKG: NSR ECHO: Mild LV hypertrophy EST: Protocol: BRUCE (peds) Max BP: 191/61 mmHg Max workload: 13.4 METS Exaggerated BP response	Cr: 0.85mg/dl Urinalysis: Normal Pr/Cr: 0.08 cANCA: <1:20 ABPM: Normal Retroperitoneal USS with doppler: Normal	He received HCT for about 1 month and continued lifestyle modification. Resolution of PAMM lesions and Retinal vein occlusion. His BP at his last visit was 125/80mmHg.
2	14y/Male/African American	Fainting during exercise	70.9kg/169.3cm/ 24.7kg/m2/93rd percentile)/130/82mmHg	EKG: NSR ECHO: Mild LVH with increased LV mass-154g/m2. Protocol: BRUCE (Peds) Max BP: 209/051 mmHg Max workload: 11.6 METS Repeat EST BP:192/62mmHg.	Cr:0.87mg/dl Urinalysis: Normal Pr/Cr:0.05 Aldosterone:4.2ng/dl Renin:0.2ng/ml/hr Retroperitoneal USS with doppler: Normal	There was resolution of LVH and increased LV mass on repeat ECHO prior to starting antihypertensives. Low dose lisinopril was started due to EESP. His BP at last visit was 144/85mmHg.

PAMM: Paracentral acute middle maculopathy, HCT: Hydrochlorothiazide

PO2089

Individualized Hypertension Management in CKD

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Background: The prevalence of hypertension (HTN) in chronic kidney disease (CKD) patients ranges from 60% to 90% with up to 50% having drug resistant hypertension.

Methods: We instituted a practice improvement project comparing hypertension Standard Care (Group B) to an Individualized Protocol (Group A) in non-dialysis CKD patients referred to our nephrology practice. The Individualized Protocol used noninvasive impedance cardiography (NICAS) and central arterial pressure waveform analysis (SphygmoCor) to define the hemodynamic state: vasoconstricted, hyperdynamic, or mixed. Recommendations for pharmacologic interventions were guided by the hemodynamic state, however, choice of specific drugs was left to the nephrologist. Group A nephrologists were trained to use the Individualized Protocol, and hypertensive patients were assigned to groups A or B during an initial 6-month period, then followed for 6 months (endpoint).

Results: There were 90 and 21 patients in groups A and B, respectively. At baseline, demographics were similar in both groups (Table 1). At endpoint, Group A had more patients at targeted blood pressure (BP) (55.6% vs 33.3% at 140/90 mmHg; 21.1% vs 19% at 130/80 mmHg), and larger reduction in both brachial and central BP parameters (Table 2). The mean (SD) of number of office visits were 3.1(1.0) and 2.9(1.1), in Groups A and B, respectively. In Group A, mean aorta compliance was increased 23.3% and 1.7% in the subgroups that met and did not meet target BP, respectively. Mean number of medications at baseline/endpoint were 1.7/2.6 and 1.9/2.0 in groups A and B, respectively. At endpoint, Group B had negligible change in distribution of drug classes, while Group A had significant increased use of calcium channel blockers (dihydropyridine) and beta-blockers.

Conclusions: Impedance cardiography is a simple, noninvasive method for evaluating underlying hemodynamic drivers of HTN. Hypertension management is more effective when guided by hemodynamic state.

Variable at Baseline	Group A (N = 90)	Group B (N = 21)
Age, mean (SD)	61.3 (15.9)	63.7 (10.7)
Female, N (%)	44 (48.9%)	13 (61.9%)
CKD 1-5, N	65 (72.2)	14 (66.7%)
SBP, mean (SD) mmHg	163.0 (16.4)	162.6 (16.4)
DBP, mean (SD) mmHg	89.9 (12.4)	88.4 (12.9)
MAP, mean (SD) mmHg	114.0 (10.5)	112.7 (10.4)
Central SBP, mean (SD) mmHg	142.2 (20.7)	142.7 (16.3)
Central DBP, mean (SD) mmHg	90.7 (15.6)	89.5 (14.0)

Table 1

Change from Baseline	Group A	Group B
SBP, mean (SD) mmHg	-22.0 (16.3)	-15.2 (21.2)
DBP, mean (SD) mmHg	-11.4 (10.0)	-6.9 (9.7)
MAP, mean (SD) mmHg	-14.7 (10.9)	-9.5 (12.4)
Central SBP, mean (SD) mmHg	-21.5 (33.8)	12.5 (18.6)
Central DBP, mean (SD) mmHg	-13.4 (21.9)	-7.0 (9.27)

Table 2

PO2090

Associations of Diuretic Use with Cardiovascular Events and All-Cause Mortality in the Systolic BP Intervention Trial (SPRINT)

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Background: It has been suggested that the beneficial effects of intensive compared to standard treatment of systolic BP (SBP) on the primary outcome of cardiovascular events (CVE) and all-cause mortality (ACM) in the SPRINT were due to increased diuretics use in the intensive arm.

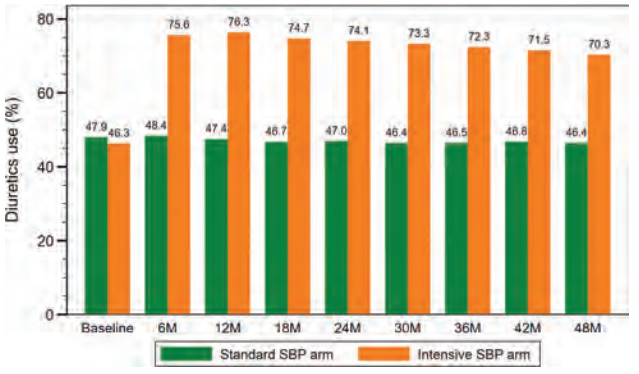
Methods: In a *post hoc* analysis of SPRINT, we used time-dependent Cox analyses to examine if adjusting for diuretic use during follow-up attenuated the effects of intensive treatment on CVE and ACM. We also examined the interactions of diuretic use with the SBP interventions to assess the presence of effect modification.

Results: Figure1 shows the percentage of intensive and standard treatment participants on diuretics over time. Intensive treatment resulted in lower CVE (HR 0.76,

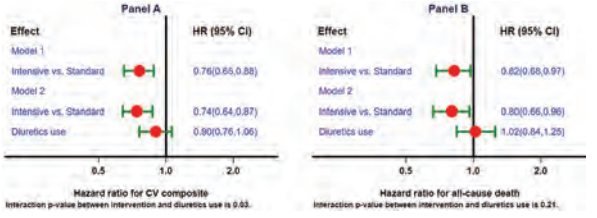
95%CI 0.65-0.88) and ACM (HR 0.82, 95%CI 0.68-0.97) compared to standard treatment. In Cox regression analyses that controlled for time-dependent diuretic use, the HR for intensive treatment on CVE (HR 0.74, 95%CI 0.64-0.87) and ACM (HR 0.80, 95%CI 0.66-0.96) were similar to main effects, whereas diuretic use was not associated with CVE (HR 0.90, 95%CI 0.76-1.06) or ACM (HR 1.02, 95%CI 0.84-1.25). However, diuretic use was associated with a lower HR for CVE in intensive arm (HR 0.69, 95%CI 0.54-0.90) but not in standard arm (HR 1.07, 95%CI 0.86-1.33), interaction p=0.03. No such interaction was found on ACM.

Conclusions: The main effects of intensive treatment on CVE and ACM were independent of time varying diuretic use. While diuretic use by itself was not associated with a lower HR for CVE in the entire cohort, it associated with lower CVE in intensive but not standard arm. Causal role of diuretic use on CVE needs further study.

Funding: NIDDK Support, Other NIH Support - NIDDK 1R01DK118219-01, NHLBI 1R21HL145494-01 and VA ORH-ORH-1439., Veterans Affairs Support



Participants on diuretics over time.



PO2091

Abstract Withdrawn

PO2092

The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on Incident Strokes in the SPS3 Trial

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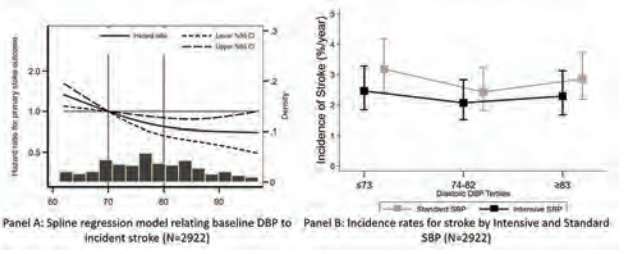
Background: In persons with low baseline diastolic blood pressure (DBP) and previous stroke, ntensive systolic blood pressure (SBP) lowering might by decreasing cerebral perfusion increase the risk for recurrent stroke.

Methods: SPS3 was a 2x2 factorial RCT that examined the effects of intensive vs. standatd (<130 vs. 130-149 mmHg) SBP control and combination versus asprin alone antiplatelet therapy on stroke outcome in 3020 participants. We examined whether the effects of intensive SBP lowering on stroke were modified by baseline DBP using spline regression models.

Results: Mean age was 63±11 yrs, 63% male and 15% black. Mean baseline SBP was 143±19 mmHg and DBP was 78±11 mmHg. There were 267 strokes over10725 person-years of follow-up. In spline regression models, those with lower baseline SBP were at higher risk for stroke (Fig1, panel A) but stroke incidence was lower in intensive vs. standard SBP arm all three baseline DBP tertiles (Fig1, panel B). In a spline regression model, there was no evidence that intensive SBP lowering increased the risk of stroke in those with low baseline DBP (Fig 2). Repeating the analysis with a cardiovascular composite (MI, CHF, stroke, or cardiovascular death) showed similar results.

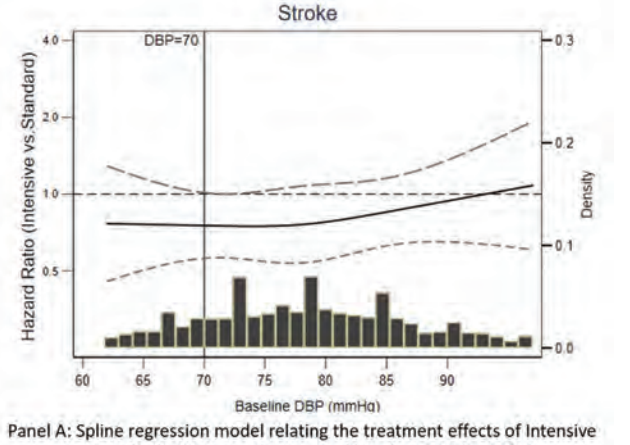
Conclusions: While observational analysis suggested higher risk of recurrent stroke with low baseline DBP, intensive SBP lowering did not increase recurrent stroke risk in those with low baseline DBP and previous stroke.

Funding: NIDDK Support



Panel A: Spline regression model relating baseline DBP to incident stroke (N=2922)

Panel B: Incidence rates for stroke by Intensive and Standard SBP (N=2922)



Panel A: Spline regression model relating the treatment effects of Intensive vs Standard SBP across the range of baseline DBP (N=2922)

PO2093

The Influence of Baseline Diastolic Blood Pressure on the Effects of Blood Pressure Lowering on Death and ESKD Outcome

Olesya Ilkun,[1] Guo Wei,[1,2] Robert E. Boucher,[1] Srinivasan Beddhu.[1,3] *[1]Division of Nephrology & Hypertension, University of Utah School of Medicine, Salt Lake City, UT; [2]Division of Biostatistics, University of Utah School of Medicine, Salt Lake City, UT; [3]Medical Service, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT.*

Background: Intensive systolic blood pressure (SBP) lowering decreased the risk of death in SPRINT. However, there are concerns in those with low baseline diastolic blood pressure (DBP) that intensive BP lowering might adversely affect kidney perfusion and increase the risk for death/ ESKD.

Methods: The African-American Study of Kidney Disease and Hypertension (AASK) trial examined the effects of two different BP goals (mean arterial pressure (MAP) < 92 vs ≥ 102-109) in African American men and women (N =1094) with kidney disease but no diabetes. We investigated whether the effectts of BP intervention on the risk of death/ESKD was modified by baseline DBP.

Results: Mean baseline age was 55 ± 11 yrs and DBP 95 ± 14 mmHg. There were 264 death/ESKD events over 4714 years of follow-up., Compared to usual BP control, low BP goal resulted in lower levels of follow-up SBP, MAP and DBP across baseline DBP tertiles (Fig 1). Despite the lower follow-up MAP and DBP values, there was no evidence that low BP goal increased the risk of death/ESKD in those with low baseline DBP (Fig 2). Interaction of baseline DBP and BP intervention for death/ESKD was not significant (p =0.22).

Conclusions: The effect of BP lowering on the risk of death/ESKD was not modified by low baseline DBP. Hence, low baseline DBP by itself should not be an impediment for intensive BP lowering in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

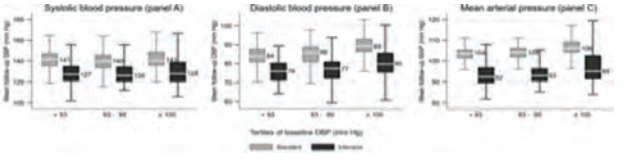


Figure 1. Mean follow-up SBP, DBP and MAP by BP arm in baseline DBP tertiles

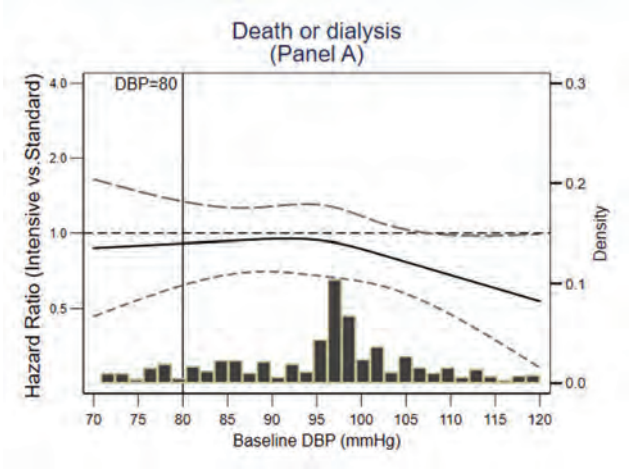


Figure 2. Spline regression model of the effects of BP intervention on death/ESKD outcome across the range of baseline DBP

PO2094

Intensive BP Control Associates with Better Kidney Outcomes in Individuals with APOL1 High-Risk Genotypes

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Background: Presence of two *APOL1* risk variants (high-risk genotypes) are associated with risk for chronic kidney disease. However, we previously reported that intensive blood pressure (BP) control may lower mortality risk in AASK trial participants with *APOL1* high-risk genotypes. Our current objective was to assess whether *APOL1* genotypes modified the effect of intensive BP control on kidney outcomes in the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD BP) trial.

Methods: We performed a retrospective analysis of the ACCORD 2x2 factorial trial which randomized participants to intensive (systolic BP <120mmHg) vs. standard BP control (<140 mmHg) and intensive vs. standard glycemic control. Presence of 0-1 *APOL1* risk alleles were considered low-risk genotypes and 2 *APOL1* risk alleles as high-risk genotypes. Cox models were used to test for interaction between intensive BP control and *APOL1* risk categories for the outcome of serum creatinine doubling or eGFR decline >20 ml/min (as defined by ACCORD). We included glycemic control assignment, age, sex, GFR, and albuminuria as covariates in adjusted models.

Results: 3,108 participants (n=2,617 White, 430 Black with low-risk and 61 Black with high-risk genotypes) were included. An interaction was present between race/*APOL1* genotype and intensive BP control (p <0.05). Whites assigned to intensive (vs. standard) BP control had a 85% higher adjusted risk of the kidney outcome (95% CI 1.67-2.06). Blacks with *APOL1* low-risk genotypes had a 37% higher adjusted risk of the kidney outcome (95% CI 1.06-1.77), while the adjusted risk of kidney function decline was not higher with intensive (vs. standard) BP control (HR 1.00, 95% CI 0.48-2.07) in Blacks with high-risk genotype. [Figure]

Conclusions: Intensive BP control to SBP <120 mmHg associated with less kidney function decline in Blacks with *APOL1* high-risk genotypes compared to Whites or Blacks with low-risk *APOL1* genotypes.

Funding: NIDDK Support

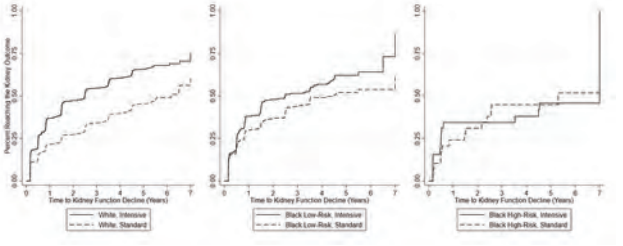

Figure – Unadjusted Kaplan Meier Curve for Risk of Kidney Function Decline with Standard vs. Intensive BP Control by race and APOL1 genotype

PO2095

Early GFR Decline with Intensive BP Lowering and the Risk of Death and ESKD: Mediation Analysis of AASK Study

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Background: Intensive BP lowering decreased the risk of death in CKD in SPRINT but there are concerns that its acute, hemodynamic kidney effects might increase ESKD risk.

Methods: AASK Study (N =1094) was a RCT of low vs. usual mean arterial pressure (≤ 92 vs.102 to 107 mmHg) on kidney outcomes. Using the change in measured iothalamate GFR from baseline to the average of months 3 and 6 (early GFR change), we examined the acute effect of the intervention on subsequent death/ESKD in a mediation analysis. We partitioned the total effect of BP intervention on death/ESKD that was mediated through early GFR change (indirect effect) and independent of early GFR change (direct effect). We also used SIMEX method to access the impact of measurement error in early GFR change on the findings.

Results: We included 976 AASK participants with GFR measurements at baseline, 3 and 6 months. Mean baseline GFR was 55±11 ml/min/1.73m². There were 223 deaths, 293 ESKD events and 445 death/ESKD events during an average of 7.2± 3.3 years of follow-up. BP separation was maintained through the trial (Fig 1, panel A) with an early decline in GFR in the lower BP group but GFRs in the two arms that were similar at the end of the trial (Fig 1, panel B). After adjustment for covariates listed in the footnote to Fig 2, we observed a borderline significant beneficial total effect of the BP intervention on death/ESKD and a slightly stronger direct effect (Fig 2). The HR for the indirect effect was slightly > 1, consistent with the possibility of a small adverse effect of early GFR change.

Conclusions: Intensive BP lowering appears to have a largely beneficial direct effect and a small deleterious indirect effect on death/ESKD in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Figure 1: Mean follow-up MAP (Panel A) and GFR (Panel B) by BP arm

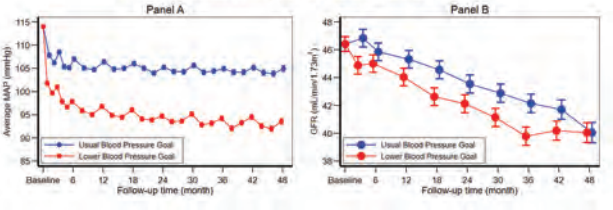
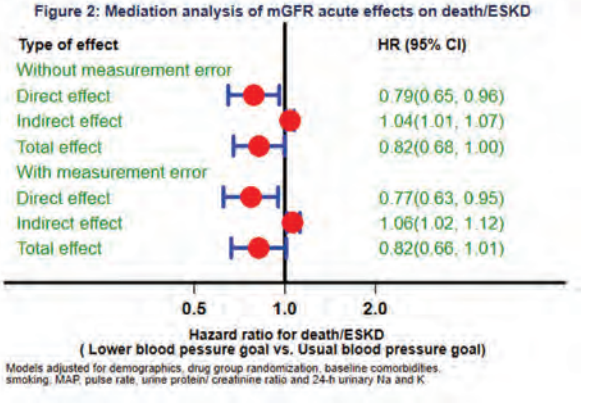


Figure 2: Mediation analysis of mGFR acute effects on death/ESKD



PO2096

A Novel Marker of Resistant Hypertension in CKD

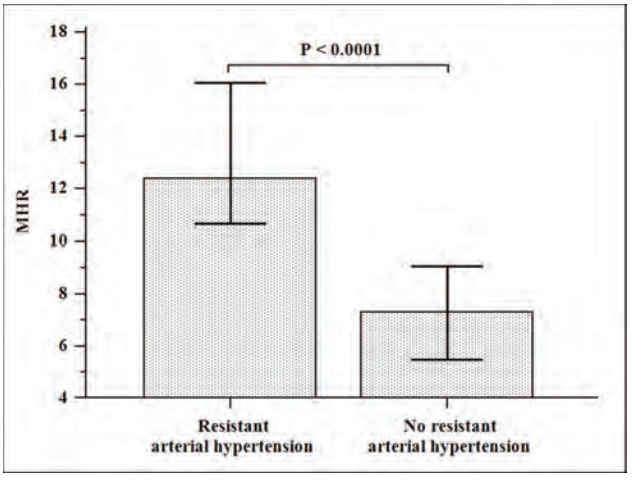
Guido Gembillo, Rossella Siligato, Valeria Cernaro, Domenico Santoro. *Policlinic G. Martino, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.*

Background: Inflammation, oxidative stress (OS), atherosclerosis and resistant hypertension (RH) are common features of chronic kidney disease (CKD) leading to higher risk of death from cardiovascular disease. These effects seem to be modulated by impaired anti-oxidant, anti-inflammatory and reverse cholesterol transport actions of high-density lipoprotein cholesterol (HDL). Recently, monocyte count to HDL-cholesterol ratio (MHR) has emerged as a potential marker of inflammation and OS, demonstrating to be relevant in CKD. Our research was aimed to assess, for the first time, its reliability in RH.

Methods: We performed a retrospective study on 214 patients with CKD and arterial hypertension admitted between January and June 2019 to the Unit of Nephrology and Dialysis of Policlinic G. Martino in Messina, Italy. 72 patients were diagnosed with RH, defined as blood pressure >140/90 mmHg despite use of three different classes of antihypertensive medications (one of which must be a diuretic) at the maximum tolerated doses.

Results: MHR appeared inversely related to eGFR (ρ = -0.163; P = 0.0172). MHR was significantly higher among RH patients compared to non-RH ones (12.39 [IQR 10.67 - 16.05] versus 7.30 [5.49 - 9.06] (Figure 1); P < 0.0001). Moreover, MHR was significantly different according to the number of anti-hypertensive drugs per patient in the whole study cohort (F = 46.723; P < 0.001) as well as in the non-RH group (F = 14.191; P < 0.001). Lastly, MHR values differed according to gender, being higher among males (9.41 [6.75 - 12.07] versus 8.02 [5.94 - 10.57]; P = 0.0463).

Conclusions: MHR may be a reliable biomarker due to the connection between HDL and monocytes. HDL prevents and reverses monocyte recruitment and activation into the arterial wall and impairs endothelial adhesion molecule expression. Our study suggests that MHR can reflect inflammatory status and OS in CKD patients with RH, in order to implement appropriate treatment strategies.



PO2097

Renal Denervation (RDN) vs. Spironolactone in the Treatment of Resistant Hypertension (RH): A Meta-Analysis

Sherida N. Edding, Monica Therese Cating-Cabral, Brian Michael I. Cabral. *St. Luke's Medical Center - Global City, Taguig City, Philippines.*

Background: Resistant hypertension (RH) is defined as blood pressure that remains above guideline-directed goal despite the concurrent use of at least three antihypertensive agents of different classes, one of which is a diuretic. Treatment of RH is focused on the addition of fourth-line therapy. Several studies revealed impressive blood pressure reductions when spironolactone was added to the therapeutic regimen. In the recent years, there has been a growing perception that controlling blood pressure in resistant hypertension is beyond the reach of existing drug therapies, leading to the emergence of device-based therapies, such as renal denervation. Our aim is to do a systematic review of randomized controlled trials that compares the use of Spironolactone and Renal Denervation in patients with RH.

Methods: A comprehensive literature search from the PubMed, Embase, Cochrane Library, and Ovid was performed with the following search terms: Resistant Hypertension, Spironolactone, Renal Denervation. The search was limited to randomized-controlled trials that compared Spironolactone to Renal Denervation in patients with Resistant Hypertension. Three prospective clinical trials were selected and analyzed using Cochrane Revman v5.3. Primary outcome were mean changes in 24-hour Ambulatory Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). Secondary outcomes include mean changes in Office SBP and DBP. Safety was assessed by changes in eGFR and potassium levels.

Results: Two trials comprising 130 patients were selected - 63 patients treated with RDN and 67 patients with Spironolactone. Pooled analysis of the 2 trials for 24H SBP and DBP showed an adjusted standardized mean difference of 0.55 mmHg (CI -0.72, 1.82; P = 0.39) and 0.32 mmHg (CI -0.72, 1.35; P = 0.55) with significant heterogeneity. No significant differences were also noted in terms of decline in eGFR (p = 0.07) and changes in serum potassium (p = 0.29) from baseline to 6 months.

Conclusions: Based on our results, RD appears to be safe and effective treatment for RH. However, additional larger studies should be done including a cost-benefit analysis to explore that possibility of RD as treatment alternative for those intolerant of spironolactone or as a possible 5th line of treatment for those already taking spironolactone.

PO2098

Primary Aldosteronism in CKD

Heather Wachtel,[1] Jae Ermer,[1] Angela C. Davio,[3] Yuta Tezuka,[3] Gregory L. Hundemer,[2] Adina Turcu,[3] Anand Vaidya,[4] Debbie L. Cohen.[1] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Ottawa Hospital, Ottawa, ON, Canada; [3]University of Michigan, Ann Arbor, MI; [4]Brigham and Women's Hospital Department of Medicine, Boston, MA.*

Background: Primary aldosteronism (PA) is a common cause of secondary hypertension. Unilateral causes of PA are potentially cured with adrenalectomy. Treatment of PA in CKD is often avoided for concerns of safety and efficacy.

Methods: We conducted a retrospective cohort study of patients with PA and CKD (eGFR <60 ml/min/1.73m^2) at 3 institutions (2009-2019). eGFR was calculated using CKD-EPI. Statistical comparison utilized the student's t-test, Chi-square test, and Wilcoxon rank-sum test.

Results: Of 250 patients included, mean age was 56.6years (±10.5), and 64% were female. Median plasma aldosterone concentration was 29.0 ng/dl (IQR:20.3-47.4); median plasma renin activity was 0.2 ng/ml/hr (IQR:0.1-0.6) and aldosterone-renin ratio was 119 (ng/dl)/(ng/ml/hr) (IQR:63.5-240.0). Median eGFR on initial evaluation was 49.0 ml/min/1.73m2 (IQR:40.3-58.2). Adrenal vein sampling (AVS) was performed in all patients; unilateral PA was diagnosed in 67.6% (n=169). Adrenalectomy was performed in 163 subjects. Surgical pathology demonstrated adrenocortical adenomas in 66.9%, nodular hyperplasia in 4.9%, and nodular hyperplasia with a dominant nodule in 10.4%. The median tumor size was 1.2 cm (IQR:1.0-1.8). No differences were detected in baseline MAP, number of anti-hypertensive medications (AHM), serum creatinine, or potassium levels between adrenalectomy patients and those medically managed. Adrenalectomy patients had significantly lower AHM requirements at 1 month (2.0 vs. 4.5, p<0.001), 6 months (2.0 vs. 3.0, p=0.002) and 12 months after surgery (2.0 vs. 4.0, p<0.001) compared with medically managed patients. Adrenalectomy patients demonstrated stable eGFR from baseline to 12 months postoperatively, while medically managed patients had a statistically significant decrease in eGFR from baseline to 12 months (p=0.040). There was no difference between groups in cardiovascular outcomes.

Conclusions: Patients with CKD and unilateral PA experience significant and durable decrease in AHM requirement and demonstrate stabilization of eGFR after adrenalectomy when compared to medically managed patients. AVS was successful despite reduced GFR. This study demonstrates that patients with CKD and suspected PA should undergo evaluation to determine whether they have surgically curable disease, as there is a clear benefit in medication reduction and stabilization of eGFR at 12 months.

PO2099

Bilateral Nephrectomy in a Patient with Refractory Hypertension Prior to Development of ESKD

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Introduction: Renal denervation (RDN) reduces increased sympathetic activation in refractory HTN (rHTN) while preserving kidney function, and trials in both the US and Europe demonstrate a 7-12 mmHg placebo subtracted reduction in systolic BP. Bilateral nephrectomy (BLN), originally performed in ESKD patients in the 1970s for rHTN is an effective treatment, but is reserved for ESKD pts. We present a case of life threatening rHTN in a pt with Stage 3b CKD that was unresponsive to open surgical renal denervation (OS RDN) but responded extremely well to BLN.

Case Description: A 43 y/o white woman with stage 3b CKD (eGFR 38 ml/min/1.73m^2) presented with a resting SBP between 180-240 mmHg on maximal doses of 8 different antihypertensive medications including spironolactone and minoxidil. She required frequent hospitalizations for symptomatic HTN with IV CCBs and beta blockers. Workup included an evaluation of all secondary causes including drug screening, urine metanephrines, renal MRI, and renin/aldo ratio. In an effort to avoid BLN, she initially underwent bilateral OS RDN by severing all neural tissue entering the kidney. Renal vein renin levels were 9.1, 7.8 ng/mL/hr pre OS RDN and 0.7, 1.4 ng/mL/hr post. Despite an initial drop in BP to 140/70 mmHg on only 2 medications, within 4 wks of OS RDN, her BP rose to 240/120 on 4 medications and she was symptomatic. At this point, BLN was performed as the only remaining option. Understanding of the need for RRT following BLN, the patient consented to proceed. Follow up BPs have been in the 130/80 mmHg range on carvedilol dose 12.5mg bid alone.

Discussion: Neither OS RDN nor pre-ESKD BLN for rHTN have been previously reported. Advancements in endovascular RDN are becoming more effective, but still only lower systolic BP by 7-12 mmHg placebo subtracted. Our case failed to respond to OS RDN, where we were guaranteed completed resection of the nerves and surrounding connective tissue, and suggests the effects of any form of RDN may be limited. BLN for rHTN for pts on RRT was started in the 1970s. Almost 50 yrs later, despite enormous improvements in medications, there is still a role for this procedure, and it emphasizes how little we still know about the etiology of rHTN. Requiring this in a patient pre-ESKD was extreme but we felt a life-saving requirement. She will be referred for transplantation.

PO2100

Rostral Ventrolateral Medullary Compression: A Rare but a Cardinal Cause of Refractory Hypertension (RfHTN)

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Introduction: RfHTN is defined as uncontrolled HTN with BP >140/90 mmHg despite ≥5 different classes of maximally tolerated antihypertensive agents, including a diuretic *and* a mineralocorticoid receptor antagonist. RfHTN may be underdiagnosed.

Case Description: A 43-year-old female with a history of mitral valve prolapse, iron deficiency anemia, mild asthma and migraines presented for management of uncontrolled severe HTN. Her HTN became increasingly resistant following use of pheniramine and fenfluramine for two years and a recent hysterectomy, with persistently elevated blood pressure (BP) up to 250/100 mmHg. Her medications included: hydralazine, lopressor, procardia, demadex, accupril, diovan, catapres and aldactone. On physical exam, her BP was 230/136 mmHg with regular pulse of 96 beats/min and no papilledema or bruits. Renal function and aldosterone levels were normal. Renal ultrasound/doppler, captopril scan, and angiograms showed no renal artery stenosis or coactation of the aorta, and 24-hour urine metanephrines were normal. Her echocardiogram showed concentric left ventricular hypertrophy with ejection fraction of 60%. Minoxidil was initiated and procardia and lopressor were maintained, with no effect on BP. A high-resolution brain MRI with spectroscopy showed a venous angioma in the right superior temporal lobe and CT angiogram showed irregularity of the basilar artery with outpouching at the left posterior communicating artery and right anterior choroidal artery. She was diagnosed with neurogenic arterial HTN from neurovascular compression (NVC) of the rostral ventrolateral (RVL) medulla. Left retro sigmoid craniotomy was performed for NVC decompression, but aborted eight hours later for fear of precipitating a massive stroke. The patient continues to have RfHTN despite maximal medical therapy and has now developed complications including a cervical ICA dissection, CKD stage 3, heart failure, and severe valvular disease.

Discussion: NVC is related to neurogenic HTN when occurring in the RVL medulla. This case highlights that brain MRI be performed in patients with intractable resistant HTN when all other secondary causes are ruled out.

PO2101

Adjunctive Mesenchymal Stem Infusion Boosts Recovery of GFR After Renal Revascularization for Atherosclerotic Renovascular Disease

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Background: Atherosclerotic renovascular disease (ARVD) reduces renal blood flow RBF, GFR and accelerates poststenotic kidney (STK) tissue injury. Renal revascularization alone often fails to restore GFR in ARVD. Whether adjunctive infusion of autologous mesenchymal stem cells (MSC) can modify reparative processes during restoration of RBF is unknown.

Methods: We measured RBF (MDCT), GFR (iothalamate clearance), systolic blood pressure (SBP), in 16 human subjects with ARVD, before and 3 mo after MSC delivery and stent PTRA. MSC were administered at 3 dose levels (1, 2.5 and 5.0x10^5 MSC/kg, n=7,5,4 patients each) into STK, after stent PTRA. A cohort with ARVD n=17 matched for age, SBP and GFR studied under identical protocol treated with stent PTRA alone served as controls.

Results: SBP decreased in MSC + PTRA and PTRA alone groups 145±20 to 135±19, P=0.022, and 147±20 to 137±16 mmHg, p= 0.02. RBF increased in both MSC + PTRA and PTRA alone treated groups following the three-month hiatus 233±121, to 291±178 ml/min, p=0.015 and 315±260, to 376±304 ml/min, p=0.017. By contrast, GFR increased In the MSC + PTRA group 64±29 to73±34 ml/min p=0.017 whereas GFR did not change in the PTRA group 63.7±30.7 to 65.0±28.6, p =0.35. The increases in RBF and GFR were higher in the group treated with the highest MSC dose Fig1.

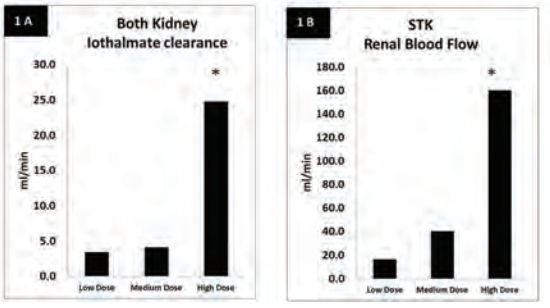
Conclusions: These data reinforce the dissociation between restoring RBF and recovery of GFR in ARVD. Adjunctive therapy with autologous MSC was associated with a dose-related increase in GFR after restoring blood flow, consistent with the ability of MSC to repair microvascular injury. Further clinical trials to characterize the durability and extent of these reparative pathways are warranted.

Funding: NIDDK Support

Table 1

Characteristics	PTRA			MSC+ PTRA		
	Visit 1	Visit 2	P-value	Visit 1	Visit 2	P-value
SBP, mm Hg	147±20	137±16	0.02	145±20	135±19	0.022
STK Cortical Perfusion, mL/min/cc	2.32±0.4	2.7±0.7	0.01	2.65±1.6	3.0±1.7	0.034
STK Cortical blood flow, mL/min	185±104	238±154	0.026	263±236	329±282	0.0068
STK Renal blood flow, mL/min	233±121	291±178	0.015	315±260	376±304	0.017
Iothalamate clearance, ml/min (Both kidneys)	63.7±30.7	65.0±28.6	0.35	64±29	73±34	0.018

STK: Stenotic kidney



PO2102

Percutaneous Angioplasty of Renal Artery Stenosis Most Beneficial in Patients with AKI Requiring Acute Hemodialysis

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Background: Treatment of atherosclerotic renal artery stenosis (RAS) is still contraversial and several studies have shown that percutaneous transluminal renal angioplasty with stenting (PTRAS) is not superior to medical treatment, and the procedure is commonly reserved for malignant hypertension, flash pulmonary edema or deterioration of kidney function. The benefit of endovascular intervention among acute kidney injury (AKI) patients requiring hemodialysis secondary to severe RAS has not been studied. We studied the effects of PTRAS in patients with atherosclerotic RAS, specifically those who presented with AKI indicated for hemodialysis.

Methods: 109 PTRAS were performed in 92 patients with RAS from 2003 to 2019 in a tertiary hospital. Eleven patients presented with AKI secondary to high grade RAS and underwent PTRAS after starting acute hemodialysis. Data collected included demographic parameters, medical background, indication for intervention, technical procedure parameters and complications and long term data including dialysis treatment and mortality. Patients were categorized as responders or non-responders based on improvement in kidney function and discontinuation of dialysis.

Results: A total of 109 procedures were performed in 92 patients with severe renal artery stenosis. Eleven patients (12%) underwent PTRAS for severe high grade stenosis causing renal hypoperfusion and hemodialysis-dependent AKI. After PTRAS, 8 of 11 patients (73%) improved kidney function and discontinued dialysis. The average time on dialysis was 17 days (range 3-35 days) to PTRAS and 22 days (range 3-42 days) to recovery of kidney function, which occurred 6.5 days (range 1-24 days) after PTRAS. Two of the 8 patients later required long term hemodialysis. Only two cases were reported with mild complications.

Conclusions: In patients with hemodialysis dependent AKI, PTRAS should be considered as a rescue treatment as kidney function may recover even after prolonged time on dialysis.

PO2103

Outcomes of Cardiac Surgery in CKD Stage 3 vs. Stage 4 and 5

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Background: Pre-operative kidney dysfunction is associated with worse outcomes following cardiac surgery. However, few studies have assessed the outcomes of advanced Stage 4 and 5 Chronic Kidney Disease (CKD) patients.

Methods: Using our Electronic CKD registry, we compared the outcomes of 988 patients with CKD stages 3 vs. 4 and 5 undergoing Coronary Artery Bypass Graft (CABG) and/or valvular cardiac surgery. We compared length of stay (LOS), ICU days, days on pressors, and days intubated as continuous values and as proportion above the 50th percentile using Kruskal-Wallis and Chi-square tests. We estimated Fine and Gray's competing risks cumulative incidence function of days to post-operative AKI requiring

dialysis (AKI-D) with mortality as a competing risk during hospitalization. We also compared the proportion developing AKI-D with Chi-square test.

Results: Among 988 total patients with cardiac surgery, 115 (12%) had CKD stage 4/5 and 873 (88%) had CKD stage 3. Average age was 71.2 ± 9.5 and 590 (59.7%) were male. Patients with CKD 4/5 had a higher proportion of diabetes (60% vs. 37%). Compared to CKD 3 patients, CKD 4/5 patients required longer intubation (33% more than 2 days compared to 20%, P=0.003), more pressors (47% more than 3 days vs. 32%, P=0.003), longer ICU LOS (median of 5 days vs. 4 days, P<0.001), longer post-operative LOS (median 12 days vs. 9, P<0.001). 24 patients (20.9%) with CKD 4/5 developed post-operative AKI-D vs. 42 (4.8%) in the CKD 3 group (p < 0.001). The cumulative incidence of End-Stage-Kidney Disease (ESKD) with death as a competing risk at 15 days was 5% (95% CI: 4, 8) in CKD 3 group vs. 24% (15, 33) in CKD 4/5 group (p < 0.001).(Table 1)

Conclusions: Advanced CKD stages 4/5 is associated with worse outcomes following cardiac surgery including prolonged ICU stay, intubation duration, days on pressors, development of AKI-D and ESKD.

Post-operative Outcomes in CKD Stage 3 Vs. Stage 4 and 5

Factor	N missing	Stage 3 (N=873)	Stage 4 or 5 (N=115)	p-value
N ICU days	11	4.0[3.0,7.0]	5.0[3.0,11.0]	<0.001b
Pressor days >3 (P50)	201	218(32.0)	49(46.7)	0.003c
Intubation days >2 (P50)	58	166(20.2)	36(32.7)	0.003c
Post AKID during admission	0	42(4.8)	24(20.9)	<0.001c
In-Hospital Death	0	32(3.7)	5(4.3)	0.72c
Post-op LOS	0	9.0[7.0,13.0]	12.0[8.0,19.0]	<0.001b

Presented as Median [P25, P75] or N (column %).

p-values: b=Kruskal-Wallis test, c=Pearson's chi-square test

PO2104

Cardiovascular Events and Mortality in Adults with Kidney Failure after Major Noncardiac Surgery

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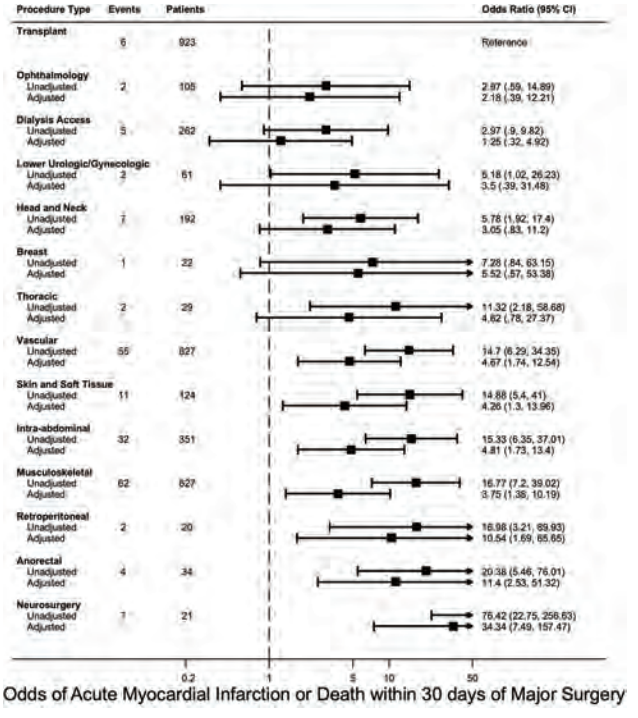
Background: People with kidney failure have a high incidence of major surgery. Despite this surgical exposure, there is a paucity of literature investigating postoperative CV events and death. We aimed to determine the risk of these outcomes based on surgery type.

Methods: This retrospective cohort study used administrative health data from Alberta, Canada from April 2005 to February 2017. Adults (≥18 years) with kidney failure (receipt of chronic dialysis or two outpatient eGFR measures <15 mL/min/1.73m^2) admitted to hospital for a surgical procedure were included. Surgery type, categorized using ICD-10 codes from hospitalization data, was examined for association with acute myocardial infarction (AMI) and death within 30 days of surgery using multivariable logistic regression. We adjusted for demographics, comorbidities, preoperative laboratory measures, procedure urgency, and kidney disease specific variables.

Results: 3398 people with kidney failure had a major surgery (1905 hemodialysis; 590 peritoneal dialysis; 903 non-dialysis). Most of the cohort was male (61.0%), the median age was 61.5 years (IQR 50.0, 72.7), and over half of the procedures were urgent (56.9%). 198 people (5.8%) had an AMI or died within 30 days of major surgery. Kidney transplantation had the lowest frequency of the outcome and were the reference group. After adjustment, vascular, skin and soft tissue, intraabdominal, musculoskeletal, retroperitoneal, anorectal, and neurosurgical procedures had statistically higher odds of AMI or death compared to kidney transplantation (Figure 1).

Conclusions: Major non-transplant surgery in people with kidney failure is associated with a high risk of AMI and death, which has implications for the direction of future perioperative research in this population.

Funding: Government Support - Non-U.S.



Odds of AMI and Death for people with kidney failure undergoing major non-cardiac surgery stratified by surgery type.

PO2105

Race Differences in Cardiovascular Events After Percutaneous Coronary Intervention-Induced AKI

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Background: AKI portends a higher risk of subsequent cardiovascular disease (CVD). Although racial differences in AKI incidence have been found, it is unclear if the risk of CVD events following AKI also varies by race.

Methods: We quantified racial differences in the association of AKI with CVD events 1-year following percutaneous coronary intervention (PCI), using the Duke Databank for Cardiovascular Disease (DDCD). The DDCD captured all patients who underwent PCI at Duke between January 1, 2003 and December 31, 2013 with a combination of structured (forms) and electronic health record (EHR) data. Patients were followed prospectively for CVD events. AKI was defined as ≥ 1.5-fold increase in serum creatinine from outpatient reference value before PCI to the peak value within 7 days post-PCI or a 0.3 mg/dl increase from the reference value within 48 hours. The primary outcome was a CVD composite including all-cause death, myocardial infarction, stroke, and revascularization. Cox models from date of AKI to outcome were adjusted for demographics, baseline cardiac comorbidities, medication use (RAAS inhibitors and NSAIDS), indication and urgency of PCI, and BP at PCI and number of stents placed.

Results: Among 9432 patients (median age 63y; 33% women; 75% white, 20% black), 865 (9%) developed AKI. Among 8699 patients with follow-up, the cumulative incidence of CVD at 1-year was 21%. After adjustment, AKI vs no AKI was associated with 1.84 greater hazards for the composite CVD outcome [95% confidence interval (CI) 1.62 to 2.10]. Compared to whites, other race (HR 0.79, 95% CI 0.63 to 0.99) but not black race (HR 1.07, 95% CI 0.95 to 1.20) was associated with lower risk of subsequent CVD. There was no interaction between race and AKI (p-interaction 0.216). Results were similar with individual components of the outcome.

Conclusions: AKI vs. no AKI following PCI is associated with greater risk for CVD events, regardless of race. Efforts to offset long-term consequences of AKI should target all patients undergoing PCI.

Funding: Private Foundation Support

PO2106

Frailty Is Associated with Higher Risk of Cardiovascular Events and Death in Adults with CKD: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Frailty is common in individuals with chronic kidney disease (CKD). In the general population, frailty is associated with increased risk of cardiovascular events and mortality, but this association has not been fully examined in the CKD population. The objective of this study is to evaluate frailty status as a predictor of cardiovascular events and death in individuals with CKD.

Methods: Among 2,537 CRIC Study participants, frailty status was assessed using five criteria (slow gait speed, muscle weakness, low physical activity, exhaustion, and unintentional weight loss). Frailty was defined as meeting ≥3 criteria, pre-frailty as meeting 1-2 criteria, and non-frailty as meeting zero criteria. Cox proportional hazards models were used to evaluate associations with atherosclerotic events, incident heart failure, and death.

Results: Baseline age was 57.5 years, 45.5% were female, mean eGFR was 46.9mL/min/1.73m^2, and median urine protein was 0.13 mg/day. Frailty was present in 21% of the participants and 66% were pre-frail. During a median follow-up of 12.5 years, there were 349 atherosclerotic events, 398 incident heart failure events, and 398 deaths. In multivariable analyses, frail individuals had a higher risk of each outcome compared to non-frail individuals. Pre-frail individuals had a higher risk of atherosclerotic events compared to non-frail individuals (**Table**).

Conclusions: In adults with CKD, frailty is associated with increased risk for cardiovascular events and death. Future studies are needed to evaluate the impact of interventions to reduce frailty in individuals with CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

Association Between Frailty Status and Outcomes

	Atherosclerotic Events	Heart Failure	Death
	Hazard Ratio (95% CI)*		
Pre-Frail	1.73 (1.12 to 2.68)	1.36 (0.91 to 2.04)	1.47 (0.99 to 2.17)
Frail	2.49 (1.56 to 3.98)	2.07 (1.35 to 3.17)	2.18 (1.44 to 3.31)
Non-Frail	Referent	Referent	Referent

*Adjusted for clinical site, age, sex, race/ethnicity, education, marital status, smoking, BMI, systolic BP, diabetes mellitus, cardiovascular disease, LDL cholesterol, HDL cholesterol, ACE/ARB, aspirin, statin, baseline eGFR, and proteinuria

PO2107

CKD Predicts Stroke Severity, Disability, and Early Recurrence in a Population-Based Cohort Study

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Background: Chronic kidney disease (CKD) is associated with cerebrovascular disease and related mortality, and with under-utilisation of acute and preventive treatments, but any impact on initial event severity and recurrence risk is unclear. We aimed to determine whether CKD is associated with worse initial stroke severity and disability, and whether CKD is independently predictive of recurrent stroke and other vascular events.

Methods: In a population-based study of all TIA/stroke (Oxford Vascular Study), we studied initial stroke severity and disability using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS), respectively, in relation to CKD in all patients presenting with TIA and stroke from April 1, 2002 to March 31, 2017. Associations between CKD and event severity, and between CKD and risk of recurrent vascular events (stroke, myocardial infarction, and sudden cardiac death) were examined using ordinal and Cox regression models, respectively, adjusted for age, sex, and known vascular risk factors, and stratified by TOAST subtype.

Results: Among 3178 patients with TIA (n=1167), ischaemic stroke (n=1802), and intracerebral haemorrhage (n=209), 1267 (40%) had CKD. CKD was independently associated with greater risk of ischaemic stroke compared to TIA (adjusted OR=1.31, 95%CI=1.11-1.56; p=0.002) and with greater initial NIHSS (adjusted OR=1.28, 1.04-1.46; p=0.018), driven mostly by those with an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 (adjusted OR=2.59, 1.44-4.66; p=0.001 for ischaemic stroke; adjusted OR=4.06, 2.04-8.06; p<0.001 for initial NIHSS). Among patients with ischaemic stroke, CKD was also associated with higher one-month mRS scores (adjusted OR=1.40, 1.13-1.74; p=0.002), driven by those with an eGFR < 30 ml/min/1.73m^2 (Adjusted OR=6.51, 3.04-13.97, p<0.001). Risk of early (< 90 days) recurrent stroke was increased with CKD (adjusted HR=1.60, 1.15-2.21; p=0.005) as was the risk of longer-term (0-15 years) composite vascular outcomes (adjusted HR=1.14, 1.05-1.46; p=0.01).

Conclusions: The consistent independent impact of CKD on initial event severity, early disability and recurrence risk suggests that there may be processes intrinsic to CKD leading to uniformly worse outcomes. Further research should determine whether there are CKD-specific treatments that may improve stroke outcomes.

PO2108

Control of Blood Pressure in Elderly Patients with Heart Failure and Risk of Mortality

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Background: Blood pressure (BP) targets in elderly patients with heart failure (HF) are unclear and guidelines are based on expert consensus and extrapolation from populations without HF. Thus, our population-based prospective cohort study assessed if BP control <140/90 mmHg is associated with a decreased risk of mortality in elderly HF patients.

Methods: We included participants of the Berlin Initiative Study, all ≥70 yrs, with HF and treated with antihypertensive drugs at baseline (2009-2011). Demographics, lifestyle factors, medication, and comorbidities were obtained in face-to-face interviews and linked with administrative healthcare data. BP status was defined as normalized BP (systolic BP <140 and diastolic BP <90 mmHg) or non-normalized BP (systolic BP ≥140 or diastolic BP ≥90 mmHg) and updated every 2 yrs, so that each patient could contribute person-time to both exposure categories during follow-up. Time-dependent Cox proportional hazards models estimated adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of cardiovascular death and all-cause mortality associated with normalized BP compared with non-normalized BP in HF patients. Analyses were repeated in non-HF patients.

Results: There were 544 HF patients treated with antihypertensive drugs (mean age 82.8 yrs; 45.4% female). During a median f/up of 7.5 yrs and compared with non-normalized BP, normalized BP was associated with an increased risk of cardiovascular death (HR, 1.79; 95% CI, 1.23-2.61) and all-cause mortality (HR, 1.48; 95% CI, 1.15-1.90). No increased risks of cardiovascular death (HR, 1.23; 95% CI, 0.87-1.74) or all-cause mortality (HR, 1.19; CI 0.95-1.49) associated with normalized BP were observed among 1079 non-HF patients.

Conclusions: BP <140/90 mmHg was not associated with a decreased risk of mortality in elderly HF patients. The increased risk requires further confirmation.

Funding: Private Foundation Support

Risk of cardiovascular death and all-cause mortality associated with normalized BP in older adults with HF

	Number of events	Person-years	Incidence rate (per 100 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
Cardiovascular death					
Non-normalized BP	56	1721	3.3	Ref.	Ref.
Normalized BP	80	1546	5.3	1.57 (1.12-2.21)	1.79 (1.23-2.61)
All-cause mortality					
Non-normalized BP	128	1751	7.3	Ref.	Ref.
Normalized BP	167	1567	10.7	1.44 (1.14-1.81)	1.48 (1.15-1.90)

PO2109

Renal Outcomes of Sacubitril-Valsartan vs. ACE Inhibitors and Angiotensin Receptor Blockers in Heart Failure: A Systematic Review and Meta-Analysis

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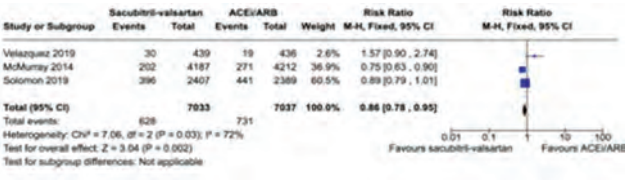
Background: Chronic kidney disease is an important comorbidity in heart failure patients through elevation in blood pressure and activation of the RAAS. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been linked to beneficial effects on clinical outcomes of HF patients with CKD; however, they have been found to increase the risks for renal impairment. Clinical trials on the angiotensin receptor neprilysin inhibitor, sacubitril-valsartan, have found that it causes kidney dysfunction less frequently. This study determined the effect of sacubitril-valsartan on renal outcomes among HF patients compared to ACEi and ARBs alone.

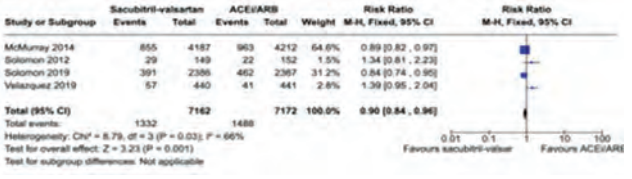
Methods: A comprehensive literature search was done through electronic databases and readings until November 2019. This analysis incorporated randomized controlled trials in which indicators of renal function of patients on sacubtril-valsartan were compared to those of patients on reference drugs--estimated glomerular filtration rate, rise in serum creatinine, and increase in serum potassium.

Results: Four RCTs were included with a total of 14,377 subjects for analysis. Two of the studies used an ACEi (enalapril), while the remaining 2 used an ARB (valsartan). Compared with ACEi and ARBs, there was a nonsignificant difference between decline in renal function (RR 0.75, 95% CI 0.55 to 1.02; participants = 14377; studies = 4; I2= 53%), but a significant difference between rise in serum potassium level (RR 0.90, 95% CI 0.84 to 0.96; participants = 14334; studies = 4; I2= 66%), and elevation of serum creatinine level (RR 0.86, 95% CI 0.78 to 0.95; participants = 14070; studies = 3; I2= 72%).

Conclusions: In HF patients, sacubitril-valsartan shows possible reduction of risks for renal impairment, and definite reduction of risks for both increasing serum creatinine and hyperkalemia, as compared to ACEi and ARBs.



Non-increase of serum creatinine



Non-increase in serum potassium

PO2110

The Accuracy of Current Ankle-Brachial Index and Toe-Brachial Index Diagnostic Criteria for Peripheral Artery Disease Among Patients with CKD

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Background: Ankle-brachial index (ABI) less than or equal to 0.9 and toe-brachial index (TBI) less than or equal to 0.7 are used as diagnostic criteria for peripheral artery disease (PAD). The sensitivity and specificity of the ABI and TBI diagnostic criteria have not been evaluated in patients with chronic kidney disease (CKD).

Methods: We performed ABI, TBI, and doppler ultrasound among 100 patients with CKD using standard methods. Color doppler ultrasound, which has a high level of diagnostic performance with a sensitivity of 93% and a specificity of 95% for diagnosing PAD, was used as the reference standard. Doppler ultrasound diagnostic criteria were determined by multiple ultrasound features including reduction in luminal diameter, monophasic waveform, peak systolic velocity ratio (PSV ratio) >2.0, and presence of special broadcasting. Stenosis greater than or equal to 50% based on doppler ultrasound imaging was used to diagnose PAD. Sensitivity, specificity, positive predictive value, and negative predictive value were estimated. The areas under the curve (AUCs) for ABI and TBI were calculated.

Results: Participants with PAD were older, and more likely to be male and have a history of cardiovascular disease. The average estimated glomerular filtration rate and proteinuria were similar among participants with and without PAD. The sensitivity, specificity, positive predictive value, and negative predictive value were 15.6%, 88.3%, 20.8%, and 84.2% for ABI and 44.8%, 93.3%, 54.2%, and 90.5% for TBI, respectively. AUCs for ABI and TBI were 0.71 and 0.73, respectively.

Conclusions: These data indicate that current ABI and TBI diagnostic criteria have suboptimal accuracy in diagnosing PAD in CKD. New ABI and TBI diagnostic criteria with both optimal sensitivity and specificity need to be developed.

Funding: NIDDK Support, Other NIH Support - P20 GM109036

PO2111

Efficacy and Safety of Roxadustat in Patients with Non-Dialysis-Dependent CKD, Anemia, and Heart Failure

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Patients with heart failure (HF) represent an important clinical subgroup of patients with CKD.

Methods: Pooled data from three pivotal, phase 3, randomized, double-blind, placebo-controlled studies of roxadustat for the treatment of anemia in patients with non–dialysis-dependent (NDD) CKD were assessed in the subgroup of patients with a history of NYHA Class I or II HF recorded at baseline. Endpoints were mean change from baseline (CFB) in hemoglobin (Hb) level averaged over Weeks 28–52 regardless of rescue therapy and time to first blood/RBC transfusion in the first 52 weeks. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs).

Results: In the NDD-CKD study population, 13% (569/4277) of patients had HF (roxadustat=312, placebo=257). Baseline characteristics were generally similar between the treatment groups. Mean (SD) Hb levels (g/dL) at baseline were 9.02 (0.86) in the roxadustat group and 9.04 (0.79) in the placebo group. Patients achieved a larger mean (SD) CFB in Hb levels (g/dL) with roxadustat vs. placebo (1.99 [0.99] vs. 0.29 [1.10]), corresponding to a statistically significant least-squares mean difference of 1.75 (95% CI: 1.54, 1.95) (p<0.0001). The risk for blood/RBC transfusion was significantly reduced in the roxadustat vs. placebo group (HR, 0.15 [95% CI: 0.08, 0.27]; p<0.0001). TEAE rates were comparable between treatment groups and similar to those reported in the overall NDD population.

Conclusions: Roxadustat was efficacious vs. placebo for increasing Hb levels and reducing the risk for blood/RBC transfusion in NDD-CKD patients with HF. The safety and tolerability profile was similar to the overall population and consistent with that observed in this patient subgroup.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO2112

Efficacy and Safety of Roxadustat in Patients with Dialysis-Dependent CKD, Anemia, and Heart Failure

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. Patients with heart failure (HF) represent an important clinical subgroup of patients with CKD.

Methods: Pooled data from three pivotal, phase 3, randomized, open-label, epoetin alfa-controlled studies of roxadustat for the treatment of anemia in patients with dialysis-dependent (DD) CKD were assessed in the subgroup of patients with a history of NYHA Class I or II HF at baseline. Endpoints were: mean change from baseline (CFB) in hemoglobin (Hb) averaged over Weeks 28–52 regardless of rescue therapy, time to first blood/RBC transfusion during the treatment period, and mean monthly IV iron use during weeks 28–52. Safety and tolerability were assessed by reported treatment-emergent adverse events (TEAEs).

Results: In the DD-CKD study population, 25% (991/3890) of patients had HF (roxadustat=499; epoetin alfa=492). Baseline characteristics were generally similar. Mean (SD) Hb levels (g/dL) at baseline were 9.59 (1.30) in the roxadustat group and 9.65 (1.29) in the epoetin alfa group. Patients achieved significantly larger least-squares mean (LSM) [SEM] CFB in Hb levels (g/dL) with roxadustat vs. epoetin alfa (1.24 [0.04] vs. 0.94 [0.04]), corresponding to a LSM difference of 0.29 (95% CI: 0.18, 0.40) (p<0.0001). The hazard ratio for first blood/RBC transfusion during the treatment period in the roxadustat and epoetin alfa groups was 0.76 ([95% CI: 0.54, 1.08]; p=0.1274). Mean (SD) monthly IV iron (mg) use was lower in roxadustat- vs. epoetin alfa-treated patients: 55.8 (288.8) vs. 68.6 (142.7) (p<0.0001). TEAE rates were comparable between treatment groups and similar to those in the overall DD-CKD study population.

Conclusions: Roxadustat was efficacious vs. epoetin alfa for increasing Hb levels and reducing mean monthly IV iron use in DD-CKD patients with HF. The safety and tolerability profile was similar to the overall population and consistent with that observed in this patient subgroup.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO2113

Roxadustat Lowers Low-Density Lipoprotein Cholesterol in Patients with Anemia of CKD

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Background: Roxadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor with positive safety and efficacy results in phase 3 studies in patients with anemia in CKD. The HIF pathway affects cholesterol metabolism; at high altitude, total and low-density lipoprotein cholesterol (LDL-C) decrease in healthy individuals. Roxadustat reduced LDL-C in phase 2 studies. We evaluated the effect of roxadustat on LDL-C in patients with anemia in non–dialysis-dependent (NDD) and dialysis-dependent (DD) CKD.

Methods: Data were pooled from three pivotal phase 3 studies in patients with NDD-CKD and three pivotal phase 3 studies in patients with DD-CKD, including the incident dialysis (ID; on dialysis <4 mo at randomization) population. Mean changes from baseline (CFB) in LDL-C (regardless of statin use) averaged over weeks 12–28 were analyzed using a mixed model of repeated measures and reported least-squares mean (LSM) treatment differences.

Results: In patients with NDD-CKD, there was a 17.2% reduction in LDL-C averaged over Weeks 12–28 in the roxadustat group (n=1994) and a 1.4% increase in the placebo group (n=1430). The LSM treatment difference was statistically significant (p<0.0001). In patients with DD-CKD, there was a 18.5% reduction in the roxadustat group (n=1650) and a 1.7% reduction in the epoetin alfa group (n=1741). The LSM treatment difference was statistically significant (p<0.0001). In patients with ID-DD-CKD, there was a 21.5% reduction in the roxadustat group (n=680) and a 4.6% reduction in the epoetin alfa group (n=691). The LSM treatment difference was statistically significant (p<0.0001).

Conclusions: Treatment with roxadustat vs. placebo or epoetin alfa lowered LDL-C in patients with NDD-CKD and DD-CKD, respectively.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

Table: LDL-C Results in NDD-, DD- and ID-DD-CKD Patients (FAS)

	NDD (001, 608, 060)		DD (002, 064, 063)		ID-DD (002, 064, 063)	
	Roxadustat (n=2368)	Placebo (n=1865)	Roxadustat (n=1929)	Epoetin alfa (n=1928)	Roxadustat (n=756)	Epoetin alfa (n=759)
LDL-C averaged over Weeks 12–28						
n	1994	1430	1650	1741	680	691
Mean (SD), mg/dL	81.8 (36.2)	97.6 (43.8)	76.7 (33.0)	91.8 (38.5)	82.7 (34.0)	100.8 (37.6)
LDL-C CFB*						
n	1994	1430	1650	1741	680	691
Mean (SD), mg/dL	−17.1 (32.9)	1.3 (32.2)	−17.3 (27.7)	−1.6 (26.1)	−22.6 (29.9)	−4.8 (27.9)
ANCOVA†						
LSM difference (SEM)	−19.8 (1.2)		−15.8 (0.9)		−17.5 (2.4)	
(95% CI)	(−22.16, −17.51)		(−17.54, −14.06)		(−22.22, −12.78)	
P-value	<0.0001		<0.0001		<0.0001	

*Baseline is defined as the last available value prior to the first dose of study treatment.
†Treatment comparison was made using an ANCOVA model with baseline Hb, baseline eGFR, baseline LDL-C as covariates, and study, treatment, study-by-treatment interaction, history of cardiovascular/cerebrovascular/ thromboembolic diseases (Yes vs. No) and region (US, Europe, Other) as fixed effects.
ANCOVA, analysis of covariance; CI, confidence interval; CFB, change from baseline; FAS, full analysis set; LDL-C, low-density lipoprotein cholesterol; LSM, least-squares mean; NDD, non-dialysis dependent; ID, incident dialysis; DD, dialysis dependent; SD, standard deviation; SEM, standard error of the mean.

PO2114

Roxadustat vs. Placebo or Epoetin Alfa Has No Clinically Meaningful Effect on Blood Pressure in Patients with Anemia of CKD

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Background: Hypertension (HTN) is a leading cause of chronic kidney disease (CKD) and often worsens as CKD progresses. Erythropoiesis-stimulating agents have been associated with an increase in blood pressure (BP) and other cardiovascular risks. Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron metabolism. We evaluated the effect of roxadustat on BP in dialysis-dependent (DD) and non–dialysis-dependent (NDD) patients with anemia of CKD.

Methods: Pooled data from three, phase 3, randomized, placebo-controlled trials in NDD patients (n=4270), and three pivotal phase 3 randomized, active-controlled trials in DD patients (n=3880), including incident-dialysis-dependent (ID-DD; on dialysis for ≤4 mo; n=1526) and stable dialysis-dependent (SDD; on dialysis for >4 mo; n=2354) patients, were assessed. All DD patients and NDD patients (data censored after dialysis initiation [NDD-NDD]) were included. Mean change from baseline (CFB) in mean arterial pressure (MAP) averaged over Weeks 20–28 (NDD-NDD, SDD) and over weeks 8–12 (ID-DD); time to first exacerbation of hypertension (SBP ≥170 mmHg or DBP ≥110 mmHg and an increase from baseline ≥20 mmHg [SBP] or ≥15 mmHg [DBP]); and adjudicated hypertensive emergency were analyzed.

Results: In NDD-NDD, the least squares mean (LSM) (SE) difference between roxadustat and placebo in MAP (mmHg) was 0.67 (0.30) [95% CI: 0.09, 1.25]. Values for ID-DD and SDD patients were −0.35 (0.66) [95% CI: −1.65, 0.95] and −0.06 (0.42) [95% CI: −0.88, 0.76]. Hazard ratios (95% CI) for HTN exacerbation in NDD-NDD, ID-DD, and SDD patients were 1.12 (0.95, 1.32), 1.02 (0.84, 1.25), and 1.06 (0.93, 1.21). Follow-up adjusted incidence rates [events/100 patient-exposure year] of adjudicated hypertensive emergency were 1.1 and 1.1 in roxadustat- and placebo-treated NDD-NDD, 2.2 and 2.5 in the overall roxadustat- and epoetin-alfa treated DD, and 1.7 and 1.7 in the subgroup of ID-DD.

Conclusions: Pooled analyses of phase 3 data across a continuum of patients with CKD and anemia showed that roxadustat did not have any clinically meaningful effect on BP, HTN exacerbation, or hypertensive emergency vs. placebo in NDD-NDD patients and epoetin alfa in DD patients.

Funding: Commercial Support - Fibrogen, Inc.; AstraZeneca plc; Astellas Pharma Inc.

PO2115

Rivaroxaban Reduces Major Cardiovascular and Limb Events in Patients with CKD and Peripheral Artery Disease with Recent Lower Extremity Revascularization: Insights from VOYAGER PAD

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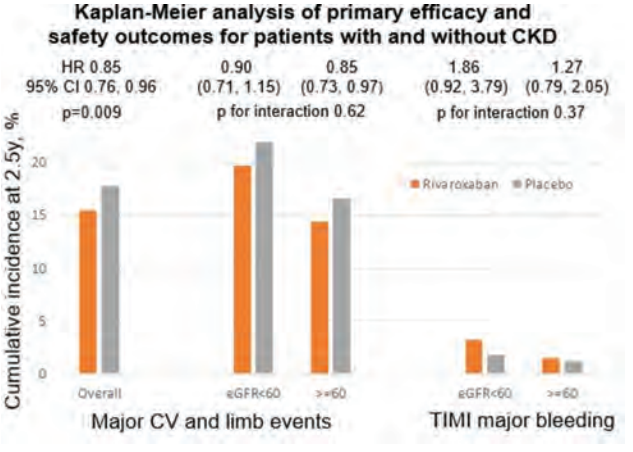
Background: In the VOYAGER PAD trial, rivaroxaban reduced cardiovascular (CV) and limb ischemic events (HR 0.85 vs placebo, 95% CI 0.76-0.96; p=0.009) in peripheral arterial disease (PAD) patients following lower extremity revascularization (LER). This analysis examines the prespecified subgroup of VOYAGER PAD patients with CKD.

Methods: VOYAGER PAD (NCT02504216) randomized 6564 PAD patients following LER to rivaroxaban 2.5 mg twice daily or placebo on a background of aspirin 100 mg daily. The primary endpoint was a composite of acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke or CV death. Intention-to-treat analyses utilized Kaplan Meier estimates and Cox proportional-hazards models.

Results: Mean baseline eGFR was 75±23 ml/min/1.72m^2 with 79, 20, 1 and <1% of patients with CKD stage ≤2, 3, 4 and 5 respectively. During 28-month median follow up, rates of major CV and limb events were higher among patients with more severe CKD (placebo group event rate: 7.4/100 patient-years for eGFR ≥60, 10.0 for eGFR 30-<60 and 9.8 for eGFR 15-<30). Rivaroxaban reduced primary endpoint events with no heterogeneity by eGFR above or below 60 (mostly CKD stage 3)(Figure). Acute limb ischemia and major amputation were significantly reduced among patients with eGFR≥60 (HR 0.77, 95% CI 0.63, 0.94) and <60 (HR 0.55, 95% CI 0.36, 0.86). Major bleeding was infrequent with no heterogeneity by CKD category.

Conclusions: Rivaroxaban reduced CV and limb events in patients with CKD, PAD following LER, a particularly high-risk population.

Funding: Commercial Support - Bayer



PO2116

No Adverse Effects of Veverimer on Volume Status or Blood Pressure in Patients with CKD and Metabolic Acidosis

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Background: Current American Heart Association guidelines recommend sodium (Na) restriction of <1.5 g/day. Drugs can be a source of Na, potentially contributing to inadequate control of blood pressure (BP) and volume. For example, each $NaHCO_3$ tablet (650 mg) contains 170 mg of Na and multiple tablets per day are required to effectively treat metabolic acidosis. Veverimer is a non-absorbed polymer that treats metabolic acidosis by binding and removing HCl from the GI tract. It is not an exchange resin and does not introduce unwanted cations such as Na or K. We hypothesized that veverimer would not increase BP, weight or induce volume overload. In Phase 3 randomized, blinded placebo-controlled trials in acidotic patients (pts) with CKD (baseline mean eGFR 29 mL/min/1.73 m^2), veverimer significantly increased serum bicarbonate (LS mean +4.7 mEq/L at Week 52) with safety profile similar to placebo (Wesson et al. *Lancet*, 2019).

Methods: We analyzed parameters related to volume status in these Phase 3 trials.

Results: In these studies, 97% and 31% of pts, had HTN and CHF, respectively and 193 pts were treated with veverimer or placebo for up to 52 weeks. Treatment with veverimer (v placebo) had no effect on weight, BP, urine Na/creatinine ratio, volume-related adverse events, or increased use of diuretics or antihypertensives (**Table**).

Conclusions: Veverimer, a novel non-absorbed HCl binder, effectively treats metabolic acidosis in CKD without adversely affecting BP or volume status.

Funding: Commercial Support - Tricida, Inc.

	Placebo (N = 81)	Veverimer (N = 112)
Mean (SD) Change from Baseline to Week 52		
BP (systolic/diastolic, mmHg)	-2.0 (7.1)/-2.9 (5.8)	-2.0 (7.6)/-2.6 (8.0)
Body Weight (kg)	0.5 (2.2)	-0.3 (2.7)
Urine Na/Creatinine (mol/mol)	1.10 (10.35)	-0.08 (13.32)
Patients with Selected Adverse Events during 52-Week Study		
Congestive Heart Failure	4 (4%)	3 (2%)
Hypertension	4 (4%)	7 (6%)
Peripheral Edema	3 (3%)	0
Patients Starting Selected Medications during 52-Week Study		
Diuretics	8 (9%)	8 (6%)
Antihypertensives	5 (5%)	9 (7%)

Data presented are mean (SD) or n (%)

PO2117

Optimal Medical Therapy Attainment by Dialysis Status in the ISCHEMIA-CKD Trial

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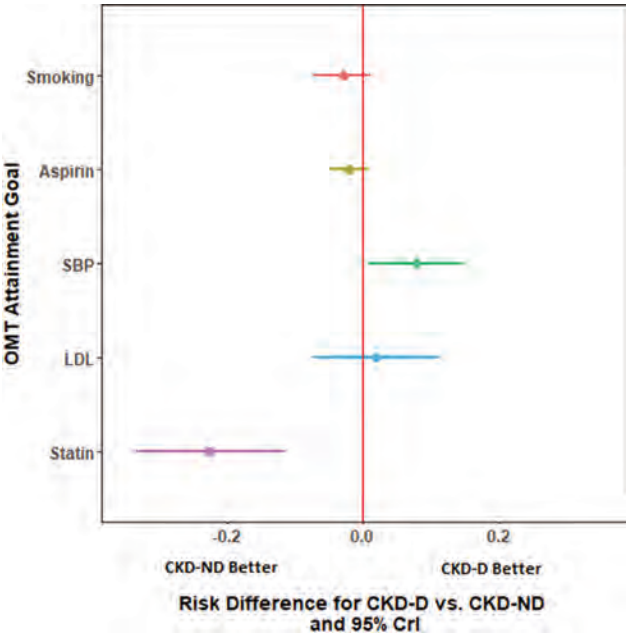
Background: The efficacy of an aggressive multiple risk factor intervention approach – optimal medical therapy (OMT) – to reduce major adverse cardiovascular events in patients with CKD has not been tested. Objective: to examine OMT goal attainment in patients with CKD on dialysis (CKD-D) and non-dialysis CKD (CKD-ND) in the ISCHEMIA-CKD trial.

Methods: OMT was recommended to all participants in ISCHEMIA-CKD. Longitudinal trajectories of individual OMT components (smoking cessation, systolic blood pressure (SBP) <140 mmHg, low density lipoprotein (LDL) cholesterol <70 mg/dL, high-intensity statin use, and aspirin use) were modeled over study follow-up. Covariate-adjusted percentage point difference in each OMT goal achieved at 24 months between CKD-D and CKD-ND groups (% difference [95% credible interval (CrI)]) was estimated.

Results: There were 415 CKD-D and 362 CKD-ND patients at baseline. CKD-D were younger (61 v 67 yrs, p<0.001) and less often diabetic (53% v 62%, p=0.023). CKD-D patients were 7.9 % (0.7%, 14.8%) more likely than CKD-ND to attain the SBP goal at 24 months (Figure). CKD-D patients were 22.7% (-33.3%, -11.4%) less likely to receive high-intensity statins. There was a steady and similar increase in proportional achievement of OMT during follow up.

Conclusions: OMT improved over time in advanced CKD-ND and CKD-D. CKD-D achieved the SBP goal more than CKD-ND, yet CKD-D were less likely to be treated with high-intensity statin. Future studies should explore systemic and patient-related barriers to attainment of OMT in this high-risk cohort.



PO2118

Cardiovascular Determinants of Physical Function in Patients with ESKD on Hemodialysis

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Background: Patients with end-stage kidney disease (ESKD) are often sedentary and decreased functional capacity associates with mortality. The relationship between physical function and cardiovascular disease (CVD) has not been fully explored. Understanding the relationships between prognostically relevant measures of CVD and physical function and capacity may offer insight into whether exercise interventions could target specific elements of CVD.

Methods: 130 patients on haemodialysis underwent cardiovascular phenotyping with cardiac MRI (left ventricular (LV) structure and function, pulse wave velocity and native T1 mapping) and cardiac biomarker assessment. Participants completed the incremental shuttle walk test (ISWT) and sit-to-stand 60 (STS60) as field-tests of physical function and capacity. Separate linear regression analyses identified CV determinants of physical function measures. Multivariate models were adjusted for age, gender, BMI and diabetes.

Results: Mean age was 57±15 years, 73% were male and median dialysis vintage was 1.3 years (0.5, 3.4). In multivariate models, NT pro-BNP and global native T1 were independent determinants of ISWT and STS60 performance. LV ejection fraction was also an independent determinant of ISWT distance. However, age, gender and diabetes had the strongest relationship with physical function. Cardiovascular markers that were signficant in multivariate models are shown in Table 1.

Conclusions: Markers of CV health could be targeted in exercise interventions to improve outcomes in patients with ESKD. NT pro-BNP, global native T1 and LV ejection fraction were independent CV determinants of physical function. The influence of age and diabetes on performance had the strongest relationship. Improving strategies for prevention and management of diabetes may ameliorate deconditioning in these patients.

Funding: Government Support - Non-U.S.

Table 1

	B (SE)	β	p-value
ISWT			
NT pro-BNP	-20.71 (8.9)	-0.19	0.02
Age	-4.65 (0.9)	-0.43	<0.01
Gender	-61.47 (28.8)	-0.17	0.03
BMI	-2.04 (2.6)	-0.07	0.43
Diabetes	-89.70 (8.9)	-0.19	0.02
STS60			
NT pro-BNP (ng/L)	-1.35 (0.6)	-0.19	0.03
Age	-0.32 (0.1)	-0.44	<0.01
Gender	-1.42 (1.9)	-0.06	0.45
BMI	-0.27 (0.2)	-0.14	0.11
Diabetes	-4.75 (1.9)	-0.21	0.01
ISWT			
LV ejection fraction (%)	3.50 (1.4)	0.20	0.01
Age	-4.92 (0.9)	-0.44	<0.01
Gender	-93.18 (30.1)	-0.24	<0.01
BMI	-1.24 (2.3)	-0.04	0.58
Diabetes	-94.65 (28.0)	-0.27	<0.01
ISWT			
Global Native T1 (ms)	-1.21 (0.3)	-0.28	<0.01
Age	-4.67 (0.9)	-0.42	<0.01
Gender	-73.58 (28.5)	-0.19	0.01
BMI	-0.66 (2.2)	-0.02	0.77
Diabetes	-102.97 (27.4)	-0.29	<0.01
STS60			
Global Native T1 (ms)	-0.06 (0.02)	-0.19	0.02
Age	-0.31 (0.1)	-2.85	<0.01
Gender	-2.10 (2.0)	-0.08	0.30
BMI	-0.14 (0.2)	-0.07	0.39
Diabetes	-5.73 (2.0)	-0.24	<0.01

PO2119

The Relationship of Cardiovascular Morbidity with Death and End-Stage Kidney Failure in Patients with Diabetes and CKD Receiving Specialist Renal Care

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Background: Patients with diabetes (DM) and CKD have worse cardiovascular, renal and mortality outcomes than those with neither and either condition alone. However, relationships between these 3 outcomes remain unclear, especially in patients receiving specialist renal care. Aims: To determine the relationship of major adverse cardiovascular event (MACE), end stage kidney failure (ESKF) and death using competing risk analysis.

Methods: CKD.QLD is a large Australian registry of patients with CKD not on RRT receiving specialist renal care. Patients with DM enrolled between 1/1/2011 and 31/12/2016 inclusive were studied. Follow-up was censored by death, ESKF, 1st MACE post enrolment, movement of patient interstate/overseas, loss to follow-up or censor date of 31/12/2017, whichever occurred first. Competing risk analysis was performed with MACE, ESKF and death in turn as the primary outcome whilst the other 2 were competing risks. Covariates examined were age, gender, ethnicity, incident status, access to services, biopsy, smoking, diabetes treatment, Hba1c, MACE prior to enrolment, eGFR, proteinuria, Hb, RAAS blocker and lipid lowering therapy.

Results: 2355 patients underwent 6615 patient-years follow-up (pyfu), mean 2.8y. The first event was MACE in 571 patients (24.2%), ESKF in 299 patients (12.6%) and death in 268 patients (11.3%), giving respective event rates of 86, 45 and 41 per 1000 pyfu. 1137 patients (48.3%) experienced no event. Table 1 summarises the results of the best fit multivariable model with each primary outcomes. $p < 0.05$ was deemed significant.

Conclusions: Despite advances in cardiovascular risk management, MACE remains the dominant clinical outcome in diabetic CKD patients who are nearly twice as likely to experience a MACE first then they are to die or develop ESKF. One hypothesis is that advances in cardiovascular risk management may also concurrently decrease risk of CKD progression and delay death. The most consistent predictors of outcome were age and MACE prior to enrolment. Of note, neither ethnicity nor access to services predicted outcome.

Table 1: summary of competing risk analysis with the different primary outcomes.

Primary outcome	Competing risks	Positive predictors	Negative predictors
MACE	ESKF, Death	Age, proteinuria, HbA1c, Prior MACE	N/A
ESKF	MACE, Death	GFR, proteinuria, prior MACE	Age
Death	MACE, ESKF	Age, smoking, prior MACE	Hb

PO2120

The Combined Prognostic Significance of Red Blood Cell Distribution Width and Vascular Calcification in Patients with ESKD

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Background: Red blood cell distribution width (RDW) is a simple parameter that reflects the degree of red blood cell volume variability. Recent evidence has shown that increased RDW is associated with adverse clinical outcomes in end-stage kidney disease (ESKD) patients. Vascular calcification (VC) is another major independent risk factor for mortality among ESKD patients. This study investigated the combined prognostic effect of RDW and VC in ESKD patients starting dialysis.

Methods: We conducted a retrospective observational cohort study of 582 ESKD patients treated at a single center from January 2006 to July 2017. VC was assessed by the aortic calcification index (ACI) using abdominal computed tomography. Patients were divided into four groups based on the median ACI (17.12) and serum RDW value (14.3) as low ACI-low RDW, low ACI-high RDW, high ACI-low RDW, or high ACI-high RDW. The association between RDW and VC on the composite of cardiovascular events (CVEs) and death was investigated.

Results: During a median follow-up of 3.1 years (range, 1.5–5.5 years), 165 (28.3%) CVEs and 126 deaths (21.4%) occurred. The Cox regression analyses showed that the patients with low ACI-high RDW (adjusted hazard ratio, 1.934; 95% confidence interval, 1.185-3.157; $P = 0.008$) and high ACI-low RDW (adjusted hazard ratio, 1.921; 95% confidence interval, 1.171-3.152; $P = 0.01$) had a greater risk of the composite endpoint than patients with low ACI-low RDW. Patients with high ACI-high RDW had the greatest risk (adjusted hazard ratio, 2.367; 95% confidence interval, 1.465-3.824; $P < 0.001$). The interaction between ACI and RDW on CVEs and mortality was statistically significant ($P = 0.043$).

Conclusions: In ESKD patients starting dialysis, the combined effect of VC and higher RDW was associated with a higher risk of CVEs and death. Also, high serum RDW amplified the risk associated with VC.

PO2121

Attention to the "Liddle" Details

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Introduction: Laboratory data provide clues to the etiology of resistant hypertension. We present one such case where in a presumptive diagnosis of Liddle's syndrome was made, and appropriate therapy initiated. Yet the hypertension failed to be controlled despite multiple antihypertensives.

Case Description: A 26-year-old African American male was evaluated 8 years ago for a history of resistant hypertension. He was compliant with five blood pressure medications yet his systolic blood pressures were greater than 180mmHg. He denied smoking or consuming licorice products. No family history of early deaths, hypertension, or strokes. He reported having early onset of puberty at around age 12, being taller than his peers and now being short as an adult. He was a thin individual with no abdominal striae. Investigations revealed hypokalemia with mild metabolic alkalosis along with low renin and aldosterone. His kidney ultrasound was normal as were his renal functions and free metanephrines. 24-hour urine cortisol was not elevated. A presumptive diagnosis of Liddle's syndrome was made and amiloride was added to his anti-hypertensive regimen, with little effect on BP control. Over the subsequent years, he was admitted repeatedly for hypertensive emergencies. This led to changes in his regimen along with a trial of Aldactone with no benefit. During one such episode, he complained of retrosternal pain. A CT was done to rule out a dissecting aneurysm, but it revealed a 5cm adrenal mass. Work up revealed high deoxycorticosterone, 11 deoxycortisol, dehydroepiandrostenedione sulphate and testosterone which was suggestive of 11-hydroxylase deficiency causing congenital adrenal hyperplasia (CAH) He was started on dexamethasone 2 mg daily and his blood pressure control began showing improvement.

Discussion: CAH due to 11-hydroxylase deficiency is commonly seen in Sephardic Jews. It presents with features suggestive of mineralocorticoid excess. The differential diagnoses are Liddle's syndrome, Chrousos syndrome, syndrome of apparent mineralocorticoid excess and Geller syndrome. This patient was wrongly diagnosed which led to repeated hospitalizations with inadequate therapy. Liddle's syndrome responds well to amiloride without the need for additional medications. The fact that he was on multiple medications in addition to amiloride should be a clue to the misdiagnosis.

PO2122

A Case of Disappearing Hypertension: Difficulties of Managing Hypertension in a Breast Cancer Survivor

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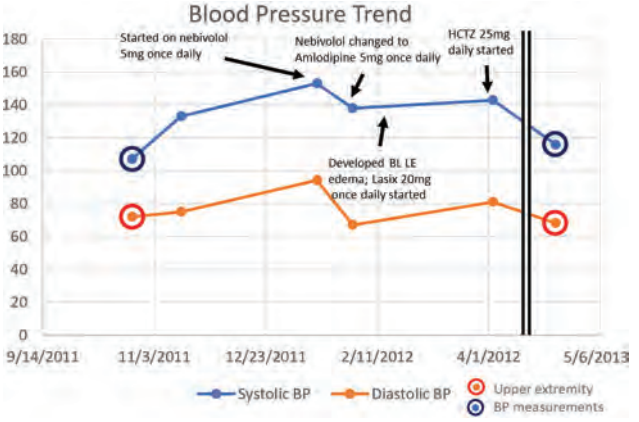
Introduction: Treating hypertension in breast cancer survivors often hold unique difficulty. These patients may have undergone sentinel lymph node biopsy (SNB) or axillary lymph node dissection (ALND), and are often advised to avoid blood pressure measurement with affected by surgery. Here we present a case of young female after mastectomy, SNB and ALND, who was diagnosed with essential hypertension after mastectomy due to inaccurate measurements from avoiding the use of sphygmomanometer cuffs on her upper extremities.

Case Description: 32-year-old female with past medical history of breast cancer status post bilateral mastectomy and hypertension who presents for hypertension management. Hypertension was diagnosed after her breast cancer diagnosis. After diagnosis, she underwent bilateral mastectomy and sentinel node biopsy and subsequently underwent left axial lymph node dissection. Average clinic blood pressure prior to breast cancer diagnosis was 102/63 including days prior to surgery where BP was 107/72. On post-operative follow ups, the patient's BP was noted to be elevated (133/75 and then 154/94) and she was started on nebivolol 5 mg daily. Blood pressure continued to be high at clinic and home, nebivolol was changed to amlodipine 5mg daily. After starting amlodipine, patient developed lower extremity edema and headaches. Furosemide 20 mg PO daily was added which resolved the edema but headache persisted. Hydrochlorothiadize was further added when the patient continued to have blood pressures in the 140s/80-90s. On evaluation with nephrology, the was noted that her blood pressures had been measured

using her lower extremities since her mastectomy. Blood pressure measured with her right upper extremity was 116/68.

Discussion: Often patient after mastectomy with SNB or ALND avoids taking blood pressure on affected limb regardless of lymphedema in order to prevent lymphedema. Despite this, the evidence for this is sparse with most recent studies reporteding blood pressure measurement in ipsilateral affected arm as not being risk factor for lymphedema.



PO2123

A Curious Case of Hypertensive Emergency and AKI

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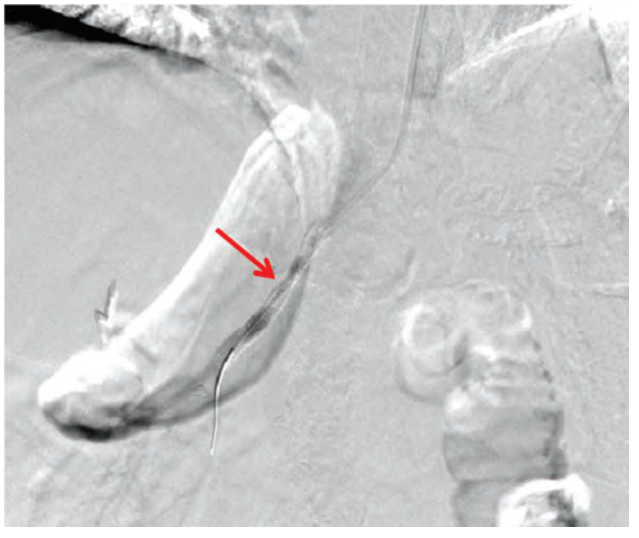
Introduction: We report a case of a 75-year-old female with history of a prior right renal artery stent (coronary bare metal stent), stage IV chronic kidney disease (baseline serum creatinine (Scr) 2.1-2.3 mg/dL (eGFR 20-23 ml/min/1.73 m2)), diastolic heart failure, and hypertension who presented with hypertensive emergency (blood pressure (BP) 220/80 mmHg) and flash pulmonary edema.

Case Description: During her hospital stay, despite treatment with up to nine anti-hypertensive medications, her systolic BP remained 180-200 mmHg. Her Scr also increased to 3.92. Work-up showed normal kidney sizes and urine protein/creatinine ratio 1.26 g/g. Renal artery duplex revealed right renal artery peak systolic velocity 267 cm/sec, renal-to-aortic ratio 2.68, and resistive index 0.7-0.9, suggestive of right renal artery re-stenosis and some intrinsic damage. Due to progressive volume overload and worsening respiratory status, she required temporary hemodialysis. As her volume status improved, she underwent CO2 angiogram and was found to have 90% diffuse in-stent restenosis with marked deformity of the previous stent. She underwent re-stenting of the right renal artery with a proprietary FDA-approved Herculink Elite® renal stent with only 8 ml of contrast. Immediately post-intervention, her BP dramatically improved and after two months, her dialysis was stopped (new baseline SCr 1.5-1.9) and she only requires two BP medications.

Discussion: This case highlights several important points. First, renal ultrasound should be considered in the work-up of patients with hypertensive emergency and history of renal stent due to the risk of re-stenosis. Second, it highlights the importance of using an appropriate FDA approved stent in the renal position as placement of coronary stents in the renal position might have a higher incidence of structural failure and re-stenosis.



Deformed stent (arrow) with severe in-stent restenosis

PO2124

Effect of Dietary Salt Reduction on Blood Pressure in Kidney Transplant Patients: A Randomised Controlled Trial

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Background: Cardiovascular morbidity and mortality are increased in kidney transplant patients. High blood pressure (BP) contributes significantly to this risk and is associated with shortened allograft survival. Dietary salt reduction is widely recommended as a strategy to lower BP in the general population and in chronic kidney disease. Due to a lack of evidence there is currently no consensus on dietary salt restriction in kidney transplant patients.

Methods: Sixty stable kidney transplant patients, ≥ 6-months post-transplantation, with BP ≥120/80 mmHg, and sodium intake ≥80 mmol/24hrs, were randomised in this parallel-designed study to receive either a regular-salt diet (target 150 mmol/24hr) or a low-salt diet (target 80 mmol/24hr) for 8-weeks. The primary outcome measure was systolic and diastolic BP. Secondary outcome measures included 24-hour ambulatory BP (ABP) and proteinuria. Dietary salt intake was assessed by 48-hour urinary sodium excretion.

Results: At baseline, patients (72% men) were 56±11 years with estimated glomerular filtration rate (eGFR) 53±18 mL/min/1.73m^2. Mean urinary sodium was 128±42 mmol/24hr, mean systolic BP was 132±12 mmHg, and mean diastolic BP was 77±10 mmHg. At the end of the intervention period sodium excretion was significantly lower in the low-salt group compared with the regular-salt group (90±37 vs. 132±51 mmol/24hr; adjusted mean difference, -36 [95% CI, -59 to -14] mmol/24hr; *P*=0.002). We found no difference in systolic BP (adjusted mean difference, -2 [95% CI, -12 to 9] mmHg; *P*=0.750), diastolic BP (adjusted mean difference, 0 [95% CI, -4 to 4] mmHg; *P*=0.887), 24-hour systolic ABP (adjusted mean difference, -3 [95% CI, -9 to 2] mmHg; *P*=0.213) or 24-hour diastolic ABP (adjusted mean difference, -2 [95% CI, -5 to 1] mmHg; *P*=0.267). There was no significant effect on proteinuria, eGFR, serum osmolality, uric acid, renin concentration, or aldosterone.

Conclusions: In this study baseline urinary sodium was lower than expected and baseline BP was well-controlled. Reducing dietary salt by 2g/day did not have a significant effect on office blood pressure readings.

PO2125

Left Atrial Reservoir Strain Is an Independent Predictor of End-Stage Renal Impairment in Patients with CKD

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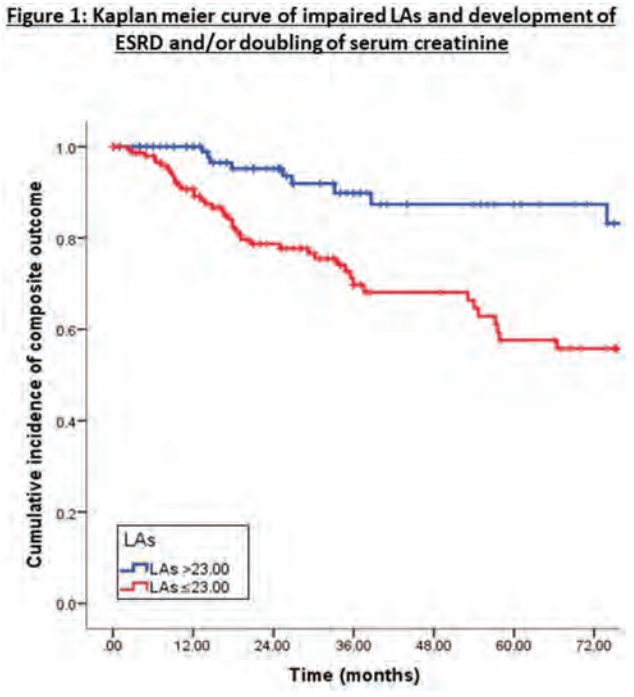
Background: Left atrial (LA) enlargement is common in patients with chronic kidney disease (CKD) and is a predictor of adverse cardiovascular events. Our study sought to evaluate the value of LA reservoir strain (LAs), a novel echocardiographic measure of LA function, as a prognostic marker of adverse renal outcomes.

Methods: Patients with stable Stage 3 and 4 CKD without prior cardiac history were prospectively recruited and underwent transthoracic and stress echocardiography. Patients with normal left ventricular (LV) function, without significant valvular disease and without ischaemia on stress testing were included and followed for up to 5 years for development of end stage renal disease (ESRD) and/or doubling of serum creatinine.

Results: 280 patients (65.8±12.2years, 63% male) were recruited and followed for a mean period of 3.9±2.7years. 56 patients developed the composite endpoint. On log rank tests, impaired LAs (Figure 1), older age, lower eGFR, anemia, diabetes mellitus, greater urinary albumin/creatinine, greater number of antihypertensive agents, higher indexed LV mass and larger LA volumes were significant predictors of the composite outcome ($p<0.01$ for all). On Multi-variable Cox proportional hazards regression analysis, impaired LAs in addition to eGFR, number of antihypertensive agents and urinary albumin/creatinine ($p<0.01$ for all) were independent predictors of ESRD and/or doubling of serum creatinine. Impaired LAs was associated with a 2.5-fold higher risk of the composite outcome.

Conclusions: LAs is an independent predictor for development of ESRD and/or doubling of serum creatine and thus has the potential to be a 'biomarker' for identification of high-risk patients, enabling early initiation of therapy.



PO2126

Weight Gain Is a Risk Factor for the Progression of Coronary Artery Calcification in CKD: From the KNOW-CKD Study

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Background: In chronic kidney disease (CKD), patients with high body mass index or weight gain have better survival. However, their cardiovascular risk is uncertain. The aim of this study was to investigate the relationship between weight changes and the progression of coronary artery calcification (CAC) in CKD.

Methods: This study analyzed 839 participants (Mean age 52.51±12.03, Males 41.12%) from the KNOW-CKD cohort. Changes in weight between baseline and 4 year follow-up period were categorized in tertiles: first tertile (T1) (-31.3kg to -1.1kg), second tertile (T2) (-1kg to 0.9kg) and third tertile (T3) (1kg to 30kg). The coronary artery calcium score (CACS) was assessed using cardiac computed tomography at baseline and 4 years after enrolment. The CAC progression was defined as increase of CACS after 4 years.

Results: The study participants' baseline median CACS was 0.0 (median) [0 (25th quartile)- 34.5(75th quartile)] and 387 (46.13%) participants had baseline CACS above 0. After 4 years, numbers of patients in each tertile was 247 (29.4%) in T1, 258 (30.8%) in T2 and 334 (39.8%) in T3. Median difference in CACS between baseline and follow-up was 2 [0 -69.3] in T1, 0 [0-47.2] in T2 and 6.4 [0-64.77] in T3. (p=0.088) Multivariate adjusted odds ratios (OR) [95% confidence interval] (95% CI) for CAC progression in T1 and T3 group compared to T2 group were 1.21 [0.79-1.85] and 1.80 [1.20-2.70].

Conclusions: Third tertile group, which gained between 1 to 30kg after 4 years, was significantly and independently associated with CAC progression compared to weight stable second tertile group in Korean predialysis CKD patients. These results suggest that preventing excessive weight gain might help prevent cardiovascular complications in CKD.

	Crude OR	Model 1	Model 2	Model 3
Weight change				
1st tertile	1.24 (0.88-1.76)	1.28 (0.86-1.92)	1.21 (0.79-1.85)	1.21 (0.79-1.85)
2nd tertile	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
3rd tertile	1.37 (0.99-1.90)	1.77 (1.21-2.60)	1.82 (1.22-2.72)	1.80 (1.20-2.70)

Model 1 : Adjusted for age, sex

Model 2 : Adjusted for age, gender, BMI, SBP, diabetes, baseline statin medication, HDL, LDL, eGFR, CRP, urine protein to creatinine ratio, calcium, phosphorus, vitamin D, PTH

Model 3 : Adjusted for age, gender, BMI, SBP, diabetes, baseline statin medication, HDL, LDL, eGFR, CRP, urine protein to creatinine ratio, calcium, phosphorus, vitamin d, PTH, current smoker, alcohol drinking frequency and Metabolic syndrome equivalent

PO2127

The Circadian Clock Provides Beneficial Effects Against the Endothelial Dysfunction to Promote Atherogenesis by Regulating Heme Oxygenase 1 Expression

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Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of HO-1 expression in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. We also confirmed that HO-1 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating HO-1 expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

PO2128

Modeling Endothelial Cell Dysfunction Using Human Induced Pluripotent Stem Cells Derived from Patients with ESRD

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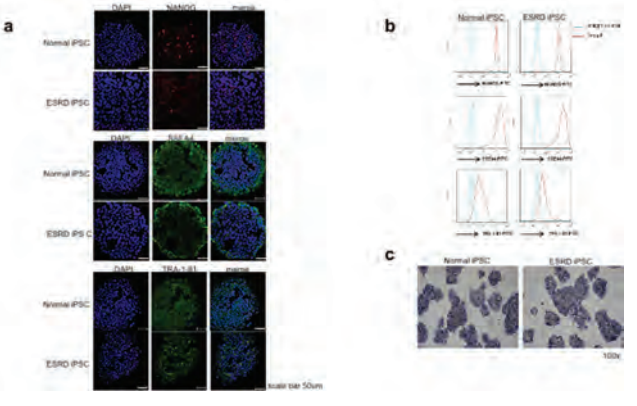
Background: Endothelial cell (EC) dysfunction is a frequent feature in end-stage renal disease (ESRD). The aim of this study was to generate human induced pluripotent stem cell-derived EC (hiPSC-ECs) from patients with ESRD as a model to investigate EC dysfunction.

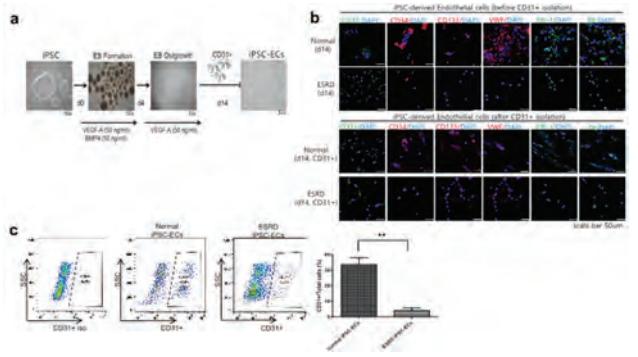
Methods: hiPSCs were obtained using peripheral blood mononuclear cells of patients with ESRD and healthy controls (HC). Next, we generated hiPSC-ECs and the expression of endothelial markers was assessed by immunofluorescence. The differentiation efficacy, EC dysfunction, and molecular signatures of EC-related genes based on microarray were compared between the ESRD and HC groups.

Results: In both groups, hiPSCs and hiPSC-ECs were successfully obtained based on iPSC or EC marker expression. However, the efficiency of EC generation from hiPSC was lower in ESRD than HCs. In addition, ESRD-hiPSC-ECs failed to form interconnecting branching point networks, unlike HC-hiPSC-ECs in the tube formation assays. In a microarray analysis, transcripts associated with oxidative stress and inflammation were upregulated and transcripts associated with vascular development and basement membrane extracellular matrix components were downregulated in ESRD-hiPSC-ECs compared with HC-hiPSC-ECs.

Conclusions: In conclusion, ESRD-hiPSC-ECs showed a greater EC dysfunction based on functional assays and molecular profiles and it can be a useful disease model to investigate EC dysfunction in ESRD.

Funding: Government Support - Non-U.S.





PO2129

Macrophage Neutrophil Gelatinase-Associated Lipocalin Has a Critical Role in Aldosterone-Induced Renal Fibrosis via the CCL5-IL4 Pathway

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Background: Neutrophil Gelatinase-Associated Lipocalin (NGAL) (or lipocalin 2) is a novel mineralocorticoid biotarget in the cardiovascular system. NGAL is also described as an acute renal lesion biomarker and NGAL serum concentration is associated with the severity of renal damages patients with a chronic kidney disease (CKD). Lipocalin2 (Lcn2) gene invalidation in a CKD mouse model protects from proteinuria and renal lesions. We hypothesized that NGAL produced from macrophages promotes expression of chemoattractant molecules involved in renal lesions induced by mineralocorticoid excess.

Methods: The role of Lcn2 was analyzed using full Lcn2 knock out mice (NGAL KO) challenged with uni-Nephrectomy, Aldosterone 200 mg/kg/day, Salt 1% (NAS model) during 6 weeks. Assessment of CCL5/IL4 in kidney fibrosis were studied using maraviroc administration (50 mg/kg/d in chow diet) or by injections of anti-IL4 antibody (600 mg/week).

Results: NAS induced a significant increase in the expression (relative values, mean±SEM, compared to 1 in the control samples, $p<0.05$) of extracellular matrix proteins such as collagen I (2.35±0.33), a-SMA (2.04±0.44) and fibronectin (3.38±0.42) in the kidney of WT mice associated with interstitial kidney fibrosis (6.49±0.70). This is fully prevented by Lcn2 deletion. Expression of macrophages markers *F4/80, CD80* and *CD86* was increased (5.11±0.46, 4.84±0.19 and 5.22±0.45 respectively) in WT NAS mice and partly prevented in Lcn2 KO mice. Macrophages isolated from Lcn2 KO or WT mice were co-treated with aldosterone (10^{-8}M) and NaCl (40mM). In WT macrophages, expression of *Lcn2* (2.81±0.30) and the *CCL5* chemokine (2.48±0.32) was increased. The increase of *CCL5* was blunted in Lcn2 KO macrophages. Similarly to Lcn2 inactivation, CCL5 receptor blockade improved renal fibrosis and reduced high levels of Th2 $CD4^+$ cell markers induced by NAS. Neutralization of IL4, a Th2 cytokine, in NAS mice injected with anti-IL4 antibody blunted kidney fibrosis and overexpression of profibrotic proteins such as collagen I, a-SMA and fibronectin.

Conclusions: NGAL produced by macrophages plays a critical role in renal interstitial fibrosis through the CCL5/IL4 pathway in mice exposed to mineralocorticoid excess.

PO2130

Water Intake and Blood Pressure in Children: Results from the SPA Project

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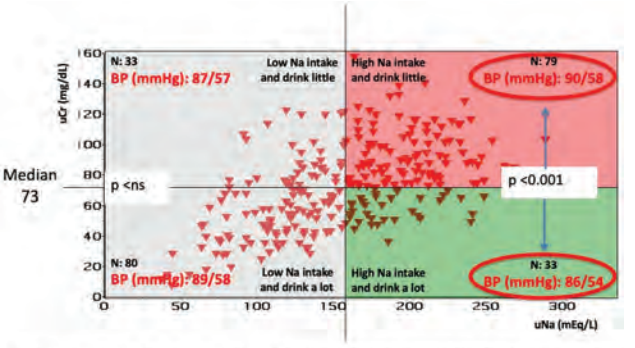
Background: Sodium (Na) intake is involved in the development of hypertension (HPT); to reduce NaI is important in the treatment of HPT, but the increase in renal Na excretion might also be a potential preventive and/or therapeutic opportunity. The SPA Project studied blood pressure (BP) in relation to water (H2O) andNa intake with the working hypothesis that an increased water I can improve renal Na handling.

Methods: 339 healthy, non-overweight children (166 girls), 5.7 years old (IQR: 5.3-6.2) were characterized for: BP (using standardized multiple office BP measurement), Na and water intake (by means of urinary Na and creatinine from 4 samples taken in 4 different days). After categorizing subjects as low/high Na and low/high water intake (based on median value), BP was compared.

Results: Among children with higher Na intake, those introducing more water, showed a significantly ($p<0.001$) lower BP (both systolic and diastolic) compared to those who drink less (figure). This difference was not observed among children with lower Na intake.

Conclusions: Our findings support the hypothesis that an increased water intake, reduces BP perhaps by increasing Na renal excretion. We speculate that this simple, highly acceptable, inexpensive and harmless measure might have a role in preventing and minimizing the epidemics of HPT and related morbidities.



Arterial blood pressure (as measured with the mOBPM and urinary parameters (mean of 4 samples taken in diffent days) in healthy, non-overweight children according to water and Na intake

PO2131

Altered Tryptophan Catabolism via the Kynurenine Pathway Associates with CKD-Accelerated Atherosclerosis

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Background: Non-traditional risk factors like inflammation and oxidative stress play an essential role in the increased cardiovascular disease risk prevalent in chronic kidney disease (CKD). Tryptophan catabolism by the kynurenine pathway (KP) is linked to atherosclerosis and renal function in both clinical studies and experimental models. However, the role of KP in the pathogenesis of CKD accelerated atherosclerosis is unknown.

Methods: 9-week old 5/6 nephrectomized (CKD) and sham-operated (CON) $LDLr^{-/-}$ mice were placed on a high-fat/high-cholesterol diet (HFD) for 16 weeks. KP metabolites were measured using targeted mass spectrometry in the plasma, urine, and tissues. Expression and activity of Indoleamine 2,3 dioxygenase (IDO1- first step of the KP) were quantified by immunoblotting, immunohistochemistry, and kynurenine to tryptophan ratio (KTR) in aortic tissue in both groups.

Results: CKD mice demonstrate increased KP metabolites compared to sham-operated mice (CON) both at baseline and after exposure to HFD for 16 weeks. Exposure to HFD for 16 weeks increases most KP metabolites in both CON and CKD mice, except for levels of tryptophan and 3-hydroxy anthranilic acid that decrease with HFD exposure. 3-hydroxy kynurenine and kynurenic acid increase with HFD exposure in CKD mice, whereas these levels tended to decrease in controls. Hepatic tissue in the CKD mice fed HFD reveals no changes in KP metabolites except increased quinolinic acid, whereas the splenic tissue and renal tissue reveals low tryptophan levels and higher KTR, kynurenic acid, and anthranilic acid. These changes in the HFD fed CKD mice are likely due to a combination of increased synthesis in specific tissues and reduced clearance. IDO expression and activity were also increased in atherosclerotic lesions of CKD mice on HFD for 16 weeks compared to control mice with intact renal function.

Conclusions: In summary, KP metabolites are altered both in the circulation, tissues, and arterial wall of the CKD atherosclerosis model implicating KP in the pathogenesis of atherosclerosis in CKD.

Funding: Other NIH Support - NHLBI

PO2132

Male Sex Hormones Drive an Increase in Renal Necrosis in Spontaneously Hypertensive Rats (SHR)

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Background: We recently published that maturation in male SHR increases necrosis which contributes to the development of hypertension. Maturation in male SHR is associated with both increases in sex hormones and blood pressure (BP). Testosterone has been shown to induce renal tubular cell necrosis in vitro. This study tested the hypothesis that male sex hormones drive maturation-induced increases in renal necrosis in male SHR.

Methods: At 4 wks of age, male SHR were randomly assigned to one of three groups: sham, gonadectomy (ORX), or treatment with the BP lowering drugs hydrochlorothiazide (HCTZ; 55mg/kg/day) and reserpine (Res; 4.5 mg/kg/day) in drinking water to prevent age-related increases in BP (n=6-8). At 8 wks of age, telemeters were implanted in a subset of rats (n=3-4/group). Rats were allowed 1 wk of recovery, then BP was continuously recorded. All rats were euthanized at 13 wks of age. Renal necrosis was quantified using FACS analysis of $7AAD^+$ cells. Data are expressed as mean ± standard error. Kidneys were isolated from additional untreated 5 and 15 wk old male SHR (pre- and post-maturation) and processed for Western blot analysis of key proteins mediating necrosis, receptor-interacting protein kinase 3 (RIP-3) and high mobility group box 1 (HMGB-1).

Results: BP was significantly lower in ORX and HCTZ/Res-treated SHR compared to sham (mean arterial BP (mmHg): Sham = 139±2; HCTZ/Res = 117±3; ORX = 126±2; $p=0.002$). As expected, renal necrosis was greatest in sham control (renal necrosis

expressed as % total gated kidney cells: Sham = 6±0.3%). ORX significantly decreased renal necrosis vs. sham, while necrosis in HCTZ/Res treated rats was not significantly altered vs. sham despite having the lowest BP (ORX = 4±0.4%; HCTZ/Res = 5.3±0.3%; p=0.003). To begin to gain insight into the mechanisms mediating maturation-induced increases in necrosis, RIP3 and HMGB1 protein expression were measured in 5 and 15 wk old SHR. Expression of RIP-3 (1±0.1 vs. 0.7±0.1; P=0.008; n=5-6) and HMGB-1 (1±0.06 vs. 0.7±0.1; P=0.005; n=5-6) were greater in 15 wk old SHR.

Conclusions: In conclusion, these data suggest that male sex hormones contribute to maturation induced increase in renal necrosis in male SHR to a greater extent than maturation-induced increases in BP. Future studies will determine the relative contributions of RIP3 and HMGB1 to renal necrosis in adult male SHR.

Funding: Other NIH Support - American heart association

PO2133

SIRPα Interacts with the IGF-1 Receptor in CKD-Induced Cardiomyopathy

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Background: A major consequence of chronic kidney disease (CKD) is associated with cardiomyopathy. Even at early stages of CKD with near normal GFR, and normal blood pressure, left ventricular hypertrophy (LVH) is present, which suggests an unidentified trigger unrelated to pressure overload. We now find that elevations of signal regulatory protein alpha (SIRPα), a substrate for tyrosine phosphatases, in cardiac muscle adversely influences insulin signaling via interactions with the insulin-like growth factor-1 receptor (IGF-1R) in CKD.

Methods: SIRPα floxed (control) vs. muscle-specific (mSIRPα) KO mice were subjected to subtotal nephrectomy. The binding affinity between IGF-1R immunoprecipitate lysates and purified recombinant SIRPα was determined based on the association rate (ka) and the dissociation rate (kdis) constants using bio-layer interferometry (BLI; Octet RED384 systems). Finally, SIRPα vs. GFP plasmids were transfected into muscle cells. n=4-6 mice/group, results are presented as mean ± SD.

Results: Control mice with CKD displayed reduced levels of tyrosine phosphorylation of IGF-1R in cardiac muscle. However, in mSIRPα KO mice with CKD there was no downregulation of IGF-1R phosphorylation despite the presence of CKD. Next, we examined the interactions of these proteins by immunoprecipitation analysis. SIRPα proteins were immunoprecipitated and immunoblotted with the IGF-1R confirming interactions. IGF-1R-SIRPα interactions were further validated using the BLI to assess protein quantities and characterization of kinetics. Specifically, IGF-1R was immunoprecipitated from cardiac muscle and the binding kinetics of Fc-tagged-recombinant SIRPα (rSIRPα) to the IGF-1R was identified via BLI. We concluded that rSIRPα was bound to immunoprecipitated IGF-1R with a kD of 147 uM, which futher validate their interactions. Lastly, SIRPα plasmids were transfected into myotubes, which led to an upregulation of SIRPα and impaired activation of insulin signaling mediators (IGF-1R and pAKT) plus worsening muscle fibrosis when compared to control transfected cells.

Conclusions: SIRPα interacts with the IGF-1R reducing receptor activities, confirming its role in regulating insulin/IGF-1 intracellular signaling in cardiac muscle while exacerbating cardiac muscle functions in CKD.

Funding: Veterans Affairs Support

PO2134

Increases in Renal CD81 and NCC Are Associated with Lipopolysaccharide-Induced Preeclampsia

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Background: CD81, a member of the tetraspain superfamily, is an important component in the pathogenesis of pregnancy hypertension while the status of renal salt transport proteins plays an important role in blood pressure (BP) regulation.

Methods: In order to explore whether there is a connection between the two in the process of preeclampsia, we studied the interaction of CD81 and Na^+-Cl^- cotransporter (NCC) *in vivo* and *in vitro*.

Results: A rat model of pregnancy hypertension was built by injecting a small amount of lipopolysaccharide (LPS, 0.5μg/kg in 2ml saline) into the tail vein of pregnant rats on GD 5. On GD 18, BPs (SBP :99.9±1.4 vs 116.9±1.8,DBP :85.9±2.0 vs 94.4±1.8,mmHg, n=7/group) and urine protein (1185±35.0 vs 3550±158.0, μg/day, n=4/group) were higher in LPS -rats relative to vehicle-rats while renal protein abundance of CD81 (186.7±20, % of vehiclel, n=4/group, same as below) and NCC (278.0±53) was increased. The interaction of CD81 and NCC was found in the co-immunoparticipation complexes from rat kidney homogenates with the antibodies against CD81 or NCC. In order to further explore the relationship between renal CD81 and NCC, we treated mouse kidney distal tubule cells with LPS for 24h to construct an in vitro experimental model. The cell viability, detected by CCK-8, was not affected at all concentrations of LPS (0, 1, 10, 20, 30, μg/ml). The toxicity of LPS, detected by LDH release studies, was increased at concentrations of 20 (108.0 ± 3.4, n=6/group) and 30μg/ml (115.5±3.3) respectively but not altered at the lower concentrations. Relative to vehicle, LPS at concentration of 10ug / ml increased the protein abundance of CD81 (161.5 ± 23.22, n=6/group) and TNF-α (207.5 ± 27.67) but did not change the protein abundance of MCP-1. The protein abundance of NCC (193.5 ± 27.86) was increased remarkably while α1-NKA was also increased slightly (134.3 ± 4.51). The mRNA expression of CD81 mRNA was increased at LPS concentrations (μg/ml) of 1(154.9 ±11.13, % of vehicle, n=6/group), 10 (134,2±10.54),20 (148.0±8.61),30 (139.3±20.9) respectively.

Conclusions: Our findings in vivo and in vitro suggest that LPS can cause an increase in protein abundance and mRNA expression of CD81 and up-regulate NCC in renal distal convoluted tubules, which may contribute to an increase in blood pressure in pregnancy rats.

PO2135

Neurogenic Tachykinin Mechanisms in Experimental Nephritis of Rats

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Background: We demonstrated earlier that renal afferent pathways combine very likely "classical" neural signal transduction to the central nervous system and a substance P (SP) dependent mechanism to control sympathetic activity. SP content of afferent sensory neurons is known to mediate neurogenic inflammation upon release. We tested the hypothesis that alterations in SP dependent mechanisms of renal innervation contribute to experimental nephritis.

Methods: Nephritis was induced by OX-7 antibodies in rats, six days later instrumented for recording of blood pressure (BP), heart rate (HR), drug administration; intrarenal administration (IRA) of the TRPV1 agonist capsaicin to stimulate afferent renal nerve pathways containing SP and implantation of electrodes for renal sympathetic nerve recordings (RSNA). The presence of the SP receptor NK-1 on renal immune cells was assessed by FACS.

Results: IRA capsaicin decreased RSNA from 62.4±5.1 mV*sec to 21.6±1.5 mV*sec (*p<0.05) in controls, a response impaired in nephritis. Suppressed RSNA in nephritic rats and controls transiently but completely recovered after systemic administration of a neurokin 1 (NK1-R) blocker. NK-1 receptors occurred mainly on CD11+ dendritic cells (DCs). An enhanced frequency of CD11c+NK1R+ cell, NK-1 receptor+ macrophages and DCs were assessed in nephritis. Administration of the NK-1R antagonist aprepitant during nephritis reduced CD11c+NK1R+ cells, macrophage infiltration, renal expression of chemokines and markers of sclerosis.

Conclusions: Hence, SP promoted renal inflammation by weakening sympathoinhibitory mechanisms while at the same time substance SP released intrarenally from afferent nerve fibers aggravated immunological processes i.e. by the recruitment of DCs.

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Renoprotective Effect of KLF2 on Glomerular Endothelial Dysfunction in Hypertensive Nephropathy

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Background: Kruppel-like factor 2 (KLF2) is a transcription factor, which regulates endothelial cell metabolism. KLF2 plays a role in maintaining normal vascular integrity by proinflammatory, anti-thrombotic, anti-angiogenic effects in endothelial cells. Endothelial dysfunction is associated with hypertension, and is a predictor of atherosclerosis development and cardiovascular events. Also, it is commonly observed in chronic kidney disease (CKD). The association between glomerular endothelial cell damage in diabetic nephropathy of KLF2 has been studied, but not in hypertensive nephropathy. Here, we present a role of KLF2 in hypertensive nephropathy.

Methods: Human primary glomerular endothelial cells were harvested and cultured under various duration, pressure condition by a rotational force device for mimic hypertensive nephropathy. We established the appropriate culture environment by confirming the pressure and survival rate applied to endothelial cells according to rotational force and evaluate the mRNA expression of α-smooth muscle actin (αSMA), KLF2 and KLF4. To induce hypertensive nephropathy in rat, 5/6 nephrectomy was done and kidney injury marker, blood pressure, KLF2 expression were evaluated. And we evaluated the KLF2 expression in hypertensive nephropathy patients' biopsied kidney tissue.

Results: The survival rate of human primary glomerular endothelial cells was maintained at a pressure of up to 4mmHg and decreased from above. After the application of 4mmHg pressure for 48hr in human primary glomerular endothelial cells, expression of KLF2 mRNA was decreased, while αSMA mRNA was increased and KLF4 mRNA was similar compared to control. 5/6 nephrectomy in rats resulted in increased blood pressure, decreased kidney function, as well as decreased KLF2 expression of glomerular endothelial cells. In addition, the expression of KLF2 in biopsied kidney tissue of hypertensive nephropathy patients was lower than that of normal kidney tissue.

Conclusions: We found that KLF2 expression of glomerular endothelial cells was reduced in both in vivo and in vitro models of hypertensive nephropathy. These findings suggest a new role for KLF2 in hypertensive nephropathy, which may be the basis for the development of new therapeutics.

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Substance P: Differential Influences on Action Potential Production in Afferent Neurons of the Kidney?

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Background: Afferent nerve fibers of the kidney play a role in controlling sympathetic activity in hypertension and cardiovascular diseases. Proinflammatory substances influence the action potential production of these neurons. Therefore, we tested the hypothesis that proinflammatory substance P (SP) released from afferent nerves inhibits the action potential production in neurons with renal afferents.

Methods: Cultured dorsal root ganglion neurons (DRG Th11-L2) of rats with renal afferents were investigated in current clamp mode to assess action potential generation during both current injections and TRRPV1 stimulation with protons (pH 6) with and without exposure to SP (0.5 μmol) or CGRP (0.5 μmol). Neuronal classification as tonic (high AP generation upon stimulation) and phasic (AP ≤ 5 upon stimulation). Additional experiments were performed in voltage clamp mode to fully assess electrophysiological properties of the neurons.

Results: Renal neurons were stimulated with current injection (14,4+/-1,5 APs/600ms, mean+/- SEM) and protons (9,6+/-1,9 APs/10s of stimulation with pH6). The co-stimulation of renal neurons with current injections and SP ***decreased*** the number of action potentials in tonic neurons (15,2+/-1,1 APs/600ms vs. 10,1+/-1,6 APs/600ms, p<0.05, mean+/- SEM), however superfusion of renal neurons with both protons (pH 6) and SP ***increased*** it (9,6+/-1,9 APs/10s vs. 16,9+/-2,3 APs/10s, p<0.05, mean+/- SEM). Addition of SP itself did not stimulate cultivated neurons. Co-stimulation with CGRP was without significant effect under any circumstances.

Conclusions: Neuronal SP influences action potential production in renal neurons in a very complex way: Both inhibition and specific increases in action potentials via a TRPV1-dependent mechanism in acid-sensitive renal neurons could be demonstrated. Afferent nerve fibers are likely to respond very specific in different conditions while influencing sympathetic nerve activity and putatively renal physiology or pathology (proinflammatory actions of SP).

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PO2138

Tonic Inhibition of Sodium Reabsorption by Na^+/K^+-ATPase in the Renal Proximal Tubule

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Background: In the renal proximal tubule (PT), Na^+/K^+-ATPase (NKA) is exclusively located in the basolateral domain. Through its classic ATP-dependent ion-pumping function, NKA generates the Na+ gradient that drives apical Na^+ reabsorption, mostly through Na^+/H^+ exchanger (NHE3). Accordingly, activation of NKA-mediated ion transport decreases natriuresis through activation of basolateral (NKA) and apical Na^+ reabsorption (NHE3). In contrast, activation of the more recently discovered NKA signaling triggers a cellular redistribution of PT NKA and NHE3 that decreases Na^+ reabsorption.

Methods: We used an *in vitro* and *in vivo* gene targeting approach to explicitly test the respective contributions of NKA signaling and ion-pumping in the control of PT Na^+ reabsorption.

Results: Knockdown of 90% of NKA in PT LLC-PK1 cells activated NHE3 (50% decrease in inhibitory phosphorylation), and increased basolateral Na^+/HCO_3^- cotransporter (NBCe1A) content. Rescue with wild-type but not Src signaling-null NKA restored NHE3 and NBCe1A to basal levels. In a hypomorphic PT $NKA^{-/-}$ mouse obtained by SGLT2-Cre/LoxP recombination, 70% decrease in PT NKA expression decreased inhibitory phosphorylation of NHE3 and increased membrane abundance of NHE3 and NBCe1A. Urine output and absolute Na^+ excretion were decreased by 65%, without histological or functional evidence of renal injury. Those changes were driven by increased PT Na^+ reabsorption, as indicated by a 65% decrease in lithium clearance and unchanged GFR. The hyper-reabsorptive phenotype of PT $NKA^{-/-}$ mice were rescued upon crossing with PT $NHE3^{-/-}$ mice, confirming the importance of NKA/NHE3 coupling.

Conclusions: Hence, NKA signaling exerts a tonic inhibition on Na^+ reabsorption by regulating key apical and basolateral Na^+ transporters. This action, which is lifted upon NKA genetic suppression in cells and *in vivo*, tonically counteracts NKA's ATP-driven function of basolateral Na^+ reabsorption. Strikingly, NKA/Src signaling is not only physiologically relevant, it is functionally dominant over NKA ion-pumping in the control of PT reabsorption. NKA signaling therefore provides a long sought-after mechanism for the natriuretic action of endogenous NKA ligands such as cardiotonic steroids.

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NPFFR2 in the Kidney via Novel Transcriptional and Posttranslational Mechanisms Triggers Molecular Responses to Salt

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Background: Hypertension and salt sensitivity is dependent on NaCl intake. The kidney maintains sodium (Na) balance and blood pressure homeostasis. Neuropeptide FF (NPFF), is involved in nociception, hormonal modulation, and body temperature control. NPFF and its receptors, *NPFFR1* and *NPFFR2*, are found in the kidney and have prohypertensive properties.

Methods: Renal restricted bolus or chronic infusion of NPFF raised blood pressure and reduced Na excretion (n=4) in C57Bl/6 mice. Silencing *NPFFR*1 had no effect but, silencing *NPFFR2* raised UNaV (3 fold). *NPFFR2* with the D1 dopamine receptor interacts. Both coimmunoprecipitated (coIP) and colocalized in human renal proximal tubule cells (hRPTCs) and whole kidney. NPFF and the D1R/D5R agonist fenoldopam (FEN) antagonized cAMP production (2.54±0.1 pmol/mg/min for FEN vs. 1.23±0.2 for vehicle vs. 1.11± 0.2 for both, n=4) and Na transport (1.78±0.1 fold with FEN, 1±0.11 for vehicle, and 1.1±0.2 for both, n=4) in hRPTCs. Mice fed a 4% NaCl diet increased (>2.5 fold) the coIP between renal *NPFFR2* and *D1R*, enabling the *D1R* to limit *NPFFR2* effects. A normal (145 μM) to low (90 μM) NaCl raised both promoter activity (~2.5 fold, n=3), mRNA and protein expression (n=4; 0–8 hr). A normal to high (175 μM) Na concentration reduced promoter activity (–0.5 fold), mRNA and protein expression of *NPFFR2* (0–8 hr). The increased coIP between prohypertensive *NPFFR2* and antihypertensive *D1R*, resulted in an increased receptor antagonism to cAMP response and Na transport (*vs* FEN or NPFF treatment [1 mM/30 min], n=4).

Results: We found a "Sodium Response Element" (NaRE), homolog of "Dehydration Responsive Element" ("TACCGACAT") in *Arabidopsis thaliana* genome, at the *NPFFR2* promoter. We measured *NPFFR2* promoter activity to test NaRE response to Na. The *NPFFR2* promoter responded to low (4.1±0.05 fold increase,) and high (0.52±0.5 fold decrease) Na with wild type NaRE, but not in the absence of NaRE (mutant *NPFFR2*). Using a selective NaRE blocker, (antigene RNA) on mouse kidneys, showed no increased *NPFFR2* response to low Na intake (<0.04 G Na/day) but a decreased systolic blood pressure caused by the low Na diet (65±0.6 mm Hg vs. 83.3±1.3, n=4).

Conclusions: Our data identified NaRE and novel transcriptional and posttranslational mechanisms by which mammalian genes respond to sodium.

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PO2140

Age-Dependent Regulation of the NCC and the Development of Salt-Sensitive Hypertension

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Background: The prevalence of hypertension (HTN) increases with age, and age-dependent HTN is associated with increased sympathetic tone and blood pressure (BP). Dietary sodium intake is a major risk factor for HTN as excessive dietary sodium intake leads to increases in BP in individuals that demonstrate the salt sensitivity of BP to evoke salt sensitive HTN (SSH). We have previously demonstrated excessive release of norepinephrine upregulates the activity of the renal sodium chloride cotransporter (NCC) to promote sodium reabsorption and salt sensitive hypertension. However, the regulation of the NCC with age remain unclear. Thus, we tested the hypotheses that 1) upregulation of NCC contributes to age-dependent HTN, and 2) aged rats develop SSH.

Methods: Three different age groups (3, 8, 16 month old (MO)) of male Sprague-Dawley (SD) rats were fed a normal salt (NS; 0.6% NaCl) or HS (4% NaCl) diet for 21 days respectively. On day 21, basal MAP and NCC activity (peak natriuresis to IV hydrochlorothiazide (2mg/kg) infusion) were measured in vivo. The expression of total NCC, phosphorylated NCC, with-no-lysine [K] kinases (WNK) 1, WNK4, STE20/SPS1-related proline-alanine-rich protein kinase (SPAK), oxidative stress responsive kinase 1 (OxSR1), and phosphorylated SPAK/OxSR1 were assessed via immunoblotting (N=6/gp).

Results: Male SD rats develop age-dependent HTN with increased NCC activity and expression, and increased WNK1 expression. Aged male SD rats developed SSH, impaired dietary salt evoked suppression of NCC activity, phosphorylation, and the expression of kinases SPAK and OxSR1.

Conclusions: These data suggest that the NCC contributes to the development of age-dependent HTN. Moreover, dysregulation of the NCC may play a pivotal role in the development of age-dependent SSH.

Variables	3 MO		8 MO		16 MO	
	NS	HS	NS	HS	NS	HS
MAP (mmHg)	124 ± 2	126 ± 3	135 ± 4#	143 ± 5#	149 ± 3#†	169 ± 1*#†
ΔUNaV to HCTZ (μeq/min)	9 ± 1	7 ± 1*	18 ± 2#	16 ± 1#	15 ± 5#	16 ± 6#
Total NCC expression (fold change)	1.00 ± 0.22	0.32 ± 0.09*	1.91 ± 0.25#	1.13 ± 0.15*#	1.82 ± 0.23#	0.75 ± 0.11*
Total pNCC153 expression (fold change)	1.00 ± 0.20	0.19 ± 0.05*	1.24 ± 0.46	0.87 ± 0.22	0.49 ± 0.18	1.73 ± 0.22*#
WNK1 expression (fold change)	1.00 ± 0.20	0.49 ± 0.06*	1.07 ± 0.34	1.36 ± 0.15	2.15 ± 0.38*†	1.60 ± 0.29#
WNK4 expression (fold change)	1.00 ± 0.11	0.86 ± 0.07	1.95 ± 0.14#	1.28 ± 0.10#	1.05 ± 0.07†	1.17 ± 0.09
SPAK expression (fold change)	1.00 ± 0.12	0.48 ± 0.09*	1.25 ± 0.09	1.30 ± 0.23#	0.42 ± 0.04*†	0.41 ± 0.13#
OxSR1 expression (fold change)	1.00 ± 0.12	0.62 ± 0.05*	1.09 ± 0.12	1.10 ± 0.06#	1.19 ± 0.20	1.17 ± 0.08#
pSPAK/OxSR1 expression (fold change)	1.00 ± 0.24	0.84 ± 0.30	0.55 ± 0.23	1.42 ± 0.24*#	1.12 ± 0.17	2.86 ± 0.43*#†

MO, month old; NS, 0.6% NaCl; HS, 4% NaCl. *p<0.05 vs. respective NS group; #p<0.05 vs. respective 3 MO group; † p<0.05 vs. respective 8 MO group.

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A Novel Genetically Defined Mouse Model of Hypertensive Nephropathy

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Background: The molecular pathways that drive hypertensive nephropathy remain poorly understood. We overcome the roadblock with a new genetically-defined mouse model of HTN that exhibit a low-renin salt-sensitive form of the disease. The mice, created by introducing activating mutations in the Ste20p-related proline alanine-rich kinase (SPAK) in a distal convoluted tubule cell-specific manner, become hypertensive solely as a consequence of constitutive activation of the thiazide-sensitive sodium chloride cotransporter (NCC) and salt retention.

Methods: For these studies, the constitutively active (CA)-SPAK and control (C57BL/6J) mice were fed control or high salt diet (HSD), and renal function was evaluated over 40 weeks, together with telemetric measurements of blood pressure. RNA-Seq was performed to evaluate changes in the transcriptional profile in the renal cortex and corroborated biochemically.

Results: Kidney function in the CA-SPAK mice began to deteriorate at 20 weeks as evidenced by significant elevation of BUN, creatinine, and frank albuminuria, which gradually increased over the next 20 weeks. HSD consumption exacerbated hypertension in CA-SPAK mice and accelerated the decline in renal function. Trichrome-staining revealed no obvious histopathological changes, including nephroangiosclerosis. By contrast, a significant change in the transcription profile was observed between CA-SPAK mice and controls at an early stage when microalbuminuria begins to develop. Remarkably, the differentially expressed (DE) genes profile was enriched in 26% of the known genes associated with albuminuria in humans. Significant downregulation of key components of the glomerular filtration barrier slit diaphragm genes (nephrin, podocalyxin, synaptopodin) and the proximal tubule protein scavenger, Cubilin, were also observed in the CA-SPAK. Pathway analysis was especially enriched for genes associated with Major Histocompatibility Complex class II, T helper 17 lymphocytes and B lymphocytes markers in the CA-SPAK mice.

Conclusions: Progression of renal insufficiency in CA-SPAK mice indicates a causal role of hypertension in nephropathy and incriminates an inflammatory component as a key driver of early damage to the glomerular filtration barrier and tubular protein reabsorption.

PO2142

Different Renal and Cerebral Vascular Responses to Angiotensin II Infusions in Anesthetized Mice: Roles of Vasodilator Prostaglandins and Nitric Oxide

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Background: Since the cerebral PO_2 is much lower than the renal, the brain requires protection from vasoconstriction while the renal circulation must adapt to physiological demands often dictated by angiotensin II (Ang II). We tested the hypothesis that renal and cerebral blood flow (RBF and CBF) are differentially regulated by vasodilator prostaglandins (PGs) and nitric oxide (NO).

Methods: Mice (n = 6 – 8 per group) were anesthetized with a-chloralose/urethane and ventilated to a PCO_2 of 33-38 mmHg. Mean arterial pressure (MAP) was recorded via an aortic cannula, RBF via a transit time blood flow meter encircling a renal artery and CBF via a blood flow meter encircling the common carotid artery with the external carotid artery ligated. Renal and cerebral vascular resistances (RVR and CVR) were recorded on line during infusion of vehicle or Ang II (40 p mol min^{-1} Kg^{-1} iv) vs vehicle. L-NAME (30 mg^{-1} Kg^{-1} h^{-1}) and/or indomethacin (5 mg^{-1} Kg^{-1} h^{-1}) or vehicle were infused iv over 50 mins to test the roles of NO and PGs in basal and Ang II-stimulated vascular resistances.

Results: In the basal state, L-NAME increased RVR (+79 ± 9%; P < 0.01) and CVR (+78 ± 8%; P < 0.01) similarly whereas vehicle was ineffective. Indomethacin alone did not modify RVR or CVR but enhanced the effects of L-NAME to raise RVR (+132 ± 15%; P < 0.05) and CVR (+134 ± 30%; P < 0.05) similarly. Thereafter, Ang II infusion increased MAP (+10 ± 2%; P < 0.05) and RVR (+33 ± 6%; P < 0.05) but did not change CVR (+2 ± 2%; NS). Neither L-NAME nor indomethacin alone modified the MAP, RVR or CVR responses to Ang II but after indomethacin given to mice infused with L-NAME, Ang II infusion caused a greater rise in MAP (+30 ± 3%; P < 0.05), and RVR (+190 ± 5%; P < 0.05) but CVR remained quite unresponsive (-7 ± 5%; NS).

Conclusions: Low basal RVR and CVR depend on PG-dependent NO generation. Whereas CVR is entirely protected from vasoconstriction with Ang II, the increase in RVR with Ang II is moderated by PG-dependent NO generation. Thus, PGs and NO exert distinct action in the renal and cerebral vasculature.

PO2143

The Intrarenal RAS Upregulates SGLT2 Expression and SGLT2 Inhibitors Attenuate Angiotensin-II Induced Hypertensive Kidney Injury in Mice

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Background: Clinical trials have shown that SGLT2 inhibitors (SGLT2i) improve both cardiac and renal outcome in several diseases. However, the mechanisms underlying regulation of SGLT2 gene expression remain unclear. Here, we studied whether the intrarenal renin-angiotensin-system (RAS) modulates SGLT2 expression and SGLT2i efficacy.

Methods: We analyzed the association between RAS-related genes and SGLT2 gene expression in the tubulointerstitial compartment of the kidneys of adult non-diabetic patients in the Nephrotic Syndrome Study Network (NEPTUNE). We compared SGLT2 expression in transgenic mice overexpressing angiotensinogen (Agt) in their renal proximal tubular cells (RPTCs)(Agt-Tg) ± RAS blockers, and wild-type (WT) mice. We administered angiotensin II (AngII, 1000 ng/kg/min subcutaneously) in WT mice ± canagliflozin (Cana, 15mg/kg/day in drinking water- for 4 weeks). We also studied human immortalized RPTCs (HK2) as an *in vitro* model.

Results: In human kidney samples (N=183 patients), SGLT2 mRNA was significantly correlated with AGT (r=0.55, p<0.001), Renin (r=0.46, p<0.001), ACE (r=0.47, p<0.001), and AT1R (r=-0.28, p<0.001), but not with AT2R. SGLT2-immunopositive staining was higher in RPTCs of Agt-Tg mice than in WT mice and this was attenuated by losartan treatment. Ang II infusion in WT mice significantly increased blood pressure, which was not reversed by Cana co-treatment. Ang II caused glomerulosclerosis, tubulointerstitial fibrosis, and albuminuria, which were all attenuated by Cana. Fractional glucose excretion was significantly higher in Ang II+Cana than WT+Cana. *In vitro*, AngII dose-dependently stimulated SGLT2 mRNA in HK2 cells, and these were inhibited by losartan.

Conclusions: Our data demonstrate that the intrarenal RAS upregulates SGLT2 expression and show that SGLT2i ameliorate AngII-induced kidney injury independent of blood pressure.

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Loss of Soluble (Pro)renin Receptor Attenuates DOCA-Salt Hypertension

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Background: Cleavage of the extra-cellular domain of the (pro)renin receptor (PRR) yields a soluble fragment (sPRR), which may be involved in mediating hypertension. We recently developed a mouse model with mutation in the cleavage site of the PRR using CRISPR/Cas9 such that sPRR is not generated and showed that absence of sPRR attenuated angiotensin-II induced hypertension and kidney damage. In this study, we examined if sPRR alters blood pressure (BP) in angiotensin-II independent hypertension using deoxycorticosterone acetate (DOCA)-salt treatment.

Methods: Mutant sPRR mice and littermate controls were treated with DOCA (50 mg/kg) and high Na^+ diet for 3 weeks. BP was monitored by radio-telemetry and metabolic balance studies performed on Day 17-18 of DOCA-salt treatment. Only male mice were studied as the PRR gene is on the X-chromosome.

Results: Compared to controls, male mutant sPRR mice had markedly lower plasma sPRR levels (control: 21.5 ± 2.5 vs mutant 0.2 ± 0.03 ng/ml) and baseline BP (systolic control: 122 ± 3 vs mutant 114 ± 3; diastolic control: 94 ± 5 vs mutant 82 ± 3 mm Hg). BP remained low in mutant sPRR mice relative to controls following 12 days of DOCA-salt treatment (systolic control: 141 ± 2 vs mutant 132 ± 5; diastolic control: 110 ± 4 vs mutant 95 ± 5 mm Hg). Mutant sPRR mice had lower body weight but similar food intake and urinary albumin excretion compared to controls (Table 1). Mutant mice had lower urine volume, water intake and urinary K^+ but not Na^+ excretion. No differences in renal histology were noted between control and mutant sPRR mice.

Conclusions: Loss of sPRR attenuates DOCA-salt mediated hypertension. The mechanisms by which sPRR might regulate BP and water/Na^+ homeostasis in DOCA-salt hypertension are currently being investigated.

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Table 1

	Control (N=6)	Mutant sPRR (N=7)
Food intake (g/day)	4.0 ± 0.3	3.6 ± 0.1
Water intake (ml/day) *	13.2 ± 1.4	8.8 ± 0.5
Urine volume (ml/day) *	10.4 ± 1.0	6.4 ± 0.5
Body weight (g)*	30.9 ± 1.5	25.0 ± 0.3
UNaV (μmol/day)	3279 ± 124	2865 ± 282
UKV (μmol/day) *	421 ± 29	335 ± 32
Urine albumin (μg/day)	77 ± 33	62 ± 36

* P value <0.05 by T-test

PO2145

Effect of Dietary Magnesium Supplementation on Tubulointerstitial Damages in Angiotensin II-Induced Hypertensive Rats

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Background: Recently, it has been epidemiologically suggested that Mg deficiency promotes progressive renal damage, and conversely, it has been reported that Mg load to Cyclosporine A-induced renal damage models attenuates renal impairment. This study aimed to investigate the ameliorating effect of high Mg diet on the renal impairment by use of hypertensive nephrosclerosis model.

Methods: Eight-week-old SD rats were subjected to continuous infusion of Angiotensine II by subcutaneously placed osmotic minipumps for 2 weeks (435 ng/kg/min) and then housed for 6 weeks. The food for animals was normal Mg diet (NMD): 4% NaCl+0.05% Mg or high Mg diet (HMD): 4% NaCl+0.5% Mg. PicroSirius Red staining was used to assess fibrosis, and immunostaining of claudin-16, which is known to be down-reguglated in the renal interstitial damage was also performed.

Results: No significant difference in mean blood pressure was seen between two groups (NMD: 97.8±7.6 mmHg vs HMD: 94.2±9.0 mmHg, n=4), and serum Mg was elevated in HMD group (NMD: 1.63±0.19 mg/dL vs HMD: 2.48±0.09 mg/dL, n=4). Analysis of PicroSirius Red staining positive area by semi-quantification showed that positive area in outer medullary resion was significantly reduced in HMD group (NMD: 1.61±0.15% vs HMD: 1.11±0.10%, n=4). Positive area of claudin-16 immunostaining in HMD was greater than NMD (NMD: 1.52±0.13% vs HMD: 1.70±0.15%, n=4).

Conclusions: Hypertensive nephrosclerosis is one of the major causes of end-stage renal failure, and its suppression is important. It was confirmed that the outermedullary fibrosis was inhibited by high Mg diet, while there was no change in the blood pressure, indicating that anti-fibrotic effect of high Mg diet seemed to be an independent mechanism from the blood pressure. We report the fact that claudin-16 expression is reduced and Mg excretion is increased in the interstitial fibrosis model (Shimizu, Magnesium Res 2018). These results suggest that high Mg diet has an inhibitory effect on fibrogenesis through suppressing the increased Mg-excretion.

PO2146

Pharmacological Sympathetic Denervation of the Kidney with Angiotensin II Receptor Blockade?

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Background: A putative interaction between angiotensin II (Ang II) and the renal sympathetic nervous system has been described. We tested the hypothesis that the angiotensin II receptor inhibitor candesartan mimicks a functional renal sympathetic denervation not distinguishable from surgical renal nerve ablation.

Methods: Measurement of arterial blood pressure (MAP), heart rate (HR), renal sympathetic nerve activity (RSNA), glomerular filtration (GFR), renal plasma flow (RPF), urine volume and urinary sodium. To assess neural control of volume homeostasis, 21 days after the induction of congestive heart failure (CHF) via myocardial infarction rats underwent volume expansion (0.9% NaCL; 10% body weight) to decrease RSNA. CHF rat and controls with or without renal denervation (DNX) or pretreated with the angiotensin II type 1 receptor antagonist candesartan (0.5 ug i.v.) were studied.

Results: CHF rats excreted only 68±5% of the volume load in 90 min. CHF rats pretreated with candesartan or after DNX excreted from 92% to 103% like controls. Decrease of RSNA induced by volume expansion were impaired in CHF rats but unaffected by candesartan pointing to an intrarenal drug effect. GFR and RPF were not significantly different in controls or CHF rendering mere hemodynamic effects on sodium and water excretion unlikely. 0.5 mg candesartan did not inhibit the pressor response to i.v. Ang II as compared to higher blood pressure lowerig doses.

Conclusions: The prominent function of increased RSNA – retaining salt and water - could no longer be observed after renal ANG II receptor blockade in CHF rats mimicking renal nerve ablation. Since inhibitors of the renin-angiotensin system are nowadays standard treatment of patients with CHF and hypertension, the role of *efferent sympathetic* denervation in these patients needs further meticulous scrutiny.

Funding: Government Support - Non-U.S.

PO2147

Extracellular Volume, Peripheral Resistance, and Cardiac Index May Be Altered in Early CKD

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Background: It is unknown if extracellular volume (ECV), cardiac index (CI), and peripheral resistance are altered in early stages of chronic kidney disease (CKD) before significant decline in glomerular filtration rate (GFR) or if these can be identified by routine laboratory measurements.

Methods: A total of 21 participants, including 13 with CKD stages 1-3 and 8 non-CKD controls, were prospectively recruited from outpatient clinics. CKD stage 3 was defined as an estimated GFR (eGFR) of 30-59 mL/min/1.73 m2, and stages 1-2 as a urine albumin-to-creatinine ratio >30 mg/g and eGFR ≥60. ECV was measured using bioimpedance spectroscopy and normalized to total body weight. CI and total peripheral resistance index (TPRI) were measured using non-invasive cardiac output monitoring. Measurements were compared using Fisher exact tests, Student's t tests, and Pearson correlations.

Results: Participants with CKD had a mean (SD) age of 65.4 (12.9) years vs. 59.8 (13.5) years for controls, *P*=0.36. Mean eGFR in the CKD group was 47.0 (17.9) mL/min/1.73 m2. In the CKD group there were 8 (61.5%) with diabetes, vs. 3 (37.5%) controls, *P*=0.39. Mean systolic blood pressure was 159.2 (22.3) in the CKD group vs. 143.1 (26.2) in the control group, *P*=0.17. Edema was present in 9 (69.2%) of the CKD group vs. 2 (25.0%) controls, *P*=0.08. Mean (SD) ECV/weight was marginally higher in the CKD group than in controls, 27.4% (3.7) vs. 24.7% (2.6), *P*=0.06. The CKD group had higher b-type natriuretic peptide (BNP), 182.8 (236.0) vs. 33.4 (35.4) pg/mL, *P*=0.04, lower CI, 2.4 (0.4) vs. 3.0 (0.5), *P*=0.04, and higher TPRI, 3800.2 (645.7) vs. 2980.8 (263.5) dyn.s.cm-5, *P*=0.001. Log-transformed BNP correlated with CI, r=-0.77, *P*=0.0002, and TPRI, r=0.50, *P*=0.04 (**Table**). ECV/weight did not correlate strongly with CI, r=-0.27, *P*=0.29, and TPRI, r=0.25, *P*=0.32.

Conclusions: In this hypothesis-generating study, patients with CKD had higher TPRI and lower CI than non-CKD controls. CI and TPRI correlated with BNP but not with ECV/weight. BNP, an easily measured and universally available test, may be used as a correlate for CI and TPRI in patients with early stage CKD. These findings need to be confirmed in larger cohorts.

Funding: Veterans Affairs Support

	CKD (N=13)	Non-CKD (N=8)	P value	Entire Cohort (N=20)		CKD (N=13)		Non-CKD (N=7)	
				Log BNP, Pearson r	P value	Log BNP, Pearson r	P value	Log BNP, Pearson r	P value
CI, L/min/m2	2.4 (0.4)	3.0 (0.5)	0.04	-0.77	0.0002	-0.64	0.02	-0.90	0.02
TPRI, dyn.s.cm-5	3800.2 (645.7)	2980 (263.5)	0.001	0.50	0.04	0.29	0.31	0.66	0.16

PO2148

Atrial Natriuretic Peptide Deficiency Alters Mitochondrial Bioenergetics in Dahl Salt-Sensitivity Rats

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Background: In the heart and fat tissue, Atrial Natriuretic Peptide (ANP) is known to affect mitochondrial bioenergetics. However, little is known about the effects of ANP on mitochondria in the kidney, especially in the context of salt-sensitivity (SS). We hypothesized that in SS hypertension ANP deficiency causes renal mitochondrial dysfunction and contributes to end-organ damage.

Methods: Hypertension was induced in male $SS^{NPPA-/-}$ (*Nppa* (encoding for ANP) knockout in Dahl SS background) and SS^{WT} (wild type Dahl SS) rats by a 21-day long high salt diet challenge (HS, 4% NaCl). Normal salt diet (NS, 0.4% NaCl) was given to age-matched control animals. A combination of *in vivo* techniques and studies on isolated renal mitochondria (seahorse respiration and spectrofluorimetry assays) were used to test the role of *Nppa* knockout in mitochondrial bioenergetics.

Results: $SS^{NPPA-/-}$ rats exhibit exacerbated salt-sensitivity of blood pressure and kidney injury when challenged with a HS diet. In order to test mitochondrial function in this model, we measured membrane potential and levels of superoxide and H_2O_2 in renal cortical mitochondria. TMRM, Amplex Red and MCLA were used to detect membrane potential, H_2O_2 and superoxide, respectively. We report a decrease in mitochondrial membrane potential in the $SS^{NPPA-/-}$ rats vs SS^{WT} (both on NS and HS diets), and an increase in mitochondrial H_2O_2 and superoxide levels in the same groups, indicative of leakage within the ETC. A Western analysis revealed that in SS^{WT} rats SOD2 levels are increased by a HS diet, while in $SS^{NPPA-/-}$ animals its expression is suppressed. In addition, we observed activation of the antioxidant capacity in the $SS^{NPPA-/-}$ rats vs SS^{WT} (on HS diet). $SS^{NPPA-/-}$ rats exhibited a difference in MCU (mitochondrial calcium uniporter) activity when compared to SS^{WT}, implying an effect on mitochondrial calcium uptake. Interestingly, seahorse analysis revealed elevation of the oxygen consumption rate (OCR) in the knockout rats on HS, while in HS fed SS^{WT} rats OCR was reduced (vs NS).

Conclusions: Lack of circulating ANP results in changes of mitochondrial bioenergetics in the renal tissue via effects on calcium uptake, and alters respiratory chain activity leading to changes in ROS production. Further studies will advance the understanding of the mitochondria-mediated mechanisms affecting renal damage susceptibility in SS hypertension.

Funding: NIDDK Support, Private Foundation Support

PO2149

Inhibition of Mineralocorticoid Receptor Ameliorates Salt-Sensitive Hypertension After Ischemic-Reperfusion Injury in Rats

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Background: The transition from acute kidney injury (AKI) to chronic kidney diseases a major pathway for progression to end-stage kidney disease. Although hypertension is reported to be associated with the clinical progression of chronic kidney disease, the mechanism by which AKI induces hypertension remains elusive. Previous studies have demonstrated that salt-sensitive hypertension occurs in rats after ischemic reperfusion injury (IRI), a rodent model of AKI, and that distal nephrons play an important role in the development of salt-sensitive hypertension. Herein, we investigated the role of the mineral corticoid receptor (MR) in the progression of IRI-induced salt-sensitive hypertension in rats.

Methods: Seven days after right nephrectomy, IRI was induced by clamping of the left renal artery for 45 min in 8-week-old male Sprague-Dawley rats. Rats were sacrificed at 7 days after IRI, and expression of MR examined. IRI rats were also given drinking water with 1% sodium chloride (IRI/NaCl), or were implanted with an osmotic mini-pump to infuse aldosterone (IRI/Aldo). Esaxerenone (3 mg/kg/day; a non-steroidal MR antagonist [MRA]), or vehicle were administrated in IRI/NaCl and IRI/Aldo rats for 6 weeks. Blood pressure and urinary protein level were measured weekly during the study period. Protein expression in renal tissues was examined by immunoblotting and/or immunohistochemistry.

Results: MR expression was increased at 7 days after IRI. Further, blood pressure and urinary protein excretion increased in IRI/NaCl and IRI/Aldo rats over the 6-week observation period, whereas these effects were negated by MRA administration. Similarly, MRA ameliorated the expression of the β-epithelial sodium channel (ENaC), γ-ENaC, and fibrotic markers, but not α-ENaC or NaCl cotransporter channel in both IRI/NaCl and IRI/Aldo rats.

Conclusions: Upregulation of MR, β-ENaC, and γ-ENaC may play a pivotal role in the development of salt-sensitive hypertension in rats after IRI.

Funding: Government Support - Non-U.S.

PO2150

The Effect of Epidermal Growth Factor Inhibition on Salt Sensitivity in Mice

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Background: Every year in the United States, more than 3 million adults are determined to have high blood pressure. Studies have shown that the epidermal growth factor (EGF) decreases the open probability of the epithelial-Na+ channel (ENaC) along the apical surface of the kidney cortical collecting duct (CCD). Yet, it is unknown whether EGF influences renal Na+ transport via the Na+-Cl- cotransporter (NCC). Our laboratory has investigated whether EGF regulates NCC. We performed various in vitro experiments using mouse distal convoluted (mDCT-15) cells and found that EGF decreases NCC surface expression with an increase in endocytosis of surface NCC. Overall, our findings and those from other researchers, collectively suggest that EGF decreases the activity of two key mediators of salt-sensitive blood pressure, ENaC and NCC. This discovery served as our rationale for investigating whether EGF inhibition affects BP, and if this response is related to dietary sodium intake.

Methods: Using radio-telemetry, we collected the systolic blood pressure (SBP) measurements in five male mice ages 7 weeks old. These animals received a low salt (LS) diet (0.4% Na chow) for 6 days and high salt (HS) diet (4% Na chow) for 8 days. Over a period of two weeks, only the experimental (E) group (n=3) received gefitinib (an EGF receptor tyrosine kinase inhibitor) at a regimen of 100 mg/kg/d given orally while the control (C) group (n=2) received a placebo.

Results: The results for the change in awake-SBP while receiving diet (0.4% Na chow) for 6 days and high salt (HS) diet (4% Na chow), showed the *experimental (E) group* had a greater increase in SBP in response to a higher dietary Na+ intake (*E group*: 7.70 ± 0.17 vs. *control (C) group*: 0.311 ± 0.29 mmHg, p<0.001). The delta for the difference in BP change when increasing the dietary Na+ intake was greater for the *E group* of mice (delta = 7.40 mmHg, p<0.001).

Conclusions: Therefore, our data strongly suggests that inhibition of EGF increases the salt sensitivity of blood pressure. This may indicate that EGFR ligands act as tonic inhibitors of tubular sodium reabsorption. Future experiments will explore the in vivo effects of EGFR inhibition on NCC, ENaC and sodium excretion.

Funding: NIDDK Support, Veterans Affairs Support

PO2151

The Effect of Epidermal Growth Factor Inhibition on Diurnal Variation of Blood Pressure in Mice

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Background: There are 78 million adults in the United States who have hypertension (HTN). HTN is a serious medical condition that serves as risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD). Blood pressure (BP) normally declines about 10% during sleep and this is called "dipping". Studies have demonstrated that an attenuated decline in nocturnal BP ("non-dipping") is associated with increased cardiovascular risks. Investigations by our group and others have demonstrated an effect of the epidermal growth factor (EGF) on sodium transport proteins and BP. However, an association between EGF and "dipping" has not been described.

Methods: Using radio-telemetry in five male mice ages 7 weeks old, we collected the systolic blood pressure (SBP) measurements over 24 hours daily for two weeks. These animals received a low salt (LS) diet (0.4% Na chow) for 6 days and high salt (HS) diet (4% Na chow) for 8 days. Only the experimental (E) group (n=3) received gefitinib (an EGF receptor inhibitor) at a regimen of 100 mg/kg/d given orally while the control (C) group (n=2) received a placebo. The change in SBP was evaluated during rest (9am-9pm) which are morning hours versus awake (9pm-9am) during evening hours since mice are nocturnal.

Results: The results showed the E group had less of a decrease in their SBP during sleep than the C group (E group: -9.7 ± 0.016 vs. C group: -14.4 ± 0.34 mmHg, p<0.001; delta = 4.7 mmHg, p<0.001). When increasing the dietary Na+ intake by giving the HS diet, once again the E group demonstrated an attenuation of their ability to lower their SBP during resting compared to the C group (E group: -7.3 ± 0.18 vs. C group: -13.5 ± 0.38 mmHg, p<0.001). Here the delta is 6.1 mmHg, p<0.001, which shows that the C group maintained a greater decrease in their resting SBP compared to the E group.

Conclusions: Overall, our results suggest that inhibition of EGF leads to decreased dipping in SBP regardless of the dietary Na intake and this effect is greater with a high dietary Na intake. Therefore, our data is the first to suggest that EGF may play a role in the nocturnal dipping of BP, which could have potential implications for managing HTN-related cardiovascular disease.

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PO2152

The Klotho Deficiency and Not the FGF-23 Rise Is Associated with Heart Failure with Reduced Left Ventricular Ejection Fraction in Patients with Preserved Kidney Function

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Background: The FGF23-Klotho axis is increasingly implicated in the pathophysiology of heart failure, especially during advanced chronic kidney disease (CKD). Our objective is to study the association between this FGF23-Khloto axis and heart failure in patients without CKD. This topic is less studied in medical literature

Methods: This is a cross-sectional study of the FGF23 assessment, Klotho and the rest of the phosphocalcic assessment covering 70 patients with normal renal function. These patients had echocardiographic exploration which made it possible to distribute them in two groups: Group HF: LVEF(Left Ventricular Ejection Fraction)<55% (n = 18); Group NoHF: LVEF> 55% (n = 52). Heart failure(HF) was exclusively of ischemic origin.

Results: These were 36 women and 34 men, average age 58 + - 10 years with an estimated glomerular filtration rate (eGFR) at an average of 92 ml / min / 1.73m^2. No difference in eGFR between the two groups. Klotho was far lower with a statistically significant difference in Group HF. FGF23 was higher in Group HF but the difference was not statistically significant. PTH (parathyroid hormone)was statistically higher in Group HF and calcemia was statistically lower in Group HF. Phosphatemia and vitamin D were not associated with heart failure.

Conclusions: Although the sample studied is not large, Klotho but not FGF23 is strongly associated with systolic heart failure. This and other results will be further discussed.

PO2153

Aetiological Subtypes of Transient Ischemic Attack and Ischaemic Stroke in CKD: A Population-Based Study

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Background: Chronic kidney disease (CKD) is strongly associated with stroke risk but the mechanisms underlying this association are unclear, and might be informed by subtype-specific analyses. However, few studies have reported stroke subtypes in CKD according to established classification systems such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. We therefore aimed to determine which transient ischaemic attack (TIA) and ischaemic stroke subtypes using the TOAST classification occur most frequently in patients with CKD.

Methods: In a population-based study of all TIA and stroke (Oxford Vascular Study; 2002-2017), all ischaemic events were classified by TOAST subtypes (cardioembolism, large artery disease, small vessel disease, undetermined, multiple, other aetiology, or incompletely investigated). Logistic regression was used to determine the relationship between CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) and TIA/stroke subtypes adjusted for age, sex, and hypertension, and then stratified by age and eGFR category.

Results: Among 3178 patients with TIA (n=1167), ischaemic stroke (n=1802), and intracerebral haemorrhage (n=209), 1267 (40%) had CKD. Although there was a greater prevalence of cardioembolic events (31.8 vs 21.2%; p<0.001) in patients with CKD, this association was lost after adjustment for age, sex, and hypertension (Adjusted

OR=1.20, 95% CI=0.99-1.45; p=0.07). Similarly, although patients with CKD had a lower prevalence of small vessel disease (8.8 vs 13.6%; p<0.001), undetermined (26.1 vs 39.4%; p<0.001), and other aetiology (1.0 vs 3.6%; p<0.001) subtypes, these associations were also lost after adjustment (Adjusted OR=0.86, 0.65-1.13; p=0.27 and 0.73, 0.36-1.43; p=0.37 for small vessel disease and other defined aetiology, respectively) for all but undetermined aetiology (Adjusted OR=0.81, 0.67-0.98; p=0.03).

Conclusions: There were no independent positive associations between CKD and specific TOAST subtypes which suggests that renal-specific risk factors are unlikely to play an important role in the aetiology of particular subtypes. Future studies of stroke and CKD should report subtype-specific analyses to gain further insights into potential mechanisms.

PO2154

Identification of Novel Biomarkers and Pathways for Coronary Artery Calcification in Non-Diabetic Patients on Hemodialysis Using Metabolomic Profiling

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Background: A better understanding of pathophysiology involving coronary artery calcification (CAC) in hemodialysis (HD) patients will help to develop new therapies. We sought to identify the differences in metabolomics profiles between HD patients with and without CAC.

Methods: This is a case-control study nested within a cohort of 568 incident HD patients from the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study. Cases were non-diabetics with a CAC score >100 (n=51), and controls were non-diabetics with a CAC score of 0 (n=48). We measured 452 serum metabolites in each participant using liquid chromatography–mass spectrometry. Metabolites and pathway scores were compared using Mann–Whitney U tests, partial least squares-discriminant analyses, and pathway enrichment analyses. Multiple logistic regression was used to examine the associations of key metabolites and pathways with CAC.

Results: Cases had a median CAC score of 466 (IQR 246-981). Compared to controls, cases were older (64±13 vs. 42±12 years) and were less likely to be African American (51% vs. 94%). We identified three metabolites in bile acid synthesis (chenodeoxycholic, deoxycholic, and glycolithocholic acids) and one metabolic pathway (arginine/proline metabolism) that were associated with CAC. After adjusting for demographics, higher levels of chenodeoxycholic, deoxycholic, and glycolithocholic acids were associated with higher odds of having CAC. Comparing the third with the first tertile of each bile acid, the adjusted OR (95% CI) was 6.34 (1.12-36.06), 6.73 (1.20-37.82), and 8.53 (1.50-48.49), respectively. Using the first principal component (PC1) score, arginine/proline metabolism was associated with CAC after adjusting for demographics [OR: 1.83 (95% CI: 1.06-3.15) per 1 unit higher in PC1 score], and the association remained significant after additional adjustments for statin use.

Conclusions: Among HD patients without diabetes mellitus, chenodeoxycholic, deoxycholic, and glycolithocholic acids may be potential biomarkers for CAC, and arginine/proline metabolism may emerge as a new pathway in the pathogenesis of CAC and could be a potential treatment target.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Science, Private Foundation Support

PO2155

NaRE: A Novel "Salt Response Element" in the NPFFR2 Gene Promoter and Antagonist of the D_1 Dopamine Receptor

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Background: The neuropeptide FF receptor R2 (NPFFR2) is one of two receptors for NPFF and is endowed with pro-hypertensive and anti-natriuretic activities. We looked for regulatory elements in the *NPFFR2* gene promoter and how it interacts with an anti-hypertensive and natriuretic protein, the dopamine type receptor (D_1R).

Methods: Human renal proximal tubule cells (hRPTCs) treated with low NaCl (90 mM) increased mRNA (2.3±0.4-fold) and protein (155±5% *vs*. 100±4%) levels of the salt-retaining NPFFR2, whereas treating the cells with high NaCl concentration (170 mM) decreased the mRNA (-0.70±0.05-fold) and protein (~50±4%, P<0.05) levels.

Results: Promoter analysis of the mouse and human *NPFFR2* genes for regulatory elements identified a single 8-bp region, aptly called "**NaRE**" for **Na**$^+$ **R**esponse **E**lement, at ~2.3 kb upstream of +1 position. This is 75% identical to the "Dehydration Responsive Element" ("TACCGACAT") in the *Rdc2a* gene of *Arabidopsis thaliana* which is a cis-acting element which responds to dehydration, low temperature, and salinity. In the presence of the wild-type NaRE, the *NPFFR2* promoter responded well to both low (4.1±0.05-fold increase) and high (0.52±0.5-fold decrease) NaCl concentrations, but not in the absence of NaRE in a mutant *NPFFR2* promoter construct. Antigene RNA to block NaRE expression in the kidneys of C57Bl/6 mice resulted in the inability of the mice to respond to a low sodium diet (<0.04 g sodium/day) and reduced further the decreased systolic blood pressure caused by the low sodium diet (65±0.6 mm Hg *vs*. 83.3±1.3, P<0.05). We then studied a mechanism by which NPFFR2 dynamically interacts with the D_1R. NPFFR2 and D_1R co-immunoprecipitated and colocalized in hRPTCs and mouse kidney. NPFF and the D_1R/D_5R agonist fenoldopam had antagonistic effects on cAMP production (2.54±0.1 pmol/mg/min for fenoldopam *vs*. 1.23±0.2 for vehicle *vs*. 1.11± 0.2 for fenoldopam and NPFF) and sodium transport (1.78±0.1-fold with fenoldopam) in hRPTCs. C57Bl/6 mice fed a 4% NaCl markedly increased (>2.5-fold) the co-immunoprecipitation between renal NPFFR2 and D_1R, thus increasing the ability of NPFFR2 to antagonize the D_1R effects.

Conclusions: Our data are the first to identify NaRE and demonstrate novel transcriptional and post-translational mechanisms by which mammalian genes respond to sodium.

Funding: NIDDK Support

PO2156

Discovery and Characterization of Small-Molecule Potentiators of $K_{ir}4.1/5.1$

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Background: Heterotetrameric inward rectifier potassium (Kir) channels composed of Kir4.1 (*KCNJ10*) and Kir5.1 (*KCNJ16*) play key roles in regulation of sodium, potassium, and water balance by the distal convoluted tubule of the renal tubule. Loss-of- function mutations in *KCNJ10* lead to EAST syndrome, which is characterized by neurological dysfunction and renal salt wasting. Here we describe the discovery and characterization of small-molecule potentiators of Kir4.1/5.1 that could potentially be used to rescue the function of EAST syndrome mutant channels.

Methods: We established a monoclonal HEK-293 cell line that stably expresses human Kir4.1 and Kir5.1 from a bicistronic vector, and developed and validated a fluorescence-based thallium-flux assay of Kir4.1/5.1 channel function in 384-well format. This assay was used to screen small-molecules from the Vanderbilt Chemistry Institute Library and confirmed with whole-cell electrophysiology.

Results: To date, we have screened more than 60,000 compounds using this assay and identified 420 putative inhibitors and 354 putative potentiators of Kir4.1/5.1. Forty-five of these potentiators increase Kir4.1/5.1-mediated thallium flux by greater than 50% and are selective for Kir4.1/5.1 over homomeric Kir4.1 channels. Fourteen (14) potentiators are active at low single micromolar concentrations with EC_{50} values less than 5 μM, while six (6) compounds appear to be highly efficacious and increase Kir4.1/5.1-mediated thallium flux by more than 100%. Importantly, we have also verified with patch clamp electrophysiology the activity of one of the first-in-class activator of Kir4.1/5.1, termed VU206. In thallium flux assays, VU206 potentiates thallium flux dose-dependently with an EC_{50} of 1.9 μM and maximal efficacy of ~50% above baseline between 10-30 μM. In whole-cell patch clamp experiments, VU206 led to maximal activation of whole-cell currents at 10 μM, complementing the thallium assay. Analysis of current-voltage relationships showed robust activation at both negative and positive test potentials without a depolarizing shift in the reversal potential suggesting VU206 potentiates Kir4.1/5.1 activity without affecting ion selectivity.

Conclusions: Findings from this study provide a novel pharmacological tool for exploring renal Kir4.1/5.1 channel integrative physiology and therapeutic potential of Kir4.1/5.1 potentiators for the treatment of EAST syndrome.

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PO2157

Improvement in Albuminuria and Hypertension in Renin Transgenic Mice by a Novel Filterable Form of Angiotensin-Converting-Enzyme 2 with Prolonged Half-Life

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Background: ACE2 is a monocarboxypeptidase that converts angiotensin (Ang) II to Ang 1-7. Its large molecular size precludes it from being filtered by the kidneys. We have developed shorter forms of mouse(619 AA) and human ACE2(618 AA) that are filterable but, like the native ACE2, have a short(hours) half-life in vivo. We bio-engineered a fused protein using an albumin binding domain(ABD) and tested its long-lasting effects in mice transgenic for an unregulated secretion of Renin(Ren TgMK).

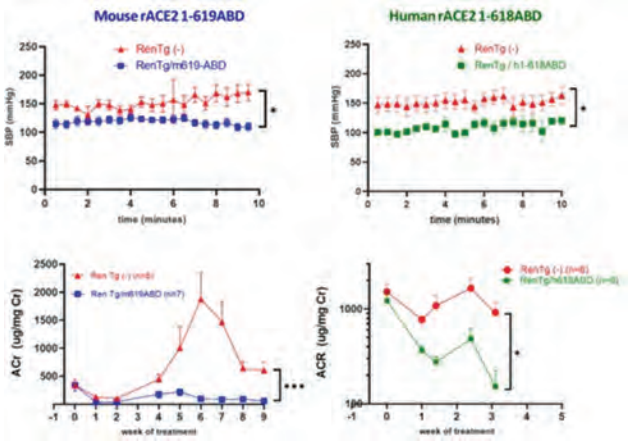
Methods: Short soluble mouse(m) and human(h) ACE2 variants were fused with Albumin-Binding Domain(ABD). In vivo pharmacokinetic was determined after i.v. and i.p. injection followed by repeated measurement of plasma ACE2 activity. Subsequently, m and h rACE2-ABD(2 mg/kg) were injected every 2-3 days i.p. to Ren TgMK mice. The endpoints included urinary albumin(ACR) and blood pressure.

Results: Administration of 619-ABD to ACE2KO mice resulted in detectability of urinary ACE2 activity which at the baseline was not detectable. Blocking proximal tubule (PT) reabsorption with L-lysine, further increased urinary ACE2 activity suggesting that the ABD-tagged ACE2 undergoes glomerular filtration and is taken up by PT. In WT mice, augmentation of plasma ACE2 activity could still be shown a week after administration. In Ren TgMK mice, both m and h ACE2-ABD markedly reduced SBP and ACR(Figure).

Conclusions: A shorter soluble ACE2 variant fused with ABD exhibits a prolonged half-life while maintaining full enzymatic activity. The protein is filterable and re-absorbable by the proximal tubule, thereby providing increased kidney ACE2 activity

as well as circulating plasma ACE2 activity. Its efficacy was documented by reduced BP and ACR in Ren TgMK, a hypertensive model due to RAS activation. Thus, this novel ACE2 variant with extended half-life offers potential for treatment of kidney disease and hypertension.

Funding: NIDDK Support



PO2158

Fibroblast Growth Factor 23 Induces Ventricular Arrhythmias and Prolongs QTc Interval in Mice In Vivo Mediated Through FGF Receptor 4

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Background: Sudden cardiac death and arrhythmias are leading causes of mortality in those with compromised renal function, such as in chronic kidney disease (CKD). Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone released by osteocytes, which becomes markedly elevated in CKD. Previously, we found that FGF23 increases intracellular Ca^{2+} in cardiomyocytes and alters contractility in mouse ventricles *ex vivo* via stimulation of FGF receptor 4 (FGFR4). Since FGF23 could disrupt Ca^{2+} homeostasis, we hypothesized that FGF23 at pathological levels would alter depolarization/repolarization of the heart and induce arrhythmias *in vivo* via a mechanism involving FGFR4.

Methods: To asses our hypothesis, CD-1 male mice (3 months old) were anesthetized and electrocardiogram (ECG) needle electrodes were inserted into the limbs. The jugular vein was cannulated for infusion of vehicle or FGF23 (9ng/ml total blood volume) with and without pretreatment with an FGFR4-specific blocking antibody (anti-FGFR4; U3 Pharma). Lead II ECG and arrhythmias were monitored at baseline and then for 30 minutes post injection.

Results: FGF23 induced premature ventricular contractions (PVCs) in 5 out of 11 mice (P=0.038 vs vehicle) with an average maximal rate of PVCs in these 5 mice of 10.2 ± 5.2 PVC/minute (P<0.01 vs vehicle). Vehicle (n=9) and FGF23+anti-FGFR4 treated (n=8) mice did not exhibit PVCs. Treatment with Isoproterenol (0.1mg/kg) after FGF23 further augmented arrhythmias to a maximal rate of 28.0 ± 21.1 PVC/minute (P<0.05 vs vehicle) and 2 out of 8 mice displayed ventricular tachycardia. Upon examination of ECG intervals, FGF23 prolonged QTc within 30 minutes (P<0.05, n=8) compared to vehicle treatment (n=9), whereas no effect was found for PR interval or QRS duration. FGFR4 blockade abrogated the QTc prolonging effects of FGF23 (n=8).

Conclusions: We conclude that FGF23/FGFR4 signaling in the heart may contribute to ventricular arrhythmogenesis and repolarization disturbances commonly observed in patients with CKD and may be an important therapeutic target to reduce cardiac mortality in CKD.

PO2159

Use of Immune Checkpoint Inhibitors in ESKD

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Background: Use of immune checkpoint inhibitors(ICI) in ESKD patients is limited. We describe our single-center experience of ICI use in ESKD patients and summarize the current literature.

Methods: Using an analytics database, we identified all patients with a minimum of one ESKD diagnosis code who received ICI therapy at our health system. Charts were reviewed manually to confirm that patients were on HD or PD during the ICI therapy. Clinical details such as demographics, comorbidities, cancer type, immune-related adverse events (irAEs), cancer disease status, and patient survival were reviewed. Further literature search was performed for all published cases of ICI use in ESKD patients and was summarized as part of the methods.

Results: In total, 8 patients with ESKD were initiated on ICI. A variety of malignancies were identified. Four patients received pembrolizumab, two received nivolumab, one received both ipilumumab and nivolumab, and the last received PD-L1 inhibitor atezolizumab. All eight patients were receiving proton pump inhibitors. The mean duration on dialysis (dialysis vintage) prior to ICI therapy was 15.8 months (range: 3-60 months). Two patients had an immunotherapy-related adverse event. In both cases, the physicians discontinued the offending ICI agent and started the patients on systemic steroid therapy. Both patients subsequently suffered from cancer progression. The remaining patients tolerated the ICIs well, without significant complication or side effect. No dose adjustments were required. In regards to cancer status, the cancer did not progress in 3 patients but progressed in the remaining five. 4 patients died. Literature review revealed total of 26 patients mostly receiving HD (92%). Interestingly, 27% of these patients were on dialysis as a result of a rejected kidney transplant due to ICI therapy, and then continued to receive ICI. Over 80% of the patients had either partial or complete response to treatment. Aside from the kidney transplant rejection preceding dialysis, a minimal number of patients had a grade 2, 3, or 4 adverse immunotherapy related event (15%)

Conclusions: Based on our series and previously published literature review, the rate of adverse events appear similar to non-ESKD patients (15-25%). ESKD may not be a contraindication to the use of ICI therapy.

PO2160

AKI as a Risk Factor for Mortality in Oncological Patients Receiving Immunotherapy

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Background: Checkpoint inhibitors (CPI) are used to treat cancer by promoting immune-mediated elimination of tumor. CPI–associated AKI (CPI-AKI) is an adverse effect and its incidence is 13-29%. The effect of CPI-AKI on patient survival is unknown. Our aim is to evaluate if CPI-AKI is a risk factor for mortality in patients with cancer under immunotherapy.

Methods: We evaluated data of all patients under CPI at our centre between March 2018-May 2019 and followed-up until April 2020. We divided them into 2 groups according the development of CPI-AKI. Kaplan-Meier and Cox survival analysis comparing patients who developed CPI-AKI with those who did not were performed.

Results: 821 patients received CPI during the study period. Mean age was 62.03 years and 59.2% men. Malignancies: lung 30.3%, urogenital 20.5%, melanoma 10.8%, others 38.4%. 54.34% patients received antiPD1, 28% antiPDL1, 1.6% antiCTLA4, 4.4% other drug, 11.7% two CPI. Mean baseline creatinine was 0.85±0.30 mg/dL. 125 patients (15.2%) developed CPI-AKI. 790 patients completed follow up and were included in the survival analysis, including all with CPI-AKI. Mean time of follow up 13.20months. 50.8% patients had died at the end of follow up, mean time after starting CPI 8.60 months. There were no differences in age/gender or basal creatinine between patients who died and those who survived. In patients who developed CPI-AKI, mortality was 70.40% vs 47.27% as compared with non-CPI-AKI (p<0.0001). Cox survival analysis including age/gender, malignance and type of CPI identified CPI-AKI as a risk factor for mortality (HR 1.597, 95%CI 1.258-2.028, p<0.001), as well as malignance (melanoma HR 1.897, 95% CI 1.290-2.793, lung HR 1.272, 95% CI 1.010-1.602 and urogenital HR 1.543, 95% CI 1.178-2.041, p=0.001) and CPI (PD1 HR 2.160, 95% CI 1.458-3.205, PDL1 HR 1.887, 95% CI 1.253-2.84 and 2 drugs HR 2.049, 95% CI 1.279-3.279,p=0.005).

Conclusions: In a study including more than 800 patients with advanced cancer receiving immunotherapy, CPI-AKI incidence was 15.2%. More than 50% of patients died during a mean follow up of 13 months. CPI-AKI development was a risk factor for mortality in our series. As far as we know, this is the first time that the association between AKI and mortality in patients receiving immunotherapy is described.

PO2161

A Single-Center Cohort Study of Nephrotoxicity due to Immune Checkpoint Inhibitors

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Background: Previous studies and case reports have demonstrated an increased risk of nephrotoxicity in patients receiving immune checkpoint inhibitors (CPIs) compared to clinical trials. The primary objective of this study was to contribute to the existing data regarding the frequency, causes of, and risk factors for CPI-induced AKI.

Methods: This was a retrospective cohort study of patients receiving at least one dose of a CPI at a health system in Central Wisconsin from 2013 to 2019. Baseline serum creatinine, defined as the average of all values obtained within 6 months of the CPI start date, was compared to all serum creatinine measurements during CPI therapy and through 60 days after the last CPI dose. Patients developing an AKI of at least three day duration were further assessed to determine the likely cause of AKI, with the incidence of potentially CPI-induced AKI being our primary outcome.

Results: A total of 936 patients received at least one dose of a CPI at MCHS during the study period. After applying exclusion criteria, a total of 910 patients were included in the analysis. A total of 8.4% of patients (76 of 910) were on dual CPI therapy (ipilimumab

and nivolumab). The incidence of AKI of any duration was 36.6% (333 of 910 patients), while sustained AKI (defined as 3 days or longer or not re-measured) occurred in 31.0% of patients (282 of 910). The incidence of presumed CPI-induced AKI was 3.2% (29/910). A total of 25.2% (71/282) of sustained AKI patients had at least one concurrent immune-related adverse effect (irAE), compared to 55.2% (16/29) of presumed CPI-induced AKI. CPI-induced AKI occurred on average 88.2 days (standard deviation 80.6) after starting the CPI, with several AKI events occurring within 60 days after stopping the CPI.

Conclusions: AKI secondary to CPI is a common side effect of CPI. In our population, it occurred at an incidence of 3.2% and sometimes occurred even after the last dose of CPI. The etiology of AKI in almost all cases of biopsy-proven CPI-induced AKI is acute interstitial nephritis. The risk appears to be increased if a patient has already developed an irAE.

Funding: Private Foundation Support

PO2162

Checkpoint Inhibitor-Related Renal Vasculitis and Use of Rituximab

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Background: The percentage of cancer patients eligible for checkpoint inhibitor (CPI) therapy has increased rapidly over the past few years and approaches 45%. As a result, more cases of CPI-related nephrotoxicity, including a rare subset with vasculitis, are being reported. To elucidate the clinical presentation of CPI-associated vasculitis with kidney involvement and its possible mechanisms, treatment options, and prognosis, we describe cases from a comprehensive cancer center and reviewed the literature for similar cases.

Methods: We retrospectively reviewed the charts of all cancer patients from 2014 to 2020 who were diagnosed with CPI-related nephrotoxicity and underwent a kidney biopsy

Results: We identified 5 cases of vasculitis with kidney involvement: 3 patients were diagnosed with renal vasculitis, 1 case with ANCA vasculitis, and 1 case with Immunoglobulin A (IgA) vasculitis. Of these cases, 4 patients were receiving nivolumab, and 1 patient was receiving tremelimumab. All patients had microscopic hematuria, four out of five had negative anti-neutrophil cytoplasmic antibodies (ANCA) serology, one patient had concurrent lung involvement and positive ANCA serology, and all had severe acute kidney injury with creatinine > 4.50 mg/dL upon diagnosis. All patients were treated by discontinuing CPI and initiating corticosteroids and rituximab. Three patients received plasmapheresis; 2 of these required renal replacement therapy (RRT) including the patient with lung involvement. All patients after rituximab had partial or complete renal response. Two patients died within 8 months of diagnosis due to malignancy progression. None of the patients had a relapse of vasculitis

Conclusions: We demonstrated that CPI can be associated with different types of vasculitis with kidney involvement that are predominantly ANCA negative and manifest as severe acute kidney injury. Despite the lack of strong evidence, treatment similar to treatment of primary ANCA vasculitis with corticosteroids and rituximab is well tolerated with favorable renal outcomes

Funding: Other NIH Support - National Institutes of Health through Cancer Center Support Grant

PO2163

AKI and Immune-Related Adverse Events (irAEs) in Patients with Genitourinary Cancers Receiving Immune Checkpoint Inhibitors (ICIs)

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Background: ICI use is associated with AKI. Patients with advanced genitourinary (GU) malignancies, including renal cell and bladder carcinoma, are at increased risk of AKI due to the high prevalence of chronic kidney disease (CKD) and frequent need for combination ICI and nephrotoxic platinum-based chemotherapy. We evaluated the incidence of AKI and irAEs in these patients.

Methods: Retrospective cohort of patients with GU-cancers receiving ICIs within a large healthcare network from 2011-2018. Cancer type, ICI class, comorbidities, baseline medications, and irAEs were determined using electronic records. AKI in the first 12 months after ICI initiation was the primary outcome. Multivariable models were used to evaluate for predictors of AKI.

Results: 639 patients with GU-cancers were included. Average age was 66 years, 72% were male, 91% were white, 50% had CKD (eGFR<60 mL/min/1.73m^2) and 51% had undergone full nephrectomy. 61% received PD1, 32% PDL1 and 7% combination PD1/CTLA4. 32% received prior platinum-based regimens or gemcitabine, and 8% received concurrent bevacizumab. 164 patients (26%) experienced AKI in the first 12 months. In a multivariable model, baseline coronary artery disease was predictive of AKI (p=0.02); prior nephrectomy, baseline CKD, and nephrotoxic chemotherapy exposure were not (Table). 185 (29%) experienced immune-related adverse events, most commonly thyroiditis (16%), gastrointestinal (7%), rash (4%), pneumonitis (4%), and hepatitis (4%).

Conclusions: AKI and irAEs are common in patients with GU-cancers receiving ICIs. Baseline CKD, prior nephrectomy nor nephrotoxic chemo use predict AKI after ICI indicating these factors should not exclude individuals from receiving treatment.

Multivariable Model for Predictors of Acute Kidney Injury

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio [95% CI]	P-value	Adjusted odds ratio [95% CI]	P-value
Demographics				
Age (≥65 vs <65)	0.89 (0.62,1.27)	0.51	0.84 (0.58,1.23)	0.37
Male	1.31 (0.87,1.96)	0.21	1.33 (0.80,1.83)	0.36
White	0.68 (0.38,1.22)	0.20	0.70 (0.39,1.27)	0.24
ICI class		0.26		
Ref (combination therapy)				
PD1	0.93 (0.47,1.84)	0.57		
PDL1	0.68 (0.33,1.40)	0.15		
Comorbidities				
Diabetes	1.12 (0.72,1.76)	0.61		
Hypertension	0.90 (0.61,1.31)	0.57		
Cirrhosis	1.25 (0.32,4.88)	0.75		
Coronary artery disease	1.47 (0.99,2.18)	0.06	1.58 (1.04,2.38)	0.03
CKD (eGFR<60 mL/min/1.73 m^2)	0.75 (0.53,1.08)	0.12		
Congestive heart failure	0.83 (0.39,1.79)	0.64		
Chronic pulmonary disease	1.28 (0.65,2.51)	0.48		
Baseline Medications				
ACEi/ARB	0.96 (0.65,1.42)	0.84		
NSAIDs	1.71 (0.93,3.13)	0.08	1.80 (0.96,3.37)	0.07
PPI	1.02 (0.67,1.55)	0.91		
Diuretics	1.41 (0.88,2.27)	0.15		
Other				
Tumor type (bladder vs RCC)	0.93 (0.65,1.33)	0.70		
Full nephrectomy	0.72 (0.51,1.03)	0.07	0.71 (0.49,1.02)	0.06
Metastatic	1.04 (0.51,2.11)	0.92		
Concurrent bevacizumab	0.81 (0.42,1.59)	0.55		
Prior platinum gemcitabine	0.90 (0.61,1.32)	0.58		
irAE	1.31 (0.89,1.92)	0.17		

In this multivariable model, age, gender, race were selected a priori for inclusion; baseline variables with a p-value < 0.1 in the univariable analysis were also included. Abbreviations: AKI = acute kidney injury, CI = confidence interval, PD1 = programmed cell death protein 1, PDL1 = programmed death ligand 1, PPI = proton pump inhibitor, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blockade

PO2164

Electrolyte Abnormalities in Patients Receiving Immune Checkpoint Inhibitors

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Background: Hyponatremia due to endocrinopathies such as adrenal insufficiency and hypothyroidism has been reported in patients receiving immune checkpoint inhibitors. Other electrolyte abnormalities such as hypocalcemia and hypokalemia have also been associated with the use of these agents. We study the incidence and predictors of electrolyte abnormalities in cancer patients receiving immune checkpoint inhibitors.

Methods: Patients who received immune checkpoint inhibitors at Massachusetts General Hospital Cancer Center between 2011 and 2018 were included. Incidence of electrolyte abnormalities were determined in the first 12 months after drug initiation and graded for severity by using Common Terminology for Cancer Adverse Events criteria. The predictors of severe electrolyte abnormalities were determined using a multivariable logistic regression model.

Results: We analyzed 2458 patients started on checkpoint inhibitors in our cancer center. Average age was 64 (SD 13) years, 58% were male and 90% were White. In the first year of follow-up, 62% experienced hyponatremia, 27% had hypokalemia, 26% had hyperkalemia, 49% had hypophosphatemia and 9% had hypocalcemia. Grade 3 or 4 hyponatremia was seen in 136 patients (6%) and occurred 164 days (SD 100) after checkpoint inhibitor initiation; only 9 cases of grade 3 or 4 hyponatremia were due to endocrinopathies. CTLA4 inhibitors were associated with a higher risk of grade 3 or 4 hyponatremia and hypophosphatemia. Patients with gastrointestinal malignancies experienced the highest risk of grade 3 or 4 electrolyte abnormalities.

Conclusions: Electrolyte abnormalities are common in cancer patients receiving immune checkpoint inhibitors. Endocrinopathies leading to severe hyponatremia are rare (<0.5%).

Funding: NIDDK Support

Electrolyte disorders	
Hyponatremia (mEq/L)	
Baseline sodium (Mean, SD)	137 (3)
Overall incidence (%)	1519 (62)
Grade 1 (130-134 mEq/L)	974 (40)
Grade 2 (125-129 mEq/L)	409 (17)
Grade 3 (120-124 mEq/L)	113 (5)
Grade 4 (<120 mEq/L)	23 (1)
Hypokalemia (mEq/L)	
Baseline potassium (Mean, SD)	4 (1)
Overall incidence (%)	677 (27)
*Grade 1 & 2 (3.0-3.3 mEq/L)	544 (22)
Grade 3 (2.5-2.9 mEq/L)	114 (5)
Grade 4 (<2.5 mEq/L)	19 (1)
Hyperkalemia (mEq/L)	
Baseline potassium (Mean, SD)	4 (1)
Overall incidence (%)	643 (26)
Grade 1 (5.1-5.5 mEq/L)	453 (18)
Grade 2 (5.6-6.0 mEq/L)	135 (5)
Grade 3 (6.1-7.0 mEq/L)	47 (2)
Grade 4 (>7.0 mEq/L)	8 (0.3)
Hypophosphatemia (mg/dL)	
Baseline phosphorous (Mean, SD)	3 (1)
Overall incidence (%)	1106 (49)
*Grade 1 & 2 (2.0-2.5 mg/dL)	757 (38)
Grade 3 (1.0-1.9 mg/dL)	329 (16)
Grade 4 (<1.0 mg/dL)	20 (1)
Hypocalcemia (mg/dL)	
Baseline calcium (Mean, SD)	10 (1)
Overall incidence (%)	213 (9)
Grade 1 (8.0-8.4 mg/dL)	145 (6)
Grade 2 (7.0-7.9 mg/dL)	63 (3)
Grade 3 (6.0-6.9 mg/dL)	5 (0.2)
Grade 4 (<6.0 mg/dL)	0 (0)

PO2165

Immune Checkpoint Inhibitor-Associated Glomerular Disease: A Systematic Review and Meta-Analysis

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Background: Immune checkpoint inhibitors (ICI) are increasingly used to treat several cancers. Kidney immune-related adverse events (IRAE) are now well-recognized, with purported incidence of 2-5%. The majority of initial data related to kidney IRAE has focused on acute interstitial nephritis (AIN). Recently various glomerular diseases have been reported; however, there is minimal data on the types and relative frequencies of glomerular diseases associated with ICI, their treatment, and outcomes.

Methods: We performed a systematic review and meta-analysis of all biopsy-proven published cases/series of glomerular pathology associated with ICI therapy. We searched the MEDLINE, EMBASE and Cochrane Central databases from inception to February 2020. We abstracted patient-level data, including demographics, cancer and ICI therapy details, and characteristics of kidney injury. We performed exploratory univariate logistic regressions for predictors of end stage kidney disease (ESKD) or death.

Results: After screening, 27 manuscripts with 45 cases of biopsy-confirmed ICI-associated glomerular disease were identified. Several types of lesions were observed, with the most frequent being pauci-immune glomerulonephritis and renal vasculitis (27%), minimal change disease (MCD) (20%), and C3 glomerulonephritis (11%). Concomitant AIN was reported among 41% of cases. The majority of patients had ICI discontinued (88%), and nearly all received corticosteroids (98%). Complete or partial remission of proteinuria was achieved in 45% and 38%, respectively. Most patients had full (31%) or partial (42%) recovery from AKI although 19% required dialysis and approximately one-third of patients died. In exploratory univariate logistic regression for predictors of endstage kidney disease (ESKD) or death, glomerular lesion, ICI class, peak creatinine and proteinuria were not significantly associated with this composite outcome.

Conclusions: Glomerular diseases associated with ICI are not uncommon. Pauci-immune glomerulonephritis, MCD and C3GN are the most frequently reported lesions. ICI-associated glomerular disease may be associated with poor kidney and mortality outcomes. Oncologists and nephrologists need to be aware of glomerular pathologies associated with ICI treatment.

PO2166

Statin Use, Renal Cell Carcinoma, and Combination Immunotherapy Increase Risk of Checkpoint Inhibitor-Induced Nephritis: A Single-Center Database Study

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Background: Immune checkpoint inhibitors (ICI) are associated with improved cancer outcomes, however immune related adverse events (irAE) develop and are poorly understood. Renal irAE (RirAE) are less common but may jeopardize effective cancer therapy, and no reliable risk factors for RirAE have been identified. Concomitant medications have been shown to play a role in response to ICI but the impact on toxicity is unknown. We report risk factors and clinical outcomes of patients who develop RirAE.

Methods: We queried a patient database with advanced cancer treated with ICI between 2010 and 2017 at Ohio State Univ for pts who developed AKI (defined as a doubling of creatinine after initiation of ICI). irAEs were reviewed by nephrologist and oncologist. Overall survival (OS) was calculated from date of initiation of ICI to death from any cause or date of last follow-up. Associations between irAE incidence and categorical outcomes were studied using chi-square or Fisher's exact test. The Wilcoxon test was used for continuous outcomes. Survival outcomes were studied using log-rank test or cox regression model.

Results: Of 1,091 pts treated with ICI, 160 (14.7%) developed AKI of any cause and 30 (2.74%) developed RirAE. PPI use (p=0.032), renal cell carcinoma (RCC) diagnosis (p=0.009) and line of therapy (p=0.033) were all associated with development of AKI, and RCC, BMI, and line of therapy remained significant in multivariate analysis[OD1]. Overall survival (OS) was 12.2 months in absence of AKI vs 10.7 months with AKI (p=0.0125). Statin use (p=0.007) and RCC diagnosis (p=0.012) were significantly associated with RirAE with a trend to higher rates in combination immunotherapy (p=0.064). These three variables were also significant in multivariate analysis. OS was not different in the RirAE group (10.8 months) vs no RirAE group (11.8 months).

Conclusions: Patients undergoing ICI therapy can develop AKI as well as RirAE. However, outcomes are worse for AKI. Survival for pts who develop RirAE does not appear to differ from patients without RirAE. AKI and RirAE share an independent risk factor in RCC. However, statin use and combination ICI therapy appear to be unique risk factors for RirAE. Further studies are needed to verify the finding regarding statin use, a drug with widespread use.

PO2167

A Potential Mechanism of Distal Renal Tubular Acidosis in Patients Treated with Immune Checkpoint Inhibitors

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Background: The main cause of acute kidney injury in patients on immune check point inhibitors(ICI) is acute interstitial nephritis(AIN). However, as their use continues to increase, we observe other renal manifestations being described. Distal renal tubular acidosis(dRTA) has been described, but the mechanism is not clear to date. We hypothesized that an alteration of H+-ATPase or anion exchanger(AE-1) in alpha intercalated cells(α-IC) in collecting duct is affected.

Methods: We present two patients with AIN and dRTA secondary to ICI: Patient#1 with metastatic adenocarcinoma of lung and patient#2 with metastatic melanoma, both treated with anti-PD1-antibodies(pembrolizumab/nivolumab). They had prominent electrolytes abnormalities consistent with dRTA(Figure 1A). Kidney biopsy was performed in each patient which showed diffuse AIN with negative routine immunofluorescence(IF) staining. Both patients had received PPI in addition to ICI therapy and had improvement in their kidney function following steroid therapy and with discontinuation of the drugs. In order to investigate the potential mechanism for developing dRTA, the kidney biopsy frozen sections from patients#1 and#2 were further stained by indirect IF for acid-base transporters in α-IC(α4 and B1)subunits of the vacuolar H+-ATPase(V-ATPase) and the AE1. In order to quantify the staining, data were normalized to a T_0 allograft biopsy as control.

Results: α-IC cell markers were decreased in both patients compared to the control as shown in Figure1B. Quantification of AE1, B1-V-ATPase and A4-V-ATPase were all reduced compared to control biopsy, however, staining for other markers of a-IC(c-kit) were not reduced. This suggests a more targeted reduction in V-ATPase subunits that may be immune-mediated.

Conclusions: The reduction in staining for V-ATPase subunit could be related to damage from AIN, however, an immune-mediated process that reduces the expression of V-ATPase in α-IC is likely. Comparing staining of V-ATPase in α-IC in patients with AIN secondary to ICI with and without dRTA in the future will be useful.

Funding: NIDDK Support

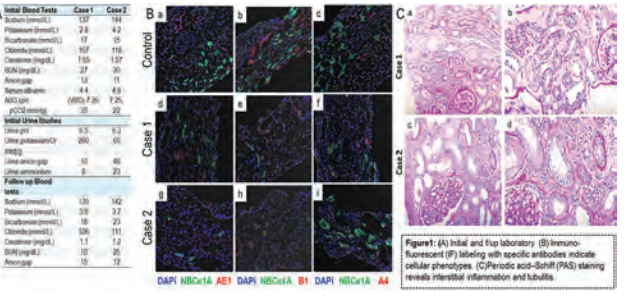

Figure1: (A) Initial and f/up laboratory. (B) Immuno-fluorescent (IF) labeling with specific antibodies indicate cellular phenotypes. (C) Periodic acid–Schiff (PAS) staining reveals interstitial inflammation and tubulitis.

PO2168

Clinical Features of AKI in Patients Receiving Tisagenlecleucel (CAR-T Therapy)

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Background: CAR-T therapy uses genetically engineered T cells to target tumor antigens, but can lead to cytokine release syndrome (CRS), neurotoxicity, and in severe cases, AKI. Prior series demonstrated 20% incidence of AKI after axicabtagene ciloleucel (Yescarta), a CD28 costimulatory domain CAR-T. Tisagenlecleucel (Kymriah) is a 41BB CAR-T that targets CD19 on B cells but has delayed toxicities, slower expansion kinetics, longer persistence, and is associated with lower rates of severe CRS. We determined incidence and clinical features of AKI in patients receiving tisagenlecleucel.

Methods: We performed a retrospective review of adults with diffuse large B cell lymphoma treated with tisagenlecleucel at our institution between Jan 2019–Apr 2020. Baseline demographics, laboratory data, and clinical outcomes were obtained from electronic health records. The primary outcome, AKI, was defined as a ≥1.5-fold rise in creatinine from pre-CAR-T baseline and staged using KDIGO criteria.

Results: Overall, 37 patients received tisagenlecleucel: average age was 60 (SD 18), 65% male, 86% white. CRS occurred in 51% (no severe CRS); neurotoxicity occurred in 24%. Thirteen (35%) required steroids, 8 (22%) received tocilizumab, and 8 (22%) received anakinra to treat CRS/neurotoxicity. AKI occurred in 2 (5%) patients; both had stage 3 AKI. One had acute tubular necrosis due to septic shock starting post-infusion day 1. The other had AKI with new-onset nephrotic range proteinuria (5-6g/g) concurrent with a hemophagocytic lymphohistiocytosis-like syndrome beginning day +8. The patient was also receiving amphotericin and acyclovir. Both patients with AKI died (days 4 and 28, respectively). Among patients without AKI, the 30-day mortality was 8.6%. Clinically significant electrolyte disorders were also common **(Table).**

Conclusions: Compared to prior reports, we found lower rates of CRS and AKI in patients receiving Tisangenlecleucel. We report a case of new-onset nephrotic-range proteinuria and AKI following CAR-T.

Clinical outcomes among patients receiving tisagenlecleucel

Outcome (Total n=37)	Count (%)
Acute Kidney Injury	2 (5)
Cytokine release syndrome	19 (51)
Grade 1	15 (40)
Grade 2	4 (11)
Grade 3/4	0 (0)
Neurotoxicity	9 (24)
Grade 1/2	7 (19)
Grade 3/4	2 (5)
Electrolyte disorders	7 (19)
Hyponatremia < 130 mEq/L	5 (14)
Hypokalemia < 3.0 mEq/L	26 (70)
Hypophosphatemia < 2.0 mg/dL	
30-day Mortality	5 (14)

PO2169

Dabrafenib-Induced Acute Interstitial Nephritis (AIN) and AKI in Patients with Cancer

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Background: BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) commonly used to treat $BRAF^{V600}$ mutant cancers have been associated with AKI. Cases of acute and chronic tubular injury and AIN have been reported with dabrafenib. We aimed to define the incidence and clinical features of AKI in patients on dabrafenib.

Methods: We conducted a retrospective cohort of patients receiving dabrafenib from 2010-2018 in a large healthcare system. Baseline comorbidities and medication use was determined by chart review. The primary outcome was AKI (≥1.5-fold-increase in baseline creatinine) within 12 months. AKI etiology was reviewed by 2 nephrologists. Multivariable modeling was used to determine predictors of AKI.

Results: Overall, 199 patients were included; mean age was 59 (SD 16) years, 56% were male, and 94% were white. 96% received trametinib (a MEK inhibitor) concurrently. Mean baseline creatinine was 0.9 (SD 0.2) mg/dL, 20 (10%) had baseline CKD (eGFR<60 mL/min/1.73m^2), and 42 patients (21%) experienced AKI at a mean of 141 (SD 116) days after starting dabrafenib. In multivariable modeling, only baseline liver disease predicted AKI. Etiology and stage of AKI are shown in Fig 1A; clear alternative causes for AKI were found in 32 of 42 cases. Ten patients (5% of total cohort, 24% of AKI) experienced AKI attributed to dabrafenib-induced cytokine release syndrome (CRS); all experienced fever, chills, gastrointestinal distress (nausea/vomiting/diarrhea) +/- rash and transaminitis within 4-6 weeks of starting dabrafenib. The majority improved with intravenous hydration and discontinuation of the drug. One patient with persistent AKI underwent kidney biopsy demonstrating granulomatous AIN (Fig 1B); he was treated with intravenous solumedrol and a prednisone taper for two weeks with full resolution of AKI.

Conclusions: AKI is common in patients on Dabrafenib (21%). A febrile systemic response or CRS after dabrafenib may explain up to 24% of AKI; we report another case of AIN after dabrafenib.

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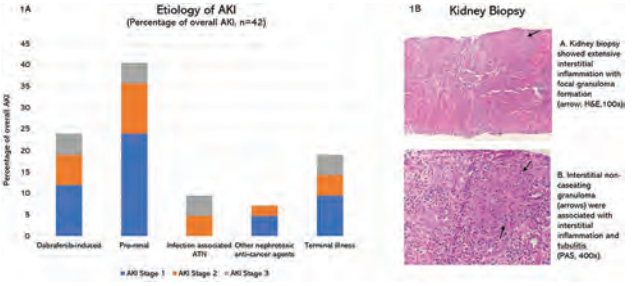

PO2170

Temporal Trends of Palliative Care Use Among Hospitalized Patients with Metastatic Renal Cell Carcinoma

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Background: Patients with metastatic renal cell carcinoma have a poor prognosis and they may suffer from hypercalcemia, venous thromboembolism, anorexia-cachexia syndrome. Little is known about the trends in the utilization of palliative care in this patient population.

Methods: We conducted a retrospective cohort study using data from 2004 to 2014, which were extracted from the National Inpatient Sample. ICD-9-CM was used to identify all diagnosis variables. We compared the baseline demographics. We assessed the annual trend over time in palliative care utilization rates. Statistical analysis was performed using STATA 16.0. We considered a two-tailed P value of <0.05 as statistically significant.

Results: We identified 181,199 hospitalizations with metastatic renal cell carcinoma from 2004 through 2014, of which 16,390 (9.0%) involved palliative care services. Inpatient palliative care utilization increased from 2.8% in 2004 to 16.3% in 2014 (p<0.001). Compared with patients discharged from non-teaching hospitals, we noticed a significantly higher rate of palliative care utilization in patients discharged from teaching hospitals [aOR 1.46; 95% CI 1.29 to 1.65]. There were higher odds of receiving palliative care in patients with private insurance (aOR 1.26; 95% CI 1.11 to 1.42). We also observed lower odds of receiving palliative care in Hispanic patients (aOR 0.83; 95% CI 0.70 to 0.98, p=0.03).

Conclusions: The rate of inpatient palliative care use in metastatic renal cell carcinoma patients sharply increased between 2004 and 2014. Our findings demonstrated improving adherence to the National comprehensive cancer network (NCCN) guidelines, which is highly encouraging. Patients from teaching hospitals and using private insurance and were more likely to receive palliative care.

Figure1: Multivariable logistic regression model predicting use of inpatient palliative care. Model also adjusted for age at admission, hospital bed-size and estimated median household income

Variables		aOR	95% CI		P value
Teaching status					
	Nonteaching	Ref			
	Teaching	1.46	1.29	1.65	<0.001
Insurance					
	Medicare	Ref			
	Medicaid	1.58	1.32	1.89	<0.001
	Private insurance	1.26	1.11	1.42	<0.001
	Self-pay	1.47	1.12	1.91	0.005
Race					
	White	Ref			
	Black	1.13	0.97	1.30	0.098
	Hispanic	0.83	0.70	0.98	0.03
	Asian or Pacific Islander	1.13	0.87	1.46	0.34
Region					
	Northeast	Ref			
	Midwest	1.23	1.03	1.48	0.018
	South	1.10	0.92	1.31	0.29
	West	1.54	1.28	1.84	<0.001

PO2171

AKI Secondary to Multiple Myeloma: Complications of Treatment with High Cut-Off Filters

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Background: Acute kidney injury is a frequent complication of MM that can affect 18 to 56% of patients and more than 10% end up needing dialysis. One of the drawbacks associated with the technique is attributed to the albumin loss. The other complications are related with the dialysis technique itself, especially infections.

Methods: We have performed 28 treatments of hemodialysis with High cut off filters (HD-HCO). The HD-HCO protocol includes daily dialysis session of 6 hours during the first 6 days to subsequently switch to dialysis every other day until free light chains levels below 500 mg / L, or until the recovery of renal function allows the independence of dialysis. All these patients have a chemotherapy regimen based on Bortezomib (25 of the 28 treatments) and Dexamethasone (28 treatments). A retrospective analysis of the 28 treatments that are performed with HD-HCO after 8 years of experience (July 2011 to May 2019) to demostrate the presence of the same complications as the conventional HD.

Results: Loss of albumin is one of the main drawbacks of the technique. Our patients had no changes in albumin levels due to the fact that our protocol includes the infusion of 2 vials of 20% albumin of 50 ml. at the end of each HD-HCO session. Another concern is intradialytic complications. We have reviewed this topic and our results show that patients in HD-HCO do not present a greater number of complications than those who dialyze with HD-HD or other conventional dialysis. The total number of sessions was 298. 21 patients developed hypotension (7%). The number of sessions in which the patient presented fever was 6 (2%), coagulation of the circuit occurred in 23 sessions (7,7%). The catheter dysfunction (when it does not allow to reach 250 ml/min of blood flow) in 26 times (8.7%) and only 13 times the replacement of the catheter (4.26%) was necessary, consequently, in those who required a greater number of dialysis sessions. In only 1 case (patient who required 27 sessions) to place a permanent Tesio catheter was necessary. Figure 1

Conclusions: Our findings indicate that the HD-HCO has the same safety profile as the conventional HD. There is no serious infectious complications in our patients despite of the fact that all of them are immunosuppressed patients (AKI secondary to Multiple Myeloma in patients treated with chemotherapy).

PO2172

Acute Myeloid Leukemia Worsens Sepsis-Induced AKI

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Background: Patients with hematological malignancies are at high risk for acute kidney injury (AKI), which is associated with high morbidity and mortality. Sepsis is the main cause of AKI in ICU patients with hematologic malignancies. However, the contributions that host or cancer cells make to systemic inflammation during sepsis-induced AKI is not known.

Methods: We created a mouse xenograft model of acute myelogenous leukemia (AML) associated sepsis AKI. Human leukemia HL-60 cells were injected into the tail vein of 6 week-old male NOD/SCID/IL-2Rγ^{null}(NSG) mice. After engraftment 2 weeks later, cecal ligation and puncture (CLP) was performed to induce sepsis (n=8-12 per group). Tumor engraftment in the bone marrow (BM) and blood tumor burden were measured by flow cytometry of human CD33 and human CD45 double positive cells. Multiple organ damage, and both mouse and human systemic cytokines were evaluated at 24 h after CLP or sham surgery.

Results: AML intensified sepsis-induced AKI. Both BUN and LDH were significantly higher in AML+CLP than CLP alone (AML+CLP vs vehicle+CLP, BUN 74.5±25.4 vs 42.7±25.3 mg/dl, LDH 3,969±1,720 vs 1,863±661 mg/dl, $p<0.05$). CLP dramatically increased the percentage of circulating leukemia cells (pre CLP vs post CLP, 2.2±1.3 % vs 20.6±13.3 %, $p<0.05$). Tumor burden in either BM or blood did not correlate with AKI severity. Systemic mouse IL-6 in AML+CLP at 24 hours after CLP was significantly higher than CLP alone (45.9±2.4 vs 15.1±2.4 ng/mL, $p<0.05$). Systemic human IL-6 in AML+CLP was higher, but not significantly, than vehicle+CLP. There was no correlation between human cytokines and severity of AKI, although human cytokines (IL-6 and TNFα) significantly correlated with tumor burden in both BM and blood at 24 hours after CLP.

Conclusions: We established a clinically relevant mouse xenograft model of human leukemia associated sepsis AKI. Leukemia intensified sepsis-induced AKI, and sepsis AKI increased the numbers of circulating AML cells. Systemic cytokines derived from the human leukemia cells correlated with tumor burden, but not with the severity of sepsis-induced AKI. Whereas malignant cells do not produce circulating cytokines that directly drive the systemic immune response to subsequent sepsis-induced AKI, cell-cell interactions in the BM niche may impact systemic inflammation indirectly, possibly through mouse IL-6.

Funding: NIDDK Support

PO2173

Acute Acquired Fanconi Syndrome (FS) in Multiple Myeloma (MM) After Autologous Hematopoietic Stem Cell Transplantation (HCT): A Case Series

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Background: Proximal tubular dysfunction can occur in patients with MM. The main clinical presentation is electrolyte abnormalities indicative of FS. The objective of the study was to describe and identify the rate and clinical predictors of developing acute acquired FS in adult patients with MM after autologous HCT.

Methods: We identified 2515 adult MM patients who underwent autologous HCT at Mayo Clinic from January 1, 2000 to December 31, 2018. 45 without research authorization were excluded. 13 patients were identified after searching for "Fanconi," "Fanconis," and "Fanconi's" in the EMR. 6 patients did not have FS. 4 patients were diagnosed with FS prior to HCT. The remaining 3 patients (0.12% of cohort) were clinically diagnosed to have FS based on features indicative of FS - hypokalemia, hypophosphatemia, hypouricemia, proximal renal tubular acidosis, and normoglycemia glycosuria - within 14 days after HCT. Of note, these patients did not have features of FS prior to HCT.

Results: The median age of the cohort was 65 years (range: 53-75). All were Caucasians. 2 were women and 1 was a man. Medical comorbidities included hypertension, dyslipidemia, CKD, hypothyroidism, and kidney stone. All had kappa-restricted light chain MM with a median M-spike of 1.2 g/dL (range: 0.4-2). All received dexamethasone while 2 received bortezomib and 1 each for cyclophosphamide and lenalidomide. They underwent HCT about 8.3 months after MM diagnosis and were clinically diagnosed with FS about 14.6 days after HCT. None underwent a kidney biopsy. All had hypokalemia, hypophosphatemia, and hypomagnesemia (<3.5, <2.5, and <1.7 respectively). 2/3 patients had AKI (≥1.5-fold increase in serum creatinine) and normoglycemia glycosuria. 1/3 had hypouricemia (low range of normal: 2.7-6.1) and proximal renal tubular acidosis (<22 and urine pH <5.3). Aminoaciduria was not checked. All received electrolyte replacement, whether PO or IV, and 2/3 received amiloride to help maintain normokalemia.

Conclusions: Although rare, severe electrolyte depletion after HCT in kappa MM patients could occur and should raise the suspicion for FS. Lenalidomide has been reported to induce FS. Concurrent GI symptoms could exacerbate these electrolyte losses, which concurrent AKI, conversely, could help correct. Timely electrolyte repletion and close monitoring are required.

PO2174

Hyponatremia Is Common After Indwelling Catheter Drainage of Malignant Ascites

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Background: Indwelling peritoneal catheters (IPCs) are frequently used to drain tense, symptomatic, malignancy-related ascites. Large-volume drainage may lead to hyponatremia due to massive salt depletion. To date, no studies have examined the epidemiology of hyponatremia after IPC placement.

Methods: We retrospectively reviewed the charts of 461 patients who had IPCs placed between 2006 and 2016 at a tertiary care hospital. Among the 309 patients with labs available pre- and post-catheter, we studied the incidence of hyponatremia and its risk factors. We also examined the management of hyponatremia and its association with mortality.

Results: The overall incidence of hyponatremia post-IPC placement was 85%, of whom 8% had severe hyponatremia with a serum sodium (sNa) sNa<120 mEq/L. The mean decline in sNa pre- versus post-catheter was 5 mEq/L (+/- 5.1) and fell by ≥10 mEq/L among 52 patients (16.8%). Patients with hyponatremia prior to catheter placement had an 8-fold (95% CI, 2.9-21.7) higher adjusted odds of having persistent hyponatremia post-catheter (Table 1). Patients with hepato-pancreatic-biliary malignancies and lower BMI also had a higher adjusted odds of hypoonatremia. Hyponatremia was either unrecognized or untreated in 61% of patients. Patients who had sNa ≤120 mEq/L had shorter median survival compared with those with a post-IPC sNa>120 mEq/L (8 versus 17 days, log-rank p value = 0.03) (Figure 1).

Conclusions: Though IPC placement is often a palliative measure, hyponatremia is common, and severe hyponatremia may be associated with shorter survival. These patients may warrant closer monitoring post-catheter placement.

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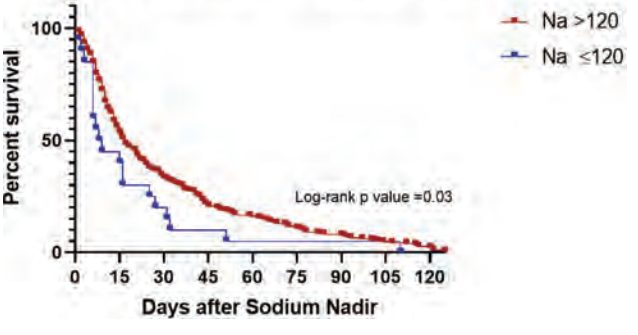
Table 1: Predictors of Hyponatremia Post-IPC

Variable	Univariable Analysis	Multivariable Analysis
	OR (95% CI)	OR (95% CI)
Age >60	0.58 (0.31,1.09)	0.60 (0.23, 1.57)
Hepato-Pancreato-Biliary Cancer	2.42 (1.05,5.60)	5.09 (1.05, 24.80)
BMI (continuous)	0.80 (0.83, 0.98)	0.90 (0.82, 0.99)
Sodium <1135 Pre-IPC	6.88 (3.39,13.95)	7.87 (2.86,21.70)

Figure 1: Survival After Sodium Nadir



PO2175

Selinexor-Associated Hyponatremia: Single-Center Real-World Data

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Background: Introduction: Hyponatremia is a commonly reported side effect in recent clinical trials evaluating the efficacy and safety of selinexor in treatment of refractory multiple myeloma (MM). With incidence ranging 7-47%. the hyponatremia was reported to be generally asymptomatic, transient, and highly responsive to medication dose reduction and sodium. The etiology for hyponatremia is not yet completely understood and speculated to be multifactorial, hypovolemia, diarrhea, poor solute intake, or pseudohyponatremia from high M protein level.

Methods: We retrospectively reviewed the medical records of all relapsed MM patients at our cancer institute. The study was approved by the institutional review board. We reviewed data relevant to hyponatremia in patients' clinical presentation, medication history, comorbid conditions, physical examination, and laboratory review.

Results: Hyponatremia was seen in 13/17 patients within 5 weeks of therapy, 8 of whom required hospitalization. Three of these hospitalized patients had grade 3 hyponatremia (serum sodium 120 to ≤130 meq/l) with severe symptoms including fall and altered mental status. Both groups of patients received antiemetics, anti-depressants and diuretics that included thiazides. Cancer related pain was observed in both groups but the hyponatremic group was on higher dose selinexor and more likely to have more gastrointestinal side effects, sepsis, hypotension. Nephrology was consulted on only 4 out of 13 patients. These were the only patients with serological and urine studies done high urine osmolarity and high urine sodium concentration that along with euvolemia favored SIAD diagnosis in 3 out these 4 patients.

Conclusions: Our observations suggest that hyponatremia is multifactorial, as the patient's co-morbidities, medications, and selinexor side effects (hypovolemia, nausea and possible unidentified factor) may contribute to hyponatremia. It is possibly dose dependent, more likely to occur with patients who had gastro-intestinal side effects, sepsis and hypotension. We recommend discontinuation of medications associated with hyponatremia prior to starting/during selinexor therapy, obtaining basic hyponatremia investigations, and early referral to nephrology to prevent potential serious symptoms

PO2176

Antiemetic Drugs and the Risk of Cisplatin-Induced AKI

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Background: Cisplatin (CIS) is an effective first line therapy for a variety of cancers. Acute kidney injury (AKI) is a common side effect of CIS seen in up to 30% of patients (Latcha et al CJASN, 2016). AKI results from the selective uptake and accumulation of CIS in proximal tubules. CIS is a highly emetogenic and fluid loss can also contribute to AKI. This retrospective study evaluated whether anti-emetics modfy the risk of AKI.

Methods: The medical records of adult cancer patients who received CIS between Jan 1, 2010 and Dec 31, 2016 (n=6,889) were reviewed. The association between use of anti-emetics and development of AKI (50% increase in serum creatinine (sCr)) was evaluated. Inclusion criteria were adults, baseline sCr, CIS dose and administration of anti-emetics. Fisher's exact test was used for univariable associations between categorical values and logistic regression analyzed multivariable associations with AKI at $p<0.05$.

Results: Out of ~8700 patients, 6889 met search criteria. A total of 3,881 (56.3%) patients received antiemetics. AKI developed after cisplatin in 1,666 (24.2 %) patients. Of those with AKI (n=1666), patients who received any antiemetic represented 52.6% (n=877), while patients with no documented antiemetic use represented 47.4% (n=789). Of patients without AKI (n=5223), patients who received any antiemetic represented 57.5% (n=3004), while patients who did not have documented antiemetic use represented 42.5% (n=2219). ($P<0.001$). Patients who received antiemetics also received a higher cumulative dose of CIS (360 vs 330 mg/m^2, $P < 0.001$). By univariate analysis older age, male gender, black race, and cumulative CIS dose were associated with higher risk for AKI ($P<0.001$). After adjusting for these variables, use of any antiemetic was protective for AKI (OR 0.84, 95% CI: 0.75, 0.94; P= 0.003).

Conclusions: Our study confirms the high rate of AKI in patients receiving CIS. While anti-emetic use appears to be associated with a lower rate of AKI, additional analyses will be needed to determine risk or benefit profiles of specific agents and/or class of agents given recent data demonstrating inhibition of kidney transporters with certain anti-emetics. Dissecting out other important covariates such as requirements for anti-emetics based on higher cumulative CIS will be necessary in prospective randomized controlled studies.

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PO2177

Acute Kidney Disease After Microinvasive Radical Cystectomy for Bladder Cancer Is Associated with CKD

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Background: Acute kidney disease (AKD) proposed in 2012 by KDIGO is getting more and more attention for its vital role in acute kidney injury (AKI) to chronic kidney disease (CKD) transition. However, no study has explored the incidence, risk factors of AKD and its impact on new-onset CKD after microinvasive radical cystectomy(RC).

Methods: The medical records of 308 patients at our hospital between January 2014 and May 2019 were reviewed. We excluded 29 patients from the study due to missing SCr preoperatively or postoperatively. AKD was diagnosed as a ≥35% decrease in eGFR or >50% increase in SCr between 7-90 days after surgery. AKI alone was defined by the 2012 KDIGO classification but failed to meet AKD criteria after 7 days. No kidney disease (NKD) was defined if patients didn't meet either criteria. Logistic regression model was used to explore risk factors of AKD, while its significance for CKD was assessed using Kaplan-Meier analysis and Cox model.

Results: We evaluated 279 bladder cancer patients, including 168 for Robotic-assisted Laparoscopic RC and 111 for Laparoscopic RC. The incidence of AKD was 14.7% whereas AKI alone was 13.6%. Risk factors for AKD included chemotherapy (odds ratio [OR]=3.245,P=0.024), robotic RC(OR=2.437,P=0.029)and operation time (OR=1.005,P=0.012). Of 150 patients without CKD history, CKD developed in 62.5% of patients with AKD,33.3% with AKI alone and 30.6% with NKD during the 30 months follow up (p=0.013). K-M analysis showed AKD patients had the highest CKD incidence(Fig.1). Cox model also identified AKD (HR=2.224,p=0.012) but not AKI alone, was independent risk factor predicting CKD, along with age.

Conclusions: The incidence of AKD was higher than AKI alone after microinvasive RC and resulted in higher risk of new-onset CKD compared with No-AKD. This persistent or repetitive injury is significantly associated with CKD.Hence, interventions for AKD are needed to improve outcomes.

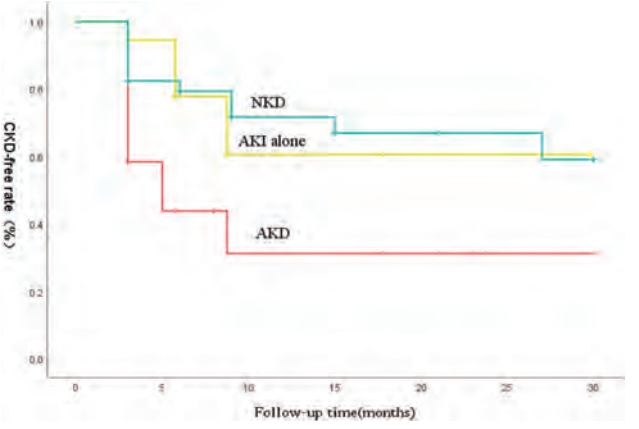

Figure 1. Kaplan–Meier analysis

PO2178

Comparative Analysis of Characteristics and Survival Outcomes of Clear Cell and Sarcomatoid Subtypes of Renal Cell Carcinoma: Results from the SEER Database 2000-2017

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Background: Renal cell carcinoma (RCC) accounts for more than 90% of kidney cancers. Clear cell RCC (ccRCC) is the commonest type, while sarcomatoid RCC(sRCC) is rare and constitutes 5% of all RCCs. sRCC is known for aggressive clinical course and poor prognosis. In this study, we sought to compare the epidemiological features and survival trends of ccRCC with sRCC, using SEER dataset 2000-2017.

Methods: The Surveillance, Epidemiology and End Results (SEER) database was used to identify all adult patients (≥18 years) diagnosed with ccRCC and sRCC between 2000 and 2017. Variables included age, sex, ethnicity, laterality, staging, histological grade, and nephrectomy. Overall survival was estimated using the Kaplan-Meier method, and compared using the Log-Rank test. Multivariable covariate-adjust cox models were used for adjusted survival analyses.

Results: A retrospective cohort study of 20248 patients (19398 ccRCC, 850 sRCC) with overall survival rate of 38% (40% ccRCC and 16.2%ssRCC). Although the two subtypes share similar demographic characteristics, including mean age (66.8±13.7 for ccRCC vs 62.9±12 for sRCC), male-female ratio (1.71:1 vs 2.3:1), and having caucasian race more affected (79% vs 82%), sRCC had a significantly worse prognosis in univariate analysis with median overall survival of 7 months vs 30 months for ccRCC. Caucausian male patients were more affected in both types. But neither sex nor race significantly affected survival in sRCC (P 0.814, 0.794 respectively), however, black americans have worse outcomes in ccRCC (HR 1.123[1.083-1.163], $P < 0.001$). On multivariate

regression analysis, advanced stage, high histological grade, and older age 65+years (HR 1.002, 95%CI [1.001-1.00], P < 0.001) were associated with worse outcomes. Patients with cancer-related death had significantly shorter survival time in both RCCs (P<0.001). Nephrectomy was associated with better survival outcomes (HR 0.486 [0.459-0.514], P < 0.001).

Conclusions: sRCC had worse prognosis. Advanced stage, high histological grade, and older age are the most important predictors of survival in both subtypes of RCC. Although caucasian male patients were more affected in sRCC, gender and ethnicity have no impact on survival. Nephrectomy imparts better survival benefits in both subtypes.

PO2179

Acid-Base Biomarkers and Cancer Mortality

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Background: Acidosis in the tumor microenvironment is associated with cancer progression in animal models. We explored the association of serum bicarbonate and anion gap – measures of acid-base balance -- with cancer mortality in community-dwelling adults.

Methods: We conducted a prospective cohort study using the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey of the US non-institutionalized population. Anion gap (mEq/L) was calculated as serum sodium (mmol/L) – (serum chloride (mmol/L) + serum bicarbonate (mmol/L). We used weighted Cox proportional hazards models to assess the associations between serum bicarbonate and anion gap with cancer-specific mortality, as recorded by the National Death Index. Multivariable models were adjusted for demographics data, BMI, smoking status, diabetes, systolic blood pressure, cardiovascular disease history, ACEi/ARB, diuretics, HIV drugs, metformin, serum albumin, total cholesterol, total protein, total calorie intake, hemoglobin, cancer diagnosis, eGFR and urine albumin to creatinine ratio.

Results: This study included total 39,137 participants [mean (SD) age, 46.83(19.25) years, 20,162(51.5%) females, 18,119 (46.3%) white]. During 4,433,277 person-years of follow up, 964 (2.46%) participants died secondary to cancer. A history of cancer at the time of enrollment was reported in 3186 (8.8%). Table 1 shows the associations between serum bicarbonate and anion gap in tertiles with cancer-related mortality. In analyses restricted to those with a history of cancer, results were 78% increased risk for cancer mortality in highest tertile compared to lowest tertile [HR 1.78; 95% CI (1.11,2.87)].

Conclusions: Increased anion gap may be a risk factor for cancer mortality. The reasons driving this association deserve further examination.

Risk of cancer mortality according to bicarbonate and anion gap as tertiles (method = weighted survey cox regression)

	Unadjusted hazard ratio	Adjusted hazard ratio
Bicarbonate T1 (10-22 mmol/l)	0.92 (0.75,1.12)	1.21 (0.94,1.57)
Bicarbonate T2 (22-26 mmol/l)	Reference	Reference
Bicarbonate T3 (26-43 mmol/l)	1.42 (1.18,1.7)	1.04 (0.82,1.32)
Anion gap T1 (< 10 mmol/l)	Reference	Refrence
Anion gap T2 (10-12 mmol/l)	1.12 (0.91,1.36)	1.21(0.94,1.57)
Anion gap T3 (> 12 mmol/l)	1.24 (0.99,1.56)	1.59 (1.21,2.07)

PO2180

In-Hospital and 1-Year Mortality Among Patients with AKI and Haematological Malignancies

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Background: Patients with haematological malignancies (HM) are at high risk for acute kidney injury (AKI), which is associated with high morbidity and mortality. The aim of this study was to identify the prognostic factors for in-hospital mortality and one-year mortality in this population.

Methods: We conducted a single centre, retrospective, observational cohort study of 101 in-hospital patients with AKI and HM between 1 January 2015 and 31 December 2019. We recorded essential demographic, clinical and laboratory data at baseline, 1 and 12 months. We classified AKI according to the KDIGO definition. Cox proportional hazard model was applied to investigate the one-year mortality, and logistic regression analysis was used to assess the in-hospital mortality.

Results: The study population included 64 males and 37 females, with a mean age of 58.7 ± 16.8 years. Multiple myeloma was present in 30.7% (n=31) of the patients, followed by non-Hodgkin lymphoma (LNH) in 27,7% (n=28). 51,5% (n=52) were admitted to intensive care unit (ICU). 60,4% (n=61) needed renal support therapy (RST). Basal GFR, one-month GFR and one-year GFR were, respectively, 65.7 ± 28.9 mL/min/1.73m^2, 57.1 ± 28.5 mL/min/1.73m^2 and 54.9 ± 28.1 mL/min/1.73m^2. Mean length of in-hospital stay was 18 days (IQR 1-88). In-hospital death was 52.5% and after one year only 26 patients were alive. In multivariate analysis, the independent predictors for in-hospital mortality were invasive mechanical ventilation (IMV) (OR 49.53; 95% CI:9.17 – 267.57; p<0.001) and sepsis (OR 5.09; 95% CI:1.18 – 21.89; p=0.029). The C-statistic was 0.93 (95% CI: 0.87 – 0.98), indicating that the equation had a great discriminatory power. The independent predictors for one-year mortality were LNH (HR 2.78; 95% CI:1.53 – 5.05; p=0.001), cancer progression (HR 2.91; 95% CI:1.56 – 5.41; p=0.001) and IMV (HR 5.79; 95% CI:3.30 – 10.15; p<0.001.). Elevated levels of albumin at the time of AKI conferred a better prognosis (HR 0.63; 95% CI:0.42 – 0.95; p=0.027).

Conclusions: Our model showed that HM patients with AKI are at high risk of sepsis and IMV, resulting in elevated in-hospital death. Elevated levels of albumin at the time of AKI correlated with a better one-year survival, while LNH, cancer progression and IMV were risk factors for death.

PO2181

Renal Recovery from AKI After Hematopoietic Stem Cell Transplant: A Systematic Review and Meta-Analysis

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Background: Patients with the recovery of renal function after an episode of acute kidney injury (AKI) have better outcomes compared to those without recovery. The current systematic review is conducted to assess the rates of kidney function recovery among patients with AKI or severe AKI requiring RRT within 100 days after hematopoietic stem cell transplant (HSCT).

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Databases were systemically searched from database inceptions through August 2019 to identify studies reporting the rates of recovery from AKI after HSCT. Random-effects and generic inverse variance method of DerSimonian-Laird were used to combine the effect estimates obtained from individual studies.

Results: A total of 458 patients from 8 cohort studies with AKI after HSCT were enrolled. Overall, the pooled estimated rates of AKI recovery among patients with AKI and severe AKI requiring RRT within 100 days were 58% (95%CI: 37%-78%) and 10% (95%CI: 2%-4%), respectively. Among patients with AKI recovery, the pooled estimated rates of complete and partial AKI recovery were 60% (95%CI: 39%-78%) and 29% (95%CI: 10%-61%), respectively. There was no clear correlation between study year and the rate of AKI recovery (p =0.26).

Conclusions: The rate of recovery from AKI after HSCT depends on the severity of AKI. While recovery is common, complete recovery is reported in about two-thirds of all AKI patients. The rate of recovery among those with AKI requiring RRT is substantially lower.

Table 2. Forest plots of the involved studies assessing renal recovery rates from AKI after HSCT

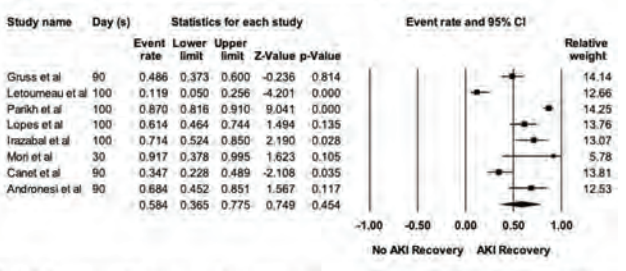
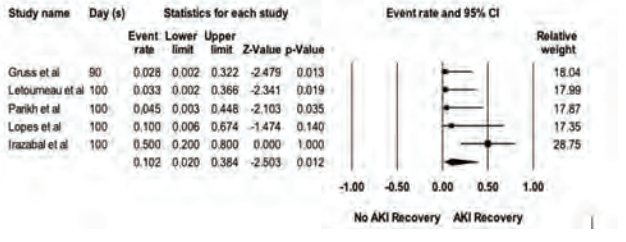


Table 3. Forest plots of the involved studies assessing renal recovery rates from severe AKI requiring RRT after HSCT



PO2182

Renal Outcomes After Autologous Stem Cell Transplant for AL Amyloidosis

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Background: Renal involvement in AL Amyloidosis is common and results in end-stage kidney disease (ESKD) in 30% of cases within 3 years of diagnosis. Newer therapeutic regimens directed at the plasma cell clone including high-dose melphalan with autologous stem cell transplantation (ASCT) are associated with improved survival but effect on renal outcome is not well established. We evaluated renal outcomes for patients who underwent ASCT and achieved a complete (CR) or very good partial (VGPR) hematologic response.

Methods: We performed a retrospective analysis of 50 AL Amyloidosis patients who underwent ASCT. Patients with renal involvement who achieved a hematologic response were included. Renal response was defined prior to transplant, according to consensus guidelines, as partial response (PR, > 30% decrease in proteinuria) or stable disease (SD, ≤ 30% proteinuria reduction). Primary endpoints were progression free survival (PFS) and overall survival (OS). PFS and OS were defined as the time from transplant to day of progression or death, respectively. Kaplan-Meier survival function estimated the PFS and OS. The log-rank test tested the equality of survivor functions between different groups of patients

Results: Following ASCT, 16 patients (32%) achieved hematological VPGR/CR after ASCT. All had renal involvement. Baseline and 1-year post-transplant proteinuria and serum creatinine (SCr) levels are shown in the Table. In the group of pts achieving VGPR/CR as hematological response PFS and OS were similar for patients having PR and SD as renal response (p=0.89 and p=0.44, respectively). No patients required hemodialysis. Median follow up for PFS was 4.1 years and for OS was 5.6 years (PR) and 11.9 years (SD).

Conclusions: Hematological response is important in AL amyloidosis and survival improves similarly with VGFR and CR. In patients with renal involvement, this study shows similar outcomes to patients who achieved a PR or SD as renal response prior to ASCT. However, our study has a small sample size and we would recommend a larger study.

RENAL RESPONSE METRICS PRE AND POST ASCT

		Partial Response (n=6)	Stable Disease (n=10)
AT DIAGNOSIS	Median 24hr Proteinuria g/d (range)	8.0 (1.9-11.3)	7.2 (2.0-15.0)
	Median SCr mg/dl (range)	3.0 (0.8-4.2)	1.3 (0.7- 4.8)
1 YR POST TRANSPLANT	Median 24hr Proteinuria mg/d (range)	2.5 (0.7-2.5)	2.2 (1.5-4.9)
	Median SCr mg/dl (range)	1.7 (0.5-3.1)	1.6 (0.6- 3.6)

Median serum Creatinine prior to ASCT in PR group was 1.2 mg/dl and 2.0 mg/dl in SD group.

PO2183

High-Dose Methotrexate (HDMTX) and Nephrotoxicity: Effect on Subsequent Dosing

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Background: HDMTX is an important part of various chemotherapeutic protocols due to its central nervous system penetrance. A key complication of HDMTX is nephrotoxicity as this leads to delayed MTX excretion and further morbidity. Nephrotoxicity in a previous cycle of HMDTX leads to an increased risk of future toxicity. Our aim was to establish how nephrotoxicity affected clinical decision making with regards to future dosing

Methods: A retrospective review of the electronic medical record was perfoemd to identify patients who developed nephrotoxicity post HDMTX from 1/1/02 to 12/31/18. We stratified the effect of nephrotoxicity by grade of AKI, according to the acute kidney injury network criteria, on resumption of MTX. In those who received a subsequent dose, we assessed whether a dose reduction have an impact on rate of Nephrotoxicity. Analysis was performed in Minitab.

Results: We identified 670 episodes of nephrotoxicity which equated to an overall incidence rate of 19% of total cycles. The majority were AKI grade 1 (79.7%). Higher grade AKI were significantly less likely to receive a future dose (p<0.001), with 71.3% of AKI N1, 59.2% of AKI N2, and 21.2% of AKI N3. Other factors associate with future dosing included elevated 48-hour MTX level (p<0.001), admission to ICU (p<0.001), and prolonged Hospital LOS (P=0.009). 449 patients received a future dose of Methotrexate with 152 (33.9%) receiving a reduced dose. The overall incidence of AKI with subsequent dosing was 33.85%. The incidence of AKI in subsequent dosing was 35.5% with no dose reduction compared to 30.3% with a dose reduction (p=0.29) (see table 1 for breakdown).

Conclusions: Nephrotoxicity had an important impact on subsequent dosing, especially with higher grade AKI. Previous AKI infers a higher rate of nephrotoxicity in future dosing with no significant reduction in incidence with reduction in MTX dose. Given the retrospective nature of the data and the many complexities to dosing calculation, this should be further explored with a prospective study.

Effect on dose reduction on subsequent AKI

	No AKI	AKI N1	AKI N2	AKI N3	Total
No dose reduction	196 (64.5%)	89 (29.3%)	18 (5.9%)	1 (0.3%)	304
Dose reduction	101 (69%)	37 (25.5%)	6 (4.1%)	1 (0.7%)	145

PO2184

Nephrology and Hematology Referral Trends in CKD Patients with Monoclonal Gammopathy and Factors Associated with Deferring Kidney Biopsy

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Background: Many patients with CKD are managed by their primary care providers (PCP). The presence of monoclonal gammopathy (MG) in the setting of CKD raises the possibility of monoclonal gammopathy of renal significance (MGRS) which would require a nephrology or hematology referral. However, rate and factors that affect specialist referral in this population remains unknown. Moreover, factors for deferring a kidney biopsy are also unknown.

Methods: We retrospectively identified adult CKD patients with MG at our center from 2017-2018. Baseline characteristics and laboratories studies were compared between nephrology/hematology referral group (RG) vs. no referral group (NRG). We also assessed the rate of kidney biopsy and the reasons for not pursuing a biopsy in the referral group.

Results: We identified 596 CKD patients with MG. Of these, 416 (69.8%) were seen by nephrologis/hematologist & 180 (30.2%) were not referred to either. Of the 180, 32% were followed by their PCP (n=57), 30% by cardiologist (n=54), and 19% by neurologist (n=35). Demographics were similar between the two groups. Patients in the NRG were more likely to have coronary artery disease, dementia, active or metastatic cancer. In multivariate analysis, 24-hr urinary protein (OR: 1.36 (1.01, 2.09)), abnormal FLC (OR 2.46 (1.29, 4.93)), and serum creatinine (OR 2.38 (1.37, 4.59)) were strong independent predictors for referral. Of 416 patients in RG, 62 (15%) patients underwent a kidney biopsy and 26 had an MGRS lesion. There were no differences in the comorbidities between the patients that were biopsied vs. those that were not. The main reason for deferring biopsy was lack of awareness of CKD or MG (142, 40%) and low suspicion for MGRS (130, 37%). In 62 patients, biopsy was not pursued as it was unlikely to change management (majority had amyloidosis). Other reasons included watchful waiting and patients' frailty.

Conclusions: Up to 30% of CKD patients with MG are not referred to a specialist. Co-morbidities lower the rate of referral whereas impaired kidney function and higher M-spike & FLC increase referral. However, once patients are referred, the comorbidities had no impact on who underwent biopsy. Most common reason for not pursuing a biopsy was lack of awareness that patient had CKD or MG.

PO2185

Efficacy of Early Use of Double Filter-Based Extracorporeal Treatment Combined with Chemotherapy in Acute Myeloma Kidney

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Background: Before the introduction of modern chemotherapy, less than 25% of patients with AKI and Multiple Myeloma (MM) who required dialysis recovered sufficient renal function to no longer be dependent on dialysis, with a median overall survival of less than 1 year. Although impaired renal function has been a marker of poor prognosis there are may others factor involved in determining patient survival. We aimed to investigate the factors related to renal recovery and to an higher survival rate in MM patients.

Methods: A monocentric retrospective study was carried out enrolling 23 patients with biopsy-proven acute myeloma kidney and sFLC levels >1000 mg/l. Patients received Bortezomib-based chemotherapy and extracorporeal treatment for sFLC removal. For each session 2 dialyzers of the same kind were used and the dialytic dose was only related to the sFLC removal. The dialyzers had high absorptive properties: PMMA (polymethylmetacrylate; Filtryzer BK-F 2.1 m2 cut-off 20 kDa); PEPA (poly ester polymer alloy; FDX or FDY 210-GW 2.1 m2, cut-off undisclosed).

Results: The factors that have been found to be significantly and independently associated with higher survival rate were: baseline serum albumin, reduction of sFLC at day 12 and day 30, reduction of sFLC at day 30 above 50%, number of session and dialysis independence.

Conclusions: Our analysis highlights the importance of the early treatment for removal of sFLC in AKI for MM. In fact the variable associated with higher survival rate are the reduction of sFLC at day 12 and at day 30 and number of session. These results indicate that the early removal of sFLC can guarantee a better outcome. Baseline serum albumin is also associated with survival rate and it demonstrates that it still carries a prognostic value in the population with AKI. This finding suggests the importance of albumin-sparing extracorporeal treatments. In fact alternative techniques, as HD-HCO, have been proposed for sFLC removal but they present high costs and albumin leakage.

Table 1: Basal patients' characteristics and 1-year survival.

	HR	[95% CI]	P
Sex	0.38	0.08 – 1.88	0.236
Age	1.04	0.96 – 1.12	0.317
Serum Creatinine	1.15	0.93 – 1.42	0.207
Proteinuria (*100 mg/day)	0.98	0.95 – 1.02	0.325
FLC pathological (mg/L)	1.00	0.98 – 1.01	0.702
Beta 2 microglobulin (mg/L)	0.99	0.93 – 1.06	0.754
Serum albumin (g/dL)	0.06	0.01 – 0.47	0.007

Table 2. Characteristics of free light chains (FLC) removal and 1-year survival.

	HR	[95% CI]	P
HD sessions (n)	1.03	1.00 – 1.06	0.035
FLC RRs (%)	0.09	0.01 - 83.7	0.879
Day 12 - RR (%)	0.95	0.91 – 0.99	0.011
Day 12 – RR ≥ 50%	0.08	0.01 – 0.78	0.028
Day 30 –RR (%)	0.97	0.95 – 0.99	0.004
Day 30 – RR ≥ 50%	0.08	0.01 – 0.34	0.003
Infections	4.8	0.9 – 26.5	0.071

PO2186

Daratumumab for Management of Bortezomib-Resistant Monoclonal Gammopathy of Renal Significance

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Background: The management of monoclonal gammopathy of renal significance (MGRS) is challenging. In our center, MGRS patients are initially treated with a bortezomib-based regimen. Patients who do not respond have very limited therapeutic options. Daratumumab is an anti-CD38 monoclonal antibody that is being increasingly used in patients with multiple myeloma with a favorable adverse effect profile, and represents a potential therapeutic option for patients with MGRS.

Methods: Retrospective review of the use of daratumumab in management of patients with bortezomib-resistant MGRS.

Results: Five patients were treated with daratumamab after receiving a variety of immunomodulatory therapies (Table 1). All received bortezomib with no response. One patient had a dramatic improvement in proteinuria with a stable renal function. One patient had resolution of glomerular monoclonal protein deposits but had persistent proteinuria due to significant damage to the glomerular basement membrane. One patient suffered from an acute kidney injury due to acute tubular necrosis (noted on biopsy) and became dialysis dependent. Two patients were started on daratumumab recently and had limited follow up, however both demonstrated a reduction in proteinuria. Daratumumab was well-tolerated and no patients required hospitalization due to adverse effects.

Conclusions: Our experience in using daratumumab for management of bortezomib-resistant MGRS suggests good tolerability and short-term response rates.

PO2187

Diffuse Background Monoclonal Light Chain Staining in Kidney Biopsies, Without Electron Dense Deposits: Is It Relevant?

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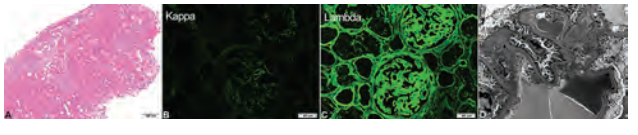
Background: Pathologic diagnosis of monoclonal gammopathy (MIg)-associated kidney disease requires specific morphologic and immunofluorescence (IF) findings with deposits on electron microscopy. We have encountered kidney biopsies showing only diffuse "background" monoclonal light chain staining the renal parenchyma, without characteristic lesions of MIg-associated kidney disease or organized/non-organized deposits on ultrastructural examination. Such staining is either overlooked if weak, or can be over-diagnosed as MIg-associated kidney disease if strong, causing dilemma over the need for immediate clone-directed therapy. We performed a clinico-pathologic study to better understand its significance.

Methods: Database search over 12-year period revealed such 32 cases. Clinical and laboratory data was retrieved along with a mean follow-up of 13 months.

Results: Out of the 32 patients, 15 (47%) had active myeloma by hematologic criteria (despite absence of myeloma casts on kidney biopsy) warranting immediate clone-directed therapy; but 11 (34%) did not have/develop myeloma-defining events till the end of follow-up period; 3 (9%) did not have detectable paraprotein; and 3 (9%) were lost to follow-up. The mean staining intensity of background monoclonal light chain was significantly higher in myeloma patients as compared to the non-myeloma patients (2.2 vs 1.5, p=0.03), but strong (2 or 3+) intensity of staining was seen in 36% (5/14) of the cases without active myeloma (Fig. 1).

Conclusions: It is important to recognize and document this isolated background monoclonal light chain staining in the biopsy report, but by itself, should not be classified as MIg-associated kidney disease. It does warrant a thorough hematologic work-up. It can help to unmask (previously unsuspected) underlying active myeloma which many patients. But it is important to note that there is a subset of patients that do not have active myeloma despite the strong background staining. Care must be taken to avoid inadvertant immediate clone-directed therapy in these patients, but periodic monitoring with hematologic and renal parameters to watch for possible malignant transformation is important.



PO2188

Immune Checkpoint Inhibitor-Induced p-ANCA Multiorgan Vasculitis

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Introduction: Use of immune checkpoint inhibitors (ICIs) has led to improved mortality in melanoma, lung cancer, and lymphoma. ICIs augment immunologic reaction against tumor cells via blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-protein 1 (PD-1), or programmed death-ligand 1 (PD-L1). Renal complications from ICI use are uncommon but can involve development of glomerular diseases and interstitial nephritis. Below we present a case of p-ANCA vasculitis in a patient on ICI therapy.

Case Description: A 52-year-old female with adenocarcinoma of the right lung (T2N2) s/p right lower lobectomy, cisplatin/vinorelbine, radiation therapy, and durvalumab was hospitalized for evaluation of new onset oral blisters, fevers, hemoptysis, skin lesions, and acute kidney injury. Her creatinine rose to 3.2 mg/dL (baseline of 0.5 mg/dL). Urinalysis revealed >180 RBCs and 17 WBCs per high power field with a urine protein to creatinine ratio (UPCR) of 2.63 g/g. ANCA titers were positive for PR-3 antibody of 4.6 units. Patient underwent renal biopsy, which revealed evidence of renal vasculitis involving all glomeruli and crescents in 4 out of 20 glomeruli. There was concern for endocarditis with vegetation seen on echocardiogram; however, with negative blood cultures the etiology was attributed to autoimmunity (vasculitis) rather than infection. The patient was aggressively treated for ANCA vasculitis with pulse steroids, plasmapheresis, and rituximab (1g given 2 weeks apart). She had a dramatic improvement in her skin lesions, hemoptysis, cardiac and renal function. Two months following her last rituximab infusion, she has not had further hematuria, her UPCR remains < 0.5 g/day, and creatinine is stable at 1.2 mg/dL. PET/CT continues to demonstrate clinical remission of her underlying cancer.

Discussion: With the dramatic cancer responses seen in patients receiving immune checkpoint therapy, there has also increased understanding associated toxicities. Although reports of ANCA positive vasculitis from ICI has been reported; this case is unique due to the multiorgan involvement of her vasculitis including the heart valves. Aggressive treatment with steroids, plasmapheresis, and rituximab has proven effective without hindering her tumor response.

PO2189

IgA Nephropathy in the Setting of Dual Immune Checkpoint Inhibitor Use

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Introduction: Acute kidney injury (AKI) is a recognized side effect of immune checkpoint inhibitors (ICPi), with acute tubulointerstitial nephritis (AIN) as the most common pathologic finding. Risk of AKI is higher with use of proton pump inhibitors (PPIs) and dual ICPi use. Glomerular disease with ICPi is infrequently found on kidney biopsy. We report a case of concomitant IgA nephropathy and AIN associated with dual ICPi blockade.

Case Description: 62-year-old male with metastatic sarcoma recently initiated on Ipilimumab and Nivolumab presented with dark colored urine for 2 days. He was recently hospitalized for neutropenic fevers with a negative infectious work up. On admission his blood pressure was 181/94 and he was afebrile. Physical exam was notable for new bilateral lower extremity edema, and no rash present. His creatinine was 2.2mg/dl (0.6-1.3), with a baseline creatinine of 0.8mg/dl. He started a PPI one month ago and denied NSAID use. Laboratory findings showed eosinophilia 7.7% (0.0-4.9) and urine eosinophils. His urinalysis had >50 RBCs and 5 WBCs per HPF and 24-hour urine protein was 5085mg. His serum complement levels were normal. Kidney biopsy showed moderate AIN and an exudative and mesangial glomerulonephritis with dominant IgA deposits. The patient was started on prednisone 60mg daily and PPI was stopped. No additional doses of immunotherapy were administered. His serum creatinine improved to 1.6mg/dl after 1 week, with plan for outpatient steroid taper. At 10mg prednisone daily, his creatinine increased to 4.5mg/dl prompting pulse steroids due to concern for ongoing interstitial inflammation versus worsening IgA nephropathy. One week later creatinine improved to 2.7mg/dl, though he developed several steroid related side effects. Due to inability to tolerate higher doses of steroids, mycophenolate was added to his treatment regimen while undergoing steroid taper.

Discussion: This case underscores the importance of considering acute glomerulonephritis as a cause for AKI in patients recently started on ICPi therapy. Risk of AKI in this patient was higher given use of PPI and dual ICPi therapy. This case is unique as the renal biopsy showed both AIN and IgA nephropathy. These findings had important implications for the treatment plan since the patient was unable to successfully stop prednisone and required a second immunosuppressive agent.

PO2190

Hypercalcemia Associated with Immune Checkpoint Inhibitors

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Introduction: Immune checkpoint inhibitors revolutionized treatment of many cancers with marked improvement in prognosis. They target CTLA-4, PD-1/PD-L1 pathways. However immune related adverse events complicate their use. Here we present the first reported case of hypercalcemia as a result of immune checkpoint inhibitors

Case Description: A 68-year old man with metastatic renal cell carcinoma underwent right nephrectomy followed by immunotherapy with ipilimumab and nivolumab. Two weeks after his second cycle of immunotherapy, he presented with inflammatory arthritis and pruritis. Work up was significant for sCa 12.8 mg/dl and Scr 3.6 mg/dl. Hypercalcemia was suspected to be malignancy related from bone metastasis or humoral stimulation. He received fluids, calcitonin and Zoledronic acid. Further investigations showed a suppressed iPTH<6.3 pg/ml, normal PTrP, low TSH 0.04 uU/ml, free T4 1.91, normal 25-OH vitamin D, elevated 1,25dihydroxy vitamin D 142 pg/ml and normal ACE level. No monoclonal proteins were detected in serum. CRP and interleukin 6 were elevated to 80 mg/dl and 176 pg/ml respectively. PET scan showed diffuse hypermetabolic lymph nodes in mediastinum, neck, and abdomen. Transbronchial needle aspiration was negative for malignancy. Inflammatory arthritis, pruritis, hyperthyroidism, nonmalignant diffuse lymphadenopathy, and 1.25 dihydroxyvitamin D induced hypercalcemia are suggestive of immune related adverse effects rather than disease progression. Patient was started on prednisone 1mg/kg/d. Hypercalcemia, AKI, pruritis and inflammatory arthritis resolved. Repeat 1,25 dihydroxy vitamin D and CRP levels were back to normal

Discussion: Hypercalcemia related to checkpoint inhibitors was previously described in setting of increased PTrP. Our patient had hypercalcemia directly related to immunotherapy likely through increased alpha hydroxylation.

PO2191

Double Trouble with Pembrolizumab: Immune Checkpoint Inhibitor-Induced Type 1 Renal Tubular Acidosis and Secondary Adrenal Insufficiency

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Introduction: Pembrolizumab is a novel immune checkpoint inhibitor (ICI) that targets programmed cell death protein (PD-1) signaling. Checkpoint inhibitor associated nephrotoxicity is an immune-mediated process that can manifest with a variety of clinical presentations. Here, we report a unique case of Pembrolizumab induced distal renal tubular acidosis (RTA) and secondary adrenal insufficiency (AI) which was successfully treated with steroids.

Case Description: A 72-year-old male with a history of stage IIIC malignant melanoma, who had recently completed 3 cycles of therapy with Pembrolizumab was admitted with generalized fatigue, weakness, and anorexia. Initial work up was notable for severe hyponatremia, and a non-anion gap metabolic acidosis (NAGMA); (Na: 120 mmol/L, Cl: 89 mmol/L, K: 3.8 mmol/L, HCO3: 20 mmol/L and creatinine 0.67mg/dL). Urine anion gap was positive at 8meq/L, urine osmolar gap was low at 57 mosm/kg and urine pH was 6.0. Subsequent laboratory work up was notable for AM cortisol of 1.0 ug/dL, serum ACTH 1.4 pg/mL and DHEA 12 ng/dl. Other pituitary hormones including LH, TSH and FSH were normal. An MRI of the sella was negative for hypophysitis. CT scan of the abdomen showed no adrenal hemorrhage or necrosis. Extensive serologic work-up including serum ANA, ANCA, anti-SSA/SSB, Hepatitis B, Hepatitis C, C3 and C4 levels were all unrevealing. A presumptive diagnosis of immune mediated central AI and distal RTA was made. A positive urine anion gap and low positive osmolar gap (<150mosm/kg) in the setting of NAGMA was highly suggestive of a distal RTA. Although this condition is associated with hypokalemia, simultaneous AI could have offset this finding. He was started on hydrocortisone 40 mg daily. This was accompanied by improvement in serum sodium and bicarbonate levels. Two days later, the patient's hyponatremia and metabolic acidosis had resolved. He was eventually discharged on a tapering dose of steroids.

Discussion: Recent studies have shown that acute interstitial nephritis is the most common type of Pembrolizumab associated nephrotoxicity. We report a novel case of Pembrolizumab toxicity, where distal RTA concurrently manifests with secondary AI. Rapid resolution of both these conditions upon initiation of steroids suggests that they are both immune mediated adverse effects associated with Pembrolizumab.

PO2192

Immune Checkpoint Inhibitor-Associated Reactivation of Primary Membranous Nephropathy Responsive to Rituximab

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Introduction: The same mechanisms that mediate immune checkpoint inhibitor (ICI) anti-tumor efficacy also increases the activity of the immune system and can lead to immune-related adverse events (irAEs). Those with preexisting autoimmune disease are particularly vulnerable. We report the first case of ICI associated reactivation of primary membranous nephropathy (MN) responsive to rituximab in a patient with mesothelioma and successful continued ICI treatment.

Case Description: A 60-year-old male with primary MN was diagnosed with stage IA malignant pleural mesothelioma (MPM) in September 2018. Shortly after receiving nivolumab his proteinuria began to increase and his nephrologist recommended conservative management. In November 2019, the patient came to nephrology clinic at MD Anderson Cancer Center for a second opinion. Notable labs included: albumin 1.9 g/dl, creatinine (Cr) 1.25 mg/dl (baseline Cr 0.82-0.91 mg/dl), and a 24-hour urine protein 13.4 g/day (<1.0 g/day prior to Nivolumab). Due to concern for reactivation of primary MN vs other causes, he underwent a renal biopsy which revealed chronic reactivated primary MN with strongly positive PLA2R stain. Consideration of immunosuppressive treatment options were discussed, and the patient was initiated on rituximab (1 g IV on Day 1 and 15), a monoclonal antibody binding specifically to CD20 on B cells. Labs one month later showed a Cr of 1.01 mg/dl, decrease in proteinuria by over 50% (4.6 g/day), and improved albumin to 2.9 g/dl. The patient restarted nivolumab in January 2020 and has stable to improved kidney function five months later. PET/CT imaging continues to demonstrate complete metabolic response and no new sites of increased FDG activity.

Discussion: Current guidelines for primary MN recommend therapy with cyclophosphamide and steroids, rituximab, or cyclosporine. All except for rituximab (in) directly suppress T cell function potentially impacting the anti-tumor effectiveness of ICI therapy. While the role(s) of B cells as pro- or anti-tumoral mediators in cancer and ICI is unknown, understanding B cell role(s) could be beneficial for those with autoimmune disease – allowing for split treatment should irAEs occur. Therapy for autoimmune reactivation should be directed by immunosuppressive mechanism in concert with goals of cancer treatment.

PO2193

Immune Checkpoint Inhibitor Therapy-Related Graft Intolerance Syndrome in a Failed Kidney Transplant Recipient on Hemodialysis

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Introduction: Immune check-point inhibitors (ICPIs) are monoclonal antibodies against inhibitory receptors on T-cells resulting in anti-cancer activity. The use of ICPIs among kidney transplant (KT) recipients with cancer is controversial, as ICPIs counter immune tolerance and is associated with a higher risk of rejection in functioning allografts. In failed allografts, the effects of ICPIs are unknown. We present a unique case of a patient with a failed KT on maintenance hemodialysis (HD) who developed graft intolerance syndrome (GIS) after ICPI therapy for metastatic renal cell carcinoma (RCC).

Case Description: Our patient is a 66-year old male with a history of diabetes, RCC and left nephrectomy in 1996. He developed end-stage kidney disease and had a deceased donor KT in 2012. His graft failed 6 years post KT, due to biopsy-proven recurrent diabetic nephrosclerosis. He was started on HD in 2018 and immunosuppression was tapered off. In 2019, he was diagnosed with renal and urothelial cell cancer in the right native kidney and underwent nephrectomy. Ten months later, distant metastasis was detected, and he was started on Nivolumab and Ipilimumab. Twenty-eight days after his 1st cycle of immunotherapy, he had good oncological response, but developed gross hematuria, pain over his allograft, malaise, and anemia consistent with GIS. Urine culture and cystoscopy were normal. A computed tomography scan of the abdomen revealed an enlarged allograft with patchy enhancement and perinephric stranding consistent with GIS. After a multidisciplinary discussion, he underwent transplant nephrectomy. Histopathology revealed grade II chronic active T-cell mediated rejection (TCMR).

Discussion: Although acute graft rejection from ICPI therapy has been documented, this is the first known report of GIS developing with ICPI therapy in a failed allograft. GIS typically occurs within 6-12 months of graft failure. Meanwhile, in functioning allografts, rejection occurs around 24 days after ICPI initiation. The temporal relation of GIS to ICPI initiation in our patient suggests the potential role of the latter as a trigger for GIS. As ICPI use becomes more prevalent in cancer management, we need to be aware of the potential complications with its use among KT recipients even with failed allografts, which requires multidisciplinary management.

PO2194

Crescentic Glomerulonephritis and Phospholipase A2 Receptor-Positive Membranous Nephropathy in a Lung Cancer Patient on an Immune Checkpoint Inhibitor

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Introduction: Acute kidney injury (AKI) occurs in 3% of patients on immune checkpoint inhibitors (ICPI), usually due to interstitial nephritis, yet the array of ICPI-mediated AKI is not fully understood, with rare reports due to Crescentic Glomerulonephritis (cGN). To date there is no known case of PLA2R-positive Membranous Nephropathy (MN) associated with ICPI. Here we report the first case of ANCA-negative cGN with PLA2R MN, which developed after initiation of ICPI, with response to rituximab (RTX).

Case Description: Nephrology was consulted for AKI and hematuria in a 67-year-old male smoker with lung adenocarcinoma. He started on pembrolizumab and pemetrexed 8 months ago, last doses 3 weeks prior to consult. He developed throat irritation from local irradiation, and pantoprazole was initiated. No NSAIDs, herbal medications or iodinated contrast exposure. Prior to treatment, baseline Creatinine (Cr) was 0.8mg/dL and urinalysis (UA) was negative for albuminuria. Blood pressure was 112/66, and no edema was present. Cr was elevated at 3.7 mg/dL. UA showed 3+ protein, >50 RBC, 10-25 WBC, and no pathologic casts. Renal sonogram was normal. Urine protein:creatinine ratio (UPC) was 1.52g/g. Complements were normal. Serology workup (pANCA/cANCA/MPO/PR3, ANA, anti-PLA2R) was negative. Kidney biopsy showed diffuse cGN [Glomeruli: necrosis (2/38), cellular crescents (10/38), and fibrocellular

crescents (6/38)], diffuse PLA2R-positive glomerular deposits, focal tubular atrophy, and minimal interstitial fibrosis/inflammation. EM showed thickened basement membranes, focal subepithelial granular deposits and early spike formation, and 30% foot-process effacement. ICPI was discontinued and prednisone 60mg daily was started. Cr nadir'ed at 2.3mg/dL, but uptrended to 3.1mg/dL over 4 weeks; UPC increased to 2.59. He then received 4 doses of RTX over 8 weeks and was started on vinorelbine. UPC and Cr improved to 2.18 and 2.5mg/dL, respectively, and NSCLC disease stabilized.

Discussion: Interstitial nephritis is often implicated in AKI related to ICPIs, but rarely other pathologies are reported. Renal biopsy should be considered in patients with atypical features suggestive of GN. Given that our patient's biopsy showed cGN and PLA2R MN, we opted to treat with RTX, which has resulted in improvement in renal function and proteinuria.

PO2195

Diffuse Large B-Cell Lymphoma Presenting with Light Chain Cast Nephropathy: A Case Report

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Introduction: Light chain cast nephropathy is caused by filtration of excessive amounts of free light chains into the renal tubules, leading to acute kidney injury (AKI). The main associated malignancy is multiple myeloma (MM). No adult case of cast nephropathy associated with diffuse large B-cell lymphoma (DLBCL) was reported

Case Description: A 55-year-old previously healthy man presented with foamy urine for 3 months and exercise intolerance. Physical exam showed pale conjunctiva, multiple neck masses, and no edema. His serum creatine (SCr) was 7.6 and 15.2 mg/dL initially and on admission 4 weeks later, whereas baseline SCr had been normal one year ago. His hemoglobin level was 7.9 g/dL, and white blood cell count was 8750/μL without eosinophilia. No active urine sediments were found. A UPCR was 7250 mg/g, and a UACR 300 mg/g. Ultrasound showed decreased kidney sizes (R 9.0, L 9.7 cm). Immunoelectrophoresis detected monoclonal λ light chain in both his serum and urine, and a serum λ free light chain level was 8830 mg/L, with a κ-to-λ ratio of 0.0024. Following a diagnosis of DLBCL (Lugano stage IV) by neck mass biopsy, a renal biopsy disclosed diffuse aggregation of amorphous eosinophilic proteinaceous casts in the tubules, with a normal glomerular compartment and mild arteriosclerosis, findings consistent with IgG-λ light chain cast nephropathy. He was treated with 4 courses of R-CHOP, hemodialysis, and a short course of plasmapheresis. λ free light chain level decreased to 2830 mg/L after plasmapheresis. A complete response for DLBCL was achieved 6 months later but he remained on hemodialysis.

Discussion: This is, in the literature, the first adult DBLCL patient presenting with proteinuria and renal deterioration proven to be light chain cast nephropathy. Standard lymphoma treatments were given, and based on limited evidence, plasmapheresis was given to reduce the light chain load (Median serum free light chain level was 6590 mg/L in MM patients as reported by Bridoux in JAMA 2017). Decreasing plasma light chain concentration leading to improvement in AKI has been reported for MM. However, this case remained dialysis-dependent despite a decline in light chain levels. To conclude, we provide a unique case of DLBCL with cast nephropathy. Clinicians could take this entity into consideration and treatment may be tailored for better outcomes.

PO2196

A Case of Mixed Cryoglobulinemia Type II with Monoclonal Gammopathy in a Patient with Chronic Hepatitis B

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Introduction: Non-Hepatitis C related mixed cryoglobulinemia Type II (MCT2) is rare. Causes include lymphoproliferative disorders, chronic infections like Hepatitis B and autoimmunity.

Case Description: A 68-year-old Chinese male presented with livedo reticularis and rapidly progressive glomerulonephritis requiring dialysis, on a background of chronic Hepatitis B (HBV) infection. Investigations showed a uPCR of 9.75g/g and serum creatinine (sCr) of 407 μmol/L (baseline sCr 82μmol/L). Rheumatoid factor was positive (>650U/ML). Both C3/C4 were low. HBV viral load was detected at 479, 452 copies/ml, while HCV, HIV and autoimmune screen were negative. A IgM kappa monoclonal band (3g/L) was detected on serum protein electrophoresis and immunofixation. Renal biopsy revealed MPGN with 28% crescents, capillary luminal hyaline thrombi, and IgM Kappa deposits. Findings were consistent with MCT2 despite negative serum cryoglobulins. Bone marrow aspiration and biopsy revealed a small clonal B-cell population confirmed on flow cytometry. Pulsed methylprednisolone followed by high-dose prednisolone, Rituximab and plasmapheresis were initiated for organ-threatening disease, together with entecavir. HBV viral suppression was observed after 1 month. Partial remission was achieved (sCr 140μmol/L; uPCR 2.39g/g) after 4 months. Development of sepsis and CMV reactivation prompted withdrawal of steroids, resulting in progressive deterioration of renal function (sCr 302μmol/L; uPCR 10.62 g/g). Commencement of Bortezomib and dexamethasone resulted in gradual improvement of renal function (sCr 107μmol/L; uPCR 4.71 g/g) after 3 cycles.

Discussion: MCT2 observed in our patient was possibly contributed by chronic HBV. However, suboptimal response despite HBV viral suppression prompted further treatment of the underlying lymphoproliferative disease causing monoclonal gammopathy of renal significance. Optimal treatment of MCT2 is not established, although immunosuppression consisting of corticosteroids with Rituximab or cyclophosphamide is required in severe renal involvement. We demonstrated a favourable outcome with Bortezomib-based clone directed therapy after achieving a non-sustained response with Rituximab/prednisolone. Long-term monitoring of the underlying low grade non-Hodgkin's lymphoma (NHL) is necessary.

PO2197

Myeloma Cast Nephropathy with Diffuse Amyloid Casts: Two Case Reports and Literature Review

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Introduction: Multiple myeloma (MM) is a plasma cell derived hematologic malignant disease. The malignant proliferating plasma cells can secrete massive monoclonal immunoglobulins which can cause various pathologic types of renal injury. Myeloma cast nephropathy (MCN) is the most common pathologic lesion with the worst renal prognosis. Rarely, the free light chains in the protein casts can form amyloid fibrils. Here, we report two rare cases of myeloma cast nephropathy with diffuse amyloid casts.

Case Description: Case 1: A 54-year-old Chinese man presented with a 4-year history of multiple myeloma, proteinuria and hematuria. He had Monoclonal IgAλ plus free λ spike in both serum and urine. He was treated with chemotherapy. His serum creatinine was normal until 11 months before admission, and he was on hemodialysis 1 month before admission. Renal biopsy showed diffuse amyloid casts in the tubular lumens, and he had no obvious amyloid deposits in other kidney compartments and no sign of extra-renal amyloidosis. The amyloid fibrils formed around mononuclear cells which were CD68 negative. The patient was maintained on chemotherapy and hemodialysis, and he died 8 months after renal biopsy. **Case 2:** A 58-year-old Chinese man presented with a one-and-a-half-year history of proteinuria and slowly rising serum creatinine. He had Monoclonal IgDλ spike in both serum and urine. Amyloid casts were observed in the tubular lumens and in the centre of some casts were mononuclear cells. There were no amyloid deposits in other kidney compartment and no sign of systemic amyloidosis. The patient also had fine granular deposits along the tubular basement membrane with λ linear staining along tubular basement membrane suggesting light chain deposition disease. The patient was treated with bortezomib-based followed by lenalidomide-based chemotherapy and achieved very good partial remission (VGPR). After twenty-seven months of follow-up, the patient still had no sign of systemic amyloidosis.

Discussion: These 2 cases of MCN with diffuse amyloid casts have different pathologic characteristics from the usual myeloma casts and tubular epithelial cells may play important roles in the pathogenesis.

PO2198

Masked Light Chain Proximal Tubulopathy (LCPT) and Focal Segmental Glomerulosclerosis (FSGS) in Multiple Myeloma (MM)

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Introduction: Patients with MM often do not have a myeloma-defining disease, and delayed recognition/treatment of a monoclonal gammopathy of renal significance (MGRS) may confer worse renal outcome. Here we report 3 patients with "masked" LCPT (one also had FSGS) and a 4th patient with both FSGS and LCPT. None had crystalline deposits. All 4 patients had a history of untreated, smoldering MM and the initial kidney biopsy interpretation in 3 of the cases reported no evidence of MGRS. Treatment of the underlying MM resulted in improvement of renal parameters in all, suggesting MM as the etiology for the renal disease.

Case Description: 73 y/o, worsening renal function (WRF), albuminuria and monoclonal proteinuria (MP). Biopsy: FSGS. Initial immunofluorescence (IF) was negative. Re-examination after protease digestion 6 months later: LCPT. Therapy for MM resulted in decreasing free light chains (FLCs), improvement of renal function, and decreased albuminuria and MP. 72 y/o, WRF and albuminuria. Biopsy: FSGS and LCPT attributed to MM. Therapy for MM resulted in decrease in FLCs, stabilization of renal function and decreased albuminuria. 75 y/o, WRF and heavy MP. Biopsy: diabetic nephropathy with interstitial inflammation. IF was negative. Following autologous stem cell transplant for progression to symptomatic MM, there was a striking improvement in FLCs, renal function and MP. 73 y/o, WRF, heavy MP and Fanconi's syndrome. Biopsy: mild glomerulomegaly and focal sparse lymphocytic infiltrates. Initial IF was negative. Re-examination after protease digestion 6 months later: LCPT. Therapy for MM resulted in decreasing FLCs, improvement of renal function and a marked decrease in MP.

Discussion: FSGS has been rarely linked to MM. In view of the connection between treatment of the MM and improvement of the renal parameters, FSGS must be considered as an additional MM-related MGRS. The presence of monoclonal light chains (LCs) in the tubular epithelial cells (TECs) should raise the possibility of this diagnosis. Because monoclonal LCs deposits in TECs may not be detectable by standard IF techniques ("masked" LCPTs), paraffin IF after protease digestion should always be performed in

kidney biopsies of patients with monoclonal gammopathies. In addition, detailed EM examination of the tubules is essential to identify the lysosomal abnormalities typical of LCPT.

PO2199

CKD After 225Ac-PSMA617 Therapy in Patients with Advanced Metastatic Prostate Cancer: A Report of Two Cases

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Introduction: A promising therapeutic efficacy has been demonstrated with targeted radionuclide therapy (TRNT) using 225Ac-PSMA617 in patients with advanced metastatic castration-resistant prostate cancer (mCRPC). However, these novel agents may be associated with significant toxicity. As seen in animal models, the multiple alpha particles generated in the decay chain of 225Ac may accumulate in the renal tubular cells, resulting in nephropathy. We report our experience with 225Ac-PSMA617 therapy in 2 patients with advanced mCRPC who developed kidney injury.

Case Description: Patient 1 is a 68-year-old man with widely metastatic mCRPC despite multiple lines of therapy and secondary chronic hydronephrosis with bilateral nephrostomy tubes. He received 3 rounds of 225Ac-PSMA617 in 2-month intervals. Baseline serum creatinine was 1.6 mg/dL (eGFR 44 mL/min/1.73m^2) and it increased up to 3.3 mg/dL (eGFR 18 mL/min/1.73m^2) after 225Ac-PSMA617 therapy. A kidney biopsy was obtained and revealed severe interstitial fibrosis with ongoing tubular injury and interstitial inflammation. A trial of corticosteroids therapy was attempted with no improvement in kidney function. 225Ac-PSMA617 therapy was discontinued because of related kidney failure. Patient 2 is a 67-year-old man with mCRPC with progression on multiple prior therapies. He first initiated Lu177-PSMA and one year later this was combined with 225Ac-PSMA617 in 2-month intervals. He received 5 rounds of 225Ac-PSMA617 in total, the last round being complicated with grade 3 cytopenias leading to cessation of treatment. Baseline serum creatinine at initiation of TRNT was 1.0 mg/dL (eGFR 82 mL/min/1.73m^2). He subsequently developed progressive CKD and serum creatinine was 1.7 mg/dL (eGFR 40 mL/min/1.73m^2) on last follow-up.

Discussion: We report 2 cases of progressive kidney disease in the setting of 225Ac-PSMA617 therapy for patients with advanced mCRPC. One underwent kidney biopsy showing tubulointerstitial injury, consistent with 225Ac-PSMA617-related tubular accumulation of toxic nuclides seen in animal models. This kidney injury was not responsive to corticosteroids therapy. Our case studies emphasized the need for careful assessment and monitoring of kidney function in patients receiving these novel agents.

PO2200

Successful Management of Chronic Ifosfamide Nephrotoxicity with Immunosuppression: A Case Series

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Introduction: Ifosfamide is an alkylating chemotherapeutic agent that causes both acute and chronic kidney injury. Ifosfamide-induced chronic tubulointerstitial nephropathy can present months after exposure, thereby delaying diagnosis and treatment. Here, we describe three cases of chronic ifosfamide nephrotoxicity, wherein the time-course and outcomes suggest that earlier recognition and initiation of immunosuppression may benefit these patients.

Case Description: Three adult patients with distinct malignancies, status-post at least 3 cycles of ifosfamide chemotherapy, presented to our onco-nephrology clinic for worsening renal function. On average, the patients were referred to our clinic ~8 months after their last dose of ifosfamide. In this period, their serum creatinine (SCr) had risen to a peak ~2.5mg/dL from ~1mg/dL. The patients reported occasional frothy urine but were otherwise asymptomatic. Urine analysis and microscopy was significant for mild glucosuria/proteinuria, sterile pyuria, and granular casts, with urine protein/creatinine ratio of ~1.2. Autoimmune serologies, complement levels, protein electrophoresis, and renal ultrasound were unremarkable. Kidney biopsies, performed 10 months after the last ifosfamide cycle, demonstrated tubulointerstitial nephritis with moderately advanced interstitial fibrosis. Cytologic atypia of the tubular epithelium was consistent with karyomegalic interstitial nephritis (KIN), previously documented in cases of ifosfamide toxicity. In all cases, prednisone therapy led to improvement and plateau of SCr ~2.1. Curiously, multiple attempts to wean corticosteroids led to worsening SCr and active urinary sediment. In 2 patients, addition of mycophenolate mofetil enabled dose reduction but not cessation of corticosteroids. In all cases, SCr remained stable at ~2.1 after 1 year of follow-up.

Discussion: These cases illustrate the latent presentation and challenging management of chronic tubulointerstitial nephritis secondary to ifosfamide. On average, prednisone was started ~10 months after the last ifosfamide dose, when significant interstitial fibrosis had already developed. Delayed therapy and/or enduring inflammation may have also contributed to the failure to stop corticosteroids. Overall, early surveillance, prompt recognition, and long-term immunosuppression is likely important in these patients to stabilize and maintain renal function.

PO2201

Hyperphosphatemia in the Setting of Fibroblast Growth Factor Receptor Inhibitors

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Introduction: Fibroblast growth factor (FGF)-23 is a phosphaturic hormone which works by reducing apical membrane expression of sodium-phosphate co-transporters in the proximal renal tubule and thus decreasing phosphate re-absorption. Fibroblast growth factor receptors (FGFR) are ubiquitously expressed in different tissues and become altered in various types of cancer. TAS-120 is one of several pan-FGFR inhibitors currently in clinical trials for use in patients with cholangiocarcinoma. Hyperphosphatemia is seen in more than 70% of patients on this therapy.

Case Description: A 44-year-old female with metastatic intrahepatic cholangiocarcinoma with progressive disease despite conventional therapy was started on TAS-120. Fifteen days into treatment she developed pain in knees and hips and was noted to be hyperphosphatemic to 7 mg/dL. She was initiated on sevelemer but given persistent hyperphosphatemia to 6.4 mg/dL, acetazolamide, calcitonin and phytonadione were added. Despite this, phosphorus remained elevated at 5.8 mg/dL; addition of alendronate 35mg weekly alongside dose reduction of TAS-120 led to sustained improvement in serum phosphorus levels. A 49-year-old male with a history of cholangiocarcinoma was started on TAS-120. Four days into treatment he developed calf pain and was noted to be hyperphosphatemic to 7.3 mg/dL. The medication was briefly stopped and he was initiated on sevelamer with improvement in phosphorus to 2.7 mg/dL. Resumption of TAS-120 led to recurrent hyperphosphatemia for which acetazolamide was initiated. Three months after initiation of TAS-120 he had ongoing hyperphosphatemia; following dose reduction of TAS-120 and starting phytonadione, probenecid and calcitonin, serum phosphorus levels remained within normal limits.

Discussion: FGFR-induced hyperphosphatemia has a similar clinical presentation as hyperphosphatemic familial tumoral calcinosis (HFTC) with debilitating join pain and tissue calcification. The current management of hyperphosphatemia relies mainly on dietary modification and gastrointestinal phosphate binding that were insufficient for our patients. The hyperphosphatemia and calciphylaxis pain was successfully treated with phosphaturic medications (acetazolamide, calcitonin) and alendronate. Phytonadione (vitamin K) interferes with matrix Gla protein, a tissue inhibitor of calcification.

PO2202

Direct Renal Infiltration in Chronic Lymphocytic Leukaemia: A Case Report

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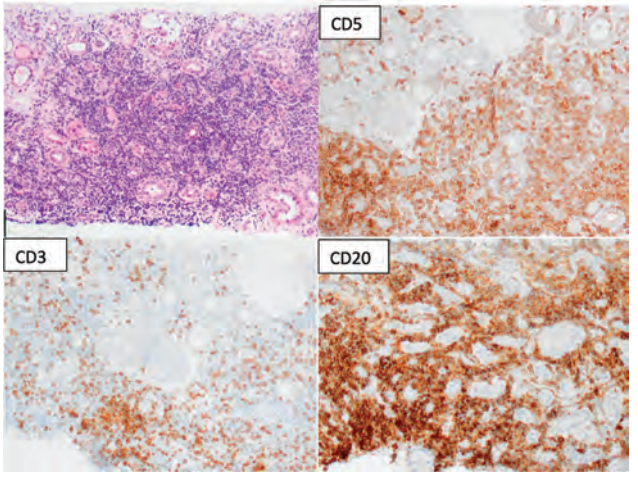
Introduction: CLL is a haematological malignancy characterised by lymphocytosis with uncontrolled accumulation of B lymphocytes. It is most commonly a disease of older adults with co-morbidities limiting treatment options. Renal involvement of CLL is common with autopsy findings showing up to 90% involvement however direct infiltration rarely causes clinically significant renal impairment.

Case Description: A 78 year old man was admitted to hospital with acute on chronic kidney injury, creatinine 759umol/l from 200umol/L. He had background of CLL and a supra-pubic catheter. His total white cell count was 33.9x10^9/L and lymphocyte count of 19x10^9/L. His SPC was draining with no recent obstruction or infection. An US showed no hydronephrosis or cortical scarring. A renal biopsy was performed and a tunnelled dialysis catheter inserted to commence haemodialysis. Biopsy showed a diffuse heavy infiltrate of lymphoid cells in the intersitium with no immune deposition and 70% fibrosis. Immunohistochemistry staining positive for CD20 and CD5. We started a tyrosine kinase inhibitor however after 3 months he remained dialysis dependent and died from COVID pneumonia.

Discussion: Renal injury is seen in approximately 16.2% of patients during disease course in CLL. This can be due to tumour lysis syndrome, immune deposits, cyroglobinaemia, obstruction to due lymphadenopathy and direct infiltration of B lymphocytes as seen in this case. Indications for commencing treatment for CLL usually involve evidence of marrow failure, massive lymphadenopathy and significant B symptoms. In this case treatment was initiated to manage the patients' renal involvement. It is important to pursue a renal biopsy in patients with CLL as it may reveal an indication to commence treatment.



H&E shows heavy infiltrate of small lymphoid cells. ICH positive for CD20 (B-cell marker) CD5 (expressed on normal T-lymphocytes but also expressed in CLL), mostly negative for CD3 (T-cell marker)

PO2203

Attack of the Clones: Leukemia and Myeloma

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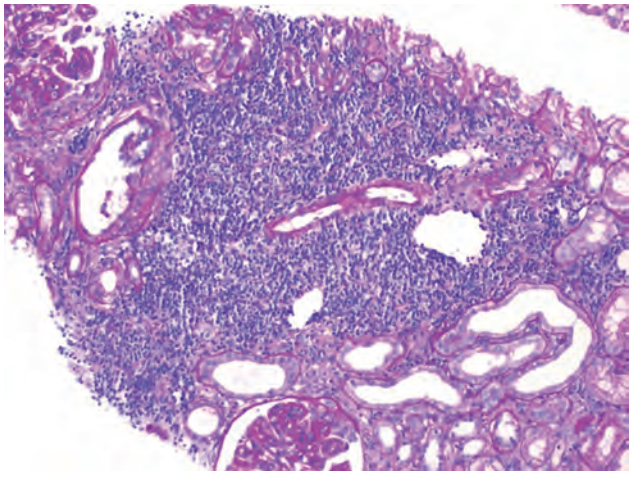
Introduction: Chronic lymphocytic leukemia(CLL) and multiple myeloma(MM) are both neoplastic diseases that are monoclonal tumors of differentiated B-cells that rarely occur simultaneously. There is disagreement and conflicting evidence as to whether these seemingly distinct disorders may arise from identical clones. In some cases MM maybe diagnosed up to 15 years after the established diagnosis of CLL. We describe a rare case of a patient with renal failure and nephrotic range proteinuria where both CLL and MM were diagnosed concomitantly from a single renal biopsy.

Case Description: 59 y/o Indian male with COPD, DM-type 2, HTN, recent pseudomonas aeruginosa pneumonia presented with bilateral temporal headaches and fevers. Work-up revealed creatitine: 1.7mg/dl, UPCR: 6.6 g/g, free kappa/lambda ratio of 0.25 and mildly depressed C3 and C4. Renal biopsy showed diffuse proliferative and crescentic g/omerulonephritis with IgG lambda light chain restriction, CD-20 positive lymphocytic interstitial infiltrate, ATN and diabetic glomerulopathy. EM also revelaed subepithelial hump-shaped depositis and abundant glomerular neutrophils suggesting a component of post-infectious GN. Both flow cytomtery and bone marrow biopsy revealed monotypic B-lymphocyte population with aberrant expression of CD5 and CD23 consistent with the diagnosis of CLL. The patient was treated with cyclophosphamide and dexamethasone and is currently stable on Ibrutinib with a creatinine of 1.3mg/dl.

Discussion: CLL is a common hematologic malignancy that has many systemic complications. Autopsies have shown that 90% of CLL pateints have renal infiltration; however there is seldom renal impairment. This is a rare case of renal CLL infiltration causing type-1 cryoglobulinemia with IgG lambda monocolonal gammopathy of renal significance. Early diagnosis with renal and bone marrow biopsy and subsequent treatment with immunosuppresive therapy is crucial.



CD20 positive lymphocytic renal interstitial infiltrate.

PO2204

Should We Give the Green Light to Green Top Tube? Reverse Pseudohyperkalemia in Leukemia Patient

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Introduction: Hewe we described a 69-year-old woman presented with hyperleukocytosis with reverse pseudohyperkalemia. This is also the first case of reverse pseudohyperkalemia in Philadelphia chromosome positive acute lymphoblastocytocytic leukemia.

Case Description: The 69-year-old woman was rushed to our emergency department due to progression of dyspnea for one week. Upon lab examination, hyperleukocytosis (> 500000/uL) with blasts that suggestive of acute leukemia. Notably, marked hyperkalemia (11.6 mEq/L) with normal renal function was noted but there is no typical electrocardiogram change. High LDH(3393 U/L) and low haptoglobin(<7.88 mg/dL) also noted. After clarification, the blood tube that had result of hyperkalemia is sodium heparin tube. We retested potassium by using serum separate tube with 5 minutes of 3000 revolutions per minute, revealing serum potassium level 3.8 mEq/L. Reverse pseudohyperkalemia was impressed. She recieved leukophresis and chemotherapy for leukostasis. The bone marrow biopsy later confirmed Philadelphia chromosome positive acute lymphoblastocytic leukemia. Reverse pseudohyperkalemia resolved after leukocyte return to normal level.

Discussion: Pseudohyperkalemia is suspected when the measured potassium is high but the patient does not manifest signs of hyperkalemia, such as abnormal electrocardiogram. Pseudohyperkalaemia is falsely elevation of serum potassium levels without elevation of plasma potassium levels, commonly occurred in patients with hematological disease. Heparin anticoagulated plasma samples provide more accurate measurement of the true potassium level in these patients and sodium heparin (green top) tube is widely used. However, in reverse pseudohyperkalemia, serum potassium is within normal range, and plasma potassium is falsely elevated, such as in our patients. The heparin in the plasma collection tube causes damage to the cell membrane during processing and centrifugation in the context of fragile cells of hematologic malignancy. Reverse pseudohyperkalemia had been reported in chronic lymphocytic leukemia patient. To our knowledge, this is the first case report of reverse pseudohyperkalemia in Philadelphia chromosome positive acute lymphoblastocytocytic leukemia patient. This case reminds us that potassium obtained using heparin tube is not panacea to get accurate level, and reverse pseudohyperkalemia is a must-known phenomenon for clinicians.

PO2205

A Rare Case of Composite Lymphoma with Kidney Infiltration of Nodal Marginal Zone B Cell Lymphoma and Three Different Types of Cast Nephropathy

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Introduction: We present an interesting case of composite lymphoma (nodal marginal zone B-cell lymphoma and multiple myeloma) characterized by the rare kidney invasion of the nodal marginal zone B-cell lymphoma and three different types of cast nephropathy present simultaneously in patient with multiple myeloma.

Case Description: A 57-year-old Chinese male was admitted to hospital for proteinuria. He reported foam urine, abdominal distension, fatigue, and weight loss of 5 kg within one month. Laboratory tests demonstrated hemoglobin 108 g/L, blood urea nitrogen 27.1 mmol/L, serum creatinine 639.1 umol/L and urine acid 547 umol/L. The 24-hour urinary protein and microalbumin was 3193.3mg and 42.3mg, respectively. Immunofixation electrophoresis (IFE) showed IgD-Lambda+Lambda monoclonal protein. MRI identified diffuse osseous lesions. Bone marrow aspirate and biopsy demonstrated a hypercellular marrow with extensive plasma cell infiltration. Besides, multiple lymphadenopathies in both axillary and bilateral Inguinal lymph nodes were noticed. Lymph node biopsy suggested a nodal marginal zone B-cell lymphoma. To explore the involvement of kidney injury, we performed a kidney biopsy. Surprisingly, we found three types of nephropathy (myeloma casts, light chain crystal structure and light chain amyloidosis). At the same time, we also found focal lymphocyte infiltration, which are confirmed of nodal marginal zone B-cell lymphoma by immunohistochemistry with various molecule markers. To further explore the relationship between the two tumors, we performed the whole genome exon sequencing of the bone marrow and lymph nodes, surprisingly we found the similar mutation sites (V1982I of ARID1A gene) in both tissues, suggesting that the two tumors might originated from the same mutation. After BCT chemotherapy and PAD-T chemotherapy, urea nitrogen and blood creatinine decreased, the patients get rid of hemodialysis.

Discussion: nodal marginal zone B-cell lymphoma infiltrate kidney only is very rare. Also three kinds of nephropathy (myeloma casts, light chain crystal structure and light chain amyloidosis). present simultaneously is also very rare. And the sequencing of the genome exon suggested that nodal marginal zone B-cell lymphoma might developed in to multiple myeloma in bone marrow micro-environment.

PO2206

Breast Cancer-Associated Podocytopathy

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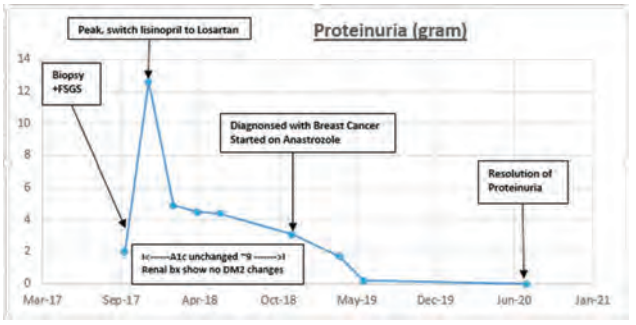
Introduction: Podocytopathies such as FSGS have not been classically associated with solid malignancy. Here we present a case of a female with a diagnosis of FSGS and its association bilateral lobular carcinoma in situ of the breast.

Case Description: A 52 year old Sri Lankan female with history of DM2 (with no prior proteinuria) was referred for sudden onset of proteinuria. The patient first reported profound foamy urine in October 2017 with workup significant for sub-nephrotic proteinuria of 2 gram with normal serum creatinine and albumin. A kidney sonogram unremarkable. Further workup was negative for infectious, autoimmune, vasculitis and para-protein etiologies. The patient was started on Lisinopril 10mg, however proteinuria worsened to 12.6 grams thereby switch to losartan (100mg daily) with slight improvement in proteinuria. A kidney biopsy was performed which showed focal global glomerulosclerosis secondary to adaptive changes with minimal fibrosis with no diabetic nephropathy related changes seen. Light microscopy showed globally sclerosis (9%) and IFTA (5-10%). Immunofluorescence microscopy showed no evidence of primary podocyte disease, immune complex-mediated disease or para-protein deposition disease. The patient was managed conservatively on anti-proteinuric agent. Almost a year after the diagnosis of FSGS, patient was diagnosed with bilateral lobular carcinoma in situ (breast) with atypical lobular hyperplasia. She underwent lobectomy and started on anastrozole. Following cancer surgery and initiation of hormonal therapy, she noticed resolution of her fatigue, urine foamy and proteinuria (repeat UP/Cr <23 mg (Figure 1)).

Discussion: Our case demonstrates a potential link of the diagnosis of lobular ductal cancer of the breast with a diagnosis of FSGS. Interestingly, the FSGS diagnosis preceded the diagnosis of the breast cancer. While the proteinuria came into partial remission with conservative management, a dramatic resolution of FSGS was noted post-surgery and hormonal therapy for the breast cancer.



PO2207

Snapshot of AKI Profile in Patients in Oncology Settings: A Single-Center Experience

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Introduction: Acute kidney injury (AKI) may result from the cancer itself, treatment of cancer or associated complications. In cancer patients with AKI complete recovery of renal function was seen in 82% and chronic dialysis was needed in 6% of patients. Overall severity of illness, age, and functional status have more of an impact on prognosis than underlying malignancy, and the presence of cancer may not be an absolute exclusion criterion for withholding RRT. Hospital mortality approaches 80% in cancer patients with AKI. Cancer associated AKI (CA-AKI) is very prevalent with reported incidence of 12% to 49%. We tried to look into incidence, etiology and outcome of AKI in a tertiary care cancer hospital.

Case Description: For two consecutive months all patients admitted in ICU at Basavatarakam Indo-American Cancer Hospital were observed for development of AKI with KGIDO criterion. We found 45 patients who developed AKI out of 83 total ICU admissions (54.21%). Chronic kidney disease was present in 17 patients (37.77%), diabetic kidney disease being the commonest (64.70%). The commonest etiology of AKI was sepsis (77.8%) and septic shock was present in majority of these patients (66.7%). Other causes of AKI were hypercalcemia (4.4%), chemotherapy associated (44.4%), obstructive nephropathy (8.9%). Metabolic acidosis was predominant finding (75.6%) with oliguria being least common (26%). Hematological malignancies were frequently associated with AKI (33.3%) followed by gastrointestinal tract tumors (24.44%). Urological malignancies were least associated with AKI (6.6%). Large number of patients required renal replacement therapy (RRT) (48.9%). SLED was commonest modality (n=15; 68.18%) of RRT followed by CRRT/CVVHDF (N=8; 34.78%). Regional citrate anticoagulation was commonest anticoagulation used (62.5%). 46% patients recovered their renal functions but creatinine did not reach baseline for 11% of patients. 29% patients with AKI died and a 14% of patients lost to follow up. CRRT was associated with better survival (n=4; 50%) followed by SLED (n=4; 26.66%).

Discussion: Incidence of AKI was higher among patients in oncological ICU with half of them required RRT. Commonest etiology of AKI was sepsis where shock state was observed in majority of patients. Although SLED was used more frequently, outcomes were better with CRRT/CVVHDF.

PO2208

A Patient with Hyper-Warburgism Successfully Treated with Peritoneal Dialysis

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Introduction: The combination of hypoglycemia and lactic acidosis in cancer patients is usually known as hyper-warburgism.

Case Description: A 74-year-old Thai man presented to our hospital with symptomatic hypoglycemia. He was previously healthy, no history of diabetes. Further investigation revealed hyperbilirubinemia, hepatosplenomegaly and first-diagnosed HIV infection. Computerized tomography of abdomen showed large liver mass with multiple intraabdominal lymphadenopathy. Liver mass biopsy showed round cell neoplasm with immunohistochemistry staining compatible with Burkitt lymphoma: positive for CD20, Bcl-6, CD10, C-myc, Ki67 100%, and negative for Bcl-2. His lymphoma was initially treated with high-dose dexamethasone. During investigation and initial treatment, our patient developed acute kidney injury (AKI) with severe lactic acidosis. Hypoglycemia persist even he received intravenous glucose 18 g/hour. Serum ketone, insulin and c-peptide were normal. We suspected that he had hyper-warburgism due to Burkitt lymphoma, which was not respond to dexamethasone. Due to HIV seropositive status, we chose automated peritoneal dialysis (PD) for AKI and severe metabolic acidosis in this patient. PD dose in this patient was 19 liters per day. After PD initiation, the patient gradually recovered, with serum lactate dramatically decreased and intravenous glucose could be stopped. Clinical and laboratory parameters, including major clinical events, were shown in figure 1. After lactic acidosis resolved, we decided to treat this patient with chemotherapy. Unfortunately, this patient died later due to fungemia, neutropenia and septic shock.

Discussion: Hypercatabolic state such as hyper-warburgism was usually treated with continuous renal replacement therapy (CRRT). Here, we presented a case of hyper-warburgism successfully treated with PD. We hoped this report might offer alternative treatment in patients who unable to undergo CRRT.

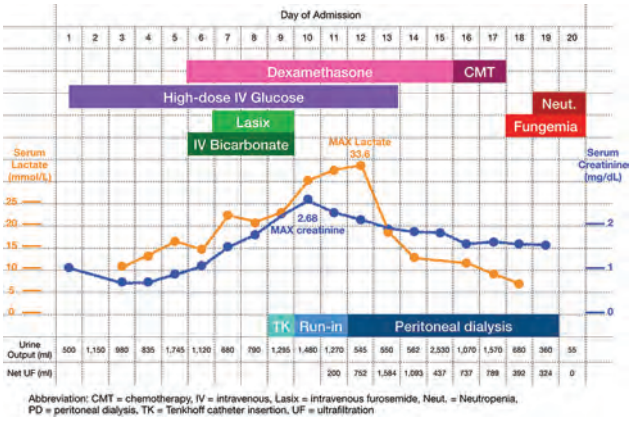

Figure 1: Clinical course of a patient with hyper-warburgism

PO2209

Narsoplimab, Another Tool in the Management of Thrombotic Microangiopathy in Stem Cell Transplant Recipients

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Introduction: Thrombotic microangiopathy (TMA) is a severe complication in recipients of hematopoietic stem cell transplants (HSCT). Its treatment remains controversial due to its complex and not fully understood mechanism. As more emerging evidence supports the role of complement dysregulation in the observed endothelial injury, anti-complement medications have emerged as a potential therapy. Narsoplimab is an anti-complement therapy that was granted FDA designations for HSCT-TMA as a breakthrough therapy. We hereby report the first case of Narsoplimab use in a HSCT adult recipient with TMA in the United states.

Case Description: A Caucasian women in her early 70s with medical history of relapsed B- cell acute lymphocytic leukemia post allogenic HSCT who was treated with Venetoclax and MiniCVD regimen with a hospital course significant for E. coli bacteremia, CMV pneumonia and acute kidney injury. Creatinine rose from 1.6 to 3.3 mg/dl, over 2-weeks, despite the discontinuation of tacrolimus and treating the sepsis. Urinalysis was significant for pyuria, hematuria, granular casts and +1 proteinuria. She had elevated C5b9 and LDH levels (363 ng/ml and 326 U/L respectively) with schistocytes noted in blood smear, suggestive of TMA. Renal biopsy was significant for ATN and acute TMA, for which we decided to treat her with anticomplement therapy with Narsoplimab. She received twice weekly doses for 4 weeks and had significant improvement in renal function (Cr improved to 0.8 mg/dl), however she developed worsening respiratory status secondary to possible diffuse alveolar hemorrhage and family withdrew care in week 4 of therapy.

Discussion: Narsoplimab is a human monoclonal antibody that inhibits mannan-binding lectin associated serine protease-2 (MASP-2) which is an essential enzyme in the complement system lectin pathway. It is designed to prevent endothelial injury without interfering with other complement pathway roles. Data from phase 2 study showed an improvement in patient survival and TMA blood markers (LDH, haptoglobin, and platelet count). It might improve renal function as well as its inhibition to lectin activation pathway can ameliorates proteinuria induced kidney injury. However she didnot have improvement in her platelet count, LDH and C5b9 levels. Further studies are ongoing (Phase 3 trials in IgA nephropathy and HSCT-TMA) to evaluate such renal benefits.

PO2210

The Histopathologic Spectrum of Kidney Biopsies in Patients with Thymoma, Myasthenia Gravis, or Both: A Report of 24 Cases from a Single Institution

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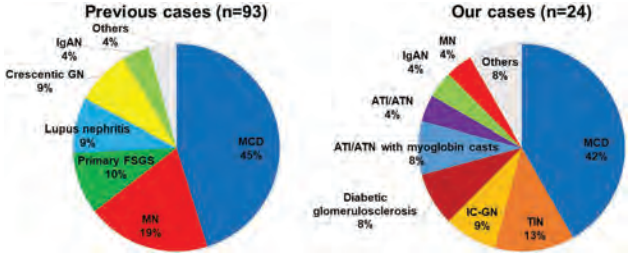
Introduction: Nephropathy in patients (Pts) with thymic diseases such as thymoma and myasthenia gravis (MG) is rare and has been the subject of case reports. Previously, 93 cases have been reported from multiple institutions, and of these, common diseases are minimal change disease (MCD; 45.2 %), membranous nephropathy (MN; 19.4 %), and primary focal segmental glomerulosclerosis (FSGS; 9.7 %). Here we characterize the spectrum of kidney biopsy findings in 24 cases from a single institution.

Case Description: Total 40,268 renal biopsy cases from 2005 through 2019 at Cedars-Sinai Medical Center were reviewed. 24 cases (0.0596 %) of Pts have history of thymoma and/or MG. Main pathological diagnoses are following: MCD (10 cases; 41.7%), Tubulointerstitial nephritis (TIN; 3 cases; 12.5 %), Immune complex-mediated glomerulonephritis (IC-GN; 2 cases; 8.3 %), Diabetic glomerulosclerosis (2 cases; 8.3 %), acute tubular injury/necrosis (ATI/ATN) with myoglobin casts (2 cases; 8.3 %), ATI/ATN (1 case; 4.2 %), IgA nephropathy (1 case; 4.2 %), MN (1 case; 4.2 %), secondary FSGS (1 case; 4.2 %), and Monoclonal Ig deposition disease (1 case; 4.2 %).

Discussion: Consistent with the previous reports, MCD is the most common renal lesion in Pts with thymic diseases. However, we experienced only one case of MN and no primary FSGS, the 2nd and 3rd common diseases in the reports. We, instead, observed kidney diseases that haven't been reported before: TIN, and ATI/ATN with myoglobin casts. Of 3 TIN cases, 1 showed granulomatous interstitial inflammation without infection; and 1 case showed acute tubulitis with immune complex deposits both in mesangium and along tubular basement membranes. In addition, 40 % of MCD cases showed an atypical feature: IC deposits in mesangial area. The possible mechanisms of thymic disease-associated nephropathy include T cell dysregulation, IC formation containing tumor antigen, and effects of tumor-releasing lymphokines. In conclusion, this is the largest and unique case series of nephropathy in Pts with thymic disease from a single institution.



PO2211

Erdheim-Chester Disease: A Rare Cause of Bilateral Renal Artery Stenosis and AKI

Monica S. Ng,[1,2] Saw Yu Mon,[1,5] Rachael O'Rourke,[4,5] Nigel Mott,[3] Touraj Taheri,[6,5] Kirk Morris,[7] Pedro H. Gois.[1,5] *[1]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [2]Faculty of Medicine and Institute for Molecular Bioscience, University of Queensland, Brisbane, QLD, Australia; [3]Medical Imaging, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [4]Medical Imaging, Prince Charles Hospital, Brisbane, QLD, Australia; [5]Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia; [6]Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [7]Department of Cancer Services, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.*

Introduction: Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis affecting multiple organ systems. We report a case of ECD with bone marrow, cardiac and vascular and renal involvement, presenting with hypertensive emergency and AKI, responsive to endovascular stenting and peg-interferon.

Case Description: A 72 y.o. female presented with hypertensive emergency and AKI. Her symptoms included fatigue, poor oral intake, 5kg weight loss and lower limb oedema. Her medical history included stage 3b chronic kidney disease secondary to hypertensive nephropathy, bilateral renal artery stenosis, coronary artery disease, rheumatoid arthritis, previous diverticulitis and osteoarthritis. Her examination was unremarkable. Her investigations showed anaemia; creatinine 2.45mg/dL (baseline 1.59mg/dL), BUN 47mg/dL; unremarkable electrolytes and liver function tests. A CT angiogram showed extensive, irregular mural thickening of the aorta present for 2 years, right atrial mass, high-grade stenosis of both renal arteries and left vertebral artery occlusion. Review of prior lower limb CT imaging showed bilateral, symmetrical sclerotic bone infiltrates in the diaphyses and metaphyses, corresponding to the regions of PET avidity, confirming the diagnosis of ECD. Echocardiogram and cardiac MRI confirmed a 21.7 x 18.3mm right atrial mass with small pericardial effusion. ECD was confirmed via right sacrum lesion biopsy showing sclerotic xantogranulomatous histiocytic(CD68+, CD163+, CD1a-) reaction. Despite taking 5 classes (7 agents) of anti-hypertensives at maximal doses, her blood pressure was suboptimally controlled. After bilateral endovascular renal artery stenting, anti-hypertensive requirement reduced to 2 agents and renal function improved to better than pre-AKI levels. She is receiving peg-interferon α2a and prednisolone for ECD.

Discussion: The disease affects renal arteries in 18-27% cases and should be considered as a cause of renal artery stenosis in older patients with multisystem anomalies. Renal artery stenting in this subset can improve hypertension and renal outcomes. The disease has characteristic radiological findings and the diagnosis is frequently reliant on imaging. Histological examination is often not sufficient to confirm the diagnosis. ECD diagnosis is essential for treatment of the underlying disease process.

PO2212

Renal Involvement as Initial Presentation of Mantle Cell Lymphoma: A Case Series

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Introduction: Mantle cell lymphoma (MCL) rarely affects kidneys. We present 2 cases with different spectrum of kidney involvement in MCL.

Case Description: The 1st case was a 63-yr old male with incidental finding of Serum creatinine (SCr) of 10mg/dL. Chronic lymphocytic leukemia was diagnosed 2 weeks prior via peripheral blood cell analysis & flow cytometry (FC) done due to constitutional symptoms and headaches for which he was using daily ibuprofen for several months. On exam he had elevated blood pressure but no signs of volume overload. Initial supportive treatment did not improve kidney function and hemodialysis was initiated due to worsening azotemia and persistent nausea and vomiting suspicious for uremia. Renal biopsy showed diffuse acute on chronic interstitial nephritis with perivascular lymphoid aggregates of monoclonal CD 20+ B-cells positive for CD5 and Cyclin-D1 consistent with MCL. No significant immunostaining was found. Bone marrow biopsy confirmed renal biopsy findings and diagnosis of MCL. Until last follow up, the patient refused chemotherapy and remained dialysis dependent. The 2nd case was a 73-yr old male with incidental founding of SCr of 1.9mg/dL in association with glomerular hematuria and grade A3 proteinuria. He had no constitutional symptoms and had normal physical exam except for presence of diffuse lymph node (LN) enlargement. Renal biopsy was obtained and showed MPGN-pattern with 25% crescents on light microscopy, presence of all immunoglobulin classes with κ-light chain (KLC) predominance in glomeruli and lymphoid infiltration with KLC in the interstitium on immunostaining. MCL was confirmed with FC and excisional LN biopsy. Prednisone/Rituximab/Bendamustine therapy led to improvement in kidney function and proteinuria.

Discussion: MCL can cause differential kidney involvement from direct tumor infiltration to MCL-associated glomerulonephritis. Therefore, correct diagnosis with renal biopsy and prospective registries are needed to generate data about differences in outcomes in MCL with various kidney involvement.

PO2213

Cystatin C Measurement Improves Renal Function Estimation with Selpercatinib Use

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Introduction: Selpercatinib (LOXO-292) is a selective RET inhibitor that is approved for the treatment of RET-dependent lung and thyroid cancers. In the LIBRETTO-001 trial of selpercatinib, a treatment-emergent increase in serum creatinine was noted in ~18% of patients. Creatinine is mainly excreted by glomerular filtration and is partly secreted via transporters such as MATE-1. Inhibitors of MATE-1, such as selpercatinib, can reduce creatinine clearance leading to an incorrect diagnosis of drug related kidney injury. Cystatin C is an alternative marker that is freely filtered, completely reabsorbed and not secreted like creatinine. It is therefore not affected by transporter inhibitors and may be a better marker of kidney injury in patients receiving Selpercatinib. We present a patient on Selpercatinib with significant difference in kidney function by creatinine and cystatin C.

Case Description: 58-year-old male with metastatic *RET* fusion-positive lung cancer who progressed on cabozantinib started selpercatinib. His pre-treatment creatinine was 0.8mg/dl and increased to 1.8mg/dl after 1 year of therapy. Urine sediment was bland with no significant proteinuria. Renal sonogram showed right sided hydronephrosis which prompted placement of ureteral stent. Creatinine did not improve with persistent hydronephrosis prompting conversion to a nephroureterostomy tube one year later. Creatinine remained elevated at 1.9mg/dl despite resolving hydronephrosis. Cystatin C levels were measured and showed significant discrepancy with serum creatinine as shown in Table below. This finding highlighted that although the patient did have chronic kidney disease, the extent was less than estimated by solely creatinine.

Discussion: This case highlights the benefit of checking both creatinine and cystatin C in patients on selpercatinib. Despite urological intervention, the persistence in elevated

creatinine is likely attributed to the drug inhibitory effect on creatinine secretion. Cystatin C may be a better measure of renal function in patients receiving MATE-1 inhibitors such as selpercatinib.

Discrepancy in Serum Creatinine and Cystatin C Trends

Clinic Encounters	Creatinine (mg/dL)	GFR (mL/min/1.73m2)	Cystatin C (mg/dL)	GFR by Cystatin C (mL/min/1.73m2)
1	1.9	38	1.2	62
2	2	36	1.4	49
3	1.9	38	1.2	61
4	1.4	55	1	77

PO2214

ALECT 2 and Hepatocellular Carcinoma: An Intriguing Association

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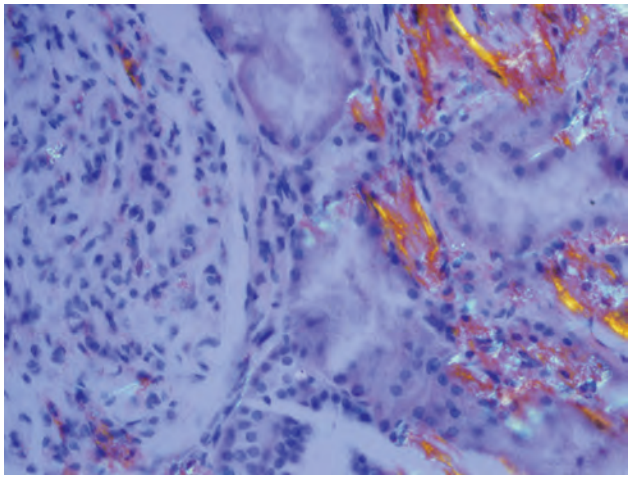
Introduction: Amyloidosis derived from leukocyte chemotactic factor 2 (ALECT2) is the third most common type of renal amyloidosis in the United States. The incidence of ALECT2 is highest among Hispanics and there is a predilection for involvement of the kidney and liver with sparing of the heart. We report a case of hepatocellular carcinoma (HCC) in a patient with ALECT2

Case Description: A 69-year-old Hispanic man with chronic kidney disease secondary to ALECT2 and monoclonal gammopathy of undetermined significance was admitted for constipation and distended abdomen. Creatinine on a dmission was 8mg/dL and he was initiated on dialysis. Imaging revealed cirrhosis, ascites and two liver masses involving the portal vein. Alpha fetoprotein was 7123ng/mL and he was diagnosed with multifocal HCC. Evaluation for hepatitis, autoimmune disease and other etiologies for chronic liver disease was negative and cirrhosis was presumed to be secondary to ALECT2. Based on the Barcelona Clinic Liver Cancer staging, he was given a stage D. His functional status precluded any liver directed therapies or systemic chemotherapy and he failed to meet the Milan criteria for liver transplantation. Following a discussion of the prognosis he was transitioned to palliative care

Discussion: ALECT2 is a recently described form of systemic amyloidosis that has quickly emerged as a common and possibly underdiagnosed cause of systemic amyloidosis particularly in patients of Hispanic ancestry. ALECT2 can involve various organs but usually spares the heart and brain. ALECT2 in association with HCC has not been reported to date. Interestingly in one study, expression of LECT2 in human HCC biopsies was significantly reduced and over expression of the gene resulted in inhibition of the tumor in an experimental model. ALECT2 is without an identifiable etiology and targeted therapy and hence, it is imperative not to misdiagnose ALECT2 as AL amyloidosis to avoid harmful chemotherapy



PO2215

A Case of Extranodal Rosai-Dorfman Disease Confirmed by Renal Biopsy

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Introduction: Perinephric stranding is typically caused by infection or obstruction. In rare cases other etiologies has been found. We present a case of the extremely rare extranodal Rosai Dorfman Disease confirmed by renal biopsy.

Case Description: A 72 yo M with CKD III was found to have perinephric stranding during CT surveillance for ascending thoracic aneurysm. Subsequent imaging revealed similar findings worisome for lymphoma. Renal biopsy was performed and revealed xanthogranulomatous inflammation with prominent plasma cells, dense histiocytic infiltrate mixed with scattered lymphoid aggregated plasma cells, histiocytoid cells with large nuclei and abundant cytoplasm. Immunostains showed histiocytoid cells to be immunoreactive to CD68 and S100 protein which is consistent with Rosai Dorfman Disease. Renal function remained stable and given unresectability of the lesion and stability of renal function, the patient was managed conservatively with serial imaging. Renal scan ruled out an obstructive process

Discussion: Rosai Dorfman Disease is an extremely rare, though benign, disease characterized by proliferation of histiocytes that typically proliferates in lymph nodes in the 2nd -3rd decades of life. While its cause is unknown, consequences of this disease are secondary to mass effect of the lesion. Rarely, RDD can present extra-nodally and pose a risk to renal function. It is important to evaluate causes of renal perinephric stranding. Rosai Dorfman Disease poses a difficult treatment dilemma given unresectability and risk of renal obstruction.

PO2216

Eculizumab for Treatment and Prevention of Recurrent Gemcitabine-Induced Atypical Hemolytic Uremic Syndrome After Gemcitabine Rechallenge: A Case Report

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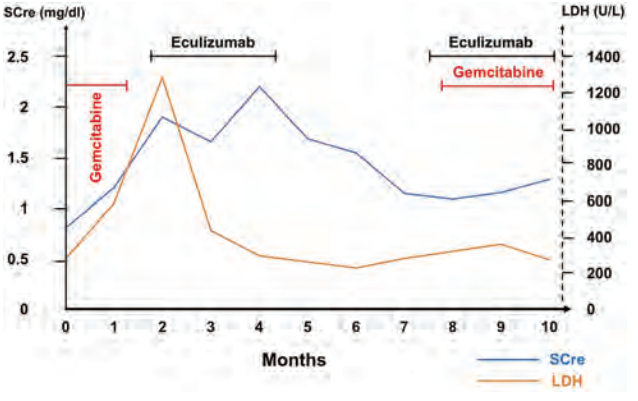
Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare side effect of gemcitabine. Here, we report a case of gemcitabine-induced aHUS successfully treated with eculizumab, with subsequent use of eculizumab to prevent recurrence of aHUS after reinitiating gemcitabine.

Case Description: A 29-year-old male with intrahepatic cholangiocarcinoma on gemcitabine and cisplatin was admitted with AKI. On presentation, he was newly hypertensive to 162/108 mmHg and edematous. His labs were notable for a serum creatinine (SCr) of 1.19 mg/dL (baseline 0.6 mg/dL), hemoglobin 8.8 g/dL (baseline of 12.6 g/dL) with reticulocytosis, platelet count 190 K/μL, LDH 635 U/L, haptoglobin <10 mg/dL, schistocytes on blood smear, and a normal ADAMTS13 level. Urine studies revealed hematuria, proteinuria, and granular casts. Gemcitabine and cisplatin were discontinued, yet his SCr continued to rise to 2.12 mg/dL, LDH to 1222 U/L and platelet count fell to 77 K/uL. Eculizumab was initiated and his creatinine improved to 1.14 mg/dl, and his LDH, platelet count, and haptoglobin normalized. Eculizumab was stopped after 2 months without subsequent recurrence. He was reinitiated on dose-reduced gemcitabine and cisplatin due to progression of his cancer despite multiple alternative chemotherapies. Eculizumab was reinitiated concurrently with gemcitabine and continued biweekly. His blood pressure, SCr, haptoglobin, LDH and platelet count remained stable. Unfortunately, he died due to cancer progression 3 months later. Figure 1 summarizes his treatment and laboratory course.

Discussion: We report a case of successfully utilizing eculizumab to prevent recurrence of gemcitabine-induced aHUS after gemcitabine reinitiation, which has not been previously reported to our knowledge. There are scarce reports of gemcitabine reinitiation without eculizumab, most of which resulted in recurrent renal toxicity. There may be utility in the use of eculizumab in patients who need to reinitiate gemcitabine. Larger studies evaluating this approach are warranted.



PO2217

A Case of Lupus Nephritis Improved by Molecular Targeted Drug Therapy for Multiple Intrapulmonary Metastasis of ROS-1 Gene-Positive Lung Cancer

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Introduction: Systemic lupus erythematosus is a multisystemic disease associated with genetic, environmental and epigenetic factors. The effect of tyrosine kinase inhibitors has only been reported in SLE model mice for imatinib. Here we report a case in which lupus nephritis was improved by a molecular targeted drug for multiple intrapulmonary metastases of ROS-1 gene-positive lung cancer.

Case Description: Thirty-one-year-old woman, who was diagnosed with SLE at the age of 14 years, had been treated with immunosuppressive agents including corticosteroids, cyclophosphamide and mycophenolate mofetil, with frequent relapses. At the age of 30 years, she was admitted to our hospital due to development of systemic erythema, which was diagnosed as drug-induced eruption with increased SLE activities. She was treated with prednisolone (PSL) 50 mg/day and remission was achieved for

SLE, however, during the systemic screening, lung adenocarcinoma was accidentally detected, and thoracoscopic right middle lobectomy was performed. Seven months after surgery, she had an exacerbation of erythema on the face and bilateral arms, arthralgia and urinary proteins, with elevated anti-ds-DNA antibodies and decreased serum complement levels. The dose of PSL was increased, but the symptoms did not improve, when multiple intrapulmonary metastases were detected, indicating recurrence of lung adenocarcinoma. The previous lung specimens revealed a high expression of PD-L1 and positive ROS-1 fusion gene, thus tyrosine kinase inhibitor (crizotinib) was selected as the anti-cancer therapy instead of anti-PD-L1 antibodies. Interestingly, urine protein and erythema/arthralgia improved as the size of lung tumor reduced.

Discussion: Crizotinib is a molecular targeting agent with non-receptor-type tyrosine kinase inhibitory action that competitively binds to the ATP binding site of EML4-ALK tyrosine kinase, resulting in signal transduction inhibition. In this case, the molecular targeting drug induced improvement of lupus nephritis along with regression of lung cancer, suggesting that tyrosine kinase inhibition may be effective for lupus nephritis.

PO2218

Paraneoplastic Minimal Change Disease Associated with High-Grade Neuroendocrine Tumor

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Introduction: Minimal Change Disease (MCD) is usually associated with Lymphoma, Leukemia and solid tumors like Lung Cancer, Renal Cell Carcinoma and Thymoma but data on incidence of paraneoplastic glomerular disease are lacking. To our knowledge, only two cases of neuroendocrine tumor (NET) presenting with Paraneoplastic MCD reported in literature. We present a 47 year-old man with duodenal NET presented with nephrotic syndrome and renal biopsy was suggestive of minimal change disease.

Case Description: A 47 year-old-man with history of well-differentiated metastatic NET (not on therapy) and HTN admitted for dyspnea and anasarca for two weeks. His labs were significant for creatinine of 3.9 mg/dL, albumin 1.9 g/dL, proteinuria of 4.3 g/day and Na 118 mmol/L. IV diuretics with albumin infusion initiated, which improved his kidney function. Serologies and proteinuria workup - negative. Renal biopsy performed for nephrotic syndrome, showed prominent podocyte foot process effacement with mild acute tubular necrosis and mild glomerular sclerosis. Diagnosed with paraneoplastic MCD from metastatic NET and treatment with steroids initiated. Chemotherapy not started because of the overall decline in his clinical status and increased tumor burden. One week after steroids, his proteinuria was 42 g/day, and steroid doses were increased. Three weeks later, proteinuria decreased to 6 g/day and his symptoms improving. Unfortunately, he suffered further kidney injury because of hypotension and hemodialysis initiated one month later.

Discussion: The most common paraneoplastic glomerular disease is membranous glomerulopathy in tumors, but MCD should be kept on the differential as well. Like membranous nephropathy, remission of MCD been reported on ablation of the tumor, suggesting a paraneoplastic process, though the precise mechanisms are not fully understood. In our case, since the patient did not qualify for chemotherapy because of increased tumor burden, steroids were initiated which helped in part to reduce symptoms. The etiology of glomerulopathy in cancer does not appear to be related to tumor burden, metastatic spread or the site or extent of invasion, but to the secretion of substances from the tumor cells. Kidney biopsy should be performed early, as prompt diagnosis is important to ensure patients do not receive ineffective and potentially harmful treatments.

PO2219

Management of IgA Nephropathy and Concomitant Breast Cancer

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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide. Although treatment guidelines have been established, there is little known about the management of IgAN in the setting of solid malignancy. Herein we describe two cases of IgAN and breast cancer diagnosed at our center.

Case Description: Case 1: 42-year-old female with newly diagnosed breast cancer 3 months ago presents to the renal clinic for acute kidney injury (AKI) with creatinine (Cr) 3.5mg/dl from baseline 1.1-1.3mg/dl. Chemotherapy was started one week ago with doxorubicin and cyclophosphamide (ddAC). Two months prior to cancer diagnosis, her doctor noted 4.9g of protein in the urine with few RBCs. She now has 4g of protein with >50 RBCs. She underwent kidney biopsy which showed IgAN (M1 E1 S1 T2 C1). She received a 3g pulse of methylprednisolone (MP) followed by prednisone taper that was shortened to 3 months in light of degree of chronicity on biopsy and concurrent immunosuppressive ddAC treatment with 4 cycles total. Creatinine stabilized at 1.8mg/dL 9 months after last ddAC cycle and proteinuria improved to 1g after re-initiation of losartan. Case 2: 38-year-old female presents to the renal clinic with AKI (Cr 1.8mg/dl from baseline 1.0mg/dl), gross hematuria and nephrotic range proteinuria that were detected incidentally in the emergency department, where she was seen for sore throat after the first 2 monthly ddAC cycles for the new diagnosis of breast cancer. She has a history of arthralgias associated with high citric citrullinated peptide, low myeloperoxidase titers and intermittent hematuria that led to a kidney biopsy demonstrating moderate focal global sclerosis without immune deposits or vasculitic lesions 4 years prior. Her symptoms improved on hydroxychloroquine which she stopped at the time of cancer diagnosis. Her kidney biopsy now shows IgAN (M1 E0 S1 T1 C2) for which she received a 1.6g pulse of MP followed by prednisone tapered over 5 months. She completed 3 cycles of ddAC. Creatinine improved to 0.9mg/dL and proteinuria receded from 7g to 0.5g.

Discussion: These cases highlight the complexity in management of IgAN while patients are undergoing treatment for a concurrent malignancy. Temporal relationship of IgAN and malignancy is unclear, but suggests potential value of cancer screening of patients with newly diagnosed IgA nephropathy.

PO2220

Sezary Syndrome with Renal Involvement

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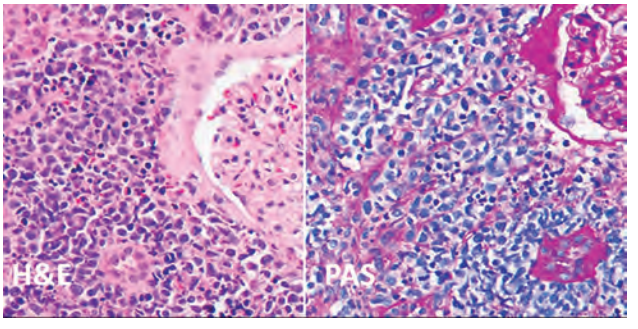
Introduction: Sezary Syndrome is a cutaneous T-cell lymphoma that presents with erythroderma, lymphadenopathy, and circulating malignant T cells. While involvement of the spleen, liver, bone marrow and lung are well documented, kidney involvement is rare. We present a case of acute kidney injury (AKI) due to biopsy-proven T cell lymphoma invasion of the kidneys

Case Description: A 69-year-old female with a history of cutaneous T-cell lymphoma was admitted to the oncology service with AKI. Serum creatinine (sCr) 3.3mg/dL (baseline 0.6mg/dL), urine protein-to-creatinine ratio 2.5g/g, urine sediment bland and renal ultrasound unremarkable. A PET scan, performed to evaluate systemic disease burden, revealed diffuse kidney enlargement with high FDG uptake throughout the renal parenchyma. A kidney biopsy was performed Light microscopy showed diffuse interstitial infiltration by atypical small lymphoid cells and prominent focal apoptosis with apoptotic bodies and focal interstitial hemorrhage. The lymphoid cells had the same immunophenotype as the cutaneous T cell lymphoma The glomeruli had slight segmental wrinkling of capillaries and glomerular basement membranes, and segmental podocyte swelling. She also had leptomeningeal involvement. Treatment included dexamethasone, systemic and intrathecal doxorubicin, methotrexate, and cytarabine. SCr returned to baseline. However, her course was complicated by severe mucositis, neutropenic fever, gastrointestinal hemorrhage and refractory shock. The patient was stabilized and opted to return home with hospice

Discussion: AKI caused by kidney involvement in Sezary syndrome has only been reported via case reports. The mechanism of AKI is thought to be tubular compression by the lymphomatous infiltrates impeding tubule function and peritubular capillary blood flow. Our patient's biopsy supports this mechanism. Her AKI resolved with urgent corticosteroids and chemotherapy. Further reporting is needed on the prevalence of this condition and nephrologists should consider renal lymphomatous invasion when evaluating AKI in those with cutaneous T-cell lymphoma



PO2221

Belatacept-Induced Post-Transplant Lymphoproliferative Disorder of the Spleen That Spontaneously Resolved on Withdrawal of the Agent

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Introduction: PTLD (Post-Transplant Lymphoproliferative Disorder) is a dreaded and serious complication of allograft transplant. Compared to CNIs, allograft rejection prophylaxis with Belatacept is less nephrotoxic, but carries a higher risk of PTLD. B-cell proliferation in PTLD is linked to EBV, and while use of Belatacept is limited to those that are EBV+ pre-transplant, prior EBV infection does not completely ensure that a patient will not develop PTLD. Patients with active PTLD characteristically show B symptoms and an increase in EBV RNA due to active viral replication. Prompt PET, BMB and blood testing must be pursued to determine a potential site of proliferation.

Case Description: 64 year AAM 2 years status-post deceased-donor transplant was admitted for altered mental status, nausea, vomiting, fever of unknown origin, and weight loss. He was found to have splenomegaly on CT without other evidence of adenopathy. LDH was elevated. Patient underwent brain MRI, PET scanning, BMB and LP, all of which were normal. A full ID work-up including CMV, EBV RNA, BK were all negative. Core biopsy of the spleen demonstrated CD20/CD45+ cells with tissue effacement, suggesting a diffuse large B-cell lymphocytic infiltration/monomorphic PTLD. The sample was EBV-negative by IHC. Belatacept was withdrawn. Subsequent splenectomy was required, which showed histopathologic evidence of infarction, but complete resolution of lymphoproliferative infiltration.

Discussion: Even in EBV recipient-positive patients, there is still a risk to develop PTLD. In our case, the patient demonstrated monomorphic PTLD which resolved spontaneously when withdrawing Belatacept. This suggests that overly aggressive immune suppression, rather than induction of dysregulated proliferation, was the culprit. The fact that the patient did not show an acute increase in EBV RNA, and EBV by ISH on core biopsy of the spleen was negative, suggests that pre-transplant serosorting based on EBV seropositivity may not be sufficient to predict risk for developing PTLD. The patient had complete resolution of AMS and B symptoms with discontinuation of Belatacept, with no subsequent recurrence of PTLD after switching to sirolimus/mycophenolate.

PO2222

Heterogeneous Manifestations of Post-Renal Transplant Lymphoma

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a serious complication occurring in 1-3% of adult renal transplant recipients (RTR). PTLD is often associated with Epstein-Barr Virus (EBV) and over immunosuppression (IS). A majority of PTLD is of B-cell origin. PTLD has a heterogenous presentation, involving the allograft, GI tract, and nervous system. We present a case series of 16 RTR who demonstrate a variety of PTLD manifestations.

Case Description: 50% of RTR were Caucasian and 38% African American. 62% of RTR received a deceased donor and 38% a living donor. 62% received Thymoglobulin induction and 38% Simulect. Maintenance IS was Prednisone, Tacrolimus, and Mycophenolate Mofetil (MMF). RTR presented with GI symptoms, abdominal pain, B symptoms, and neurological deficits. At diagnosis, average time from transplantation was 96.8 months (<1-20 years); 56% of RTR were <60 years old and 44% were >61years old. 31% were EBV mismatched and 12.5% were Cytomegalovirus mismatched. PTLD involved a single site in 44% and multiple sites in 56%. PTLD localized to the GI tract (10), lymph nodes (9), CNS (4), bone marrow (3), lungs (2), mediastinum (2), skin (2), retroperitoneum (1), and native kidney/ureter (2). 6 RTR had purely extranodal involvement. PTLD was EBV+ (8), monomorphic/monoclonal (14), and of B-cell lineage (13; Diffuse Large B Cell Lymphoma in 11). Non-Hodgkin's Lymphoma was diagnosed in 7 RTR. 3 RTR had T-cell PTLD. IS agents (MMF, Tacrolimus) were discontinued in all RTR at diagnosis; maintained on steroid monotherapy. Treatment was chemotherapy either alone or in combination with radiation (2), resection (2), and salvage therapy (1). Post treatment, all RTR remained on steroid monotherapy or with Everolimus (3), Tacrolimus (1), or Azathioprine+Rituximab (1) added. Treatment was complicated by Tumor Lysis Syndrome and infections. 50% of RTR developed renal insufficiency and 31% received dialysis. The mortality rate was 44%, <4 years after diagnosis.

Discussion: PTLD that was EBV-, had T-cell involvement, and localized to the CNS/bone marrow presented with aggressive disease and a higher mortality. Thymoglobulin induction, deceased donor, and donor EBV+ status are potential contributing risk factors for PTLD development; further analysis is still being conducted. Physicians should be aware of the various PTLD manifestations and assertive in management of renal transplant recipients.

PO2223

Richter Transformation (RT): A Rare Complication in Renal Transplant

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Introduction: RT is conversion of B-cell chronic lymphocytic leukemia (CLL) into diffuse large B-cell lymphoma (DLBCL). We present a rare case of RT in a renal allograft.

Case Description: A 68 year old male was admitted for a syncopal episode and acute renal failure. He had significant medical history of ESRD secondary to diabetes and hypertensive nephrosclerosis, deceased donor renal transplant in 2015 on Mycophenolate and Tacrolimus, CLL diagnosed in 2017 on Ibrutinib, Stage III CKD of allograft with baseline creatinine 1.5 mg/dl. Initial work up revealed orthostatic hypotension and AKI with creatinine of 3.3 mg/dl. Urinalysis and microscopy was negative for proteinuria, hematuria, pyuria, casts or crystals. Renal ultrasound showed the size of transplant kidney was 10.7 x 5.8 x 4.3 cm with normal renal cortex and no demonstrated mass, cyst or hydronephrosis. Administration of IV NS and holding antihypertensive medications to correct orthostasis failed to improve renal function with creatinine rising up to 4.02 mg/dl. Transplant renal biopsy was done. Pathology results revealed no evidence of allograft rejection but extensive infiltration of renal parenchyma with atypical lymphocytes with high Ki-67 expression suggesting transformation to DLBCL in a patient with a known history of CLL. Lymphocytes retained their positivity for CD5 and CD23 which supported diagnosis of RT rather than post-transplant lympho-proliferative disorder (PTLD). Patient was continued on Ibrutinib, Tacrolimus, Prednisone 5mg daily and started on weekly Rituximab infusion. Mycophenolate was discontinued. Patient's renal function returned to its baseline after 2 doses of Rituximab. He was planned to continue Rituximab infusion as an outpatient.

Discussion: Transplant patients have high risk of RT due risk factors including concomitant immunosuppression, Eptstein-Barr virus infection and some with genetic susceptibility. While PTLD is a well-recognized complication of patients with renal transplants, RT is not that common. Immunochemotherapy is usually the preferred treatment for older patients with RT while allogeneic bone marrow transplantation may be curative in younger patients. Discussion between transplant physician and oncologist should be held, taking into account the new molecular prognostic markers prior to renal transplant. This may help in risk stratification of patients for conversion of CLL to RT.

PO2224

Longitudinal Assessment of Unilateral Ureteral Obstruction Kidney Injury by Relaxometry and Spin-Lock Exchange MRI

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Background: Non-invasive imaging technique allows longitudinal and repetitive assessment of renal disease progression. In this study, we assessed the utility of a new MRI technique, quantitative relaxometry and Spin-lock exchange MRI, in detecting renal pathology in unilateral ureter obstructed (UUO) kidneys, focusing on destructive tubular injury (dilatation) and renal fibrosis, the pathological changes commonly observed in progressive kidney disease.

Methods: BALB/c mice (n=6-8) were imaged before and after (day 5, 10 and 15) UUO surgery at 7T magnet. Spin-lock images were acquired in a transverse plane using a fast spin echo sequence preceded by a preparatory spin-lock cluster. The dispersion of $R_{1\rho}$ with locking frequency was fit to Chopra model. The fits provided regional values of transverse relaxation rates R_{2fit}, $R_{1\rho}$ at infinite spin-lock frequency ($R_{1\rho}^{\infty}$), and an exchange rate-weighted parameter S_ρ. Since cortex and outer stripe of outer medulla (OSOM) were clearly identified with T_2-weighted image, even with UUO kidneys, these regions were selected for analysis. Paraffin tissue sections were stained using picrosirius red or anti-collagen I antibody. Histological scores for tubular dilatation and fibrosis, based on luminal space and positive fibrotic areas in sections, were computationally measured and the correlation between MRI parameters and histological scores were assessed.

Results: In histology, evident tubular enlargement was observed at UUO day 5, while tubulointerstitial fibrosis was mild at this stage. Both histological changes became more evident on progression and fibrosis showed larger increases from day 5 to day 15 (tubular dilatation ~25% increase, fibrosis ~3 fold increase). Relaxation rates R_{1obs}, R_{2obs} and $R_{1\rho}$ were progressively dropped (25-50%) in UUO kidneys. Interestingly, R_{1obs} showed the highest sensitivity to tubular dilatation, while S_ρ showed the highest correlation with renal fibrosis.

Conclusions: Relaxation parameters showed high detectability to tubular dilatation and overall changes in UUO progression. S_ρ best detected fibrotic changes. This would be because it depends mainly on the average exchange rate between water and other chemically shifted resonances such as amides and hydroxyls, sensing collagen accumulations. These new MRI parameters could be used for the assessment of kidney disease progression.

Funding: NIDDK Support

PO2225

Kidney-Specific Landscape of Aging Mitochondrial DNA Mutations by Duplex Sequencing

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Background: Accumulation of mutations in the mitochondrial genome (mtDNA) is a potential mechanism of aging in the mitochondrial rich kidney, where mtDNA damage also increases with diabetes, CKD and AKI. Accurately detecting low level somatic mtDNA mutations within the cellular complexity of the kidney was previously confounded by variable levels of mtDNA heteroplasmy. Using ultra-sensitive Duplex Sequencing (DS), a modified next-gen sequencing (NGS) technique, we decreased the error rate relative to conventional NGS by $>10^4$x, allowing us to accurately characterize mtDNA mutation patterns unique to the aging kidney relative to other organs.

Methods: We compared mtDNA mutations in kidneys from cohorts of aged (26-m.o.) and young (5-m.o.) NIA C57Bl/6j mice to multiple organs with high mitochondrial content (heart, eye, liver, skeletal muscle and brain). In both ages, kidney carried the highest burden of mtDNA point mutations. Mutation spectrum analysis showed that mtDNA point mutations in the kidney increased significantly with age and were primarily G>A/C>T, indicative of polymerase error ($2.5x10^{-5}$ $p > 0.0001$ relative to all other tissues) with G>T/C>A mutations, indicative of oxidative damage, the second most common type. Aged kidneys were further separated into glomeruli or tubule-rich whole cortex fractions to determine regional mutation burden.

Results: Glomeruli had ~25% fewer total mtDNA mutations ($p= 0.002$) and specifically ~80% fewer oxidative lesions (G>T/C>A, G>C/C>G, $p= 0.02$). Furthermore, differential accumulation of mtDNA mutation between kidney fractions does not appear to be randomly distributed across the genome but is instead gene-specific as demonstrated by significantly reduced mutations in glomeruli of mt-rRNA gene mtRnr1 but not mtRnr2, and of Complex IV gene mt-Co2, but not mt-Co1 or 3. Finally, we sequenced kidneys from aged mice treated systemically for 8 weeks with SS-31, a mitochondrial therapeutic peptide that reduces oxidative stress in the kidney, and found that mutations stemming from oxidation, but not polymerase error, were significantly reduced.

Conclusions: These data suggest that renal mtDNA mutation is cell specific and that even in old age, accumulation of some mutations is tractable with therapeutic intervention.

Funding: Other NIH Support - NIA K01 AG062757, UOHS Nathan Shock Center Pilot Award, NIA P01 AG001751, Other U.S. Government Support, Private Foundation Support

PO2226

Integrated Analysis of the DNA Methylome, Transcriptome, and Proteome in Human Glomerular and Tubulointerstitial Compartments

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Background: The interplay between the human DNA methylome, transcriptome, and proteome in the kidney glomerulus and tubulointerstitium is incompletely understood. Promoter sequence methylation is often thought to contribute to gene and protein expression regulation. We hypothesized that promoter sequence methylation would explain differential protein expression between the glomerulus and tubulointerstitium.

Methods: Nine reference nephrectomies underwent laser microdissection of the glomeruli and tubulointerstitium. DNA methylation sequencing, RNA sequencing, and mass spectrometry quantification of peptides was completed for both compartments in the samples. Datasets were dimensionally reduced to match expressed proteins (N = 4600). Regions of hypermethylation in promoter sequences, introns, and exons were assessed and compared to corresponding protein and mRNA expression.

Results: At least three patterns of hypermethylation were observed across the methylome: promoter sequence, intronic, and exonic methylation. In many cases, promoter sequence or exonic methylation of the tubulointerstitium correlated with a higher glomerular to tubulointerstitial protein and mRNA expression ratio. Likewise, increased tubulointerstitial protein or mRNA expression was associated with glomerular hypermethylation of promoter or exonic regions. For example, Uromodulin (UMOD) protein and mRNA expression were higher in the tubulointerstitium than the glomerulus. The strongest regions of uromodulin hypermethylation were observed in exons 9 and 10 of the glomerular compartment, although hypermethylation was also observed in the promoter sequence and two intronic regions of the tubulointerstitium. In contrast, regions of hypermethylation of Apolipoprotein L1 (APOL1) were exclusively confined to the tubulointerstitium, distributed in all three patterns.

Conclusions: Promoter sequence methylation alone does not explain differential expression patterns between the glomerular and tubulointerstitial compartments. Hypermethylation of exonic regions also contributes to expression regulation.

Funding: NIDDK Support

PO2227

Single-Cell Transcriptomics of the Peripheral Blood Revealed Inflammation and Infection Were Associated with IgAN

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Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide. Due to the diverse clinical manifestations and the complex pathological features, IgAN patients have different response to therapy, and the optimal treatment for IgAN remains controversial. Our study investigated the pathogenesis of IgAN by single-cell transcriptome sequencing.

Methods: Single-cell transcriptome sequencing was performed on peripheral blood monocytes derived from 3 IgAN patients and 1 healthy control, and differential gene expression profiles of peripheral blood single-cell were established. Functional analysis was performed to explore the pathogenesis of IgAN. Meanwhile, RT-PCR was used to validate the differential expression of mRNA and miRNA.

Results: According to quality control and cell selection, we characterized 21739 cells using unbiased single-cell RNA sequencing. 3 IgAN patients included 7847, 5389 and 6609 cells, respectively, and the helthy control included 1894 cells. We used unsupervised clustering to cluster cell clusters. In addition, cells were divided into 14 cell groups, including B lymphocytes and T lymphocytes, based on cell markers (Figure 1). Functional analysis revealed that differential genes were extensively enriched in inflammation / infection-related pathways in each cell type (Figure 2), and the EBV infection pathway focused on antigen presentation (Figure 3). RT-PCR of B lymphocytes demonstrated that SPI1, MXD1 and S100A9 mRNA levels were higher in IgAN patients than controls (Figure 4), which showed the reults of single-cell transcriptome sequencing was avalible.

Conclusions: Differential gene expression profiles of IgAN in peripheral blood single cells were successfully established, and it demonstrated that the inflammation/ infection pathway was associated with IgAN.

Figure 1

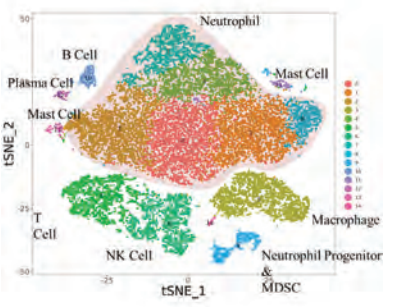


Figure 2

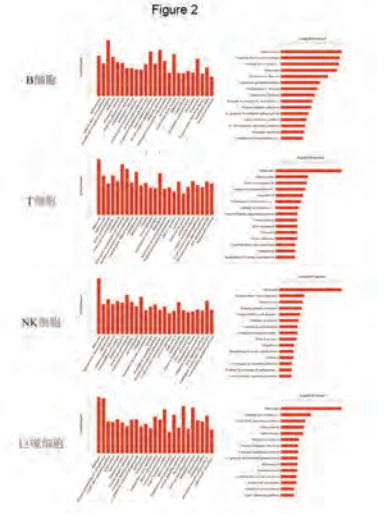
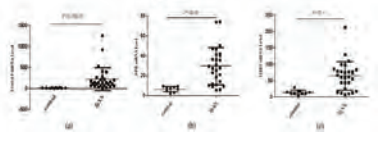


Figure 3

Figure 4



PO2228

Analysis of Urinary Exosomal RNAs After Treatment of Rats with an Nrf2 Activator

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Background: Renal NF-E2-related-factor 2 (Nrf2) is known to be increased in the presence of oxidative stress. Administration of an Nrf2 activator has also been reported to lessen the degree of renal damage. However, biomarkers for detection of Nrf2 activation in the kidney are largely unknown. Urinary exosomes, a subset of extracellular vesicles released by renal epithelial cells, contain RNA molecules that are expected to be biomarkers for renal disease. Thus we analyzed urinary exosomal RNAs after administration of bardoxolone methyl (BARD), an Nrf2 activator, in rats.

Methods: Male Sprague-Dawley rats were randomly divided into two groups; the BARD group, intraperitoneally receiving 10 mg/kg BARD, and the control group, receiving only vehicle (100% DMSO). The urine was obtained for 6 hours just after administration, and exosomes were isolated from the urine. At 6 hours after administration, rats were sacrificed and the kidneys were removed. Thereafter RNAs were extracted from the kidneys and urinary exosomes. The RNAs (27,012 mRNAs amd 1,218 miRNAs) were analyzed with microarrays.

Results: BARD altered expression of 98 renal mRNAs and 357 urinary exosomal mRNAs with more than 2.0-fold relative to the control. BARD also changed expression of 15 renal miRNAs and 3 urinary exosomal miRNAs. The correlation coefficients between renal and urinary exosomal mRNAs as well as miRNAs were both less than 0.1. mRNAs that were commonly changed in both the kidney and urinary exosomes were 13. Among them, 8 genes are known to be targets of Nrf2 including Akr1b8, Akr1c19, Bach1, Ephx1, Hmox1, Pir, Slc40a1 and Ugdh. Of 8 genes, Akr1b8 and Pir were increased more than 10-fold in the kidney and more than 4.0-fold in urinary exosomes. For miRNA, only rno-miR-877 was changed in both the kidney and urinary exosomes.

Conclusions: The correlation coefficients between renal and exosomal RNAs were less than 0.1, suggesting that specific RNAs were selectively loaded into exosomes. In addition, Akr1b8 and Pir expression was dramatically increased in both kidney and urinary exosomes. Therefore, they could be potential biomarkers to detect their renal expression changes by renal Nrf2 activation.

PO2229

Urinary Excretion of Extracellular Vesicles in 24 Hours: Time Point Collection and Normalization Strategy

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Background: Urinary extracellular vesicles (uEVs) are an ideal source of biomarkers for kidney diseases. Despite the interest generated, little is known about collection time and normalization approach. The majority of the studies on uEVs focus on spot urine collection based on the assumption that it accurately reflects the renal function. However, the practice to collect spot urine does not allow for calculating and standardizing the uEV excretion rate and then assessing the renal function. Moreover, no research has been carried out yet to show the difference between spot urine and 24h collections. The aim of this study is to compare uEVs excreted in all 24 hour urine void as single spot and compare it with 24 hour collection.

Methods: Each single spot void urine was collected and 20% of the volume was used to to create the 24 hours collection. uEVs were enriched by differential centrifugation. Transmission electron microscopy (TEM), western blot (WB), nanoparticle tracking analysis (NTA), tuneable resistive pulse sensing (TRPS), imaging flow cytometry (iFC) and miRNA (miR16 and miR200b) quantitation by qPCR were used to quantify uEVs markers variation during the 24 hour. Creatinine, urine osmolality and particle concentration (NTA, TRPS) were used to normalize the analytes.

Results: TEM showed a heterogeneous population of EVs and WB confirmed the presence of EVs marker (TSG101, ALIX and CD9). RNA was extracted by a column-based method (miRNA extraction kit Qiagen) and cel-39 miRNA was spiked in each sample. A multiparametric detection of nephron markers podocalyxin (PODXL), aquaporin-2 (AQP2) and uEVs pan tetraspanins (CD9 + DC63 + CD81) was performed in imaging flow cytometry. Whereas the uEV composition of did not change across the 24 hours analysis, the quantity of uEVs and related markers (miRNA and protein) fluctuated during the day depending on the hydration and excretion rate. Creatinine, urinary osmolarity and particle count normalization failed to normalize "outliers"

Conclusions: In conclusion, this study represents the very first report which compares single void urine versus 24 hour uEV analysis. We concluded that the 24 hour collection is the preferred choice for a robust and rigorous assessment of uEVs and its associated markers.

PO2230

Ultra-Fast Clearing Protocol for 3D Optical Renal Pathology

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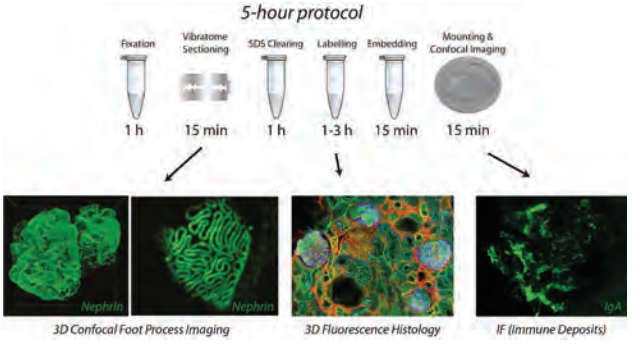
Background: Kidney pathology involves three separate microscopy workflows. *Histology*, typically carried out on paraffin-embedded sections, used to optically visualize large-scale renal morphology. *Immunofluorescence*, used for mapping presence of specific molecular variations, carried out on paraffin-embedded or fresh-frozen thin sections. To visualize renal ultrastructures, *electron microscopy* is applied, with elaborate preparation protocols on ultra-thin sections.

Methods: We have modified published protocols in order to simplify and speed up the workflow of routine optical kidney imaging. The presented protocol induces a slight swelling of a cleared sample, and increase effective resolution enough for 3-D confocal visualization of filtration barrier structures. The duration of the protocol is only 5 hours from harvesting the tissue until full image acquisition.

Results: Our simple and fast protocol can resolve foot processes in mouse and human tissue using standard lab equipment and conventional 3-D confocal microscopy. Importantly, the protocol can be used to visualize various large-scale histopathological features as well as immune deposits in human patient material too. Compared to others, our tissue protocol is simpler and faster, and allow better 3-D in situ imaging capabilities.

Conclusions: We conclude that our simple and fast protocol, allow researchers and pathologists to use a single preparation and microscopy technique, to visualize both renal ultrastructure, histology and protein expression. Our protocol has the potential of, not just to complement, but also merging workflows used today while adding accessing to in situ depth information on all scales.

Funding: Government Support - Non-U.S.



PO2231

A Novel Model of CKD and Heart Failure with Preserved Ejection Fraction

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Background: Chronic kidney disease (CKD) has high cardiovascular mortality. We developed a model of CKD that shows major pathological features: low GFR (+/- 60 ml/min), renal inflammation, fibrosis, microvascular disease, and hypertension. We aim to define the cardiac phenotype of the model and, if present, the pathological traits involved

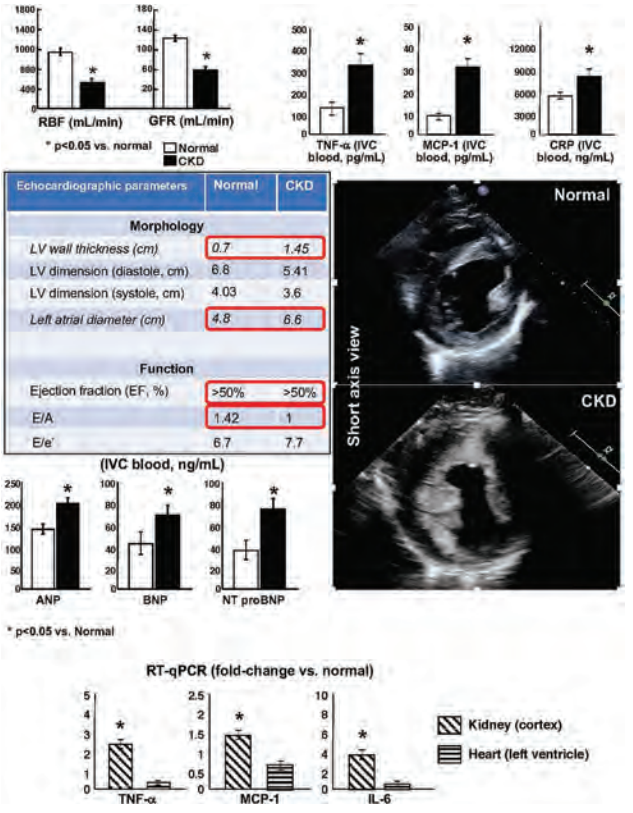
Methods: CKD was induced in 6 pigs (bilateral renovascular disease and dyslipidemia) and observed for 14 weeks. Renal hemodynamics (RBF, GFR) were quantified by multi-detector C, cardiac morphology and function by echocardiography, and mean arterial pressure (MAP) by telemetry. Blood was collected to measure circulating inflammatory cytokines (TNF-α, MCP-1), markers of inflammation (C-reactive protein), and biomarkers of heart failure (ANP, BNP, NT-proBNP). Pigs were then euthanized and kidneys and hearts collected for *ex vivo* studies. Normal pigs were used as time-matched controls

Results: Loss of renal function was accompanied by left ventricular hypertrophy, left atrial dilatation, diastolic dysfunction (E/A ratio) with preserved ejection fraction (pEF), elevated ANP, BNP, and NT-proBNP, and hypertension (MAP of 131.2 mm/Hg, $p<0.05$ vs. normal). CKD also increased renal (but not cardiac) mRNA expression of TNF-α, MCP-1, and IL-6, accompanied by increased circulating inflammatory cytokines (Figure)

Conclusions: CKD leads to cardiac abnormalities that meet the criteria of heart failure with pEF (HFpEF). Our data suggest that hypertension and inflammatory mediators (possibly from kidney origin) target the heart and may contribute to HFpEF

pathophysiology. HFpEF associates with CKD in about 50% of cases and has no specific treatment. Our study offers a new experimental platform to increase our understanding of CKD-HFpEF and to test new treatments in a translational fashion

Funding: Other NIH Support - NHLBI-HL095638 and American Heart Association IPA34170267, Private Foundation Support



PO2232

Pathophysiological Insult of the Liver by Gadolinium-Based Contrast Agent Treatment

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Background: The advent and overuse of gadolinium-based contrast agents (GBCAs) lead to consequent iatrogenic systemic fibrosis. Gadolinium may accumulate in tissues in every organ. GBCA treatment induces dyslipidemia and insulin resistance (Do C et al, Toxicol Appl Pharmacol 2019 Jul 15;375: 32-45). Therefore, the impact of gadolinium on the liver was investigated.

Methods: Wild-type male and female C57/BL6 mice were randomized by age and weight to untreated (n = 20) or GBCA-treatment (n = 20) (Omniscan, 2.5mmol/kg, intraperitoneally, 20 doses over 4 weeks). Tissue were isolated, specimens fixed in glutaraldehyde or snap frozen in liquid nitrogen. Metabolites were profiled by capillary electrophoresis mass spectrometry (Human Metabolome Technologies, Japan).

Results: Liver from the GBCA group demonstrated ballooned hepatocytes, lipid-laden vacuoles, and reduction in glycogen. Furthermore, GBCA treatment promoted hepatic steatosis. Gadolinium reduced expression of lipid metabolism and transport metabolites g-butyrobetaine, prostaglandin E2, O-acetylcarnitine, malonylcarnitine, isobutyryl CoA divalent, hexanoic acid, lauroylcarnitine, and decanoic acid (P < 0.05). GBCA treatment alters metabolite expression of metabolites from other pathways, including glycolysis, histidine metabolism, and purine metabolism. Furthermore, gadolinium treatment altered the urea cycle.

Conclusions: GBCA treatment alters several metabolic pathways, particularly lipid metabolism and lipid transport pathway intermediates. GBCA treatment induces ultrastructural and metabolic disruptions that mimic nonalcoholic fatty liver disease. These studies are the first to demonstrate GBCA mediates metabolic perturbations in the liver. GBCAs are not biologically inert.

Funding: NIDDK Support, Veterans Affairs Support

PO2233

Expression of Immunoglobulin G in Human Proximal Tubule Epithelial Cell and Its Role in Epithelial Mesenchymal Transformation

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Background: Our previous studies showed that human mesangial cells and podocytes can synthesize and secrete IgA and IgG respectively, participating in cell viability and adhesion. Proximal tubular epithelial cells (PTECs) mediate transcytosis of IgG through neonatal Fc receptor (FcRn). Whether PTECs express IgG has not been reported. The aim of this study was to explore whether PTECs express immunoglobulins

Methods: Kidney cortical tissues were obtained far from the tumor of patients undergoing nephrectomy as a result of renal carcinoma. Immunohistochemical (IHC) staining was used to assay the IgG expression in PTECs. Single PTECs were sorted by FACS from the cell suspension of the cortexes. 10×Genomics and nested PCR combined with Sanger sequencing were used to detect the transcripts and repertoires of Igs in single PTECs. An immortalized PTEC cell line (HK-2) was used to detect Igs protein expression and potential roles in tubular epithelial mesenchymal transformation.

Results: IHC showed positive staining of IgG but not other Igs in PTECs of kidney cortex. High throughput single cell RNA sequencing by 10×Genomics only detected Ig γ transcripts in few PTECs without V(D)J rearrangements. Nested PCR amplified Ig γ transcripts in 82% (91/111) manually picked single PTECs. Sanger sequencing showed that PTEC-derived Ig γ variable region displayed classic V_HDJ_H rearrangements but predominant VH1-24/DH2-15/JH4 sequence, biased VH1 usage and less diversity than B cells derived IgG. Western blot and immunofluorescence staining demonstrated Ig γ (including Ig γ4), Ig κ and Ig λ in HK-2. RP215, which specifically recognizes non-B cell-derived Ig γ, can identify the Ig γ in HK-2. The Ig γ was upregulated by TGF-β1 and accompanied by the up-regulation of α-smooth muscle actin and the down-regulation of E-cadherin. In addition, the transcripts of recombination activating gene 1/2 (RAG1/2, essential for V(D)J rearrangement) and activation-induced cytidine deaminase (AID, essential for class switch recombination) were detected in HK-2.

Conclusions: Our study suggests that PTECs can express IgG in a similar way as B cells. TGF-β1 can upregulate the expression of IgG in PTECs. PTEC-derived IgG may be involved in tubular epithelial mesenchymal transformation and interstitial fibrosis.

Funding: Government Support - Non-U.S.

PO2234

A Plasma Creatinine- and Urea-Based Equation to Estimate Glomerular Filtration Rate in Rats

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Background: Monitoring renal function is a vital part of kidney research involving rats. Measurement of Glomerular Filtration Rate (GFR) with an exogenous filtration marker is laborious and does not easily allow serial measurements. Plasma concentrations of creatinine and urea are often used as surrogate, although their correlation with GFR has not been thoroughly investigated in a large cohort of rats. Goal of this study was to develop an eGFR equation for rats.

Methods: We used an in-house collected database of 691 experiments in male rats with gold-standard GFR measurement (inulin clearance, mGFR) and plasma creatinine, plasma urea, weight, and strain (Lewis, Fawn-Hooded, Sprague-Dawley, Wistar). The equation was derived in a development cohort (n=442) and validated in a validation cohort (n=249). Subsequently, we measured plasma cystatin C in a random subset (n=242) to test its added value to the model.

Results: All parameters that were included during model development correlated to mGFR (weight, R^2=0.065; creatinine, R^2=0.756; urea, R^2=0.633; strain, R^2=0.014; all p<0.001). Using linear regression with a piece-wise linear spline for creatinine, we developed the following equations in the development cohort. *Plasma creatinine <48 (μmol/L):* $eGFR=833*W^{0.677}*C^{-0.585}*U^{-0.425}$ *Plasma creatinine ≥48 (μmol/L):* $eGFR=8173*W^{0.677}*C^{-1.175}*U^{-0.425}$ ***eGFR**= estimated GFR (μL/min), **W**= weight (gram), **C**=creatinine (μmol/L), **U**=urea (mmol/L).* Subsequent evaluation in the validation cohort yielded similar precision and accuracy (R^2=0.872, p_{30}=69%) as in the development cohort (R^2=0.801, p_{30}=73%). Inclusion of strain in the model increased neither precision nor accuracy. Although plasma cystatin C correlated with mGFR (R^2=0.242,p<0.001), it did not add predictive power to the model (R2-change=0.0004, p=0.64), and therefore not measured in the entire dataset nor included in the model.

Conclusions: We are the first to develop an equation to estimate GFR in male rats. This equation allows a less labour intensive and invasive repetitive estimation of GFR in rats, and may reduce experimental animal numbers. Validation in an external cohort, in females, and in other disease models is required.

PO2235

Long-Term Mitochondrial Protection Reduces Proteinuria in Obese Aged Mice

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Background: In humans, obesity is associated with higher rates of kidney disease, which is compounded by aging. As an energetically demanding tissue, it has been proposed that preventing mitochondrial dysfunction is one key to reducing renal decline. Previously, we showed that an 8-week systemic treatment of aged 24-month-old (m.o.) mice with a mitochondrial targeted protective tetrapeptide, SS-31, significantly reduced the burden of age-induced glomerulosclerosis by 26-m.o. and preserved podocyte integrity.

Methods: To determine if SS-31 aging protection also applied with a comorbidity of obesity, 18-m.o. male NIA C57bl/6j mice were fed regular chow (RC) or a high fat, high sucrose diet (HFHS) for 10 months and treated with SS-31 injected 5x/wk (3 mg/kg) or saline vehicle (n= 20/group).

Results: Mice were weighed weekly. RC mice averaged 33g with no change from age or treatment. HFHS mice gained weight in the first month but by 5 mo. of diet, SS-31+HFHS mice weighed significantly less relative to HFHS untreated mice (40.4g vs. 45.9g p= 0.047). Spot urine was collected monthly for albumin/creatinine ratio (ACR μg/mg). At 18-m.o. baseline, ACR averaged 48μg/mg. In RC mice, ACR increased modestly, and not significantly, with age although SS-31 RC mice had lower ACR at endpoint (28-m.o. control 125.9 vs. SS-31 60.0). HFHS untreated mice displayed more renal dysfunction by 23 m.o. (ACR: RC = 32.6 vs HFHS = 243.2, p = 0.003), climbing significantly to an average of 519.8 μg/mg at 28-m.o. ACR increased in SS-31 HFHS mice but leveled off by 23-m.o. (5 mo. treat.), averaging 146.1 μg/mg with no significant increase by 28-m.o. By 9 mo. of treatment, ACR was significantly lower in HFHS+SS-31 treated mice. Preliminary quantification of podocytes by p57 nuclear stain and PAS counter stain (n=4-7) showed that HFHS mice, regardless of treatment, had a 30% decrease in podocyte density relative to RC mice. Control HFHS mice trended to higher tuft volume (glomerular hypertrophy) than in SS-31 HFHS mice. However, results were not significant likely due to small sample size.

Conclusions: Combined with improved ACR our results suggest that podocyte integrity, if not number, may be preserved in mice fed a Western diet by SS-31 intervention and that long-term mitochondrial protection is a potential therapeutic target to preserve renal function with age.

Funding: Other NIH Support - NIA K01 AG062757, NIA P01 AG001751

PO2236

Bacterial and Fungal Communities Entombed Within Calcium Oxalate, Struvite, and Brushite Human Kidney Stones

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Background: Mechanisms of human kidney stone formation are poorly understood. More than 70% of stones are composed of calcium phosphate and/or oxalate. Recent studies have shown that kidney stone formation follows a continuum of complex biogeochemical transitions and is strongly influenced by the presence of human host and microbial organic matter.

Methods: Kidney stones, removed via percutaneous nephrolithotomy, were prepared as 25-μm thick doubly polished petrographic thin sections and analyzed using brightfield, confocal and super-resolution autofluorescence microscopy. DNA was extracted from 18 calcium oxalate stones, 1 struvite stone, and 1 brushite stone for Fluidigm™ PCR amplification. Paired-end sequencing of bacterial 16S rRNA gene sequences and fungal internal transcribed spacer (ITS) regions was completed using Illumina™ MiSeq. Reads were correlated with patient metadata and analyzed using DADA2, phyloseq v1.22.3 and R software.

Results: A 153-amplicon sequence variant (ASV) fungal community, dominated by *A. niger* (92% of total reads), was present in 11 of 20 total sequenced stones and correlated with higher patient urine calcium excretion (335 ± 131 vs 175 ± 108 mg/day, p=0.01). Petrography of 30 stones documented entombed coccoidal and rod-shaped bacterial cells in the struvite stone and well-preserved fungal borings and hyphae in one calcium oxalate/apatite stone. Entombed bacterial sequences were most closely affiliated with *Acinetobacter* and *Cutibacterium*. The brushite stone microbiome community contained *Capnocytophaga* and *Humibacter* and the struvite stone microbiome community included *Pseudomonas* and *Staphylococcus*.

Conclusions: This study presents the first evidence of a low-diversity fungal and bacterial microbiome community entombed and preserved within calcium oxalate, struvite, and brushite human kidney stones. The macromolecules secreted by the fungal and bacterial communities may play crucial roles in human kidney stone growth, dissolution, and recrystallization, similar to processes that have been documented in natural geologic stone growth.

Funding: NIDDK Support, Other U.S. Government Support

PO2237

Targeting of Factor D in Cfh-/- Mice Does Not Relieve C3 Glomerulopathy due to the Action of C3(H2O)

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Background: C3 glomerulopathy (C3G) is an ultra-rare kidney disease defined by underlying complement dysregulation and characterized by complement C3 deposition on kidney biopsy. Dysregulation of the alternative pathway (AP) is fundamental to disease expression, although terminal pathway dysregulation is also common. Treatment of C3G with eculizumab is unsuccessful in the majority of patients, consistent with the fact that eculizumab targets the terminal complement cascade while leaving up-stream C3 complement dysregulation untouched. Of up-stream targets, factor D (FD) is appealing because it circulates in the plasma at low concentrations and has a single function, to cleave its substrate, factor B, to generate C3 convertases of the alternative complement pathway. Mice with a targeted deletion of factor H (FH; *Cfh*-/- mice) develop features of C3 glomerulopathy (C3G).

Methods: To assess the impact of FD inhibition, we studied *Cfh*-/-;*Cfd*-/- mice. After crossing the *Cfd*-/- and *Cfh*-/- mice, *Cfh*+/-;*Cfd*+/- progeny were backcrossed to C57BL/6 for 10 generations. Littermates of *Cfh*-/-, *Cfd*-/-, *Cfh*-/-;*Cfd*-/- and wildtype were used for assessing complement dysregulation and renal pathology.

Results: The C3G phenotype in the *Cfh*-/- mouse is not rescued by removing FD. Instead, *Cfh*-/-;*Cfd*-/- mice develop a subtype of C3G and nephrogenic diabetes insipidus. We used serum from the *Cfh*-/-;*Cfd*-/- mouse to show that residual AP function is present when both FD and FH are missing and that hemolytic activity is increased *in vitro* and *in vivo* due to the action of C3(H2O). Therefore, uncontrolled tick-over leads to slow activation of the AP in the *Cfh*-/-;*Cfd*-/- mouse. While a tiny amount of FD suffices to activate complement, a minimal threshold of FH is needed to prevent tissue deposition of C3 in the absence of FD.

Conclusions: These findings suggest that efforts to block AP activity by targeting FD may lead to unanticipated outcomes in subgroups of C3G patients. Sustained complete and persistent FD blockade may be difficult to maintain, and due to the action of C3(H20) might not completely suppress complement activation; substantial breakthrough complement activation may then occur as even minuscule amounts of free FD become available.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute

PO2238

A Mutation in Complement Factor B Causing Massive Fluid-Phase Dysregulation of the Alternative Complement Pathway Can Result in Atypical Hemolytic Uremic Syndrome

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is an ultra-rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. Pathogenesis is driven most frequently by dysregulated *cell-surface* control of the alternative pathway (AP) of complement secondary to inherited and/or acquired factors.

Case Description: We present two unrelated aHUS patients (a 5-year-old female and a 55-year-old female) who presented with the classic signs of thrombotic microangiopathy associated with renal failure with the additional finding of an undetectable C3 level. Circulating levels of C5 and properdin were also low, consistent with over-activity of both the alternative and the terminal pathways of complement. Genetic testing identified a heterozygous novel variant in the complement factor B gene (*CFB* c.1101 C>A, p.Ser367Arg). Functional studies demonstrated strong fluid-phase C3 cleavage when normal and proband sera were mixed. Cell-surface C3b deposition was strongly positive when patient serum was supplemented with C3. *In vitro* control of C3 convertase activity could be restored with increased concentrations of factor H.

Discussion: *CFB* p.Ser367Arg is a gain-of-function pathogenic variant that leads to dysregulation of the AP in the fluid-phase and increased C3b deposition on cell surfaces. This report highlights the complexities of complement-mediated diseases like aHUS and illustrates the importance of functional studies to characterize variants of unknown significance and to gain insight into the disease phenotype.

PO2239

Efficacy of Low-Intensity Pulsed Ultrasound on CKD-Associated Cachexia and Muscle Wasting Prevention in a Mouse Model

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Background: Low-intensity pulsed ultrasound (LIPUS), a therapeutic ultrasound, is recognized to elevate the bone fracture repair process and help in some soft tissue healing. Here, we tested the prevention of chronic kidney disease (CKD)-associated cachexia and sarcopenia by LIPUS in a renal ischemia/reperfusion injury (IRI) mouse model.

Methods: Adult C57BL/6J male mice were used. A model of unilateral IRI with nephrectomy of the contralateral kidney with or without LIPUS treatment (3 MHz, 0.1 W/cm^2, 20 minutes/day) 5 days before and 14 days after surgery was performed. The CKD-related cachexia/muscle wasting in mice was evaluated. Mice were euthanized 14 days after IRI.

Results: LIPUS treatment significantly alleviated the decrease in the serum albumin/globulin (A/G) ratio and the increases in the serum levels of blood urea nitrogen (BUN), creatinine, cystatin C, and fibroblast growth factor (FGF)-23, and the renal pathological changes and fibrosis in CKD mice ($p<0.05$, n=8; for A/G ratio and FGF-23). The development of epithelial-mesenchymal transition and the induction of senescence-related molecular signals and the decreased protein expressions of α-Klotho and endogenous antioxidant enzymes in the kidneys of CKD mice were significantly alleviated by LIPUS treatment ($p<0.05$, n=4). LIPUS treatment could also significantly reverse the decreased muscle mass, grip strength, and cross-section areas (CSA) of muscle fibers ($p<0.05$, n=8; for soleus muscle weight, hindlimb grip strength), and the increased muscular protein expressions of atrogenes, Atrogin1 and MuRF1, and phosphorylated AMP-activated protein kinase (AMPK), and the decreased muscular protein expressions of phosphorylated Akt, peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α), and mitochondrially encoded cytochrome c oxidase I (MT-CO1) in CKD mice ($p<0.05$, n=5 or 6).

Conclusions: LIPUS treatment showed the benefits for renal and muscular protection in a CKD mouse model via inhibition of renal fibrosis, restoration of antioxidant enzymes, and attenuation renal senescence/aging, and muscle mass loss via prevention of muscular mitochondrial dysfunction, AMPK activation, and Akt downregulation. LIPUS treatment may be potentially applied to an alternative non-invasive therapeutic intervention on CKD-associated cachexia/muscle wasting therapy.

PO2240

Mechanisms of Suppressed Autophagic Flux in the Kidney Caused by Sham Surgery and Unilateral Nephrectomy

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Background: Compensatory renal hypertrophy resulting from loss of nephron mass has been implicated in promoting further nephron damage. Unilateral nephrectomy (UNX) is a model of compensatory hypertrophy in the remaining kidney. We previously reported that in the remaining mouse kidney that both sham surgery (SS) and UNX vs. normal kidney (N) resulted in increased mTORC1/2, decreased lysosomal function, suppressed autophagic flux. P62/SQSTM1, is an autophagy receptor that links cargo proteins with the autophagosome membrane. p62 is destroyed by the lysosome and is a marker of autophagic flux, a decrease usually indicating increased autophagic flux. The aim of the study was to measure p62 and other potential mechanisms of suppressed autophagy caused by SS and UNX.

Methods: C57BL6 mice. p62 and ERK was measured by quantitative immunoblot analysis. Cytokines were measured by MesoScale. Mice were treated with the MEK1/2 inhibitor Trametinib (T) (1 mg/kg/d for 3 days) that is a potent ERK1/2 inhibitor

Results: There was an increase in p62 in SS and UNX kidneys. p62/GAPDH (densitometry units) was 0.6 in N, 1.0 in SS ($P<0.05$ vs N) and 1.0 in UNX kidneys ($P<0.05$ vs N). p62 is known to modulate pro-inflammatory cytokines. In the serum, there were increases (fold) in IL-1b (50), IL-4 (10), IL-6 (100), IL-8 (5), IL-12 (5), GMCSF (2), IFNγ (2), IL-10 (0), TNFα (0) in SS and UNX vs N. Pro-inflammatory cytokines can activate ERK1/2, a known autophagy suppressor. There was a large increase in ERK1/2 in SS and UNX kidneys. Phospho/total ERK (densitometry units) was 0.2 in N, 1.4 in SS ($P<0.001$ vs N) and 2.0 in UNX kidneys ($P<0.001$ vs N). Trametinib blocked the increase in pERK in sham surgery and UNX kidneys and resulted in a significant decrease in p62. Phospho/total ERK (densitometry units) was 1.0 in N, 0 in SS+T ($P<0.001$ vs N) and 0 in UNX+T kidneys ($P<0.001$ vs N). p62/GAPDH (densitometry units) was 1.6 in N, 0.4 in SS +T ($P<0.05$ vs N) and 0.4 in UNX+T kidneys ($P<0.05$ vs N).

Conclusions: The mechanism of suppressed autophagy with SS and UNX may be related to an intense systemic inflammatory response and an ERK-mediated increase in p62. It is important that researchers are aware that changes in ERK1/2, systemic pro-inflammatory cytokines and autophagy can be caused by sham surgery as well as the kidney injury/disease itself.

Funding: Veterans Affairs Support, Other U.S. Government Support

PO2241

Differential Role of NAD$^+$ Deficiency in Acute and Chronic Kidney Disease

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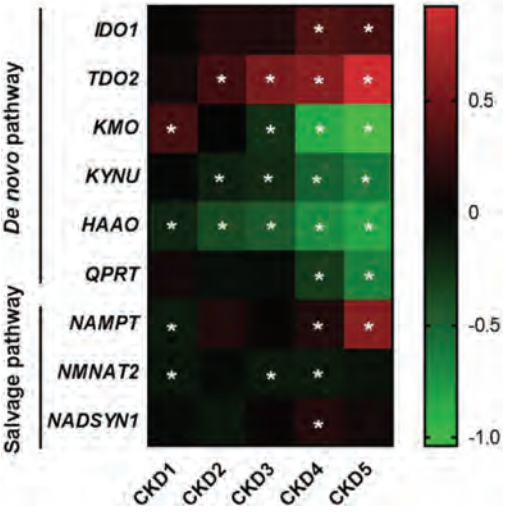
Background: Nicotinamide adenine dinucleotide (NAD$^+$) is a ubiquitous coenzyme involved in electron transport and a co-substrate for sirtuin function. NAD$^+$ deficiency has been shown in acute kidney injury (AKI), but few is known about chronic kidney disease (CKD).

Methods: We studied the expression of key NAD$^+$ biosynthesis enzymes in kidney biopsies from allograft patients during reperfusion, mimicking AKI, and in patients with CKD at different stages. We used ischaemia–reperfusion injury (IRI) and cisplatin injection to model AKI, unilateral ureteral obstruction (UUO) and tubulointerstitial fibrosis induced by proteinuria (POD-ATTAC) to investigate CKD in mice. Then we assessed the effect of a potent NAD$^+$-replenishment therapy, the nicotinamide riboside (NR), in both AKI and CKD models.

Results: RNA-sequencing analysis of human kidney allograft biopsies during reperfusion showed that the NAD$^+$ *de novo* synthesis is impaired in the immediate post-transplantation period. This decrease in *de novo* NAD$^+$ synthesis was confirmed in two mouse models of IRI where NR supplementation prevented plasma urea and creatinine elevation and tubular injury. In biopsies from CKD patients, the NAD$^+$ *de novo* synthesis was impaired according to CKD stage, with better preservation of the salvage pathway (Figure 1). Similar alterations in gene expression were observed in UUO and POD-ATTAC mouse models. NR supplementation did not prevent CKD progression in contrast to its efficacy in AKI.

Conclusions: Impairment of NAD$^+$ synthesis seems to be a hallmark of AKI and CKD. An oral NR supplementation showed protective effects on AKI but had no effect on CKD in mouse models. This study shows the dual role of NAD$^+$ deficiency in AKI and CKD and the potential of NAD$^+$-replenishment therapies as a preventive strategy for human AKI.

Funding: Private Foundation Support, Government Support - Non-U.S.



PO2242

Plasminogen Activator Inhibitor 1 (PAI-1) Induction During Kidney Injury Promotes Epithelial Dysfunction via TGF-β1 Receptor Signaling and Klotho Downregulation

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Background: Persistent PAI-1 induction is evident in several nephropathies in mice and humans. Although PAI-1 is an established CKD promoting factor, the precise role of PAI-1 in disease progression is unclear and, surprisingly, this fibrogenic response appears to be mediated by uPA-independent mechanisms. Expression of the anti-aging gene klotho is lost during renal injury, predisposing to CKD, and recombinant klotho administration in mice suppresses progressive fibrosis. Whether kidney tubular PAI-1 induction promotes maladaptive repair and orchestrates klotho downregulation is currently unknown.

Methods: To mimic sustained renal epithelial PAI-1 expression during renal injury, we stably expressed PAI-1 via lentiviral transduction in HK2 human kidney epithelial cells (CMV-PAI-1); western blotting confirmed PAI-1 overexpression relative to vector controls (CMV-Con). Double-transgenic cells engineered to express both PAI-1 and klotho were used to assess pathological interplay between PAI-1 and klotho in renal fibrosis.

Results: PAI-1 expressing HK-2 cells robustly upregulated pro-fibrotic factor expression/secretion (fibronectin and collagen-1) and exhibited dedifferentiation (loss of E-cadherin and increased vimentin expression), G2/M growth arrest and susceptibility to apoptosis, evident by increases in pHistone-H-3, pH_2AX, p21 and p53 expression, caspase3 cleavage and annexin V-positivity compared to the CMV-Con population. PAI-1-transductants had increased TGF-β receptor 1/2 levels and SMAD2/3 activation relative to vector controls. TGF-β1 receptor-1 kinase inhibition with SB431542 attenuated the PAI-1-driven fibrotic phenotype, independent of TGF-β1 ligand synthesis. Interestingly, sustained PAI-1 expression also downregulated klotho protein levels compared to controls. Rescue of klotho expression in CMV-PAI-1 cells attenuated fibrogenesis and reversed the proliferative arrest.

Conclusions: Persistent PAI-1 expression promotes a fibrotic maladaptive repair orchestrated, in part, via TGF-β1-receptor1/2 hyperactivity and klotho loss. Our studies identify not only a novel role for PAI-1 in renal tubular dysfunction but also in klotho deregulation in renal fibrosis.

Funding: Other NIH Support - Capitial District Medical Research Institute; Friedman Foundation, Other U.S. Government Support, Private Foundation Support

PO2243

Percutaneous Renal Biopsy Using an 18-Gauge Automated Needle Is Not Optimal

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Background: As percutaneous renal biopsies (PRB) are increasingly performed by interventional radiologists, an increase in the use of the smaller 18-gauge automated biopsy needle has been observed. The use of smaller gauge needles stands to compromise adequacy, ideally >20 glomeruli per biopsy. We compare the adequacy and safety of PRB with a 14, 16 and 18-gauge automated needles.

Methods: PRB of 592 native (N) and 1023 transplant (T) kidneys was performed by a nephrologist or a supervised nephrology fellow at Rush University Medical Center from 1/2002 to 12/2019 using real-time ultrasound guidance. Baseline clinical and laboratory data, biopsy sample data (number of cores, total glomeruli per biopsy (glomeruli on light + immunofluorescence + electron microscopy) and total glomeruli per core) and outcome data (hematoma on renal US 1-hr post-PRB and complications requiring a transfucion or procedure post-PRB) were collected prospectively. PRB with N14g (n=337) vs N16g (n=255) and T16g (n=892) vs T18g (n=131) needles were compared. A P value of <0.05 was significant.

Results: PRB with an 18g needle yielded the lowest number of total glomeruli per biopsy (N14g vs N16g: 33±13 vs 29±12, P<0.01 and T16g vs T18g: 34±16 vs 21±11, P <0.0001 and N16g vs T18g, P <0.001). PRBs with 18g needle were also less likely to have ≥20 total glomeruli per biopsy (N14g vs N16g: 85% vs 82%, P=0.4 and T16g vs T18g: 83% vs 46%, P<0.0001). The number of cores per biopsy was: N14g-2.3±0.7, N16g-2.2±0.6, T16g-2.8±0.7 and T18g- 2.2±0.6. Adjusting for the number of cores obtained, the total glomeruli per core was significantly less with 18g needle (N14g vs N16g: 15±8 vs 14±6, P=0.1 and T16g vs T18g: 13±6 vs 10±5, P<0.001 and N16g vs T18g, P <0.001). A hematoma by routine screening renal US 1-hr post-PRB was similar for native (14g-35% vs 16g-29%, P=0.2), and transplant biopsies (16g-10% vs 18g-9%, P=0.9) irrespective of needle size. The complication rate for native (14g-8.9% vs 16g-7.1%, P=0.5), and transplant biopsies (16g-4.6% vs 18g-1.5%, P=0.2) as well as the transfusion rate for native (14g-7.7% vs 16g-5.8%, P=0.4), and transplant biopsies (16g-3.8% vs 18g-0.8%, P=0.1) were not significantly different irrespective of needle size.

Conclusions: The use of the smaller, 18g biopsy needle compromises the adequacy and thus, quality of the PRB while not enhancing safety.

PO2244

Deep Neural Network Facilitated Immunofluorescence Assessment of Glomerular Diseases: A Preliminary Report

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Background: Immunofluorescence (IF) tests of renal tissue are important in diagnosing glomerular diseases. Deep neural network were used to facilitate analysis of pathologic images recently, but not in IF assessment. We proposed a novel Convolutional Residual Dense Network (CR-DenseNet) to facilitate IF assessment of glomerular diseases.

Methods: A dataset with 614 IF images of glomerulus, including IgA Nephropathy, IgAN (n=319), Idiopathic Membranous Nephropathy, IMN (n=211) and Secondary Membranous Nephropathy, SMN (n=84) from Peking Union Medical College Hospital, PUMCH were used for training of CR-DenseNet. Additional 78 IF images from PUMCH (35 IgAN, 15 IMN and 28 SMN) and 98 IF images (36 IgAN, 34 IMN and 28 SMN) from other 3 hospitals were used for validation and human tests. These images were annotated by two nephropathologists independently. Convolutional residual dense blocks were introduced. Each of them consisted of a dense block with a convolutional skip connection to fully exploit the dense local features (Figure 1). Performance was evaluated by overall accuracy, sensitivity, specificity and F1 score. F1 was computed as 2×True Positive, TP / (2×TP + False Positive + False Negative).

Results: The proposed CR-DenseNet outperformed the state-of-the-art method with overall 85.3% recognition accuracy. For the validation data from PUMCH, the sensitivity of recognizing IgAN, IMN and SMN were 78.3% to 93.3% and the specificity were 88.9% to 97.4%. For the validation dataset from other hospitals, the sensitivity and specificity were 79.2% to 93.5% and 88.5% to 98.2%, respectively. Eight nephrologists' average accuracy for recognizing each classification were 50.0% to 76.0%. The F1 score were 0.542 to 0.802. CR-DenseNet demonstrated superior performance. The corresponding accuracy and F1 score were 80.0% to 84.6% and 0.762 to 0.880, respectively.

Conclusions: Our data showed that CR-DenseNet model were useful in IF assessment of typical glomerular diseases.

Funding: Government Support - Non-U.S.

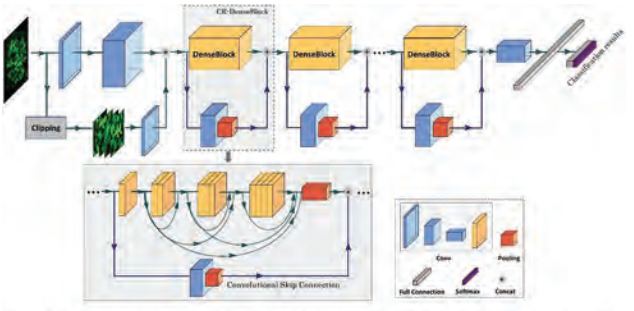

Figure 1. The overview of the proposed Convolutional Residual DenseNet (CR-DenseNet). The input consists of the immunofluorescence image and the local clipped parts of the IF image. The convolutional residual dense block (CR-Denseblock) is composed of traditional dense block and a long convolutional skip connection.

CR-DenseNet Overview

PO2245

Prognostic Glomerular Morphometric Phenotype Discovery via Clustering Across Large Datasets

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Background: Microscopic glomerular assessment is diagnostic and prognostic for a diverse array of renal parenchymal disorders. Digital renal pathology enables complex morphometric studies that may identify prognostic information imperceptible to the human eye. We use clustering and feature enrichment to discover morphometric phenotypes that may relate to patient prognosis.

Methods: A convolutional network extracted glomeruli from 29 Periodic acid-Schiff stained transplant biopsies. 315 features were calculated on each glomerulus and clustered with a modularity-based community detection algorithm available in Seurat. Clusters were compared with patient outcome (eGFR decline at 1 year). A Wilcoxon rank sum test identified features enriching each cluster. Uniform manifold approximation and projection (UMAP) was used to visualize the clusters in low dimension.

Results: Clustering revealed 5 glomerular populations (Fig. 1A), and glomeruli of different patients were well admixed across clusters (Simpson's Diversity Index: 0.78 - 0=no diversity, 1=infinite). Patients were separated in two classes (eGFR≥5 or <5 mL/min/year), and these labels were projected into the cluster space (Fig. 1B). We observed the clusters show different frequencies of glomeruli from patients with higher eGFR decline. Two of the clusters (2 and 4) had >90% of their morphometrically similar glomeruli solely from slower eGFR decline patients. The distribution of two example features (glomerular area and total nuclei) per cluster are shown in Figs. 1C & D, though the full analysis revealed hundreds of significant features enriching each cluster.

Conclusions: The adoption of an –omics style analysis for renal histology may be feasible to mine prognostically significant morphometric information.

Funding: NIDDK Support

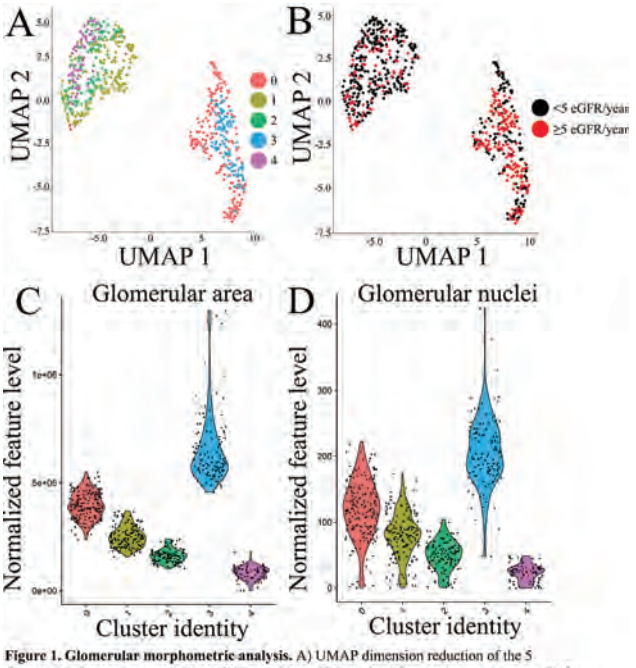

Figure 1. Glomerular morphometric analysis. A) UMAP dimension reduction of the 5 discovered glomerular populations. B) Same glomeruli from A with progression status overlaid as color. C) Normalized glomerular area difference between the clusters. D) Normalized glomerular nuclei between the clusters.

PO2246

IgA Staining Patterns Differentiate Between IgA Nephropathy and IgA-Dominant Infection-Associated Glomerulonephritis

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Background: Differential diagnosis of primary IgA nephropathy (IgAN) and IgA-dominant infection-related glomerulonephritis, particularly Staphylococcus infection-associated glomerulonephritis (SAGN), on a kidney biopsy can be challenging because of similar morphologic findings by light microscopy, immunofluorescence and electron microscopy. Clinical management approach however, is very different. Immunosuppressive therapy is contraindicated in SAGN because it can lead to sepsis and even death. Antibiotics constitute the first line of therapy. In contrast to that, primary IgAN is treated either with conservative management or with immunosuppression. There are no specific biomarkers to distinguish between these two diseases.

Methods: Kidney biopsies from patients with IgAN or SAGN were analyzed. Immunofluorescence with an antibody to IgA was performed on sections of frozen and paraffin embeded tissue.

Results: In total, 75 biopsies (45 with IgAN and 30 with SAGN) were evaluated. All 75 biopsies showed distinct granular staining for IgA in the non-sclerotic glomeruli (Figure 1). Globally sclerosed glomeruli were identified in 47 biopsies (29 with IgAN and 18 with SAGN). Among the 29 biopsies of IgAN, 20 (69%) had positive granular staining for IgA in the globally sclerosed glomeruli and 9 (31%) cases did not. Among the 18 kidney biopsies with SAGN, only one case (5.6%) showed positive staining for IgA in globally sclerosed glomeruli, whereas the remaining 17 (94.4%) did not (Table 1). The sensitivity of positive IgA staining in globally sclerosed glomeruli for kidney biopsies with IgAN was 68.97%, specificity was 94.44%.

Conclusions: Evaluation of IgA staining in sclerosed glomeruli can help to differentiate between primary IgAN and SAGN in the right clinical context, and aid in patient management in most cases

Table 1. Distribution of staining for IgA in sclerotic glomeruli between cases with IgAN and SAGN

IgA staining in sclerotic glomeruli	IgAN	SAGN	Total
Positive	20	1	21
Negative	9	17	26
Total	29	18	47

PO2247

The Spectrum of Biopsy-Proven Glomerular Diseases in Mexico: Experience at a Tertiary Hospital

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Background: Glomerular diseases are still one of the leading causes of end-stage renal disease. The diagnosis of these diseases relies on the interpretation of the renal biopsy.

Methods: This investigation was performed in a tertiary hospital. We assessed the main demographic, clinical and histological data of individuals who underwent native kidney biopsies in one tertiary hospital in Mexico. From January 2011-December 2019, totally 1,541 patients first received renal biopsy. After excluding allograft biopsies, inadequate sampling, and failed interpretation, there are still 853 cases with a clear diagnosis.

Results: We evaluated 853 renal biopsies: female 65.3%, elderly (>60 years) 16.4%. The most frequent biopsy-proven diseases were secondary (59.1%) and primary (28.7%) glomerulonephritis (GN), tubulointerstitial nephritis (TIN) was observed in 2.5 % and vascular diseases in 1.5%, hereditary disease in 1.2%. Among primary GN the most frequent diagnosis were focal segmental glomerulosclerosis (FSGS) (17.2%), membranous GN (MGN) (5.7%) and IgA nephropathy (IgAN) (4.8%). Among secondary GN, lupus nephritis (LN) represented 38.9%, diabetic nephropathy 8.1% and pauci-immune crecentic GN 4.9%. The most common diseases in patients with nephrotic proteinuria were LN 14.8%, FSGS 5.8%, MGN 4.1%. Ultrasound needle guidance was used in 97.8%. The frequency of serious complications was approximately 2.5%.

Conclusions: This report provides representative population-based data on native biopsy-proven renal diseases in Mexico. FSGS and LN are the most frequent primary and secondary GN respectively. FSGS and MGN were the most common diseases in patients with nephrotic proteinuria.

PO2248

Clinical Context and Outcomes of Kidney Biopsy in Pregnant Women: An Institutional Review

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Background: Kidney biopsy is an excellent method of gaining insight to causes of renal decline but is not without risk, particularly in pregnant patients. While we await the era of biomarkers which enhance our ability to diagnose diseases of pregnancy, biopsy remains the most inclusive way of reaching a diagnosis. Clinical manifestations warranting biopsy include gross deterioration in renal function, de novo development of nephrotic syndrome, or suspicion for glomerulonephritis. A recent metanalysis found that the risk of complications during pregnancy was 7% and should be limited to patients in whom the diagnosis would warrant urgent therapy. We sought to explore indications for biopsy and histopathology in patients evaluated at our institution.

Methods: Our surgical pathology database was searched for renal biopsy specimens interpreted from 2008 to mid-2020. Patients were either pregnant at the time of biopsy or within 3 months postpartum. Indiana University IRB approved the study. A chart review was completed to obtain lab data at the time of biopsy and post procedure.

Results: We identified biopsy specimens from 38 women who were pregnant during the specified time period. Histopathologic diagnoses included lupus nephritis (n=4), FSGS (8), diabetic kidney disease (3), allergic interstitial nephritis (1), IgA (10) and minimal change disease (3). Chart information was available for 19 women including 15 Caucasian and 4 African American patients, with a mean age of 28.6 years. Eight specimens were obtained during pregnancy and 11 during the postpartum period. Proteinuria was present in 17 patients with a mean value of 3.5g/d. Hematuria was also present in 14 of the patients. Mean serum creatinine was 2.6mg/dL.

Conclusions: Renal biopsy is a procedure with high risk and morbidity for pregnant women. At our institution, biopsy was performed for either worsening renal function or proteinuria. Our population showed diverse diagnoses which justified need for biopsy, including requiring urgent intervention. Our study highlights the need of judicious biopsy in pregnant women. Further studies can be done to determine long term kidney outcomes in pregnant women.

PO2249

Prevalence and Risk Factors Associated with Nephrosclerosis in Renal Parenchyma Specimens of Patients Undergoing Partial or Radical Nephrectomy

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Background: Evaluation of non-neoplastic renal parenchyma in nephrectomies is part of the College of American Pathologists (CAP) Cancer Protocols. We evaluated the prevalence of histological abnormalities and nephrosclerosis and its association with clinical factors in patients undergoing nephrectomy for any cause at our institution.

Methods: Two nephropathologists evaluated the status of the renal parenchyma in 813 patients who underwent either partial (41%) or radical nephrectomy (59%) between 2013 and 2017. Age-adjusted global glomerulosclerosis (GS), interstitial fibrosis (IF), tubular atrophy (TA), and arteriosclerosis (AS) were evaluated by light microscopy. Nephrosclerosis was defined as the presence of ≥ 2 histologic variables. Clinical, demographic, and pathological data were collected by chart review. Logistic regression analysis was used to evaluate the association between clinical parameters and nephrosclerosis.

Results: The mean age was 60 ± 14 years. 38% were female, 44% were Hispanics. 59% had hypertension, 22% had diabetes mellitus and 24% had a smoking history. The pre-nephrectomy eGFR was 73 ± 27 ml/min/1.73m^2 and 31% had an eGFR <60 ml/min/1.73m^2. The prevalence of age-adjusted GS was 82%, any TA was 80%, more than 5% IF was 78% and any AS was 95%. The prevalence of nephrosclerosis was 88%. Lower pre-nephrectomy eGFR (adjusted odds ratio [OR] per 10 units decrease in eGFR, 1.12 [95% confidence interval (CI), 1.02-1.23]), and age (adjusted OR per 10 years increase, 1.97 [95% CI, 1.64-2.39]) were significantly associated with nephrosclerosis. Gender, history of hypertension, diabetes, and smoking were not associated with nephrosclerosis (p>0.05 for all).

Conclusions: Nephrosclerosis is highly prevalent in renal parenchyma of patients undergoing nephrectomy. Lower pre-nephrectomy eGFR and older age were independently associated with significantly greater odds of nephrosclerosis. Future studies should evaluate the association between nephrosclerosis and post-nephrectomy eGFR.

PO2250

Evaluation of Preexisting Renal Disease in Nephrectomies

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Background: Evaluation of non-neoplastic renal parenchyma in nephrectomies is part of the College of American Pathologists (CAP) Cancer Protocols. We aimed to determine the prevalence of pre-existing renal diseases in all patients who underwent nephrectomy for any cause in our center.

Methods: The surgical pathology protocol for nephrectomies was modified with a) additional sampling of non-tumoral renal parenchyma, b) Hematoxylin and eosin, Periodic acid-Schiff, trichrome and silver stains, and c) addition of the expanded checklist for reporting nephrectomy from the Renal Pathology Society recommendations. All samples were reviewed by 2 trained nephropathologist (NP). A total of 813 nephrectomies (49% partial and 51% radical) performed between 2013 and 2017 were evaluated and included in the study. Reasons for nephrectomies were malignancy in 645 (79%) of patients, of which 528 (82%) had renal cell carcinoma, 100 (16%) urothelial carcinoma, and 168 (21%) benign lesions (42 oncocytomas, 34 pyelonephritis, 13 trauma, and 8 nephrolithiasis). Clinical, demographic, and pathological data were collected by chart review.

Results: The mean age was 60 ± 14 years. 62% were male and 44% Hispanics, 59% had hypertension, 22% had diabetes mellitus, and 24% had a history of smoking. Baseline eGFR was 73 ± 27 ml/min/1.73m^2 and 31% had an eGFR < 60 ml/min/1.73m^2. Only 41 patients (5%) had a documented pre-operative consult to nephrology. 296 (36%) patients had at least one renal disease diagnosis and only 62 (8%) had a single diagnosis. 374 pathological diagnoses were reported including focal segmental glomerulosclerosis (FSGS) (157), mostly NOS variant (88%), diabetic glomerulosclerosis (57), interstitial nephritis (66), arterionephrosclerosis (39), pyelonephritis (36), acute tubular injury (10), chronic sclerosing glomerulonephritis (4), amyloidosis (1) and atheroembolic renal disease (1).

Conclusions: Pre-existing renal disease are frequently identified in nephrectomy specimens. FSGS was the most common diagnosis. A collaborative effort involving nephrologists, urologists and pathologists is warranted to improve the care of patients undergoing surgical nephrectomy.

PO2251

Kidney Filtration Markers in Human Saliva: Accuracy and Reproducibility of Novel Salivary Cystatin C Measurements

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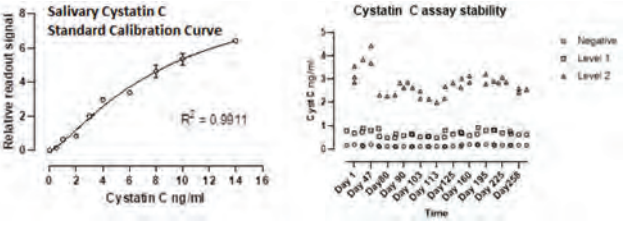
Background: Invasive phlebotomy followed by laborious blood specimen processing is the only reliable approach to assess routinely measured kidney filtration markers including cystatin C (CysC). Non-invasive testing of these markers is urgently needed particularly during the COVID-19 pandemic to enhance social-distancing.

Methods: We developed novel Enhanced Enzyme and Immunoassay-based Lateral Flow (ELF) assays to measure concentrations of CysC in human saliva. Highly selective binding reagents were screened for optimum specificity, followed by applying sample treatment steps to mitigate sample to sample variability using healthy donor saliva samples spiked with known levels of the filtration markers. Standard calibration curves (SCCs) for each marker was developed with nonlinear 4-parameter logistic curve fitting to triplicate measurements at each spiked concentration level. Accuracy/fit of the SCC was assessed using the coefficient of determination (R^2). Intra-assay repeatability was assessed using coefficient of variation (CV) and studies of inter-assay repeatability over time (over ~8 days) examined reproducibility of whole experimental protocol.

Results: SCC fitted to relative optical intensities (ratio of test to control lines vs. spiked CysC (0-14 ng/ml) was excellent (R^2=0.991) and provided accurate estimates of spiked/ true CysC levels (R^2=0.994). Assessment of intra-assay variation showed that repeatability is very good with CV <10% throughout the dynamic range of measurements. Assessment of inter-assay variation (measurements over 8 days) showed that reproducibility is acceptable with CV <13% throughout most of the dynamic range. Preliminary assessment of long-term reproducibility (stability) out to 258 days indicated similar performance. [figure]

Conclusions: We demonstrated feasibility of CysC measurements in human saliva samples with acceptable ELF assay characteristics including accuracy, repeatability, reproducibility, and long-term stability. Validation studies are ongoing to optimize the saliva testing framework for kidney function markers.

Funding: NIDDK Support



PO2252

Examining Accuracy and Reproducibility of Novel Creatinine and Urea Rapid Measurements in Human Saliva

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Background: Rapid and frequent point-of-care kidney filtration markers that do not require laborious blood specimen draws/processing can improve CKD patient care. The use of saliva as a non-invasive biofluid for monitoring kidney function biomarkers such as Creatinine (Cr) and Urea, addresses a clinical need in support of telemedicine.

Methods: We developed novel Enhanced Enzyme and Immunoassay-based Lateral Flow (ELF) for quantitative measurement of 2 kidney filtration markers in human saliva using highly selective reagents for optimum specificity. We used healthy donor saliva samples spiked with known levels of Cr and Urea. Standard calibration curves (SCCs) for each marker were established with nonlinear 4-parameter logistic curve fitting in triplicate at each spiked level. Accuracy/fit of the SCC was assessed using the coefficient of determination (R^2).

Results: SCC fitted to relative optical intensities (ratio of test to control lines vs spiked Urea (0-180 mg/dL) and Cr (0- 6 mg/dL) showed excellent correlation (R^2=0.992 and 0.999 respectively). Intra-assay variation showed that repeatability is very good with CV <15%, and CV <10% for Cr and Urea, respectively, throughout the dynamic range of measurements. Assessment of inter-assay variation (measurements over 8 days) showed that reproducibility is acceptable with CV <10% and <13% for Cr and Urea, respectively, throughout most of the dynamic range. Preliminary assessment of long-term reproducibility (stability) up to 91 and 216 days for Urea and Cr assays, respectively indicated similar performance.[figure]

Conclusions: Cr and Urea can be measured in human saliva with acceptable ELF assay characteristics including accuracy, repeatability, reproducibility, and long-term stability. Future validation studies may lead to a saliva testing framework for kidney function markers and a potential paradigm-shift in CKD monitoring.

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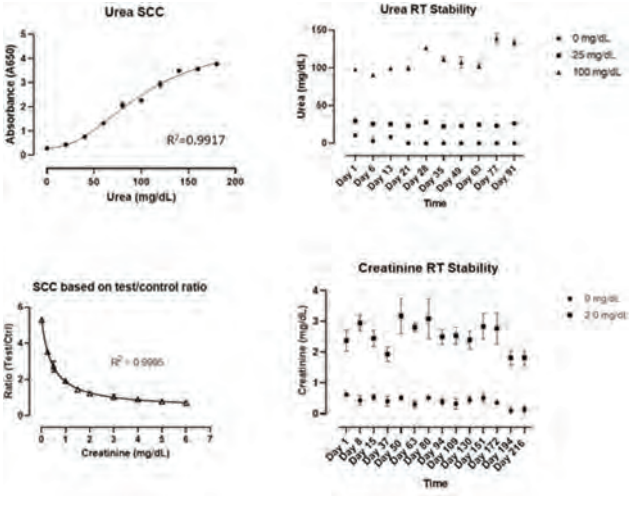

PO2253

Comparison of Creatinine-Based Estimated Glomerular Filtration Rate Equations with DTPA GFR in Healthy Adults

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Background: Measurement of Glomerular filtration rate (GFR) is a reliable technique but is expensive and cumbersome for routine use. GFR is routinely estimated (eGFR) with serum creatinine. These equations are not widely validated in Indian population.

Methods: The cross-sectional study was done on live kidney donors. DTPA was used to measure GFR, 24 hour creatinine clearance (CrCl) was measured and creatinine based eGFR was calculated using Cockcroft-Gault (CG), Modification of Diet in Renal Disease-fourvariable (MDRD-4), Modification of Diet in Renal Diseasesix-variable(MDRD-6), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations

Results: 88 subjects were included, of whom 29.5% were male, with a mean age of 46.8 yrs, and BMI of 25.7 kg/m2. Mean GFR (± standard deviation) obtained by CKD-EPI, MDRD-4, MDRD-6, CG, CrCl, and DTPA GFR were 99.8 (±15.2), 96.2 (±17.9), 106.1 (±20.2), 88.3(±38.7), 89.3(±29.2) and 93.6(±11) ml/min/1.73m^2 respectively. The mean absolute difference in GFR and percentage variation between calculated and measured GFR for CKD-EPI, MDRD-4, MDRD-6, CG, CrCl were 14.7 (16.5%), 16.2 (17.9%), 19.8 (22.2%), 33.2 (36.5%), and 23.6(25.7%) respectively. Percentage of valueswithin 20%of DTPA GFR in each equations were CKD-EPI - 69.32%, MDRD-4 – 70.45%, MDRD-6 -54.55%, CG- 38.64%, and CrCl- 45.45%. There was no significant co-relation between the measured GFRs and eGFR using any of the above equations.

Conclusions: All the equations used (CKD-EPI, MDRD4, MDRD6, CG) and CrCl did not correlate significantly with the measured GFR. Among the equations, CKD-EPI had the least variation with about 69% confirming within 20% of DTPA GFR, and about 86% and 97% confirming within 30% and 50% of DTPA GFR.

Table 1: Percentage of eGFR estimations ocurring within 20%, 30%, and 50% variation of DTPA GFR values

Equation	20% of GFR	30% of GFR	50% of GFR
EPI	69.32%	86.36%	96.59%
MDRD4	70.45%	82.95%	95.45%
MDRD6	54.55%	72.73%	93.18%
CG	38.64%	53.41%	62.50%
CrCl	45.45%	68.18%	90.91%

PO2254

Fecal Calprotectin Correlates with Serum Albumin in Patients with CKD

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Background: Persistent inflammation, a characteristic feature in chronic kidney disease, contributes to decreased serum albumin levels and plays a central role in the Malnutrition, Inflammation and Atherosclerosis (MIA) syndrome, which is associated with poor clinical outcomes. Altered bowel habit is also a highly frequent status among patients with chronic kidney disease potentially due to their low fiber and fluid intake, medications, multiple comorbidities and dysbiosis of the gut microbiota. In this study, we have explored whether measurement of fecal calprotectin, a commonly used marker for increased neutrophil migration and local inflammation in gastrointestinal diseases, could reflect a state of low serum albumin in patients with chronic kidney disease.

Methods: Clinical and biochemical data including stool samples for calprotectin were collected from 579 cases of patients with no history of inflammatory bowel disease.

Results: Fecal calprotectin was not different according to estimated glomerular filtration rate, degree of proteinuria and medication of polystyrene sulfonate and ferrous sulfate. However, it was significantly and negatively correlated with serum albumin in patients (r=-0.107, p=0.010). Patients with higher tertile of fecal calprotectin were older and likely to have lower hematocrit. Multivariable linear regression analysis showed that fecal calprotectin was significantly correlated with serum albumin (β=-17.702, P=0.010).

Conclusions: These observations that serum albumin were significantly correlated with fecal calprotectin in patients with chronic kidney disease, suggest that the bowel inflammatory response may be another contributing factor.

PO2255

A Case of Sevelamer-Induced Colon Perforation

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Introduction: Sevelamer is an anion exchange resin used to treat hyperphosphatemia in patients with chronic kidney disease. It does not cause hypercalcemia or vascular calcification associated calcium based phosphate binders. Common adverse effects include nausea, vomiting, diarrhea, dyspepsia and constipation [1]. Case reports of sevelamer associated bowel perforation have been reported in the literature[2]. Here we report a case of sevelamer induced colon perforation.

Case Description: 61 year old Caucasian male with history of ESRD from diabetic nephropathy on automated peritoneal dialysis presented to the emergency department with abdominal pain. Physical exam was notable for epigastric tenderness. Labs were unremarkable except for hyperglycemia of 427 mg/dL. CT scan abdomen showed cholelithiasis and moderate ascites. PD fluid analysis ruled out peritonitis. Patient's abdominal pain persisted despite several days of supportive care, prompting repeat CT scan abdomen which revealed large pneumoperitoneum with possible colon perforation. Patient was emergently taken for exploratory laparotomy requiring right hemicolectomy with ileocolic anastomosis. Histopathological exam of the resected colon showed scattered yellow eosinophilic, acellular crystalline material with "fish scale" morphology within the lumen suggestive of sevelamer resins. Patient was on sevelamer 800mg TID for several years. Patient improved with appropriate medical management. Sevelamer was discontinued prior to discharge.

Discussion: Sevelamer is composed of a non-absorbable hydrogel with ammonia on the hydrochloride (Renagel) or the carbonate (Renvela). In the acid milieu of stomach, the polymer dissociates from its anion, is protonated to ammonium which is available to bind phosphate in the intestine[3]. The exact pathogenesis of intestinal perforation remains unclear. It is hypothesized that presence of sevelamer crystals in the gastrointestinal tract was associated with mucosal abnormalities including inflammation, ischemia and necrosis. Recognition of characteristic sevelamer crystals (typically seen as bright pink linear accentuations with a rusty yellow background and irregularly spaced fish-scales) on pathology along with the supporting clinical history clinches the diagnosis. It is important for clinicians to be aware of this rare but a serious potential complication of bowel perforation associated with sevelamer.

PO2256

Case of Pulmonary-Renal Syndrome Involving Goodpasture Disease and Granulomatosis with Polyangiitis

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Introduction: Wegner's granulomatosis and Goodpasture's disease are two rare causes of pulmonary-renal syndromes syndromes. Both have similar presentation and differentiation is crucial for early management. WG is a systemic vasculitis syndrome that affects the respiratory and renal systems and associated with C-ANCA (PR3) antibodies. Goodpasture's disease is an autoimmune condition that is characterized by rapidly progressive glomerulonephritis (RPGN) and severe alveolar hemorrhage. It is most often related to IgG antibodies against type 3 collagen in the glomerulus and renal basement membranes. It is noted that 5% of all ANCA + patients are also positive for anti-GBM and of all the anti-GBM about 1/3rd also have ANCA but that does not always correlate with active clinical disease. This leads to a significantly poor prognosis and worse renal outcomes than either disease process alone.

Case Description: We present a 59-year-old female with initial complaint of weakness, lethargy and sinus congestion. She had a history of untreated hypertension. She was noted to be hypoxic and had rales and rhonchi bilaterally. Labs revealed WBC of 35, Hg 5.6, Hct 15.5 and platelets 594. She had sodium of 98, Potassium 5.8, Bicarbonate 18, BUN of 58 and Creatinine of 8.5. Chest x-rays showed bilateral opacities resembling CAP. Further hypoxemia prompted intubation, revealing copious amounts of alveolar hemorrhage. Vasculitis was in the differential given alveolar hemorrhage and renal failure and she was promptly started on plasmapheresis, high dose IV steroids as well as cyclophosphamide. Complement levels and immunofixation were normal as were studies for lupus and hepatitis B and C. She had + ANA, Anti-GBM and c-ANCA antibodies. Renal biopsy showed predominant sclerosis and >90% focal necrotizing crescentic GN and severe interstitial scarring. Immunofluorescence (IF) demonstrated linear staining of glomerular BM as well as ANCA mediated changes.

Discussion: This case illustrates that both WG and GP can occur in the same patient. Such patients can present with CAP that rapidly deteriorates. Early recognition of pulmonary involvement was crucial to start proper treatment by plasmapheresis and immunosuppressant. Although these patients with severe glomerular involvement will be lifelong dependent on dialysis, their 1- and 2-year survival can be significantly improved with appropriate therapy and follow up.

PO2257

Fibromuscular Dysplasia Masquerading as Polyarteritis Nodosa in a Patient with Raynaud Syndrome

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Introduction: Fibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic vascular disease primarily affecting renal and cerebral arteries. Polyarteritis nodosa (PAN) is a small to medium vessel vasculitis that can be fatal if not promptly diagnosed and treated. Both conditions are commonly diagnosed by angiographic findings which may appear similar.

Case Description: A 49-year-old Caucasian woman with a past history of Raynaud's disease presented to the emergency department with acute onset periumbilical abdominal pain. She was mildly hypertensive on presentation; metabolic panel showed no electrolyte abnormalities; urinalysis showed proteinuria and hematuria; ESR was 7 and CRP 22.7. Notably, she had been on prednisone for a skin rash after poison ivy exposure 5 days prior to presentation. Family history was pertinent for rheumatoid arthritis. CT abdomen and pelvis with contrast revealed multiple right renal infarcts. Subsequently a CT angiogram was obtained. During renal arteriography, the right renal artery developed dissection with minimal catheter manipulation suggestive of significant underlying abnormality. The procedure was aborted given risk for further complications including rupture and hemorrhage. Radiology reported findings consistent with medium vessel vasculitis. Autoimmune workup showed positive ANA, Scl 70 and rheumatoid factor, supporting suspicion for systemic vasculitis such as PAN. However, mesenteric vessels were normal. She was advised to continue on prednisone while additional workup was completed. Carotid dopplers were obtained and demonstrated partial dissection of the mid right internal carotid artery, with subsequent CT angiogram of the head and neck showing findings consistent with FMD throughout vertebral arteries and left internal carotid artery. Initial renal CT angiogram was reevaluated by Radiology, with renal artery

beading noted, consistent with a diagnosis of FMD. The patient's creatinine remained stable throughout her hospital stay, and she was initiated on lisinopril prior to discharge.

Discussion: Fibromuscular dysplasia can be diagnosed by histopathology or angiography. It may manifest as a systemic vascular disease involving multiple vascular beds, mimicking systemic vasculitis. Since treatment of PAN and FMD is vastly different, it is important to consider both differentials and have definitive diagnosis prior to initiation of therapy.

PO2258

Asymptomatic Spurious Hyperuricemia Related to Waldenstrom Macroglobulinemia

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Introduction: Increased IgM has been shown to result in underestimation of uric acid levels and pseudo-hypouricemia; however, there are no reported cases of hyperuricemia in the setting of paraproteinemia. We present a case of Waldenstrom's Macroglobulinemia (WM) resulting in marked elevation of uric acid level in the absence of tumor lysis syndrome (TLS).

Case Description: A 73-year-old man with history of WM was incidentally noticed to have very high uric acid level of 37.2 mg/dl. He had no history of crystal arthropathy or chronic kidney disease. He was started on Acalabrutinib because of high serum viscosity and elevated IgM level. After 30 days of treatment, his serum viscosity and uric acid levels improved significantly, however the treatment had to be discontinued due to development of potential drug related adverse events. After discontinuation of Acalabrutinib, his serum viscosity and uric acid level gradually increased back to the previous level. Laboratory parameters were not suggestive of TLS and potassium, calcium and phosphorus were all normal. 24-hour uric acid excretion was noticed to be low normal (341 mg/24 hours). He was treated with allopurinol and monitored in clinic with serial uric acid checks. He continued to remain asymptomatic despite of having a uric acid level consistently above 35 mg/dl. He was not treated with Rasburicase due to lack of symptoms and potential false elevation of uric acid in the setting of paraproteinemia.

Discussion: Paraproteins often cause factitious biochemical measurements by forming opaque precipitates with the test reagents and interfering with various automated assays. These interferences may be difficult to anticipate as they are intermittent and patient specific. Ultrafiltration of paraproteins, dilution or deproteinization of the samples can sometimes help correct these measuring errors. WM and other paraproteinemia may cause true hyperuricemia in the setting of TLS. However, the absence of other concomitant laboratory abnormalities should raise a suspicion of factitious results. An observant clinician should be aware of these findings in order to avoid unwarranted testing and treatment. Also, a very high level of uric acid in the absence of symptoms may point towards a possibility of undiagnosed paraproteinemia.

PO2259

Is the Well-Recognized Intravascular Tamm-Horsfall Protein Polyp a Misnomer? A Case Report from a Patient with Obstructive Uropathy and Hematuria

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Introduction: Tamm-Horsfall protein (THP), a renal epithelial glycoprotein, was originally isolated from normal urine and can be the primary constituent of many urinary casts. The phenomenon of THP polyp formation in obstructive uropathy first appears in the literature about 1978. The polyps are described in these reports as being located in veins or sometimes lymphatics. Our case is the first to confirm the location of a THP polyp by immunohistochemical (IHC) analysis.

Case Description: A 64-year-old Caucasian male presented with bilateral flank pain and persistent gross hematuria. On admission, he had mildly elevated BUN (26.0 mg/dL) and serum creatinine (3.2 mg/dL). Urine analysis showed red blood cells > 182 /hpf with negative leukocyte esterase and negative nitrates. He developed azotemia during the hospitalization with the highest creatinine of 7.4 mg/dL on day 3 of admission. Renal ultrasound indicated mild-moderate hydronephrosis with a collapsed bladder. Renal biopsy was performed given lack of proper explanation for his presentation. Biopsy showed Periodic acid-Schiff (PAS) positive THP with polyp formation distended the markedly dilated tubules (confirmed by positive Pan-cytokeratin and negative CD31 immunohistochemical (IHC) stains). The THP polyp also contains delicate elongate-appearing endothelial cells. There was diffuse interstitial edema with mild fibrosis without tubular atrophy, and mild to moderate to focally intense inflammation with numerous eosinophils surrounding the involved tubules. The walls of the inflamed tubules are densely infiltrated by inflammatory cells and has focal fibrinoid necrosis. No significant glomeruli or vascular pathologic changes were identified. The renal pathology findings of acute to subacute tubulointerstitial nephritis with THP polyps consistent with obstructive uropathy.

Discussion: There were a total of four cases of intravenous THP polyps identified in the patients with obstructive uropathy and persistent gross hematuria. It was theorized that acute hydronephrosis may increase the intratubular pressure, with extravasation of THP into the veins forming tubulovenous communications. However, our study suggests that this theory may not be true due to the misidentification of the markedly distended renal tubules as renal veins.

PO2260

Vedolizumab-Induced Acute Interstitial Nephritis and Acute Tubular Necrosis

Abdulrahman Muzib, Rushang Parikh, Vanesa Bijol, Nupur N. Uppal, Mala Sachdeva. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY.*

Introduction: Vedolizumab is a humanized monoclonal antibody used in the treatment of ulcerative colitis. To date there has been no reported case of vedolizumab associated acute interstitial nephritis (AIN) and acute tubular necrosis (ATN). We report the first such case.

Case Description: A 58 year old female with history of ulcerative colitis on vedolizumab for one year, primary hyperparathyroidism and calcium oxalate nephrolithiasis presents due to acute kidney injury. Patient received her last dose of vedolizumab two months prior. She had been receiving 300mg IV every eight weeks, making her last dose her seventh dose. Her pre-medication creatinine (Cr) was 0.9mg/dL. Approximately one week prior to admission she was found to have a Cr of 2.0 mg/dL. She denied any NSAID, PPI, antibiotic or herbal use. Her physical exam was unremarkable. Her admission labs were notable for a Cr 2.25mg/dL, potassium 3.1mmol/L, bicarbonate 15mmol/L, phosphorus 2.2mg/dL, uric acid 1.3 mg/dL, urinalysis specific gravity 1.011, pH 6.5, glucose 500 mg/dL, small blood, protein 30 mg/dL, negative leukocyte esterase, nitrite negative, 2 RBC, 4 WBC, negative urine culture, and spot protein/cr of 1.1. Further workup revealed urine electrolytes: Cr 39mg/dL, sodium 77mmol/L, potassium 20mmol/L and phosphorus 22.9mg/dL. FePhos was 61% suggesting renal wasting. Serologic workup was negative for ANA, ANCA, nl c3, nl c4 and spep. Renal sonogram showed normal sized kidneys with two nonobstructing calculi in each kidney. Renal biopsy revealed focal degenerative changes in the tubules with flattening of the epithelium consistent with mild ATN. The interstitium had diffuse inflammation with mononuclear cells and frequent eosinophils consistent with AIN. EM showed tubuloreticular inclusions. She was started on prednisone which was tapered over 8 weeks. Creatinine downtrended to 1.1mg/dL

Discussion: Vedolizumab reported AIN and mild ATN has not thus far not been reported. Here we report the first case which seemed to have a cumulative dose response. Whether this patient has a mild proximal RTA due to this medication remains to be elucidated, as the phosphorus wasting could have been due to her primary hyperparathyroidism. Clinicians should be made aware of such reported associations so that both a timely renal biopsy and therapy could be instituted without delay.

PO2261

An Unusual Case of Granulomatous Interstitial Nephritis (GIN)

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Introduction: A 28 Y/O man was admitted with stage 5 CKD. He was entirely asymptomatic with a negative PMH except for recent HTN & proteinuria. Entire proteinuria w/u was negative. PE was unremarkable. Kidney biopsy showed advanced glomerulosclerosis wtih chronic non-caseating GIN. Etiology was uncertain except for history of BCG vaccination. BCG induced GIN was proposed. He was given a trial of ACE-I's, but ultimately required long term hemodialysis (HD).

Case Description: A 28 Y/O Hispanic male with 1 yr PMH of untreated HTN & proteinuria presented with BUN 88, Cr 7.85. 1 day after foot surgery Cr increased to 8.14 & Renal was consulted. 1 yr ago he was diagnosed with HTN & proteinuria but never received f/u or treatment. PMH was negative. FH was significant for a cousin with ESRD s/p kidney transplant & an uncle with diabetes. Full proteinuria w/u was (-). Renal US revealed normal size kidneys & increased cortical echogenicity c/w medical renal disease. He was started on lisinopril with improvement in BP, but no improvement in renal function & was then started on HD. Kidney biopsy revealed acute tubular injury without regeneration changes, acute & chronic interstitial nephritis with a few granulomas, 75% global glomerulosclerosis, mild tubular atrophy & interstitial fibrosis. GMS & AFB stains were negative for fungus & mycobacteria. No electron dense deposits (EDD's) were see on electron microscopy. Further discussion with patient revealed he received BCG vaccine when 2 weeks old.

Discussion: Bacillus Calmette-Guerin (BCG) vaccine is a live but attenuated strain of *Mycobacterium bovis* used to protect against TB in many countries with a high prevalence of TB. BCG has been implicated in the development of granulomatous disease in multiple organs, but rarely in the kidneys. Our patient received an intra-dermal BCG injection 2 wks after birth & had no sequelae or side effects. The historical (-) PMH, absence of prior medications or infectious process, (-) serologic w/u, (-) history of environmental exposures made the incidental discovery of asymptomatic stage 5 CKD with proteinuria all the more surprising. The unexpected finding of GIN raised the consideration for stimulated immunity & granuloma formation from latent BCG vaccine. While literature documents granuloma formation in other organs, its occurrence in kidneys & potential contribution to progressive CKD seems less common, but should not to be overlooked.

PO2262

A Chimeric Case of AKI

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Introduction: New-onset nephrotic syndrome often requires kidney biopsy for diagnosis. Pathology is at times insufficient.

Case Description: An 81-year-old Hispanic female with HTN, CKD stage III presented with rash, fever, peripheral eosinophilia, AKI and diagnosed with DRESS

syndrome due to allopurinol started 3 weeks ago. Urinalysis showed pyuria, hematuria. Spot urine Pr/Cr was 3.8 with serum albumin 2.5g/dL. Admission creatinine was 4.3mg/dL, increased to 6.5mg/dL prior to starting dialysis. Serologic findings shown below. Steroids were started for DRESS and suspected AIN. Genetic testing for HLA-B*5801, seen in severe cutaneous adverse reactions to allopurinol, was positive. Skeletal survey demonstrated no lesions. Blood counts revealed anemia and thrombocytopenia. Bone marrow biopsy did not show a plasma cell dyscrasia. Kidney biopsy noted amyloidosis (Congo red positive deposits in glomeruli, vessels, interstitium) with 56% global glomerulosclerosis and >60% severe IFTA. Mild interstitial inflammation with occasional eosinophils suggested resolving AIN. Severe findings of hypertensive sequelae noted. Immunofluorescence was 2+ for IgG and kappa. Electron microscopy showed 10nm fibrils and severe podocyte foot process effacement. Mass spectrometry diagnosed ALECT2 amyloidosis.

Discussion: Our case is unusual in having three simultaneous pathologies, namely AIN and ALECT2 amyloidosis superimposed on a background of hypertensive changes; the recognition of disproportionate proteinuria was essential to question the diagnosis and avoid early closure on AIN. Concurrent renal pathologies are a common finding in patients with ALECT2 amyloidosis, underscoring the utility of kidney biopsy in these patients who often have mixed clinical pictures. Circumstances leading to this case raise suspicion for preceding immune dysregulation, in the form of DRESS/steroids, that may have triggered amyloidogenesis. A prior case report describes a patient who developed ALECT2 amyloid after steroids for allergic symptoms. This potential interplay between genetic and environmental factors requires further investigation.

UPEP, urine immunofixation	No monoclonal protein
SPEP, serum immunofixation	Polyclonal
Kappa/lambda light chains	8.42
Beta-2 microglobulin	20.2 mg/dL
ANA, ANCA, anti-GBM	negative
Hepatitis B and C, cryoglobulin	negative
Complements	normal

PO2263

ALECT2 Amyloidosis with Cardiac Involvement Complicating Renal Transplantation

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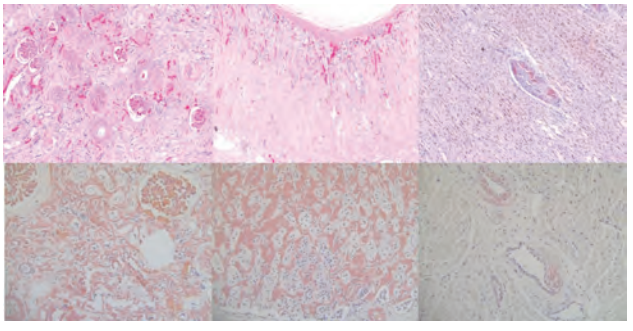
Introduction: ALECT2 amyloidosis may be associated with slowly progressive renal failure that is clinically unsuspected at the time of transplantation. While this is typically not clinically significant, we report a case with extensive systemic ALECT2 amyloidosis that also involved the myocardium, contributing to perioperative death post renal transplantation.

Case Description: A 72-year-old Hispanic woman presented for renal transplantation due to ESRD from hypertension. She was bradycardic on admission. Cardiac workup prior to transplantation had not identified an infiltrative process. Post-transplant hypotensive bradycardiac arrests lead to multiorgan failure, anoxic brain injury and death. Autopsy revealed massive amyoid deposition in the native kidneys, adrenals, spleen, and less extensive infiltration of liver and myocardium. Cardiac intramural vasculature from venules to capillaries, arterioles and arteries showed amyloid deposition. Mass spectrometry revealed ALECT2 as the amyloidogenic protein.

Discussion: ALECT2 is a systemc amyloidosis that typically involves kidneys, adrenals, spleen and liver. It may be clinically unsuspected at the time of renal transplantation and should be considered in older patients, especially from higher ALECT2 amyloid prevalence populations. Complications related to systemic disease may add to morbidity or mortality post-transplantation. Cardiac involvement in ALECT2 amyloidosis has not been previously identified as a significant clinical or autopsy finding, but our case demonstrates that the cardiovascular system may indeed rarely be involved by ALECT2 amyloidosis and be associated with clinical sequelae.



Diffuse amyloid deposition in native kidneys, adrenals and involving vasculature of the myocardium.

PO2264

Cell-Based C5b9-ELISA to Identify Patients with Atypical Hemolytic Uremic Syndrome

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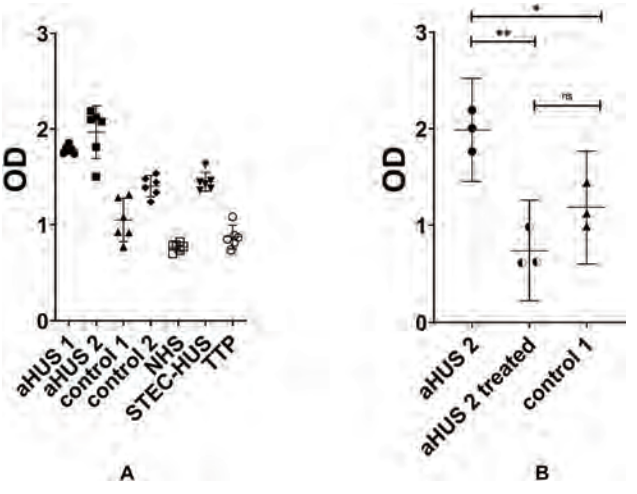
Background: Discrimination between different diseases in patients suffering from thrombotic microangiopathies is often challenging. Measuring C5b9 deposit on endothelial cells using confocal microscopy have been shown to be convenient in diagnostic and therapy monitoring of Atypical hemolytic uremic syndrome (aHUS) but methods are complex and costly.

Methods: We developed a cell-based C5b9-ELISA to measure C5b9-deposits on activated endothelial cells. Patients with suspected aHUS and other thrombotic microangiopathies were identified in early disease stage. Serum was drawn and tested versus healthy controls. After confirmation of the diagnosis aHUS therapy efficiency was monitored using the assay.

Results: In patients with the clinical diagnosis of aHUS we were able to show up to six-fold higher C5b9-deposits in contrast to normalized human serum (NHS) (p-value < 0,0001). In comparison to healthy controls, patients suffering from either Shiga-Toxin-HUS or Thrombotic Thrombocytopenic Purpura (TTP) we could demonstrate a two- to three-fold higher deposit (p-value=0.0103 and below). After onset of eculizumab treatment, the amount of C5b9-deposits becomes lower than in healthy controls, proving the efficiency of the therapy. One-Way-ANOVA shows significant differences between aHUS-groups and controls, but not between aHUS patients using Tukeys-multiple comparisons test.

Conclusions: We described a novel, fast and reproducible ELISA to identify aHUS-patients by measuring C5b9-deposits and monitor disease activity. This can give a rise to diagnostic speed and therapy decisions. Further investigation and validation are needed to show interactions with other complement diseases like systemic lupus erythematosus.



ELISA-results with 95 % CI. A: C5b9-deposits in different patients. B: C5b9-deposits before and after two doses of eculizumab in patient 2 compared to healthy control 1.

PO2265

Chronic Neurological Impairment in Patients with Thrombotic Thrombocytopenic Purpura: Preliminary Findings in a Comprehensive MRI Protocol

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Background: Thrombotic thrombocytopenic purpura (TTP) is a life-threating blood disorder characterized by insufficient activity in ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13). This protein prevents blood clotting, so in TTP there is spontaneous clotting throughout the microvasculature. Treatment includes plasma exchange therapy and immunosuppressants to improve fever, thrombocytopenia, and kidney failure. However, neurological changes, such as seizures and confusion, persist. There is limited research on TTP on the brain but it is known that TTP presents similar pathology to stroke. This study aims to better understand the long-term impact of TTP on the brain using a comprehensive magnetic resonance imaging (MRI) protocol and cognitive testing.

Methods: 13 patients (5 male, mean age 44.5) in hematological remission were recruited. Participants had a 65-minute MRI scan (Siemens mMR Biograph 3T) based on best-practice guidelines for imaging stroke. The protocol included five qualitative acqusitions and three quantitative acquisitions. Participants also completed a 40-minute cognitive test (Cambridge Brain Sciences) to assess cognitive impairment.

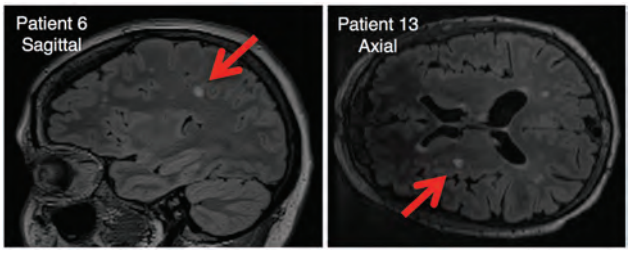
Results: Table 1 summarizes the findings across qualitative acquisitions. The most salient findings were the white matter hyperintensities seen in the T2 FLAIR in Image 1. 12 participants completed the cognitive testing and there is evidence of cognitive impairment.

Conclusions: Patients will be scanned again at six and twelve months. Age-matched healthy controls will be recruited before drawing conclusions on quantitative metrics, namely the amount of white matter. These early results are promising for better understanding the implications of TTP on the brain.

Funding: Private Foundation Support

Summary of qualitative findings

Sequence	Number of Participants with at Least One Abnormality	Example of Abnormality
T2-Weighted (FLAIR)	10	White matter hyperintensity
T1-Weighted	7	Atrophy of white matter or gray matter
Angiography	5	Thrombus
Susceptibility-Weighted	3	Microbleed
Diffusion-Weighted	1	Siderosis



PO2266

Persistent Coagulation Abnormalities in ESRD After 1 Year of Follow-Up

Emily Bontekoe, Vinod K. Bansal, Fakiha Siddiqui, Debra Hoppensteadt, Jawed Fareed. *Loyola University Medical Center, Maywood, IL.*

Background: Common to end-stage renal disease (ESRD), coagulation abnormalities can lead to severe bleeding events or excessive thrombi formation and engender increased morbidity and mortality in this population. Repeated heparin administration to ESRD patients during maintenance hemodialysis may also contribute to changes in the coagulation system. Thus, profiling coagulation parameters in ESRD patients over 1-year may provide insight to long-term coagulation dysfunction in this population.

Methods: Blood samples were collected at baseline and 1-year from ESRD patients undergoing maintenance hemodialysis (n=95) 48-hours post-dialysis. Plasma samples were analyzed using clot-based methods including activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT). Chromogenic assays measured heparin levels by anti-Xa and anti-IIa methods. Patients were categorized by heparin administration during dialysis (n=44) and compared via statistical method and percent change.

Results: In the clotting and chromogenic assays, all parameters were elevated in the baseline and 1-year ESRD cohorts compared to controls, as shown on Figure 1. Only anti-IIa levels demonstrated a significant difference in ESRD patients after 1-year ($p<0.0001$). Heparin administration varied in aPTT, TT, and anti-Xa ($p<0.05$).

Conclusions: These results suggest ESRD patients on dialysis exhibit a long-term, hypo-coagulable state as shown by prolonged aPTT and TT. Elevated parameters maintained over 1-year suggests persistent dysregulation of clotting factors in ESRD patients. Circulating levels of heparin, as evidenced by anti-Xa and anti-IIa assays may be due to impaired clearance of heparin components via dialysis.

PO2267

Using Skin Biopsies to Measure Target Occupancy of a Renal Antifibrotic Monoclonal Antibody (mAb) in a Phase 1 Clinical Study

Rowann Bowcutt,[1] Geoffrey I. Johnston,[1] Linghong Huang,[1] James Z. Song,[2] Tim S. Schmidt,[1] Alison L. Bigley,[3] Graham Ogg,[4] Eric Wong,[1] Elizabeth S. Thomson,[1] Jane Y. Chan,[1] Anastasiia Raievska,[5] Timothy S. Johnson.[1] *[1]UCB Pharma, Slough, United Kingdom; [2]Prisys Biotechnology, Shanghai, China; [3]OracleBio, Chapelhall, United Kingdom; [4]University of Oxford, Oxford, United Kingdom; [5]Veramed, London, United Kingdom.*

Background: Defining the optimal dose of drug required to bind to its mechanistic target (target occupancy, TO) and affect a measurable distal event (target engagement, TE) in damaged kidney is a challenge in the development of anti-fibrotic therapies for chronic kidney disease (CKD). We aimed to identify an accessible surrogate human tissue to predict TO in the kidney, prior to application in a Phase 1 study.

Methods: We developed a 'biopsy-on-biopsy' approach in skin: a 3mm biopsy initiated a wound healing response; a 6mm biopsy at the same site, up to 6 days later, provided tissue where active healing/fibrotic processes were ongoing. This method was used to measure the TO of zampilimab, a humanized mAb specific for human transglutaminase 2 (TG2), in development for fibrosis in CKD. Primate skin TO was correlated with kidney TO and TE in a unilateral ureteric obstruction (UUO) model, before application in a single dose Phase 1 study (NCT02879877). Following dosing of zampilimab, TO in skin biopsies and kidney was measured using a competitive immunofluorescence assay on cryosections. A TRITC-labeled mouse parent of zampilimab (DC1) and a FITC-labeled anti-TG2 antibody binding a distant epitope (DH2) were used. TO was measured by comparing the relative binding of DC1 (competitively inhibited by zampilimab administered *in vivo*) to DH2. TE in kidney was measured using a TG2 *in-situ* activity assay.

Results: In a primate UUO-CKD model treated prophylactically with zampilimab, the 'biopsy-on-biopsy' method showed excellent correlation between TO in the kidney and healing skin (3 days post first biopsy). Importantly, TO and TG2 inhibition (TE) in the kidney were also highly correlated. Subsequent use in the zampilimab Phase 1 study generated data directly comparable to the preclinical model.

Conclusions: Our 'biopsy-on-biopsy' approach allows early identification of a dose range in Phase 1 studies where the target organ is inaccessible, and is applicable to other therapeutic mAbs intended for treatment of fibrotic kidney disease. A Phase 1/2 study of zampilimab in patients with post-renal transplant fibrosis is ongoing (NCT04335578).

Funding: Commercial Support - UCB Pharma

PO2268

Standardized Grading of Chronicity in Native Renal Biopsies: A Single-Center Experience

Yuan Huang, Paul J. Lee, Diping Wang. *University of Cincinnati, Cincinnati, OH.*

Background: Chronic changes in native kidney biopsies are important in predicting prognosis and guiding treatment. In this retrospective single-center study, we investigated the applicability of histological chronicity grading in native kidney biopsies, using a newly proposed standardized grading system by Sethi *et. al.* and with modifications.

Methods: 52 consecutive patients (46.8 ± 16.1 yrs, 53.8% F) from January 2017 to December 2019 were recruited and 44 cases were deemed adequate. 9 categories of histopathology were evaluated and scored independently and blindly by two renal pathologists. An accumulated score (Sum1) was obtained from 4 categories the paper proposed. The other 5 categories were included to provide additional histopathologic information, which generated Sum2 score (Figure). Interrater agreement was measured by kappa statistics. eGFR levels both at the time of biopsy and at the end of 12 to 18-month follow-up were obtained from electronic medical records. The correlations between the calculated total scores and continuous variables were determined by bivariate correlation analysis.

Results: Interrater agreement was almost perfect based on the Landis and Koch scale with a kappa value 0.89. Among the 44 analyzed cases, mean baseline eGFR was 39.6 ± 29.7 mL/min/1.73m^2 . At the end of follow-up, eGFR was 47.8 ± 29.3 mL/min/1.73m^2. Sum1 and Sum2 scores were significantly correlated with both baseline eGFR levels ($R=-0.34$, $p<0.05$, and $R=-0.44$, $p<0.01$, respectively) and those at the end of follow-up ($R=-0.56$, $p<0.01$ and $R=-0.44$, $p<0.01$, respectively).

Conclusions: We demonstrated that the modified criteria were comparable to the original criteria; both had good interrater agreement and correlated well with eGFR levels. The modified criteria could provide standardized grading of additional clinically relevant histopathology. Application of standardized chronicity grading will benefit prognosis evaluation and clinical management of renal diseases.

Funding: Clinical Revenue Support

GS (Glomerular Sclerosis)	IF (Interstitial Fibrosis)	TA (Tubular Atrophy)	CV1 (Vascular)	ME (Mesangial expansion)	SS (Segmental sclerosis)	FS (Fibrous crescent)	CV2 (Vascular)	ah (Arteriolar Hyalinosis)
0 <10%	<10%	<10%	Intimal thickening <thickness of media	None	No segmental sclerosis	No fibrous crescents	None	None
1 10-25%	10-25%	10-25%	Intimal thickening ≥thickness of media	≤25%	Segmental sclerosis present	Fibrous crescent present	≤25%	Mild to moderate ≥1
2 26-50%	26-50%	26-50%		26-50%			26-50%	moderate to severe >1
3 >50%	>50%	>50%		>50%			>50%	Severe in many
Sum1=GS+IF+TA+CV1				Sum2=GS+IF+TA+ME+SS+FS+CV2+ah				

PO2269

Inadequate Tissue for Renal Biopsy Analysis Has Significantly Increased Since the Switch to Interventional Radiology (IR)

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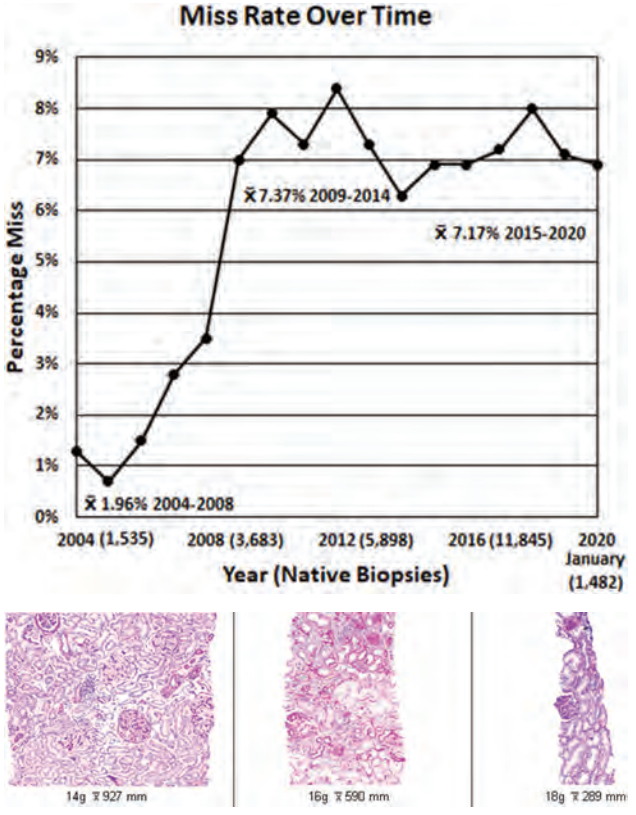
Background: The aim of this study was to determine the incidence of inadequate native renal biopsy (Bx) samples in our laboratory over time.

Methods: A retrospective study of native kidney biopsy adequacy from 2004 through the first month of 2020 was done. Adequacy was defined by the number of glomeruli for light microscopy (LM) as follows: 1. Ideal ≥20; 2 Adequate 10-19; Limited 4-9; Miss ≤3. An in-depth study of kidney biopsies received in 2004 and April-August of 2018 was done to compare Nephrologists (Neph) vs Interventional Radiologists. In 2004, there were 1,535 native Bx's: Neph 1,489 (97%); IR 46 (3%). In the 20-week 2018 study, there were 5,134 native needle Bx's: Neph 250 (5%); IR 4,884 (95%).

Results: The mean miss rate changed from 2% in 2004-2008 to 7% in 2009 through 2020 (figure). This correlates with the change from Neph to IR as operators. The miss rate deep (medulla) v miss rate shallow (peri-renal tissue) also significantly changed from 10% deep in 2004 to 90% deep in 2018. The needle gauge significantly changed from 14g 20%, 16g 73%, 18g 7% in 2004 to 14g 0%, 16g 14%, 18g 86% in 2018. This has resulted in significantly less volume available for serial sections and special stains (Figure).

Conclusions: The availability of advanced tissue analysis techniques and more importantly, the increase in therapeutic options has made the renal biopsy an even more

important diagnostic tool. The change to IR as primary operators has significantly reduced tissue adequacy. An extraordinary educational outreach to IR is needed.



Biopsy Widths 14g, 16g and 18g

PO2270

Value of Immediate Post-Kidney Biopsy Ultrasound in Excluding Major Hemorrhagic Complications

Alian Albalas, Ammar Almehmi, Sloan Almehmi, Michael Allon. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: Hemorrhage is the most serious potential complication of percutaneous kidney biopsy. Patients are typically observed for at least 6-8 hours after a kidney biopsy, with serial measurements of vital signs and hemoglobin to monitor for major hemorrhage. This study assessed whether an immediate post-biopsy ultrasound can reliably predict major hemorrhage.

Methods: We retrospectively evaluated the clinical outcomes in 147 patients undergoing an outpatient native kidney biopsy at a large medical center during a 2.5 year period (January 2017 to June 2019). All patients underwent a standardized post-biopsy ultrasound. We extracted from the medical records vital signs and hemoglobin values obtained before the biopsy and at 2, 4, and 6 hours after it, and ascertained whether the patient developed a major hemorrhage requiring hospitalization.

Results: Each patient underwent 2 or 3 biopsy passes. The mean patient age was 48±17 years, 49% were female, 37% were black, 53% had hypertension and 16% had diabetes. Five patients had evidence of a perinephric hematoma on the ultrasound and were hospitalized. The remaining 142 patients had no evidence of bleeding on ultrasound. Their blood pressure, heart rate, and hemoglobin remained stable during 6 hours of observation. All were discharged after 6 hours, and none had a late bleeding complication.

Conclusions: If the immediate post-kidney biopsy ultrasound does not show hemorrhage, the patient is extremely unlikely to develop a major hemorrhagic complication (negative predictive value, 100%). Such patients can be discharged home safely after a 2-hour observation, thereby simplifying their management.

PO2271

Morphologic Evidence of Excretory Function in Human Mesonephros

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Background: Human mesonephros develops at 4 weeks of gestation and regresses at approximately 16 weeks of gestation. It is not clear if the human mesonephros has excretory function. Our goal was to assess morphologic evidence of primordial glomeruli, and renal tubules suggestive of excretory function using special staining and immunohistochemical staining methods.

Methods: Five mesonephric kidneys from human embryos found in miscarriage (missed abortion) or ectopic pregnancy specimens were studied. They were obtained from 4 weeks to 10 weeks gestation. In addition, 8 early metanephric kidneys from 10 weeks to 21 weeks of gestation were identified from our surgical pathology and autopsy cases for comparison with mesonephric specimens. Beside routine hematoxylin and eosin staining, the sections were stained for Periodic Acid Schiff (PAS) to detect proximal tubules (PT) brush borders and glomerular basement membranes (GBM). Furthermore, mesonephros and metanephros sections were immunohistochemically stained for CD133 for progenitor cells, GATA3 for mesangial cells and distal tubules, P504S for proximal tubules, and kidney injury molecule-1 (KIM-1) for PT injury.

Results: CD133 was positive in mesonephric glomerular and tubular structures at 4 weeks but this expression disappeared in the mesonephros from 5 weeks to 10 weeks, implying gradual maturation. GATA3 staining was positive in Wolffian duct, mesangial cells of primordial glomeruli (at 7 weeks the GBM was PAS+) and distal tubules, but not in PT. PT were positively stained for P504S. PT of mesonephric kidneys revealed brush borders on PAS stained sections from 7 to 10 weeks suggestive of reabsorption capacity. The PT of mesonephros at 7 weeks stained positively for KIM-1, suggestive of acute tubular injury during abortion processes. The metanephros showed expression of markers in respective renal compartments, similar to those in mesonephros.

Conclusions: Human mesonephros can have GATA3+ mesangial cells in the glomeruli. Although structures are simplified (no loop of Henle and collecting ducts), the human mesonephric nephrons include primitive glomeruli, PT showing brush borders and distal tubules, having morphological features similar to those of advanced metanephric stages with excretory function. They have react to injury, at least during 7 to 10 weeks of gestation based on identification of brush borders and KIM-1 expression in PT.

PO2272

Monogenic Causes of Nephrolithiasis or Nephrocalcinosis in Korean Children

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Background: Nephrolithiasis (NL) or nephrocalcinosis (NC) can be the early manifestation of hereditary nephropathy in children and early detection of hereditary nephropathy gives us chance to provide therapeutic and preventative intervention. In this study, we present genetic characteristics of NL/NC in pediatric patients who were treated in tertiary medical center in Korea.

Methods: The medical records of pediatric patients (age of 0-18 year) who had NC/NL and underwent genetic test under suspicion of hereditary nephropathy from March of 2013 to January of 2020 in Samsung Medical Center in Korea were reviewed. When specific disease was suspected, the sanger sequencing was done. The whole exome sequencing was performed when suspected mutations were not detected in sanger sequencing or when the disease could not be specified. DNA was extracted from whole blood or saliva. The novel mutations were evaluated by clinical findings and bioinformatics analysis such as *in silico* prediction.

Results: Total 20 patients underwent genetic test and two of them were sibling. The median age at the time of NC/NL detection was 4.8 year and male was predominant (M/F=2.3). Genetic diagnosis was done at the median age of 5.5 year. Three patients had family history of NC/NL (15%). Total 13 pathogenic gene mutations were detected in 16 patients (80%); 5 genes (SCL3A1, GRHPR, CLCN5, OCRL1, CLCNKB) were known to cause monogenic forms of NL/NC and 8 genes (PAX2, PKD1, HNF1B, SCN11A, SLC36A2, BUB1B, VPS33B, PHEX) were not. Three pathogenic autosomal recessive mutations were detected in 3 individuals; BUB1B (n=1), GRHPR (n=1), VPS33B (n=1). We also detected pathogenic mutations in 6 autosomal dominant genes in 7 individuals; CLCNKB (n=1), SLC3A1 (n=1), PAX2 (n=1), HNF1B (n=2), SCN11A (n=1), PKD1 (n=1), SLC36A2 (n=1). Two X-linked recessive genes were detected in 5 individuals; CLCN5 (n=4), OCRL1 (n=1). In one patient, X-linked dominant gene was detected; PHEX. Eight of 16 detected mutations (50%) were novel mutation that have not been previously reported in database of human disease causing mutation.

Conclusions: In conclusion, NL/NC can be the clue to detect monogenic cause of hereditary nephropathy in children. Further large population study is needed to evaluate NL/NC as indicator for genetic analysis to detect monogenic hereditary nephropathy in children.

PO2273

Trans IL-6 Signaling Does Not Distinguish Between Pediatric Patients with and Without Scarring After Febrile Urinary Tract Infection

Sudipti Gupta, Sara E. Lautzenhiser, John D. Spencer, Brian Becknell, Christina B. Ching. *Nationwide Children's Hospital, Columbus, OH.*

Background: The inflammatory response generated in response to infection is believed to be largely responsible for the development of renal scarring after UTI. IL-6 is a cytokine known to be induced during UTI with a pro-inflammatory pathway, known as *trans* signaling. We hypothesized there would be differences in markers of *trans* IL-6 signaling between patients with a history of febrile urinary tract infection (UTI) who had subsequent renal scarring as compared to those with a history of febrile UTI who did not develop renal scarring.

Methods: Urine samples were collected on consenting/assenting pediatric patients with a history of febrile (≥38°C) UTI (urine culture >50K uropathogen) with documented presence or absence of renal scarring on imaging. Patients were not actively infected at time of sample collection. Enzyme-linked immunosorbent assays were performed on samples for markers of *trans* IL-6 signaling: IL-6, soluble (s)IL-6 receptor (R), and soluble

(s)gp130, a buffer in *trans* IL-6 signaling. Values were normalized to urine creatinine. Results were analyzed by t-test or Mann-Whitney *U*. Spearman rank correlation was used. A p-value of <0.05 was considered significant.

Results: 50 urines from patients with a history of febrile UTI were collected: 23 with and 27 without scarring. The groups were not significantly different in age or gender. Urine IL-6, sIL-6R, or sgp130 were not significantly different between those with and without scarring. While IL-6 values significantly correlated with sgp130 values (p=0.0004) in those without renal scarring, the values did not correlate in those with scarring (p>0.05). Ratios of IL-6:sgp130 and sIL-6R:sgp130 were not different between groups.

Conclusions: There is a suggestion of altered buffering of *trans* IL-6 signaling in those with renal scarring compared to those without due to a lack of correlation of sgp130 with IL-6 in those with scarring. The absolute values and ratios of these markers of *trans* IL-6 signaling, however, are not significantly different between individuals with a history of febrile UTI with and without renal scarring in the non-acute setting.

Funding: NIDDK Support

PO2274

Markers of Trans IL-6 Signaling Are Not Differentially Induced During Febrile and Afebrile Urinary Tract Infection

Sudipti Gupta, Sara E. Lautzenhiser, John D. Spencer, Brian Becknell, Christina B. Ching. *Nationwide Children's Hospital, Columbus, OH.*

Background: Febrile urinary tract infections (UTIs) are generally thought to be evidence of tissue inflammation such as pyelonephritis as compared to afebrile UTIs which are thought to be more localized to the bladder. As such, generally the concern for renal damage is more in those with febrile UTI and thought to be a result of the inflammatory response generated. IL-6 is a known mediator of inflammation, particularly through its *trans* signaling pathway. We hypothesized there would be differences in markers of *trans* IL-6 signaling in the urine of children with febrile compared to afebrile UTI.

Methods: Pediatric patients with signs of active UTI were consented/assented for participation. Urine was collected at time of evaluation for active UTI in the urology or nephrology office or at hospitalization and were divided into those with a fever (≥38°C) compared to those without (<38°C). Patients were included for analysis if they had a positive urine culture (>50K CFU of a uropathogen) and for those without a fever if they had urinary symptoms such as dysuria, urgency, frequency, and/or new or worse urinary incontinence. Those with fever were termed a febrile UTI and those without a fever were termed afebrile UTI. Enzyme-linked immunosorbent assays were performed on samples for markers of *trans* IL-6 signaling: IL-6, soluble (s)IL-6 receptor (R), and soluble (s) gp130. Results were normalized to urine creatinine. Results were analyzed by Mann-Whitney *U*. A p-value of <0.05 was considered significant.

Results: 17 patients with febrile UTI and 23 patients with afebrile UTI were included. Two of the patients with febrile UTI were male while all of the afebrile UTI patients were female (p=0.1258). The groups did not differ significantly based on age (p=0.6218). While we found that those with a febrile UTI had a higher IL-6 in their urine at the time of collection (p=0.0479), there was no significant difference in expression of sIL-6R or sgp130. Ratios of these markers also were not significantly different.

Conclusions: Markers of *trans* IL-6 signaling, either as absolute values or ratios, are not different between individuals at the time of febrile or afebrile UTI.

Funding: NIDDK Support

PO2275

Human Neutrophil Peptide 1-3 Protects the Urinary Tract from Uropathogenic *Escherichia coli* Invasion in Humanized Mouse Model

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Background: Urinary tract infection (UTI) susceptibility is defined by heritable genetic differences associated with the innate immune system development and efficiency. DNA copy number variations in the alpha-defensin *DEFA1A3* locus are associated with UTI susceptibility in children with VUR. In humans, *DEFA1A3* is expressed in neutrophils as well as in the kidney. However, how *DEFA1A3* protects the urinary tract in some individuals is unknown. We hypothesized that *Defa*$^{+/+}$ humanized mouse would be resistant to experimental UTI.

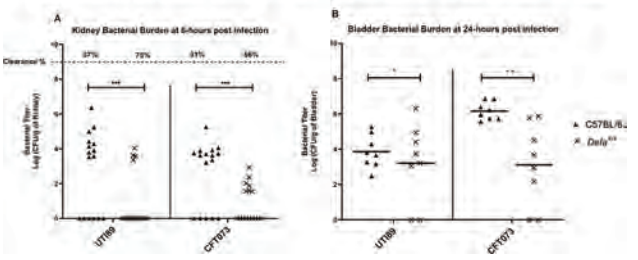
Methods: We induced UTI with two uropathogenic E. coli (UPEC) strains in wild-type (WT) C57Bl/6J and *Defa*$^{+/+}$ transgenic mice, which express human *DEFA1A3*. Bacterial suspension was inoculated with a catheter transurethrally. To asses the colony-forming-unit (CFU) burden, kidneys and bladders were homogenized and colony forming units and clearance were determined by quantifying the plating serial dilutions grown overnight on LB plates at various time points.

Results: Results are presented in Figure 1: Comparing the *Defa*$^{+/+}$ mouse to WT (n=8 for each group), at 6-hours post infection, bacterial burdens were lower in the *Defa*$^{+/+}$ mice kidneys for both UPEC strains (A). At 24-hours after inoculum, the mean bladder Log (CFU/g) was significantly lower in the *Defa*$^{+/+}$ mouse in comparison to the C57Bl/6J group (B).

Conclusions: Our findings support the early protective role of *DEFA1A3* from UPEC challenge in the humanized mouse kidney and bladder when compared to the absence of the antimicrobial peptide in the wild-type mouse. Further investigation is needed to determine whether renal or extra-renal expression of *DEFA1A3* is critical in shielding and clearing UPEC UTIs.

Funding: NIDDK Support

Figure 1. Kidney and Bladder colony-forming-unit burden upon UPEC transurethral inoculation



Kidney and Bladder CFU Burden upon UPEC inoculation

PO2276

Ribonuclease 6 Is an Intracellular Antimicrobial Peptide That Thwarts Bacterial Cystitis and Pyelonephritis

Hanna H. Cortado, Birong Li, Ashley R. Jackson, Sudipti Gupta, Christina B. Ching, John D. Spencer, Brian Becknell. Nephrology and Urology Research Affinity Group *Nationwide Children's Hospital, Columbus, OH.*

Background: Ribonuclease 6 (RNase 6) is a highly conserved cationic peptide with potent microbicidal activity toward uropathogenic *Escherichia coli* (UPEC) *in vitro*. Here, we determined the cellular sources of RNase 6 along with the consequences of its gain and loss of function during experimental urinary tract infection (UTI).

Methods: We generated female mice with a *Rnase6*^{EGFP} knock-in allele, human *RNASE6* transgene, or controls on a C57BL/6J genetic background. We identified cellular sources of RNase6 by flow cytometry and microscopy. We transurethrally inoculated *Rnase6*$^{EGFP/EGFP}$, *RNASE6* transgenic, and control mice with UPEC strain CFT073 and enumerated bacterial burden. The role of RNase 6 during intracellular killing of UPEC was investigated in bone marrow derived macrophages (BMDM) by gentamicin protection assay.

Results: *Rnase6* is expressed by tissue resident macrophages and circulating monocytes that are recruited to the infected bladder and kidney within hours of UPEC inoculation. *Rnase6* deficiency leads to increased renal UPEC burden relative to controls, whereas *RNASE6* transgenic mice exhibit reduced UPEC burden. *Rnase6* macrophages localize within the urothelium and its underlying stroma at baseline and during UTI. RNase 6 is not secreted by macrophages; instead, it is retained intracellularly within the endolysosomal system. *RNASE6* over-expression in macrophages leads to increased killing of phagocytosed UPEC.

Conclusions: RNase6 is a monocyte/macrophage derived antimicrobial peptide that acts intracellularly to kill phagocytosed UPEC and limit bacterial UTI.

Funding: NIDDK Support

PO2277

Risk Factors for Urinary Tract Infection Caused by Extended-Spectrum Beta-Lactamase Gram-Negative Bacteria in Infants

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Background: Community-acquired extended-spectrum beta-lactamase (ESBL) producing bacterial infections are an evolving public health problem. Urinary tract infections (UTIs) due to ESBL-producing bacteria are increasing even in infants rarely exposed to antibiotic. We aimed to identify risk factors for UTI caused by ESBL-positive bacteria in infants.

Methods: We retrospectively analyzed the medical records of hospitalized infants with the first episode of UTI from 2018 to 2019. Data includes demographic characteristics, birth history, previous use of antibiotics, febrile event, urinalysis results, and urine isolated organisms. Multivariate regression analysis was used to quantify independent risks associated with ESBL-positive UTI.

Results: UTIs were diagnosed in 266 patients at a median age of 3.6 (interquartile range (IQR) 2.3-5.4) months. Sixty-two (30.4%) patients were diagnosed with UTI caused by ESBL-producing bacteria. When we divided patients according to ESBL status, there was no difference in gender, age, birth history, milk type, and use of postpartum care centers. Maternal use of antibiotics during pregnancy and previous antibiotic exposure to patients was higher in the ESBL-positive group than in the ESBL-negative group (32.3% vs. 10.3%, P <0.001, and 22.6% vs. 12.3%, P =0.044, respectively). *Klebsiella* species was more frequently identified in the ESBL-positive group than in the ESBL-negative group (19.4% vs. 4.9%, P =0.002). In multivariate analysis, maternal use of antibiotic during pregnancy (odds ratio (OR), 3.817; 95% confidence interval (CI) 1.812-8.040, P <0.001), previous antibiotic exposure to patients (OR 2.418; 95% CI 1.071-5.461, P =0.034), and *Klebsiella* species as a causative organism (OR 6.222; 95% CI 2.396-16.158, P <0.001) were associated with ESBL positivity. In a comparison of clinical courses of patients, the ESBL-positive group showed severe leukocytosis (WBC 16,795 /μL vs. WBC 14,620 /μL, P =0.04), and stayed longer in hospital than the ESBL-negative group (7.0 days vs. 4.5 days, P <0.001).

Conclusions: In this study, the high rate of ESBL positivity was detected in infantile UTI. Antibiotics exposure on both patients and mothers was associated with UTI caused by ESBL producing bacteria. Identification of underlying risk factors could improve treatment and preventive strategies.

PO2278

Urinary Sodium to Potassium Molar Ratio in Pediatric Stone Patients

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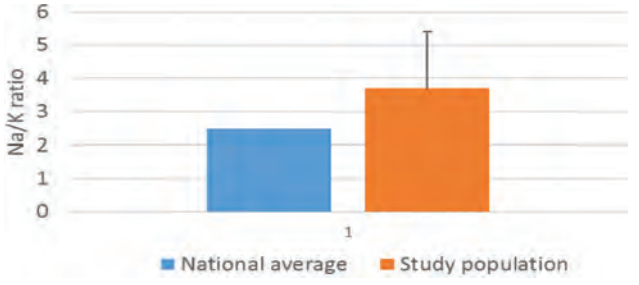
Background: The incidence of pediatric stone disease is on the rise. Dietary elements including high salt intake and reduced water consumption remain the major risk factors for stone formation. Urinary stone profile in pediatric literature remains limited. The purpose of the study is to get data on 24 hr urinary mineral excretion in pediatric stone formers with particular emphasis on these two research questions 1, How does urinary sodium/potassium (Na/K) molar ratio in pediatric stone patients compare to the national average intake data in USA? 2, How does risk factors of stone formation such as hypercalciuria correlates with dietary risk factors in pediatric stone formers?

Methods: This retrospective cohort study included all Pediatric stone patients who attended outpatient Nephrology clinic from 03/1/2014 to 10/1/2018. Children with known metabolic/genetic causes for stone disease, incomplete 24 hr urinary collection or on medications that affect mineral excretions were excluded from the study.

Results: 150 patient charts were screened and 89 included in the study. Average age of the study population was 12.7 years with 58% females and 42% males. Mean Na/K molar ratio in pediatric stone patient was 3.7, statistically significantly higher than the national average of 2.5 using one sample T test ($P < 0.001$). Urinary calcium excretion showed a strong linear correlation with sodium excretion (r 0.545, $P < 0.001$). Multiple regression model using urinary calcium excretion as the dependent variable showed correlation with Urinary sodium excretion (P 0.004), urinary volume ($P < 0.0001$) and urinary Ph (P 0.001)

Conclusions: 24 hr urinary sodium potassium molar ratio is significantly higher in stone formers indicating a higher salt and lower potassium consumption when compared to national average intake. Water intake, salt consumption and alteration of urinary Ph remains the main dietary modality to alter calcium excretion and hence reduce risk of stone formation



PO2279

Keratin 5^{+} Urothelial Cells Are Developmental and Tissue Repair Progenitors in the Bladder

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Background: Urothelium is nearly quiescent during homeostasis, but injury engages a robust regenerative capacity. Several progenitor cell candidates have been implicated, but prevailing models demonstrate conflicting roles discrete urothelial subpopulations. We recently demonstrated that Keratin 5 (K5)-expressing UCs are temporally restricted renal urothelium progenitors. It is unclear whether similar temporal restrictions are imposed on bladder K5-UCs, and whether an investigation into the temporality of the K5-UC progenitor may clarify bladder progenitor models. The objective of this study was to determine temporal progenitor-progeny relationships responsible for bladder urothelium generation and regeneration.

Methods: Using *Krt5*^{CreERT2};*Rosa*^{tdT} mice, K5-UCs were inducibly and permanently labeled with tdTomato (tdT). Tamoxifen (TMX) was administered at postnatal day (P)1, P7, P14, P21 or P41. Mice were sacrificed (SAC) at P42 or subjected to a single round of urothelial injury (cyclophosphamide) and euthanized 2 weeks later. Immunofluorescence microscopy was used to visualize and quantitate tdT, K5, (uroplakin), Upk and K20 expression.

Results: Fate mapping analysis found that 22% (TMX^{P1}-SAC^{P42}) and 23.5% (TMX^{P7}-SAC^{P42}) of neonatal tdT^{K5} UCs differentiated into adult Upk+ UCs (tdT^{K5+};$Upk^{+,}$ mostly intermediate cells) by P42 compared to 9% (TMX^{P14}-SAC^{P42}) or 2.25% (TMX^{P21}-SAC^{P42}) of juvenile tdT^{K5} UCs, and 0% adult (TMX^{P42}-SAC^{P56}) ($P<0.01$, ANOVA). Following urothelial injury, 63% (TMX^{P7}-Cyc^{P42}), 54.33% (TMX^{P14}-Cyc^{P42}) and 69% (TMX^{P21}-CYC^{P42}) of umbrella cells expressed tdT^{K5} (tdT^{K5+};$K5^{-}$;Upk^{+};$K20^{+}$). Adult (TMX^{P41}-CYC^{P42} & TMX^{P35}-CYC^{P42}) tdT^{K5} UCs rarely formed umbrella cells.

Conclusions: K5-UCs form intermediate and superficial cells, but the capacity for K5-UCs to form these derivatives is lost over time. In response to acute adult bladder urothelium injury, neonatal and juvenile tdT^{K5+} UCs regenerate umbrella cells, while adult tdT^{K5+} UCs did not. These studies establish that bladder K5-UCs are context dependent progenitors - responsive to temporal and pathologic cues. Our findings support an intermediate cell acute injury progenitor model, and show that intermediate cells formed by neonatal and juvenile K5-UCs repair acutely injured bladder urothelium.

Funding: NIDDK Support

PO2280

Perinatal Cystatin C as Biomarker of Nephron Endowment

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Background: Nephron endowment has a wide individual variability and plays a crucial role in drug toxicity, outcome of kidney diseases and pathogenesis of arterial hypertension (AH), but nephrons count is technically impossible in vivo. During acute dehydration, subject with reduced nephron mass (unilateral renal agenesis or renal hypoplasia) exhibit increased levels of biomarkers of renal function compared to healthy subjects. We hypothesized that healthy newborns with reduced nephron endowment will have high levels of cystatin c (Cys-c) during perinatal dehydration. The aim of the study was to compare Cys-c level during physiological perinatal dehydration in healthy term infants with hypertensive fathers (HF) and normotensive fathers (NF).

Methods: Healthy, Caucasian, born at term neonates were enrolled: infants with fathers on antihypertensive therapy were compared to infants with normotensive fathers > 40 yo. Enrolled infants underwent Cys-c capillary determination at time of expanded newborn screening.

Results: We enrolled 40 infants with HF and 80 infants with NF. Basic characteristics were not different between the two groups except for the number of hypertensive grandparents, that was higher among infants with HF. Cys-c levels was determined at a median of 62.5 hours of life (IQR 55-71) without any difference between groups. Cys-c was significantly higher in infants with HF (1.6 ± 0.3 mg/L vs 1.4 ± 0.3 mg/L; $p < 0.001$), Linear regression analysis corrected for confounders (type of feeding, delivery mode, weight loss velocity) confirmed that paternal hypertension was the only variable significantly associated with high Cys-c level (mean difference 0.2 mg/L, IC 95% 0.1-0.3 in; $p < 0.001$).

Conclusions: Our results support the key role of nephron endowment in the pathogenesis of AH and suggest the possibility of identifying at-risk subjects at birth. This opportunity opens up specific and targeted preventive health measures very early in life.

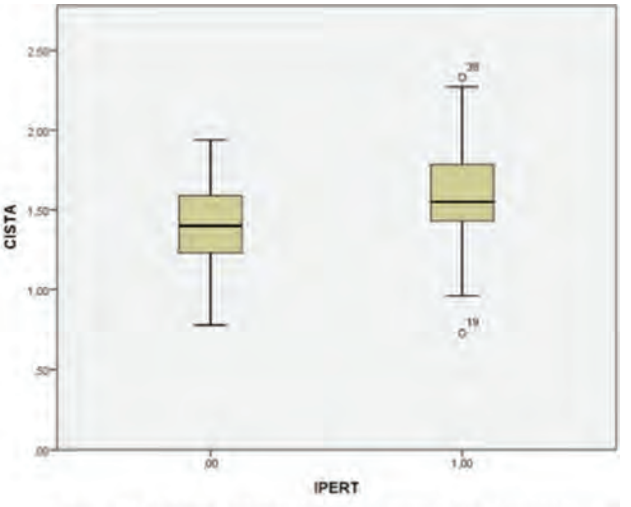

Figure 1: Perinatal Cistatine C in babies born to normotensive and hypertensive fathers.

PO2281

Elevated Urinary Neutrophil Gelatinase-Associated Lipocalin Predicts Postoperative AKI

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Background: Post-operative acute kidney injury (AKI) in neonates remains understudied despite occurring frequently. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) offers promise as a novel predictive biomarker for AKI, yet clinical utilization lags behind in neonatology.

Methods: Infants undergoing a general surgical procedure, excluding gastric tube placement alone, were prospectively enrolled. uNGAL samples were obtained prior to surgery and over post-operative days (POD) 0-3 at six time points. AKI was defined by the 2014 neonatal modified Kidney Diseases: Improving Global Outcomes (KDIGO) definition. Samples were processed using The NGAL Test® (BioPorto, Denmark). Generalized additive mixed effect model (GAMM) was utilized to study the longitudinal trajectory of log transformed uNGAL values. The ability to predict AKI was assessed using receiver operating characteristic curves (AUC-ROC).

Results: A total of 141 neonates underwent 192 surgical procedures. AKI occurred in 18% (35/192). Infants with AKI were more likely to have undergone an emergent procedure (63% vs. 31%, p=<0.001) and had higher uNGAL levels (Table 1). Pre-op uNGAL did not differ between AKI and no AKI patients (26ng/mL vs 59ng/mL, p=0.12). uNGAL levels were higher at all post-op time points even when controlled for pre-operative AKI (p values <0.001 to 0.0356). The AUC-ROC for predictability of post-operative AKI using uNGAL at 24 hours was 0.8 (95% CI: 0.71,0.88).

Conclusions: Post-op uNGAL predicts AKI. In patients undergoing emergent procedures, careful monitoring of renal function should be performed and uNGAL offers clinical utility. In all post-operative patients uNGAL trends could allow clinicians to better understand renal injury in real time and adjust treatment plans and/or avoid or restart nephrotoxic medications.

Funding: NIDDK Support, Private Foundation Support

Table 1: Comparison of predicted uNGAL values (95% CI) following Emergent and Routine Procedures

	Preoperative uNGAL (ng/mL)	12 hour uNGAL (ng/mL)	24 hour uNGAL (ng/mL)	36 hour uNGAL (ng/mL)	48 hour uNGAL (ng/mL)	72 hour uNGAL (ng/mL)	96 hour uNGAL (ng/mL)
Emergent Procedures (95% CI)	270 (164-403)	270 (181-403)	244 (164-365)	244 (164-330)	221 (148-330)	164 (110-244)	121 (81-181)
Routine Procedures (95% CI)	30 (22-40)	33 (25-45)	37 (27-49)	40 (30-55)	40 (30-55)	40 (30-55)	37 (27-49)

PO2282

AKI in Neonatal Congenital Diaphragmatic Hernia

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Background: Acute kidney injury (AKI) occurs in about 30% of hospitalized neonates and is independently associated with mortality. Infants with congenital diaphragmatic hernia (CDH) are frequently exposed to nephrotoxic medications, fluid shifts, surgery, cardiopulmonary compromise, and extracorporeal life support (ECLS). As such, they are cited to have an increased AKI incidence. We sought to determine prenatal characteristics and postnatal exposures associated with an increased risk of AKI in neonates with CDH during the first 30 days of life, as well as the impact of AKI on selected long-term outcomes.

Methods: We performed a single-center retrospective review of neonates with CDH from 2009 to 2017. AKI was defined by the modified neonatal Kidney Disease Improving Global Outcomes serum creatinine criteria. Differences in prenatal characteristics, patient demographics, and long-term outcomes were assessed between those with and without AKI. We used longitudinal models with and without lagged predictions to determine associations between postnatal exposures and AKI.

Results: 90 infants with CDH were included. In the cohort, median gestational age was 38 weeks [IQR: 36, 38], median birthweight was 2.89 kilograms [IQR: 2.5, 3.19], 56% were male, and 50% were outborn. AKI occurred in 34 (37.8%) infants during the first 30 days of life. Specifically, 15 (44%) had stage 1, 10 (29%) had stage 2, 9 (26%) had stage 3, and 8 (24%) received renal replacement therapy. Antenatally, infants with AKI had lower estimates of lung volume (percent predicted lung volume, total lung volume, lung to head ratio, observed to expected lung to head ratio) and higher occurrences of liver up. Postnatally, ECLS, nephrotoxin exposure, CDH repair, abdominal closure, and 10% fluid overload significantly increased the odds of AKI development at varying time-points in the lagged predictions model. Those with AKI had increased mortality and almost two times greater length of stay and duration of mechanical ventilation.

Conclusions: AKI is common among neonates with CDH. In our cohort, greater CDH severity assessed antenatally conferred greater odds of AKI, and those with AKI had worse long-term outcomes. Attention to kidney function should be paid to neonates with fluid overload, on ECLS, exposed to nephrotoxins, or in the post-operative period, given the increased odds of AKI in such situations.

PO2283

Modification of the Renal Angina Index for Identifying Need for Renal Replacement Therapy in Critically Ill Pediatric Patients

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Background: Severe acute kidney injury (AKI) is a common and serious problem affecting critically ill children that lacks effective treatment options. Currently, there are no treatment options for AKI other than supportive care. Continuous renal replacement therapy (CRRT) is employed to reduce fluid overload (FO) burden and treat metabolic disturbances in AKI. Identifying patients upon admission who may require CRRT has potential clinical care implications.

Methods: The analytic cohort consisted of patients who required CRRT and illness severity score matched controls who did not require CRRT at a single center. Patients who required CRRT had higher mortality rates, length of stay, and use of ventilatory and inotropic support. Test characteristics assessed and compared the discriminatory accuracy of three scores: 1) the renal angina index (RAI), 2) serum-creatinine based AKI on day 0 (Day_0AKI) and 3) modified RAI created with an additional RAI injury tranche that corresponded to severe stage 3 AKI serum creatinine (sCr) elevation.

Results: The optimal cutoff for creatinine-based Day_0AKI was found to be stage 3; the optimal cutoff for RAI was identified as ≥ 8. AUCs were comparable at 0.78 (95% CI: 0.70, 0.87) and 0.76 (95% CI: 0.69, 0.82) respectively, although each scoring measure differed in sensitivity and specificity. The modified RAI had an optimal cutoff of ≥ 10 and had the highest AUC (0.79; 95% CI 0.72, 0.85) with a high sensitivity and moderate specificity for prediction of CRRT requirements (table 1).

Conclusions: As a more accurate tool for discriminating patients in need of CRRT, a modified RAI has numerous potential implications. Identifying patients who ultimately require CRRT at an earlier timepoint may influence timing of CRRT initiation in an attempt to avoid further FO, or may influence nephrotoxin administration. Furthermore, the diagnostic capabilities of the modified RAI may be further refined by the addition of urinary biomarkers. These findings should be validated in a larger cohort.

Table 1

Predictor	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Youden	AUC (95% CI)
Day0 AKI	Stage 3	0.63 (0.45, 0.79)	0.93 (0.87, 0.97)	0.76 (0.56, 0.90)	0.89 (0.82, 0.94)	0.57	0.78 (0.70, 0.87)
RAI 12 hours	≥8	0.94 (0.81, 0.99)	0.57 (0.47, 0.66)	0.41 (0.30, 0.52)	0.97 (0.89, 1.00)	0.51	0.76 (0.69, 0.82)
Modified RAI 12 hours	≥10	0.91 (0.77, 0.98)	0.65 (0.56, 0.75)	0.46 (0.34, 0.58)	0.96 (0.89, 0.99)	0.57	0.79 (0.72, 0.85)

Abbreviations: Renal Angina Index (RAI)

PO2284

Peritoneal Dialysis (PD) as the Primary Renal Replacement Modality in Pediatric Shiga Toxin-Producing *Escherichia coli*-Associated Hemolytic-Uremic Syndrome (STEC-HUS): A Single Center's 12-Year Experience

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Background: Half to 2/3 of children with STEC-HUS require renal replacement therapy. The modality is chosen based on a center's individual experience and its associated complications.

Methods: We performed a retrospective cohort analysis using electronic medical records and chart review of 80 patients with STEC-HUS identified through billing data from July 1, 2008 to May 30, 2020. Cases of Streptococcal pneumoniae associated HUS and atypical HUS were excluded.

Results: Dialysis was required in 47 patients (59%). Except for one patient, acute PD was chosen as the initial modality. 43 patients (91%) received PD successfully immediately after the catheter was placed. Four patients required a modality change to either hemodialysis (HD) or continuous renal replacement therapy (CRRT). Leaking of dialysate around the catheter exit site was noted in only 5 patients, out of which only one underwent a catheter revision and resumed PD successfully, two were switched to HD, and two patients had renal recovery allowing for cessation of dialysis. Peritonitis occurred in a single patient but did not lead to a change in modality. In two patients, PD was unsuccessful due to severe intestinal ischemia/colitis, and these patients were switched to CRRT. A central venous catheter (CVC) was often placed at the time of the PD catheter (40 patients). 46 patients had thrombocytopenia (<100,000/mm3) prior to PD catheter and/or CVC placement. Despite having a mean preoperative platelet count of 42,100/mm3, only 6 patients received a platelet transfusion. Furthermore, 15 patients with preoperative platelets between 15,000 – 35,000/mm3 did not have a bleeding event and did not receive a transfusion.

Conclusions: During a time when HD and CRRT have become the more preferred modalities for acute dialysis in children in the US, acute PD is safe and successful in STEC-HUS. We describe a low complication rate, despite immediate use of the PD catheter, indicating that acute PD can be performed before the exit site heals. Platelet transfusion carries the potential to worsen HUS. We demonstrate that children with STEC-HUS do not have bleeding complications despite low platelets at the time of PD catheter and CVC placement.

PO2285

Post-Operative Fluid Overload Is Associated with AKI and Elevated Urinary Neutrophil Gelatinase-Associated Lipocalin Values

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Background: Positive fluid accumulation (FO) in neonates is associated with increased morbidity and mortality and may represent underlying acute kidney injury (AKI). AKI defined by changes in serum creatinine (SCr) and urine output (UOP) can be unreliable in the setting of FO. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) offers promise as an alternative biomarker in assessing AKI in patients with FO.

Methods: Infants undergoing a general surgical procedure, excluding gastric tube placement alone, were prospectively enrolled. uNGAL values were obtained pre-op and on post-op days (0-3) at six time points. FO was defined as 10% weight increase from pre-op weight during PODs 0-5. Percent FO was calculated using post-op net fluid balance(L)/pre-op weight(kg)x100. Adjusted SCr was calculated by SCrx(1+[Net fluid balance post-op(L)/(0.8*Pre-op weight(kg))]). Associations between uNGAL values and

post-op FO and no FO groups were evaluated by Mann-Whitney U tests. Ability to predict FO was assessed by receiver operating characteristic curves (AUC-ROC).

Results: A total of 141 infants underwent 192 procedures. FO occurred after 46% (88/192) procedures (mean %FO = 27±10). Previous medical history of AKI was associated with development of post-op FO (35% vs. 14%, p=<0.001). Development of post-op AKI was also associated with FO even when controlled for pre-op AKI (69% vs. 31%, p=0.005). When SCr was adjusted for FO, AKI increased from 35 to 38 events and stage of AKI increased in 8 events. In FO patients, elevations in uNGAL were higher at all time points (Table 1). The AUC-ROC for uNGAL to predict post-op FO was 0.7 (95% CI: 0.63-0.78).

Conclusions: FO is an indicator of reduced renal function and is associated with AKI. uNGAL offers utility as an additional biomarker to assist in prediction of post-op FO and inability to maintain acceptable fluid balance. Post-op FO should be monitored closely for in all surgical patients, and particularly patients with a previous history of AKI.

Funding: NIDDK Support, Private Foundation Support

Median [IQR] uNGAL values in FO and non FO patients

	Pre-op uNGAL (ng/mL)	12 hour uNGAL (ng/mL)	24 hour uNGAL (ng/mL)	36 hour uNGAL (ng/mL)	48 hour uNGAL (ng/mL)	72 hour uNGAL (ng/mL)	96 hour uNGAL (ng/mL)
All	(n=125)	(n=163)	(n=175)	(n=172)	(n=170)	(n=172)	(n=154)
FO (n=88)	48 [9, 128]	95 [17, 699]	150 [25, 501]	132 [25, 593]	100 [18, 603]	56 [20, 276]	72 [23, 213]
No FO (n=104)	24 [9, 89]	24 [10,49]	28 [10, 120]	36 [14, 86]	32 [12, 106]	30 [12, 79]	31 [11, 78]
p value	0.1106	<0.0001	<0.0001	<0.0001	0.0003	0.006	0.0018

PO2286

Use of B-Type Natriuretic Peptide as a Quantitative Marker of Fluid Overload in Neonatal Renal Replacement Therapy

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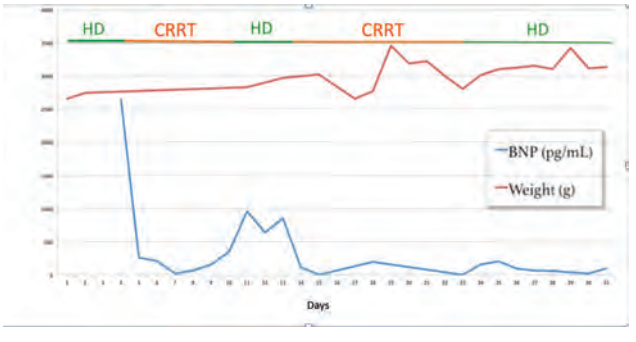
Introduction: Neonatal renal replacement therapy (RRT) remains one of the most challenging dialysis scenarios in Pediatric Nephrology. Evaluation of dry weight can be particularly difficult as fluid overload may be mistaken for adequate nutritional weight gain. Physical exam is insensitive in assessing hypervolemia until significant fluid overload develops. Non-invasive BP measurements are often difficult to obtain as upper extremities are typically used for IV access and the patient's lack of cooperation alters measurement. B-type natriuretic peptide (BNP) has long been used in the evaluation of heart failure and has even been reported to be a marker of fluid overload in adult hemodialysis patients. In this study, we evaluate the role of BNP as a quantitative marker of fluid overload in a neonate with ESRD.

Case Description: A 3 week old child with bilateral renal agenesis required emergent RRT. Following the failure of peritoneal dialysis in this 2.19 kg child, RRT modality was converted to hemodialysis (HD). Despite daily 3 hr HD treatments with ultrafiltration (UF) goals guided by weight, physical exam findings and blood pressure, patient developed bilateral pulmonary edema and an enlarged cardiac silhouette at 3 weeks of age. BNP was found to be > 5,000 pg/mL and RRT modality was changed to CVVHDF. BNP normalized after 4 days of CVVHDF, but upon transition to HD, she again developed fluid overload and required placement back on CVVHDF. Thereafter, BNP was utilized as a quantitative marker of fluid overload with UF goal guided by pre- and post-dialysis BNP levels. Applying this technique, the patient had no further episodes of fluid overload.

Discussion: Providing successful dialysis in infants is more problematic than in older patients. To assess fluid overload in children on dialysis, traditional tools include clinical assessment, serial weights and measuring blood pressure. In this infant, measurement of serial BNP levels allowed for an objective assessment of volume status, which was helpful in maintaining dry weight and lead to successful dialysis therapy.



PO2287

Comparison of Nafamostat Mesylate and Regional Citrate Anticoagulation for Anticoagulation in Pediatric CRRT

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Background: Regional Citrate Anticoagulation (RCA) is the preferred anticoagulant for CRRT in the US in children. Nafamostat Mesilate (NM), a synthetic serine protease, has been widely used for CRRT anticoagulation in Japan and Korea. While NM is considered safe and effective, there is a paucity of evidence in pediatric literature. We describe the safety and efficacy of NM compared to RCA for pediatric CRRT.

Methods: Using one children's hospital in Japan and one in the US, medical records of patients <21 years who received CRRT between 2017-2019 were reviewed. Patients receiving CRRT concurrently with ECMO were excluded. Basic demographics, CRRT characteristics, and outcomes were analyzed between the RCA and NM groups. Filter life (FL), defined as the number of hours a single CRRT filter was in use, was the primary efficacy outcome of efficacy. For Kaplan Meier analysis, circuits were censored for elective filter discontinuation. Safety is assessed by anticoagulation complications.

Results: 28 pts (100 filters) received RCA and 36 pts (90 filters) received NM. Baseline Table1. There was no difference in median FL (42.6h in RCA vs 42h in NM, p=0.17). Kaplan-Meier curves of time to spontaneous filter failure shown in Figure1. The mortality and bleeding rate did not differ between the groups.

Conclusions: NM provides similar efficacy compared to RCA for FL. No significant difference in safety was observed between the two groups.

Patient Demographics	RCA(N=28)	NM (N=36)	p-value
Age [Years; median (IQR)]	11.5 (4-21)	1.7(0.5-6)	<0.001
Baseline disease	BMT (21.43%)	Liver disease (27.8%)	
CRRT Indication	AKI (64.3%)	Metabolic (51.4%)	
CRRT duration Days; median (IQR)]	6 (3-12)	4.5 (2.5-6)	0.12
Filter Data:	RCA (N=100)	NM (N=90)	
Mode of CRRT	CVVHDF (99%)	CVVHD (49%)	
Filter life [Hours; median (IQR)]	42.6(17.3-69.0)	42.0(22.0-89.0)	0.17

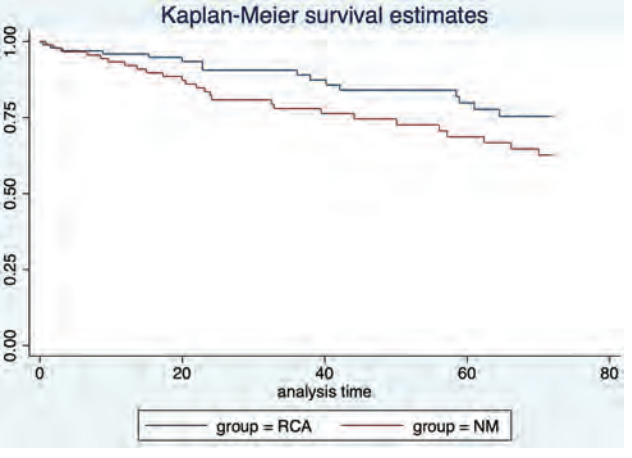

Fig. 1 Kaplan-Meier curves of time to spontaneous filter failure (p=0.085)

PO2288

Renal Replacement Therapy and Mortality Rates for Children with Posterior Urethral Valves and Prune Belly Syndrome

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Background: Posterior Urethral Valves (PUV) and Prune Belly Syndrome (PBS) cause congenital obstructive uropathy and dysplasia in infants. Resulting chronic kidney disease and pulmonary hypoplasia may lead to renal replacement therapy (RRT), mechanical ventilation and death.

Methods: This retrospective cohort study queried The Pediatric Health Information System (PHIS) database to identify patients with PUV or PBS who were born at or admitted to a PHIS hospital by 3 months of age between 1/1/2006 and 9/20/2016. Ethnicity, race and insurance were investigated as predictor variables for time to RRT or in-hospital mortality. Prematurity and mechanical ventilation were evaluated as predictors of in-hospital mortality.

Results: 1673 PUV and 236 PBS patients met inclusion criteria. There was no difference in time to RRT or mortality based on ethnicity, race, or insurance. 212 patients (11.1%) required RRT by 2 years of age. There was no difference in RRT requirement between the PUV and PBS groups. 130 patients (6.8%) died during the initial admission:

98 PUV patients (5.9%) and 32 PBS patients (13.6%), with a median time to death of 6.5 days and 2.5 days, respectively. PBS patients had an increased risk of death (Adjusted Relative Risk (ARR) 2.12, p <.00001). The difference in median time to death was not significant. Of 381 (20%) premature patients, 79 (20.7%) died prior to discharge. 696 patients (36.5%) required mechanical ventilation, and of these, 118 (17%) died. Prematurity and mechanical ventilation were associated with an increased risk of death (ARR 2.3, p <.0001 and ARR 9.9, p<.0001 respectively).

Conclusions: The severity of the sequelae associated with PUV and PBS is affirmed by the 11.1% risk of early RRT and 6.8% in-hospital mortality. PBS patients did have an increased mortality rate compared to PUV patients. Prematurity or the requirement of mechanical ventilation was associated with an increased mortality rate. Future large, prospective studies will enable investigation of early morbidity and mortality associated with PUV and PBS, as well as long-term outcomes.

PO2289

Preterm Birth in Mice Results in Differential Gene Expression and Premature Cessation of Nephrogenesis

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Background: Neonates born preterm are at risk of developing chronic kidney disease (CKD). In humans, nephron development is completed by 36 weeks' gestation and the successful formation of nephrons is dependent on self-renewing niches of cells which reside directly under the kidney capsule in the nephrogenic zone (NZ). Little is known about the fate of these progenitor cells or the other compartments of the kidney following premature birth. The objective of this study was to characterize the effect of premature birth on kidney development in murine model of prematurity. We hypothesize that preterm mice will have a shorter period of postnatal nephrogenesis and gene expression profiles will reflect premature differentiation.

Methods: Timed pregnant CD-1 dams were stratified into 2 cohorts. The preterm group was comprised of 59 pups born by Cesarean section at 18 days post-conception (dpc) and the term group contained 79 pups delivered vaginally at 20 dpc. The mice were euthanized on 20-27 dpc. The presence of the nephrogenic zone was determined on histological sections. Genome-wide expression profiles of 20 dpc mice kidneys were evaluated with RNA-seq in both preterm and term groups (n=3 per group).

Results: At 25-27 dpc, kidney to body weight ratios were significantly lower in preterm cohort. In the kidney, the cap mesenchyme was not detectable in the preterm mice a full day (23 dpc) prior to its cessation in the term mice (24 dpc). The expression profiles of 20 dpc kidneys in the preterm group showed distinct alterations compared to the term group. The differentially expressed genes were enriched in a fat-soluble vitamin (including vitamin A and D) metabolic process related pathways.

Conclusions: In a mouse model of prematurity, there is an early differential expression of genes that may be important in nephrogenesis. The shortened window of nephrogenesis may result in a lower nephron number and future risk for CKD in neonates born preterm.

PO2290

Gestational Age (GA) Affects Urine Biomarkers by Postnatal Age but Most Converge by 34 Weeks Post-Menstrual Age (PMA)

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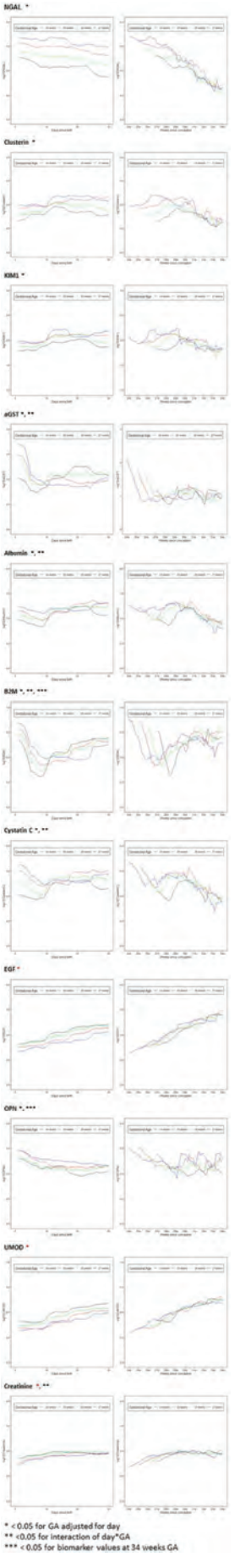
Background: Urine biomarkers may improve our understanding of kidney development and disease in premature neonates. We evalute how 1-week differences in GA impact 11 biomarkers by postnatal age and PMA.

Methods: Neonates were grouped by GA. Urine was collected on postnatal days 1, 3, 5, 7, 9, 14, 28; on PMA of 30 and 34 weeks; and discharge in 750 neonates without stage 2/3 AKI. Neutrophil-gelatinase associated lipocalin (NGAL), Clusterin, kidney injury molecule 1 (KIM-1), alpha glutathione S-Transferase (a-GST), albumin, beta-2-microglobulin (B2M), cystatin c, epithelial growth factor (EGF), osteopontin (OPN), uromodulin (UMOD), were evaluated by electrochemiluminescence; creatinine by mass spectrometer. Biomarkers are displayed as 7-day rolling mean (day X ± 3 days) on log10 scale. GEE models with mother as a clustering variable were used to determine the association between day, GA, and day*GA for each biomarker. T-tests evaluated differences in 34-week (± 3 day) PMA values.

Results: Figure: Left side plot biomarkers by postnatal age; right side plot biomarkers by PMA. When exploring the values by postnatal age, the most premature neonates have higher NGAL, clusterin, KIM-1, aGST, albumin, B2M, Cystatin C, OPN, and lower EGF, UMOD and Creatinine ($p<0.05$; * in Figure) after adjusting for day. The association of biomarker and time is significantly modified by GA for aGST, Albumin, B2M, Creatinine and Cystatin C (interaction term $p<0.05$; ** in Figure) over the first 30 postnatal days. Only B2M and OPN differ by GA at 34 weeks PMA ($p<0.05$; *** in Figure).

Conclusions: Urine biomarkers differ and are modified by GA during first 30 postnatal days. Most biomarkers converge and are not significantly different by 34 weeks PMA.

Funding: NIDDK Support, Other NIH Support - NINDS



PO2291

The Association Between Infantile Pulmonary Hypertension, Sildenafil, and AKI During Hospitalization

Emily E. Zangla, Emily L. Joyce. *University Hospitals, Rainbow Babies and Children's Hospital, Department of Nephrology, Cleveland, OH.*

Background: Pulmonary hypertension (pHTN) is a nidus for poor organ perfusion, and is an understudied potential risk factor for acute kidney injury (AKI) in infants. Neither the association between pHTN and AKI, nor treatment with phosphodiesterase-5 inhibitors (i.e. sildenafil) on renal recovery have been elucidated. We sought to describe AKI in a cohort of hospitalized infants with pHTN.

Methods: A retrospective chart review was performed on 18 infants (less than 1 year of age) during the initial hospitalization for diagnosis of pHTN over one year at a single institution. Adapted neonatal KDIGO criteria was utilized to determine presence of AKI during the hospitalization for each patient.

Results: Out of 18 infants with pHTN, 50% developed AKI during hospitalization. Those who developed AKI were older at the age of diagnosis of pHTN ($p = 0.04$) and more likely to be treated with sildenafil ($p = 0.02$). Within the cohort, 7 (39%) were treated with sildenafil. On univariate analysis, treatment with sildenafil was associated with increased odds of developing AKI (OR 6.7, 95% CI 0.81-55.0). Of those treated with sildenafil who developed AKI, 80% (4/5) developed AKI before initiation of treatment and 20% (1/5) developed AKI after initiation of treatment.

Conclusions: AKI is prevalent in infants diagnosed with pHTN. The increased odds of developing AKI in patients treated with sildenafil is likely a reflection of severity of illness, as most patients developed AKI prior to initiation of treatment. Further research is needed to evaluate the association between pHTN and AKI, as well as determine the role of sildenafil treatment in preventing AKI or promoting renal recovery.

Descriptive Characteristics

	No AKI N = 9/18 (50%)	AKI N = 9/18 (50%)	p-value
Age at diagnosis (mos), mean	1.6 ± 2.1	3.8 ± 2.1	0.04
Gestational Age (weeks), mean	33 ± 6.8	30 ± 7.3	0.36
Males, N (%)	5 (56%)	4 (44%)	0.64
Length of stay (days), mean	170± 195	169 ± 95	0.99
Treated with Sildenafil, N (%)	2 (29%)	5 (71%)	0.07
Mortality, N (%)	0	1 (11%)	0.30

PO2292

Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action) Transfusion Rates

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Background: Acute kidney injury (AKI) is associated with poor outcomes in neonates. Nephrotoxic medication (NTM) exposure is a common cause of AKI. Nephrotoxic Injury Negated by Just-in-time Action (NINJA) identifies patients with high NTM burden and recommends daily creatinine (Cr) screening. In neonates, concern for iatrogenic anemia decreases AKI screening. We monitored transfusion rates in our project modeled off the neonatal NINJA adaptation, Baby NINJA.

Methods: Critically ill neonates with high NTM exposure initially received modified Cr monitoring (only with routine labs) before transitioning to standard daily Cr monitoring. Patients transfused 3 days into & up to 7 days after Baby NINJA exposure periods counted as an associated transfusion. Statistical process control methods were used to detect changes from baseline. X^2 and Poisson regression analyses were used to compare metrics between SCr monitoring eras.

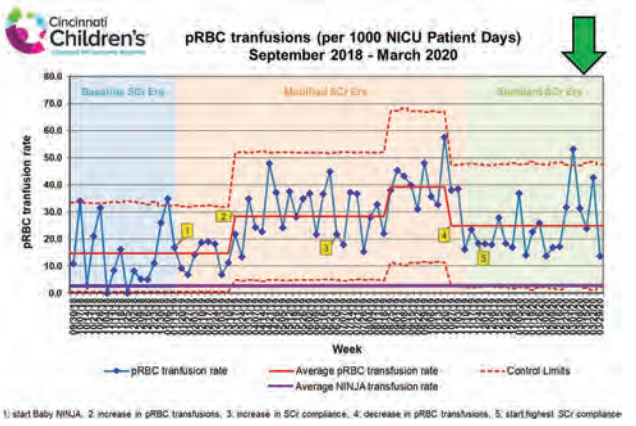
Results: Figure 1 shows an increase in transfusions 15 weeks before an increase in Cr compliance. A decrease in transfusions was sustained through the standard Cr era where the highest rate of Cr compliance was seen. The rate of NINJA-associated transfusions was unchanged. Table 1 shows that Cr compliance increased during each era, transfusions decreased between modified & standard Cr eras, NINJA-associated transfusions remained stable, and transfusion rate changes were independent of NINJA-associated transfusions.

Conclusions: There was no association between transfusion rates and daily Cr testing with Baby NINJA implementation; therefore, critically ill neonates with high risk NTM exposure can safely be screened for NTM associated AKI.

Table 1

	Baseline Era	Modified Cr Era	Standard Cr Era	p-value*	p-value**	p-value***
Cr compliance (%)	43.1	49.1	82.6	0.04	<0.01	<0.01
All RBC transfusion rate (per 1000 NICU patient days)	14.6	28.8	24.3	<0.01	<0.01	<0.01
NINJA RBC transfusion rate (per 1000 NICU patient days)	2.1	3.4	2.9	0.13	0.52	0.36
All RBC - NINJA RBC transfusion rate (per 1000 NICU patient days)	12.5	25.4	21.3	<0.01	0.04	<0.01

*baseline vs modified, **modified vs standard, ***baseline vs standard



U chart depicting transfusion rates

PO2293

Elimination of Intravenous Phthalate Exposure Abrogates Most Neonatal Hypertension in Premature Infants

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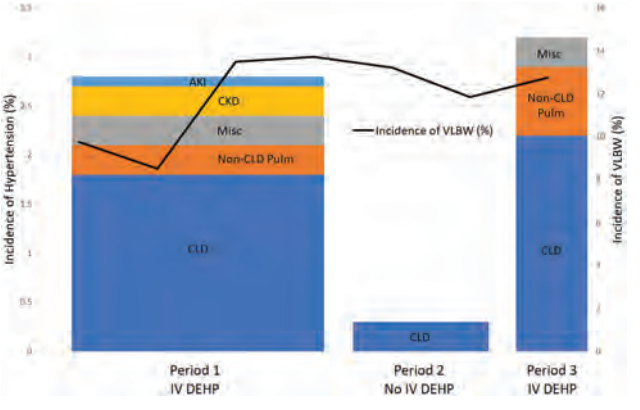
Background: The incidence of hypertension in premature infants in a neonatal intensive care unit (NICU) was noted to transiently drop during a 2-year period when the IV fluid (IVF) temporarily changed to a phthalate-free IVF. The objective of the study is to quantify the effect of varying periods of IVF phthalate exposure on incidence of hypertension in premature infants.

Methods: A chart review was performed of all hypertensive premature infants born at one NICU during the last 6 years including a 3-year baseline period, a 20-month phthalate-free IVF period, and a 10-month period when the original phthalate-containing IVF returned to use. Patients born during 4-month transitions between periods were excluded. Incidence of hypertension for each period were compared for significant difference using Chi-Square analysis.

Results: Incidence of hypertension decreased from 9.7 cases per year (baseline) to 1.2 cases per year when IVF was phthalate-free, rising back to 12.0 cases per year when phthalate-containing IVF returned to use. Most cases met criteria for the pulmonary category of hypertension – for these infants the incidence of hypertension dropped from 7.3 to 1.2, then increased to 10.8 cases per year when evaluated for the same periods of varying phthalate exposure.

Conclusions: Serendipitous removal of IVF containing phthalates resulted in near elimination of hypertension in one NICU – an effect reversing entirely after the same brand of phthalate-containing IVF returned to clinical use. These results suggest that phthalate exposure from IVF plays a major role in neonatal hypertension, especially for those infants in the pulmonary category.



Cases of Neonatal Hypertension by etiology during three time periods, plotted with incidence of very low birthweight during the same time.Width of each bars is scaled according to duration of the time period. Period 1: 36 months, Period 2: 20 months, Period 3: 10 months.

PO2294

Children with a History of Low Birth Weight (LBW) Show Greater Reduction in Kidney Function Than Previously Described Using the Updated Schwartz Equation

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Background: There is a higher risk of reduced kidney function in adults born with LBW (birthweight<2500g). A study using the Counahan-Barrat (CB) eGFR estimation described a modest risk increase in adolescents with LBW. However the CB equation is only validated in children with CKD and underestimates the burden of CKD. Utilizing the updated Schwartz equation, a more sensitive calculation of eGFR validated in healthy children, we sought to assess the prevalence of reduced kidney function in adolescents born with LBW.

Methods: We performed a cross sectional analysis of children aged 12-15 from the National Health and Nutrition Examination Survey from 1999-2016. Reduced kidney function was defined as eGFR <90mL//min/1.73m^2. Participant characteristics were described as weighted sample means and proportions. We constructed logistic regression models adjusted for important sociodemographic factors to evaluate the association of LBW with reduced kidney function.

Results: A total of 6345 individuals were analyzed, representing 13,760,132 adolescents of whom 8% had a history of LBW. Of those born with LBW, the mean age was 13.6 years, 49% were males, 49% were white, 25% were black, 19% were Mexican-American, and 7% were other race. A higher percentage of children with LBW was seen in worse poverty groups. Mean eGFRs in those born LBW were 103 and 107mL/min/1.73m^2 using the updated Schwartz and CB equation, respectively. The prevalence of reduced kidney function in those born LBW was greater using the updated Schwartz equation compared to the CB equation, 30% vs 21.4%. The updated Schwartz equation showed a greater association of LBW and reduced kidney function OR 1.51 (95% CI 1.16-1.97) compared to the CB equation, OR 1.44 (95% CI 1.06-1.96). In an adjusted analysis, the odds of reduced kidney function in adolescents with LBW remained significant OR 1.46 (95% CI 1.1-1.97 using Schwartz but not the CB equation.

Conclusions: A higher prevalence of reduced kidney function was seen in children born with LBW utilizing updated Schwartz compared to the CB equation. The higher risk was sustained in adjusted analyses. These findings may support development of guidelines for CKD screening during long term follow up in the pediatric population with LBW.

PO2295

FCGG Renal Biopsy Network: First Epidemiological Report on Pediatric Renal Disease

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Background: In 2016, a regional renal biopsy network was founded as a collaboration between renal pathologists and nephrologists in order to standardize diagnosis and therapy. Uniform renal biopsy request and renal biopsy report forms were introduced, together with a new comprehensive list of renal pathology diagnoses for coding purposes. The 2017-2018 epidemiological data of the pediatric patients (age 0-17 years) are presented.

Methods: Following informed consent and in compliance with GDPR, data registration consists of basic patient and categorical renal data, semi-structured medical information of renal disease, structured information of renal histopathology, and the clinical renal disease.

Results: In 2017 and 2018, 92 renal biopsies were performed in pediatric patients (age = 0-17 years) or 3.6 per 100,000 pediatric inhabitants per year. Three clinical patterns were equally represented: only proteinuria >1g/day; only hematuria; and combination of proteinuria and hematuria. Acute or chronic renal failure were rare. In the youngest age group (0-5 years; N=26) minimal change disease predominated, followed by Henoch-Schönlein nephritis. The middle age group (6-11 years; N=32) mainly presented with diseases characterized by hematuria: IgA nephropathy, Henoch-Schönlein nephritis and Alport's disease. A more diverse renal disease spectrum was present in the highest age group (12-18 years; N=34): IgA nephropathy, different forms of proliferative glomerulonephritis and of nephrotic syndrome of childhood. Patients with a Caucasian descent presented with IgA nephropathy, while a nephrotic syndrome was more common in those without a Caucasian descent. Alport's disease was particularly diagnosed in female patients, IgA nephropathy in male patients, and the gender distribution was equal in minimal change disease.

Conclusions: The FCGG network provides a better cross-talk between renal pathologists and nephrologists. For the first time, reliable estimates of pediatric renal diseases based on histology are available; genetic analyses are not yet included. Efforts to coordinate clinical care of pediatric renal diseases in the region are ongoing.

PO2296

Developing a Strategy for Routine Reporting of Estimated Glomerular Filtration Rate on Pediatric Laboratory Results

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Background: Routine calculation of estimated glomerular filtration rate (eGFR) is not present in laboratory reporting for children, potentially leading to low recognition of decreased eGFR. The study aim was to define options for pediatric eGFR reporting that optimize accuracy and minimize the impact of missing concurrent height in routine lab reporting.

Methods: Data was extracted from the Michigan Medicine Data Warehouse on all patients aged 1-19 years with serum creatinine between 2017-2018. Creatinine-cystatin C-based CKiD (Cr-CysC, Schwartz, 2012) and creatinine-based 'Bedside' (Schwartz 2009) equations were used to calculate eGFR. Correlations were tested between eGFR calculated with same day height values against eGFR calculated with height imputation of 50th percentile for age and sex or patient-specific historical height percentiles. Scatterplots, Pearson's correlation coefficients, and predictive characteristics were calculated.

Results: There were 109,090 serum creatinine measurements, and 35% had concurrent heights. There were 1770 Cystatin C measurements. eGFR by Bedside equation was abnormal (<90 mL/min/1.73m2) in 25% of measurements. Cr-CysC (r=0.99) and Bedside (r=0.98) equations had excellent correlations for measured vs imputed 50th percentile height eGFRs (Figure). Patient-specific height percentile imputed for the Cr-CysC (r=0.99) and Bedside (r=0.99) eGFR also had tight correlations. Discrimination of abnormal eGFR was excellent for the Cr-CysC (94% sensitivity and 95% specificity) and Bedside (90% sensitivity and 97% specificity) equations using 50th percentile height.

Conclusions: Imputation of 50th percentile or patient-specific historic height percentile enables eGFR calculation that correlates with eGFR using same day height. For ease of implementation and with high sensitivity and specificity, use of 50th percentile height may be the preferred approach for pediatric eGFR reporting when patient-specific heights are not available.

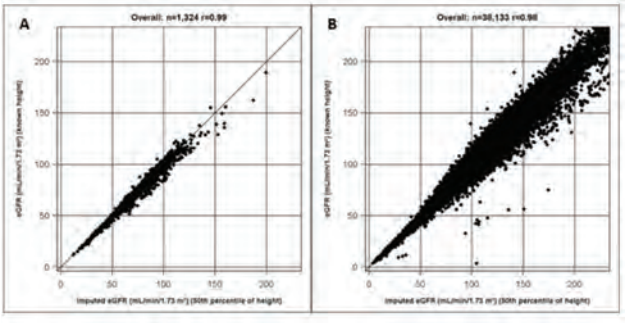

Figure. Concordance of 50th percentile height imputed eGFR compared to eGFR using same day height by creatinine-cystatin c-based CKiD equation (A) and "Bedside Schwartz" (B) equations

PO2297

Factors Related to Significant Albuminuria or Low Glomerular Filtration Rate in Adolescents from a Population with a High Prevalence of CKD of Unknown Origin

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Background: Chronic kidney disease (CKD) of unknown origin has been recognized as the leading cause of kidney disease in young adults in some underdeveloped countries. In Aguascalientes Mexico we report a high prevalence of treated CKD (1997 pmp), with more than half (54%) of unknown cause. The peak of prevalence is between 20 - 30 years (45%), being in that group 73% CKD of unknown origin. For this reason, a CKD screening study was designed in high school students in the state. The aim of this report is to describe the findings of a pilot study obtained in the first three schools.

Methods: Cross-sectional study of high school students. Determination of albumin/creatinine ratio was performed in isolated urine sample and standardized serum creatinine to calculate GFR with Schwartz formula, an abnormal albumin/creatinine ratio>30 mg/gr and GFR≤75 ml/min were defined as CKD. Students and parents were questioned about potentially risk factors. For the multivariate analysis, only students with complete questioning were included.

Results: During March 2020, three high schools in the municipality of Calvillo (Aguascalientes) were visited, accepting entry to the study 187 students out of 260 (72%). The average age was 13.3 years (IQR 12-14) with a predominance of males (n = 109, 58.2%). 33 students with pb CKD were detected (17.6%), 32 of which were due to the presence abnormal albumin/creatinine ratio. Only two patients had low GFR, one with 43 ml/min and the other with 75 ml / min. Four patients presented macro albuminuria, the rest microalbuminuria. In the multivariate analysis, next varibles remainad significant: economic income less than 4,000 Mx$, (OR 4.4, 95% CI, 1.3 - 14.7), frequent NSAID intake (OR 3.8 95% CI 1.16 - 13, p= 0.02), ≥ sweetened beverages per day (OR 4.3, 95% CI1.2 - 14.5, p = 0.01), use of clay dishes by parents and grandparents (OR 4.3 95% CI 1.4 - 12.9, p = <0.01), and BMI <17 kg / m2 (OR 5.8, 95% CI, 1.8 - 18.7, <0.01).

Conclusions: The frequency of abnormal albuminuria or low GFR in adolescents in Aguascalientes is high; follow-up is necessary to confirm these findings. The associated factors significantly guide possible toxics that may be associated with the high prevalence of CKD of unknown cause in our state.

PO2298

Measurement of GFR and Vasoactive Substances in Children with Sickle Cell Anemia

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Background: Patients with sickle cell anemia (SCA) have a high risk of developing renal disease. Sickle cell nephropathy is thought to begin in childhood with higher than normal glomerular filtration rates (GFRs) known as hyperfiltration that can lead to proteinuria, sclerosis of the glomeruli, decreased GFR, and eventual renal failure. This model of sickle cell nephropathy has not been validated in clinical studies. This study measured directly the GFRs of patients with sickle cell anemia and age matched control patients. In addition, urinary vasoactive substances were measured to correlate with the GFR.

Methods: Children with sickle cell anemia (SCA) and sickle-β0-thalassemia (HbSb0) were recruited for the study from the Sickle Cell Clinic at Children's Medical Center of Dallas. These sickle cell disease genotypes are phenotypically similar and are the most severe. Healthy siblings of children seen in the Pediatric Nephrology Clinic at Children's Medical Center of Dallas were recruited to serve as controls. GFR was measured directly from iohexol clearance. Urine was obtained to measure vasoactive substances.

Results: Subjects: SCA:32 and Control:13 The GFR of the sickle cell group was 148 ± 36 ml/min/1.73 m² (Mean and SD) and the control group was 130 ± 17 ml/min/1.73 m². The p-value (un-paired t-test) is 0.089 and thus is not statistically significant. However, the SCA group had 21/32 with a GFR ⟩130 while the control group had only 3/13 (p=0.019). Thus, there were more patients in the SCA group with hyperfiltration. There was no difference in urinary cGMP or PGE2. However, PGF2α was higher in the control group. Surprisingly, the urinary angiotensinogen (factored for urinary creatinine) was lower in the SCA group than in the controls (see table).

Conclusions: In conclusion, we have shown that although the GFR in patients with SCA might not be elevated, there appears to be a population of SCA patients with higher than normal GFR. The intrarenal renin-angiotensin system appears to play a role in this hyperfiltration. Further studies are needed to continue to understand this phenomenon.

Urine Angiotensinogen / urine creatinine

	Mean	SD
HbSS	8.0	6.5
Control	14.6	8.3

HbSS urine angiotensinogen/creatinine was significantly lower than control (p<0.005).

PO2299

Food Insecurity During COVID-19 in Children with ESKD: The Second Wave?

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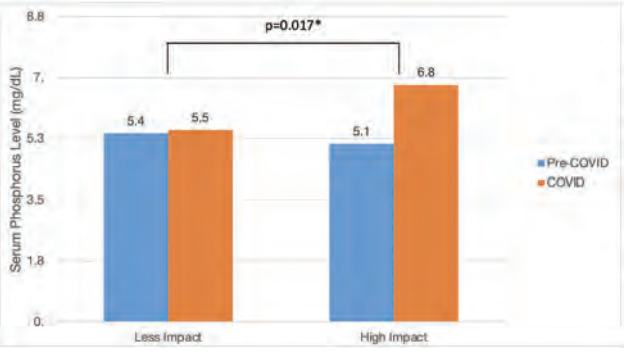
Background: Food insecurity (FI) affects 1 in 6 children in the US and has increased three-fold during the COVID pandemic. Children with end-stage kidney disease (ESKD) may be at even higher risk of FI due to complex care needs, medication burden and dietary restrictions. A pre-COVID study assessing FI in pediatric hemodialysis (HD) patients described 70% prevalence. No data exists describing the effects of the COVID pandemic on FI in pediatric HD patients.

Methods: We assessed FI among families of patients age 0-18 years with ESKD on chronic HD at a single academic pediatric center. Families were screened for FI by using the Hunger Vital sign, a validated 2 question tool. We assessed impact of COVID on FI. Using demographic features, clinical parameters and medical utilization, we compared "pre-COVID" (2/2020) to "during COVID" (5/2020).

Results: A total of 14 families were enrolled. 12 of 14 (86%) of children with ESKD were FI, and all 12 (100%) reported that COVID had worsened their FI status. The prevalence of FI in our HD unit was five times higher than the general population (86% vs. 15%,p<0.001). Patients with FI had an increase in phosphorus during COVID (5.0 to 5.9 mg/dL, p=0.031). Patients with FI self-described as highly impacted by COVID were more likely to have an increase in serum phosphorus levels during COVID (mean increase of 1.7 vs. 0.1 mg/dL, p=0.017).(Fig 1) No patients with FI highly impacted by COVID had serum phosphorus levels within range compared to those less impacted (0% vs. 38%, p=0.040).

Conclusions: FI is common among children with ESKD on HD and was worsened by the COVID pandemic. The prevalence of FI in COVID was significantly higher than community reported rates and published pre-COVID rates in children with ESKD. FI was associated with increased serum phosphorus levels. Further exploration into how FI during the COVID pandemic influence management and impact outcomes for children with ESRD is essential.



Serum Phosphorus Levels in Children with ESKD and Food Insecurity

PO2300

Incidence of Hypercalcemia with Calcitriol Compared with Paricalcitol in Pediatric Patients Receiving Hemodialysis

Rohan Dwivedi, Jennifer L. Morris, Jessica Geer, Poyyapakkam Srivaths, Sarah J. Swartz. *Texas Children's Hospital, Houston, TX.*

Background: At our institution, both calcitriol and paricalcitol are available for use. Paricalcitol is generally used when adverse effects of calcitriol are observed or during times of calcitriol shortage. There are limited data on the efficacy and safety of vitamin D analogs in pediatric (ped) hemodialysis (HD) patients (pts) to support preference of either agent. This study evaluated the incidence of hypercalcemia in ped HD pts receiving calcitriol compared to paricalcitol.

Methods: Single-center, retrospective review of ped pts on HD treated between January 2012 – December 2018 who received in-center doses of calcitriol or paricalcitol. Pts were excluded if they received in-center doses of both paricalcitol and calcitriol or if they had incomplete data. Pts were not excluded from either group if they had an active prescription for oral calcitriol for home. Data were collected for 6-months from the date of the first in-center calcitriol or paricalcitol dose. The primary objective was to evaluate the incidence of hypercalcemia in those receiving calcitriol compared to paricalcitol. Secondary objectives included the incidence of hyperphosphatemia, high calcium-phosphorus product, and hyperparathyroidism (iPTH). Data were evaluated using descriptive statistics, Mann-Whitney-U and Fisher's Exact test.

Results: 34 pts met the criteria for the study (calcitriol group = 15; paricalcitol group = 19). The groups had no statistically significant differences at baseline. Patients in the paricalcitol group received an average weekly dose of 14 ± 7 mcg, equivalent to 4.67 ± 2.33 mcg of calcitriol compared to 2.36 ± 1.51 mcg in the calcitriol group (p=0.002). There were no differences between the time averaged serum calcium, phosphorous, calcium-phosphorus product, and iPTH between the two groups. Between the paricalcitol and calcitriol groups the incidence of hypercalcemia events per patient (EPP), based on age-related normal calcium was 1.11 and 0.53 (p=0.23), hyperphosphatemia EPP was 3.74 and 2.67 (p=0.20) and high iPTH EPP was 2.63 and 2.2 (p=0.38).

Conclusions: The incidence of hypercalcemia in patients receiving paricalcitol compared to calcitriol was high but did not reach statistical significance. There is no clear advantage seen with the use of paricalcitol when compared to the calcitriol group in peds population.

PO2301

Associations Between Short Stature, Emotional-Behavioral Functioning, and Adaptive Skills in Children with CKD

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Background: Short stature impacts quality of life (QOL) for children with chronic kidney disease (CKD). Little is known about how short stature impacts emotional-behavioral functioning and adaptive skills in this group of children.

Methods: Baseline and longitudinal data from the Chronic Kidney Disease in Children study were used to evaluate associations between emotional-behavioral functioning, adaptive skills, and short stature (height z score <-2) in children with mild to moderate CKD ages 10+ years. Linear mixed models were used to determine if short stature predicted emotional-behavioral outcomes, using data from both the parent- and self-report BASC2 rating scales. Models were adjusted for sociodemographic and disease-related covariates.

Results: Baseline parent-report data were available for 737 participants (61% male; median age 13 [IQR=11,16]; 32% glomerular CKD; median eGFR 52 ml/min|1.73m2 [IQR=39, 66]; 10% short stature; 8% growth hormone use). BASC2 self-report was available for 229 participants. For BASC2 parent-report, short stature was not associated with the summary scales of internalizing symptoms (e.g., anxiety, sad mood; β=1.46,

CI=-0.51, 3.42; p=.15), adaptive skills (e.g., social skills, adaptability; β=-1.03, CI=-2.95, 0.89; p=29), or behavioral symptoms (e.g., hyperactivity, conduct problems; β=-0.02, CI=-1.63, 1.60; p=.98). Short stature was associated with the clinical subscale of somatization (child health complaints of pain, poor physical health, and illness; β=2.41, CI=0.31, 4.5; p=.02). There was a marginal, but nonsignificant, association with the depression subscale (β=1.73, CI=-0.09, 3.54; p=.06). Short stature was not related to any of the BASC2 self-report ratings.

Conclusions: For most measures of emotional-behavioral functioning and adaptive skills, short stature was not associated with an increase in parent- or self-reported internalizing or externalizing symptoms or adaptive skills. Short stature was associated with parent-reported, but not self-reported, somatization. The present findings offer some reassurance that while short stature may be related to poorer QOL and somatization, preliminary findings suggest that it is not associated with more significant psychopathology or concerns regarding adaptive skills.

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PO2302

Urine Biomarkers of CKD Progression in Children

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Background: Biomarkers of tubular injury, repair, and inflammation may improve the ability to identify children at high risk of rapid kidney function decline and help elucidate the pathophysiology of CKD progression. In this study, we investigated whether the urinary biomarkers EGF, KIM1, MCP1, YKL40, and alpha1 microglobulin are prognostic of CKD progression in children.

Methods: In the prospective CKiD study, children aged 6 months to 16 years old with an eGFR of 30-90 were enrolled and eGFR was assessed annually. We measured urine biomarkers collected 5 months after study enrollment. Urine biomarkers were indexed to urine creatinine. The primary outcome was CKD progression, defined as a composite of a 50% decline in eGFR or ESKD.

Results: Of the 375 children included, median age was 12 years [IQR, 8-15], 227 (61%) were male, and baseline eGFR was 44 [IQR, 35-56]. Overall, 187 children (50%) reached the primary outcome over a median follow-up time of 6.2 years [IQR, 3.0–10.3]. All biomarker levels were higher in children with CKD progression, except for EGF which was lower in those with CKD progression (p for all <0.05). After adjustment for confounders, children with urine EGF concentrations in the highest quartile were at a significantly lower risk of CKD progression compared to those with EGF in the lowest quartile [EGF aHR; 0.20 (95% CI: 0.11-0.39)] (Table). Children with urine KIM1 and MCP1 in the highest quartile were at a significantly higher risk of CKD progression compared to those in the lowest quartile [KIM1 aHR; 2.6 (95% CI: 1.6-4.1), MCP1 aHR; 2.8 (95% CI: 1.7-4.7)].

Conclusions: Low urine EGF and elevated urine KIM1 and MCP1 concentrations are independently associated with CKD progression in children.

Funding: NIDDK Support

Table. Unadjusted and adjusted hazard ratios for the risk of CKD progression according to baseline urine biomarker levels

Biomarkers	Biomarker alone		Adjusted Model (plus age, gender, glomerular diagnosis, BMI z-score, hypertension status)		Adjusted Model (plus log2 uPr/Cr)		Full Adjusted Model (plus eGFR)	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
EGF								
Per Doubling*	0.63	(0.59, 0.69)	0.63	(0.57, 0.69)	0.85	(0.59, 0.71)	0.72	(0.64, 0.80)
Quartile 1	1.0	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Quartile 2	0.54	(0.38, 0.78)	0.55	(0.38, 0.8)	0.58	(0.4, 0.85)	0.72	(0.49, 1.07)
Quartile 3	0.27	(0.18, 0.4)	0.24	(0.16, 0.38)	0.27	(0.17, 0.42)	0.39	(0.24, 0.65)
Quartile 4	0.16	(0.1, 0.25)	0.13	(0.07, 0.22)	0.12	(0.07, 0.21)	0.20	(0.11, 0.39)
KIM-1								
Per Doubling*	1.43	(1.31, 1.56)	1.47	(1.33, 1.63)	1.28	(1.15, 1.43)	1.33	(1.18, 1.49)
Quartile 1	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Quartile 2	1.53	(0.96, 2.44)	1.38	(0.87, 2.21)	1.37	(0.86, 2.19)	1.45	(0.90, 2.32)
Quartile 3	2.08	(1.31, 3.29)	1.94	(1.22, 3.08)	1.43	(0.89, 2.29)	1.68	(1.04, 2.71)
Quartile 4	3.78	(2.45, 5.83)	3.66	(2.33, 5.74)	2.49	(1.56, 3.99)	2.55	(1.59, 4.09)
MCP-1								
Per Doubling*	1.30	(1.20, 1.40)	1.33	(1.22, 1.44)	1.23	(1.12, 1.36)	1.21	(1.11, 1.33)
Quartile 1	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Quartile 2	2.23	(1.36, 3.65)	2.37	(1.44, 3.9)	1.69	(1.01, 2.81)	1.57	(0.94, 2.63)
Quartile 3	3.16	(1.95, 5.14)	3.13	(1.9, 5.13)	1.93	(1.16, 3.23)	2.34	(1.39, 3.94)
Quartile 4	4.40	(2.75, 7.05)	4.38	(2.7, 7.12)	2.94	(1.75, 4.93)	2.79	(1.67, 4.68)
YKL-40								
Per Doubling*	1.07	(1.02, 1.13)	1.15	(1.08, 1.22)	1.06	(1.00, 1.14)	1.02	(0.95, 1.09)
Quartile 1	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Quartile 2	1.26	(0.75, 2.13)	1.54	(0.9, 2.63)	1.79	(1.04, 3.1)	1.38	(0.79, 2.41)
Quartile 3	1.57	(0.95, 2.6)	2.74	(1.54, 4.86)	2.55	(1.45, 4.5)	1.81	(1.03, 3.2)
Quartile 4	1.82	(1.1, 3.02)	3.73	(2.08, 6.69)	2.0	(1.06, 3.76)	1.28	(0.67, 2.44)
a1M								
Per Doubling*	1.24	(1.12, 1.37)	1.53	(1.36, 1.72)	1.32	(1.15, 1.53)	1.09	(0.93, 1.28)
Quartile 1	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Quartile 2	1.36	(0.83, 2.23)	1.96	(1.16, 3.31)	1.78	(1.04, 3.04)	1.41	(0.82, 2.43)
Quartile 3	1.84	(1.14, 2.96)	2.85	(1.73, 4.71)	2.21	(1.31, 3.72)	1.30	(0.75, 2.27)
Quartile 4	2.56	(1.62, 4.05)	6.35	(3.72, 10.84)	3.61	(1.94, 6.71)	1.75	(0.9, 3.43)

*Data are presented as HR (95% Confidence Interval). Adjusted for age, gender, glomerular diagnosis, BMI z-score, proteinuria/creatinine ratio, hypertension status, baseline eGFR. *, Per doubling HRs are for a continuous $\log_2$ change in biomarker levels. The primary outcome of CKD progression is defined as a composite of 50% decline in eGFR or ESKD. Abbreviation: EGF, epidermal growth factor; KIM-1, kidney injury molecule-1; MCP-1 monocyte chemoattractant protein-1; a1M, alpha-1 microglobulin*

PO2303

Effect of Cholecalciferol Supplementation on FGF-23 in Children with CKD

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Background: Cholecalciferol increases total vitamin D levels in children with chronic kidney disease (CKD), but by increasing serum phosphate levels may also increase levels of fibroblast growth factor 23 (FGF23), which is associated with adverse outcomes in both adults and children with CKD. Our objective was to quantify changes in FGF23, α-klotho and vitamin D binding protein (VDBP) in children participating in a vitamin D supplementation trial.

Methods: We utilized stored serum samples from a 4-week pilot randomized controlled trial of supplementation with 4000 (high dose) vs. 400 (DRI) IU per day of cholecalciferol in children with mild-to-moderate CKD. Intact and C-terminal FGF23, soluble α-klotho, and VDBP were measured using commercially-available ELISAs in the Johns Hopkins Institute for Clinical and Translational Research Core Laboratory. Statistical analyses conducted using Stata 14.

Results: Thirty-four children were included in the analysis; 17 received the intervention dose of 4000 IU cholecalciferol, and 17 received the control dose of 400 IU. The mean (SD) age of the cohort was 10.9 (5.8) years, 26.5% female, 23.5% black, 58.8% white, and 17.7% other race. Mean (SD) GFR at baseline was 60 (17.6) ml/min/1.73m^2. Median (IQR) baseline total vitamin D level was 29 (20, 34) ng/ml in the control arm and 32 (23, 39) in the intervention arm. Total vitamin D level did not change significantly after 4 weeks of supplementation in the control arm, but was increased to 38.5 (31, 50) in the intervention arm (p=0.001). The table compares baseline and 4-week FGF23, α-klotho, and VDBP levels in the control and intervention arms, and no significant differences were noted between the groups who received DRI vs. high dose cholecalciferol.

Conclusions: Cholecalciferol supplementation of 4000 IU/day in children with CKD was not associated with significant differences in FGF23, α-klotho, or VDBP levels compared to children who received only the DRI.

Mean (SD)	400 IU	4000 IU	p-value
C-terminal FGF23, B (RU/ml)	44.5 (32.8)	46.5 (38.6)	0.76
C-terminal FGF23, W (RU/ml)	39.5 (26.9)	45.3 (30.1)	0.61
Intact FGF23, B (pg/ml)	19.1 (14.4)	18.7 (12.9)	0.93
Intact FGF23, W (pg/ml)	20.3 (12.9)	19.6 (11.9)	0.89
α-klotho, B (pg/ml)	3,321.9 (4,4221.82)	1,944.7 (1,257.1)	0.22
α-klotho, W (pg/ml)	3,340.4 (5,146.3)	1,959.4 (1,598.1)	0.36
VDBP, B (ng/ml)	327,437.5 (58,516.6)	332,400 (86,243.1)	0.78
VDBP, W (ng/ml)	328,666.7 (72,235.4)	352,661.5 (74,871.8)	0.40

B=baseline

W=4 week

PO2304

Improving Metabolic Acidosis in Patients with CKD

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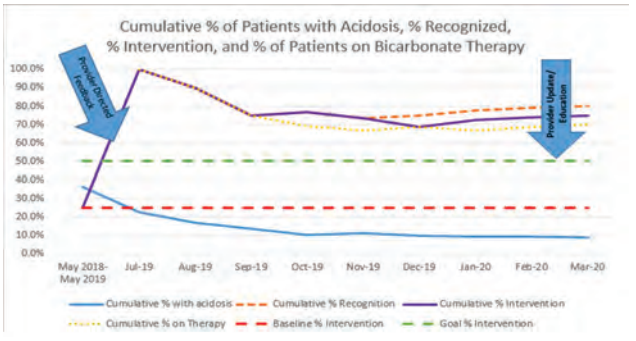
Background: Pediatric chronic kidney disease (CKD) is characterized by multiple metabolic derangements including metabolic acidosis. Untreated acidosis is associated with bone disease, increased mortality, and CKD progression[1,2]. Current guidelines

recommend bicarbonate supplementation for CKD patients with serum bicarbonate < 22mmol/L[3]. Review of our nephrology division's clinical practice in the past year found that 36% of patients with CKD stage 3-5 were acidotic, although only 25% of these received an intervention to address the acidosis. Our aim is to increase the percentage of interventions for acidosis in this population from 25% to 50% by June 30, 2020.

Methods: Monthly reports were generated for patients with CKD stage 3-5 and acidosis in the nephrology clinic. Our outcome measure is the percentage of acidotic patients. Process measures include the percentage of acidosis recognition, appropriate intervention, and patients on bicarbonate treatment. The balancing measure is patients with alkalosis (bicarbonate > 28mmol/L) while on supplementation. A multidisciplinary team identified multiple root causes and baseline data identified that lack of provider recognition of mild acidosis (bicarbonate 20-22) was the primary driver why treatment was not initiated. Countermeasures were developed to address this gap.

Results: Using PDSA cycles, we have implemented 2 countermeasures. Initially, we utilized provider directed feedback to notify those who had patients with untreated acidosis in the past month. Then, an education session was completed in March 2020. Our goal of increasing interventions for acidosis to 50% was exceeded by March 2020 (75%). There was also decrease in the number of acidotic patients, increase in provider recognition and bicarbonate treatment, with no increase in patients with alkalosis (Figure 1).

Conclusions: Utilizing provider directed feedback along with educational sessions have effectively increased the percentage of CKD stage 3-5 patients who are appropriately treated for acidosis. Further interventions are ongoing.



PO2305

Factors Influencing Duration of Dialysis in Children with Shiga Toxin-Producing *Escherichia coli*-Associated Hemolytic Uremic Syndrome (STEC-HUS) at a Single Center

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Background: More than half the children with STEC-HUS require renal replacement therapy. Several factors influence the duration of dialysis.

Methods: We performed a retrospective cohort analysis using electronic medical records and chart review of 67 patients with STEC-HUS identified through billing data from July 1st 2008 to August 30th 2015. Cases of atypical hemolytic uremic syndrome (HUS), *Streptococcal pneumoniae* associated HUS were excluded.

Results: The mean age at presentation with STEC-HUS was 4.9yrs (range 0.99-17.16yrs). 44 (66%) were females compared to 23 (34%) males. Data on intravenous fluids (IVF) administration prior to diagnosis of HUS was available in 54 subjects of which 39 (72%) received IVF anytime during four days prior to presentation, and 15 (28%) did not. Of the patients receiving IVF, 22 (56%) required dialysis for an average duration of 11.4d whereas in subjects without IVF, 7 (47%) required dialysis for an average duration of 14.7d. 9 of 55 subjects received NSAIDS during the illness, and six of the nine required dialysis. For these 6 subjects, the average duration of dialysis was 17d compared to 10.3d in subjects without NSAID exposure. We also evaluated patients for antibiotic exposure before and after the diagnosis of HUS. In 30 (53%) subjects without any antibiotic exposure the average duration on dialysis was 9.8d. For 11 (19 %) subjects receiving antibiotics before the diagnosis of HUS average duration of dialysis was 13.6d. Dialysis duration in the 12 (21%) subjects receiving antibiotics after the diagnosis of HUS was 13.3d.

Conclusions: To our knowledge our study is first to evaluate the impact of NSAIDS on the severity of HUS, and demonstrates that the use of NSAIDS in STEC-HUS increases the duration of dialysis significantly. Confirming previous literature, the use of antibiotics results in prolongation of dialysis regardless of the timing of administration. We also note that IVF administration in the first 4 days prior to the diagnosis of HUS may result in a shorter time on dialysis.

PO2306

Determining the Optimal Dose of Cholecalciferol Supplementation for Children with CKD (C_3 Trial): An Open-Label Multicentre Randomized Controlled Trial

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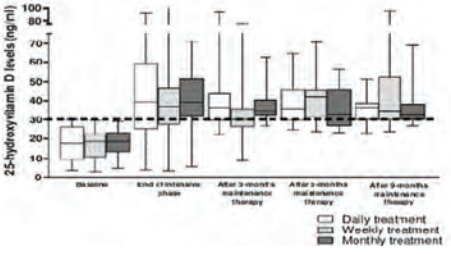
Background: The optimal treatment regimen for correcting 25-hydroxyvitamin D (25OHD) deficiency in children with CKD has not been established. We studied oral cholecalciferol treatment regimens that achieve and maintain 25OHD levels above 30ng/ml in children with CKD stages 2-4.

Methods: We performed an open label, multicentre randomized controlled trial in children with 25OHD <30ng/ml, randomized 1:1:1 to oral cholecalciferol as 3000IU daily, 25,000IU weekly or 100,000IU monthly for 3months intensive phase therapy. A maximum of 3 courses of intensive phase treatment were allowed if 25OHD was <30ng/ml. Patients achieving normal 25OHD entered maintenance phase with 1000IU cholecalciferol daily for 9 months. Primary outcome was achieving 25OHD levels ≥30 ng/ml at end of intensive phase therapy.

Results: Of the 150 children screened, 90 were 25OHD deficient and randomised to daily(n=30), weekly(n=29) or monthly(n=31) treatment arms. Age, gender, renal disease, eGFR and baseline 25OHD were comparable between treatment arms. At end of the intensive phase 68.8% achieved 25OHD ≥30ng/ml with comparable levels between arms(median 44.3 39.4 and 39.3 ng/ml p=0.24) on daily, weekly, monthly regimens respectively. The time taken to achieve 25OHD ≥30 ng/ml was comparable between treatment arms (p=0.28) with 7.7% not achieving normal 25OHD after 3 courses. Irrespective of treatment arm, median 25OHD were lower in children with glomerular disease than non-glomerular disease [25.8 vs 41.8ng/ml; p=0.007]. There was no significant difference in 25OHD between treatment arms at end of intensive(p=0.24) or maintenance phase therapy (p>0.05)[Figure]. There was no hypercalcaemia or hypercalciuria.

Conclusions: Intensive phase therapy with oral cholecalciferol as daily, weekly or monthly regimens achieved similar 25OHD levels without toxicity. Children with glomerular disease require higher doses of cholecalciferol compared to non-glomerular disease.

Figure: Serum 25OHD levels at different time points.



PO2307

ESRD Risk in Type 1 vs. Type 2 Childhood-Onset Diabetes Mellitus

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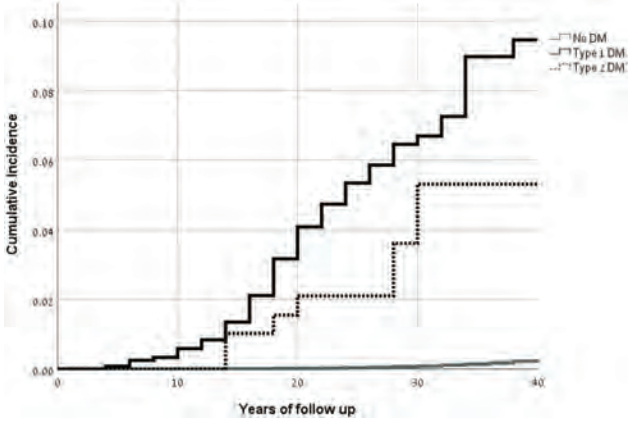
Background: Diabetic kidney disease (DKD) is becoming increasingly common among children. We aimed to estimate the risk of end-stage renal disease (ESRD) and mortality among adolescents with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and normal renal function compared to non-diabetics. We hypothesized that childhood onset T1DM vs T2DM would be associated with a different risk profile for developing ESRD and its complications.

Methods: A nationwide, population-based, retrospective cohort study, including 1,500,522 adolescents examined for military service between 1967-1997, which were classified according to the presence and type of diabetes. Data were linked to the Israeli ESRD registry. Cox proportional-hazards models were used to estimate the hazard ratio (HR) for ESRD.

Results: At study enrolment, 1,183 adolescents had T1DM and 196 had T2DM. ESRD developed in 2,386 non-diabetic individuals (0.2%) compared to 72 individuals (6.1%) with T1DM, and 8 individuals (4.1%) with T2DM. Participants with T1DM were younger at ESRD onset than participants with T2DM (median age: 36.0 vs. 40.5 years, P<0.05). In a multivariate model adjusted for age, sex, paternal origin, enrollment year, BMI, and blood pressure, T1DM and T2DM were associated with HR of 36.4 (95% CI,

28.3-46.9) and 19.3 (95%CI, 9.6-38.8) for ESRD, respectively. Stratification according to sex, ethnicity, immigration and socioeconomic status did not materially change the HR. During the follow-up period, mortality rates were higher in T2DM as compared to T1DM and controls (8.7 %, 2.2% and 2.7% respectively).

Conclusions: T1DM and T2DM in adolescents with normal renal function confer a significantly increased risk for ESRD. T1DM is associated with younger age at ESRD onset while T2DM is associated with higher mortality rate.



Cumulative ESRD incidence

PO2308

Prevalence of Renal Dysfunction in Youth with Epidermolysis Bullosa

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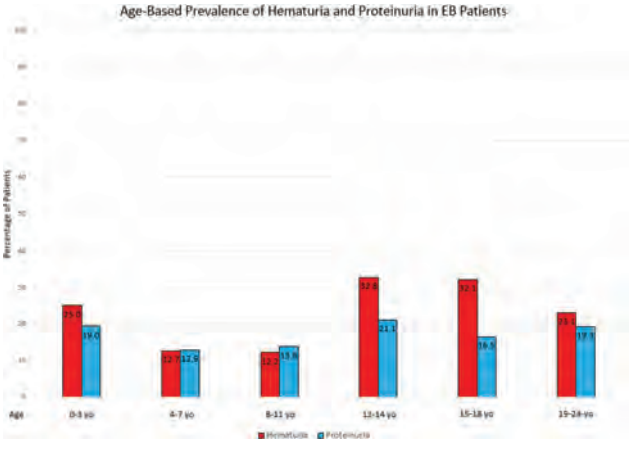
Background: Little is known regarding the prevalence of renal disease in youth with epidermolysis bullosa (EB), which we describe here.

Methods: We conducted a retrospective review of electronic health records of 170 (48.8% female, 51.2% male) EB patients aged < 25 years followed by our institution within years 1986-2019. We report the age-based prevalence of hematuria (≥ 1+ on urinalysis [UA] or ≥ 5 red blood cells per high power field) and proteinuria (≥ 30 mg/dL). We also describe the outcomes of those with persistently abnormal UAs, defined as hematuria and proteinuria or nephrotic-range proteinuria on ≥ 2 consecutive tests. Finally, we compare mortality in EB youth with versus without acute kidney injury (AKI), defined per Kidney Disease Improving Global Outcomes.

Results: The overall prevalence of microscopic hematuria was 22.7%, with no significant difference between sex (p = 0.10). Age-based microscopic hematuria followed a bimodal distribution, with increased prevalence among younger (0-3 years) and older (>12 years) children (p=0.003) [Fig. 1]. The overall prevalence of proteinuria was 16.9%, with no significant differences between sex (p = 0.35) or age (p = 0.73) [Fig. 1]. 10 patients (5.9%) had persistently abnormal UAs and were diagnosed with: C3 glomerulopathy (4), urethral stricture (2), infection (2), IgA nephropathy (1), and acute tubular necrosis (1). AKI occurred in 19 patients (11.2%) and was significantly associated with mortality (47.4% in the AKI cohort versus 20.0% in the non-AKI cohort, p = 0.01). Identified causes of death in AKI patients were multiorgan failure including renal failure (3), renal failure alone (1), respiratory failure (1) and severe malnutrition (1).

Conclusions: Many youth with EB have hematuria and/or proteinuria, suggesting glomerulonephritis and/or urologic abnormalities may be underdiagnosed in this population. AKI is significantly associated with mortality in EB youth, with renal failure as a potential common cause of death.



PO2309

Clinical Relevance of Fluid Volume Status Assessment by Bioimpedance Spectroscopy in Children on Maintenance Dialysis

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Background: Bioimpedance spectroscopy (BIS) has been used as a noninvasive method to evaluate body fluid volume status in dialysis patients. However, reports in pediatric dialysis patients about the effectiveness of this method are rare. We asked if there is a correlation in the results of BIS and clinical characteristics, and if there is a subsequent change of cardiovascular characteristics in patients whose dialysis prescription was modified based on BIS.

Methods: Medical records of children on maintenance dialysis who were evaluated by multifrequency BIS between January 2016 and December 2019 were reviewed. Their first result of BIS was assessed and fluid overload status was correlated with hypertension, number of oral antihypertensive medications and echocardiography results. In patients with fluid overload, change of dialysis prescription and clinical characteristics over time were reviewed.

Results: Among the 47 patients (male:female 28:19, hemodialysis:peritoneal dialysis 17:30) with a median age of 13.5 years, 13 children were overhydrated with the proportional overhydration relative to extracellular water more than 15%. Majority of children (76.9%) with fluid overload were taking two or more oral antihypertensive medications, while less than half of those without fluid overload were. 11 out of 13 overhydrated children changed their dialysis prescription to reduce their target body weights. Subsequent BIS in overhydrated children revealed a significantly decreased amount of fluid overload (initial: median 22.9%, follow-up: median 13.4%). However, their mean blood pressure (initial: 89.8 mmHg, follow-up: 84 mmHg) and the number of antihypertensive medications [initial: median 2 (0-4), follow-up: median 2 (0-5)] did not significantly change. Also, none of the children initially overhydrated had their left ventricle hypertrophy changed.

Conclusions: While BIS might be a useful and noninvasive method to assess fluid status, implementation of this tool did not lead to clinically meaningful improvement of cardiovascular characteristics in the children on maintenance dialysis. Long-term follow-up of a larger population and correlation with a more objective clinical indicator of fluid overload such as serum brain natriuretic peptide would be necessary to verify the clinical effectiveness of BIS in pediatric dialysis patients.

PO2310

Variants of SLC34A1, SLC34A3, and AGXT in an Infant with Nephrocalcinosis and Hypercalcemia

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Introduction: Idiopathic infantile hypercalcemia (IIH) is a rare genetic disorder that can lead to neonatal nephrocalcinosis. It is typically caused by loss of function mutations in *CYP24A1* or less commonly in *SLC34A1*. *SLC34A1* encodes the NaPi-IIa transporter which aids in phosphate reabsorption in the renal proximal tubules. Defects in *AGXT* are responsible for primary hyperoxaluria type 1 (PH1). Defects in either *AGXT* or *SLC34A1* can lead to infantile nephrocalcinosis and subsequent renal damage.

Case Description: A term male infant had bilateral hyperechoic kidneys on prenatal ultrasound. Postnatal labs showed hypercalcemia, hypophosphatemia, high 1,25 dihydroxyvitamin D3 and acute kidney injury. The patient was treated with fluids, furosemide, and calcitonin without significant change in serum calcium. Pamidronate was given which decreased serum calcium and worsened hypophosphatemia. Phosphate supplementation was initiated. Whole exome sequencing revealed two variants in *SLC34A1*, one of which was pathogenic, and a variant in *SLC34A3* of unknown significance. Incidentally, this patient was compound heterozygous for three variants in *AGXT:* one pathogenic and two benign. After these results, patient was found to have generalized aminoaciduria and mild hyperoxaluria for age. Serum calcium decreased with maintenance of adequate plasma phosphate levels.

Discussion: Compound heterozygous mutations of *SLC34A1* can cause IIH type II, and the variant in *SLC34A3* could be contributing to this patient's clinical phenotype in a unique trialleic pattern. The pathologic *AGXT* gene variants could cause this patient to develop PH1. The combined effects of IIH and PH1 could significantly impact the clinical course of this patient. Mutations in both *AGXT* and *SLC34A1* have not been previously described in the literature. During acute severe hypercalcemia, it might be necessary to use pamidronate to lower serum calcium to levels that are safe for the administration of phosphate supplements.

Events	Days after initial presentation	Calcium (8.0-10.5 mg/dL)	Phosphorus (4.2-6.5 mg/dL)	1,25 Dihydroxyvitamin D3 (15-90 pg/mL)	25-Hydroxyvitamin D (30-120 ng/mL)
Initial Presentation	1	15	3.5	32	18
After 1st Pamidronate infusion	10	11.2	2.3		
	23	11.2	4		
After 2nd Pamidronate infusion	24	10.5	3.6		
After Phosphate Supplementation	47	9.6	5.2	212	24
	75	10.5	4.4		
	138	10.4	5	122	34

PO2311

Dent Disease Phenotype Caused by Immunodysregulation Polyendocrinopathy Enteropathy X-Linked (IPEX) Syndrome: Due to Anti-Tubular Basement Membrane Antibody Disease

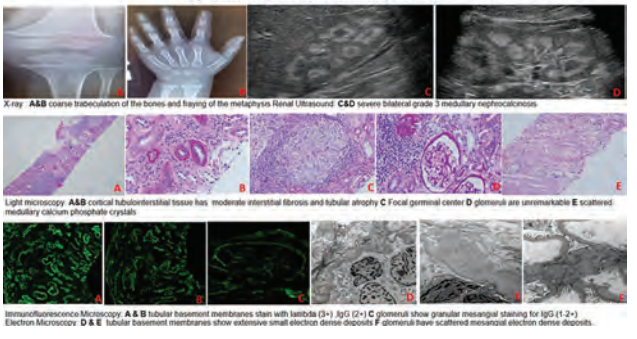
Raja Dandamudi, Keith A. Hruska. *Washington University in Saint Louis School of Medicine, Saint Louis, MO.*

Introduction: Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) recessive disorder caused by loss-of-function mutations forkhead box protein 3 gene (FOXP3) transcription factor affecting the function of circulating regulatory T cells. Previously described renal manifestations were immune complex deposition in a membranous- pattern and interstitial nephritis. Here we report novel renal manifestations of IPEX syndrome.

Case Description: 5-year-old male ipresented at the end of the first month of life, with type 1 diabetes mellitus, hypothyroidism, and chronic diarrhea and diagnosed by IPEX syndrome by c.434C>T; p. Ala 145Val mutations in the FOXP3 gene. He underwent stem cell transplant at 6 months of age from a fully matched unrelated donor. Post stem cell transplant he has had mixed chimerism with low but relatively stable donor T cells. He remained relatively stable until 4 years of age when he presented with the clinical picture of Dent's disease: nephrocalcinosis, tubular proteinuria, Fanconi syndrome (proximal RTA, phosphaturia, calciuria, glycosuria and aminoaciduria) and renal insufficiency. No disease-causing mutations in CLCN5 gene or the OCRL1 gene were identified on genetic testing. Renal biopsy demonstrated non-sclerotic glomeruli with no capillary loop spike formation, no crescent formation, no endocapillary proliferation, or segmental necrosis. Immunofluorescence showed tubular basement membranes stain with IgG, C3, kappa and lambda. Glomerular basement membranes were negative. Tubular basement membranes show extensive small electron dense deposits without substructure.

Discussion: In this case report we presented child with confirmed IPEX syndrome with nephrotic-range tubular proteinuria, proximal RTA, phosphaturia, calciuria, medullary nephrocalcinosis, and renal insufficiency, in addition to the classical triad of enteropathy, dermatitis and polyendocrinopathy. Our report is the first to document the anti-tubular basement disease clinically manifesting as the Dent's disease phenotype in association with IPEX syndrome.

Fig. 1 Radiological and Renal biopsy findings



X-ray **A&B** coarse trabeculation of the bones and fraying of the metaphysis Renal Ultrasound **C&D** severe bilateral grade 3 medullary nephrocalcinosis

Light microscopy **A&B** cortical tubulointerstitial tissue has moderate interstitial fibrosis and tubular atrophy **C** Focal germinal center **D** glomeruli are unremarkable **E** scattered medullary calcium phosphate crystals

Immunofluorescence Microscopy: **A & B** tubular basement membranes stain with lattibda (3+) *IgG* (2+) **C** glomeruli show granular mesangial staining for IgG (1-2+)
Electron Microscopy **D & E** tubular basement membranes show extensive small electron dense deposits **F** glomeruli have scattered mesangial electron dense deposits.

PO2312

Severe Hyperkalemia in a 4-Month-Old Female due to Cullin-3 Mutation

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Introduction: Pseudohypoaldosteronism (PHA) type II, also known as familial hyperkalemic hypertension, is a rare autosomal-dominant disorder that causes renal tubular acidosis (RTA) type 4, characterized by late-onset hypertension, hyperkalemia, non-gap metabolic acidosis, and low or low-normal plasma renin and aldosterone levels. We present a case of a female infant with PHA type II who presented with asymptomatic severe hyperkalemia due to Cullin-3 Mutation. Treatment with thiazide diuretics resulted in rapid correction of her hyperkalemia.

Case Description: A 4-month-old former term female with an unremarkable past medical history presented for management of right neck abscess. Family history was significant for an unspecified seizure and movement disorder in her older sister. She had appropriate growth for her age, with weight, length, and head circumference all measuring around the 20th percentile. Vital signs including blood pressure were normal. Admission laboratories revealed high potassium level of 8.4 mEq/L, low bicarbonate level of 10 mEq/L (normal for age is 19–24), high chloride level of 116 mEq/L (normal for age is 97–108). Anion gap was normal at 10 mEq/L. No electrocardiogram changes were noted. Additional studies revealed positive urine anion gap of 40 mEq/L, a normal serum aldosterone level of 22 ng/L and a low renin activity of 0.2 ng/ml/hr (normal for age is 2–37). She received intravenous calcium gluconate, sodium acetate, and sodium polystyrene sulfonate for hyperkalemia management. Whole exome sequencing revealed a de novo heterozygous c.1376A>T (p.K459M) mutation in the Cullin 3 (*CUL3*) gene consistent with PHA type II. She was treated with thiazide diuretics, which quickly corrected her metabolic abnormalities.

Discussion: Our case of PHA type II with a CUL3 pathogenic variant is exceptionally rare, especially given the patient's age at presentation and the negative family history. Her diagnosis could have been easily missed were she not hospitalized for her neck abscess. Without genetic evaluation and prompt thiazide diuretic treatment, she may have eventually suffered from failure to thrive and hypertension at a later point in life because of chronic hyperkalemia and metabolic acidosis. Primary care physicians and nephrologists should consider the possibility of PHA type II in any child who presents with hyperkalemia and metabolic acidosis with or without hypertension.

PO2313

A Rare Pediatric Case of Karyomegalic Tubulointerstitial Nephritis

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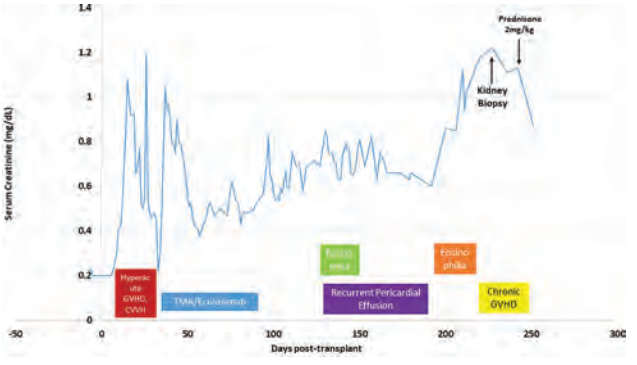
Introduction: Karyomegalic tubulointerstitial nephritis (KIN) is a rare type of interstitial nephritis that often progresses to chronic kidney disease. The pathogenesis is unclear but speculated to result from disruptions to tubular epithelial cell division by genetic predisposition or external insults. Only 6 pediatric cases have been reported and perhaps this condition is underdiagnosed.

Case Description: A 2-year-old male with history of refractory AML received a matched unrelated donor stem-cell transplant following busulfan, fludarabine, and single fraction total body irradiation. His post-transplant course was complicated by engraftment syndrome, hyperacute graft versus host disease (GVHD), thrombotic microangiopathy, and acute kidney injury. He required ICU stay, treatment with eculizumab and two weeks of renal replacement therapy. His kidney function improved but serum creatinine stayed higher than baseline (picture). Four months post-transplant, he was treated with cefepime, acyclovir, ibuprofen for enterococcus bacteremia and pericardial effusion. Seven months post-transplant, while off all immunosuppression, he developed eosinophilia, renal tubular dysfunction with increased serum creatinine. Eosinophilia resolved spontaneously. Bone marrow was negative for leukemia and infectious workup was negative. Eight months post-transplant, he developed GVHD, diagnosed with skin biopsy. He also had persistent high serum creatinine with normal urinalysis. Ultrasound showed echogenic kidneys. Kidney biopsy was performed because of unexplained high serum creatinine. Specimen tissue showed tubulointerstitial nephritis with widespread karyomegaly in medullary tubules. Glomeruli were unaffected. Some cortical tubules showed ultrastructural myelinosomes. His renal function improved with steroids.

Discussion: Our case highlights that KIN can develop in children after chemotherapy. Diagnosis requires high index of suspicion and thorough pathological examination of kidney biopsy specimen. A trial of corticosteroid therapy may be considered.



PO2314

Rescue Therapy with Eculizumab for Catastrophic Antiphospholipid Syndrome in Juvenile Systemic Lupus Erythematosus

Patricia A. Arroyo Parejo Drayer, Malek Al Barbandi, Marissa J. Defreitas, Chryso P. Katsoufis, Jayanthi Chandar, Carolyn L. Abitbol, Wacharee Seeherunvong. *University of Miami School of Medicine, Miami, FL.*

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening condition, and is associated with acute multiorgan failure, small vessels thromboembolism, and elevated markers of antiphospholipid syndrome (APL). Early recognition and promptly treatment can improve the outcome. We present a case of juvenile systemic lupus erythematosus (SLE), who presented with CAPS, refractory to conventional treatment, but rescue with Eculizumab

Case Description: The patient is a 10yo female, previously diagnosis with systemic lupus erythematosus (SLE) without renal involvement and treated with hydroxychloroquine and low dose steroid, who presented with acute kidney injury and hypertensive crisis. On exam, her weight was 31.3 Kg, height 133 cm. Her BP was 185/127 mmHg and pulse 118/min. Initial investigation showed hemoglobin of 7.2 g/dL, platelet count of 182/uL, BUN 99 mg/dL, Cr 7.86 mg/dL, haptoglobin < 10 mg/dL. Urine protein to creatinine ratio was 5 mg/mg. Serum complements were low and had positive serology for Anti-DSDNA, Lupus anticoagulant, Anti-beta2 glycoprotein, and anticardiolipin. The presumptive diagnosis was CAPS associated with SLE and thrombotic microangiopathy (TMA) which was confirmed by kindney biopsy. She underwent Methylprednisone, therapeutic plasma exchange (TPE), renal replacement therapy amd Nicardipine infusion. After 7 sessions of TPE, Methylprednisone, Rituximab, and Mycophenolate Mofetil, her renal function improved and was taken off hemodialysis. Blood pressure was still uncontrolled. She had evidence of on-going hemolysis with undetectable haptoglobin and elevated LDH. Repeat TPE did not control her BP or hemolysis, thus Eculizumab was administered as

a rescue therapy for TMA associated with CAPS. After 2 weekly doses Eculizumab, her renal function, blood pressure and hemolytic markers were much improved. Currently, her serum creatinine was 1 mg/dL, without significant proteinuria. She remained on 3 antihypertensive medications with good BP control

Discussion: This is a rare but challenging case of juvenile SLE, complicated with CAPS and TMA, who responded partially to conventional treatment. Eculizumab served as a rescue therapy with good result. Our case supports the use of Eculizumab for refractory CAPS in SLE.

PO2315

Hypertensive Crisis in an Infant: The Mass Effect

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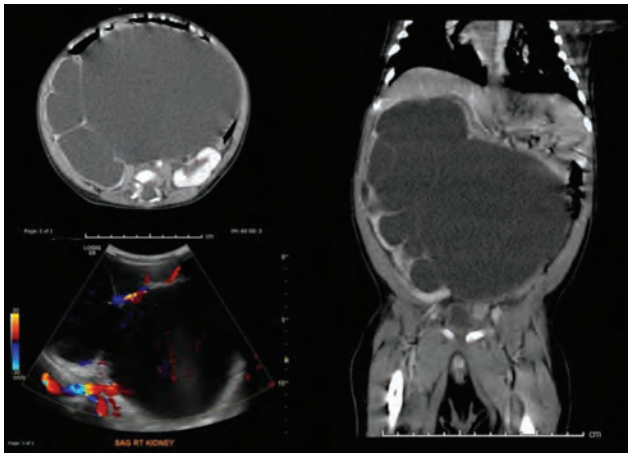
Introduction: It is unusual for congenital hydronephrosis to present with a hypertensive crisis. Recognition of this etiology and prompt urologic intervention to relieve the acute mass effect is critical to prevent further morbidity and mortality.

Case Description: A 3 month-old male with known, mild, right-sided hydronephrosis secondary to ureteropelvic junction obstruction (UPJO) presented to the ED with one week of poor feeding, emesis, and abdominal distension. His recent urine output had been normal. Right upper extremity blood pressure (BP) was recorded as 140/79 mmHg in the ED. Labs were unremarkable with a normal urinalysis and serum creatinine of 0.3 mg/dL. Abdominal ultrasound revealed massive pelvocaliectasis of the right kidney with the kidney parenchyma stretched and thinned over the massively dilated central collecting system. Findings were confirmed on abdominal CT which also revealed profound mass effect on abdominal organs and vessels, specifically compressing and displacing the aorta and inferior vena cava. He was admitted to the pediatric ICU for BP management, which was controlled with IV hydralazine. Pediatric urology placed a percutaneous nephrostomy tube and drained over one liter of urine from the right collecting system. At discharge, the patient was normotensive off medications. A right pyeloplasty was completed shortly following discharge.

Discussion: UPJO is the most common cause of antenatally detected hydronephrosis. The renal pelvis of infants exhibits increased compliance and can accommodate large urine volumes. Kidney function may be preserved or could undergo deterioration depending on UPJO severity. If missed prenatally, infants with UPJO may present with a palpable abdominal mass, urinary tract infection, hematuria, or failure to thrive. Kidney failure and hypertensive crises are rare presentations but are indications for prompt surgical intervention to prevent permanent damage and reduce blood pressure. Infants with preserved function can be monitored conservatively with serial imaging.



PO2316

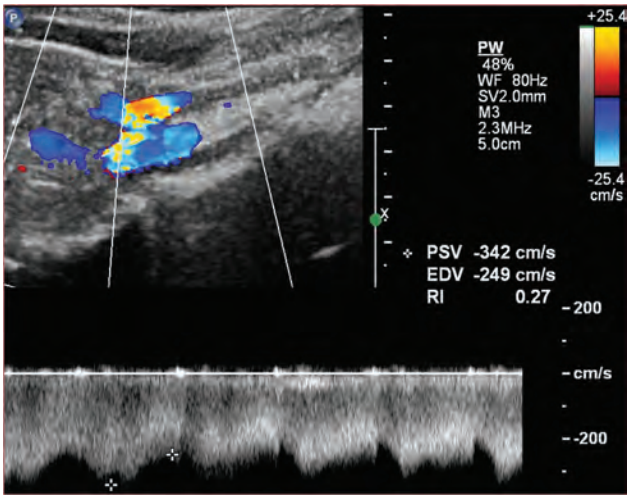
Missed Diagnosis: A Case of Asymptomatic Isolated Orthostatic Proteinuria from Nutcracker Phenomenon

Anna R. Gaddy, Ranjani N. Moorthi. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: In children, proteinuria which exceeds 100 mg/m2 per day or 150 mg per day is considered abnormal. Isolated proteinuria is relatively common, but persistent proteinuria is abnormal and should be investigated. Persistent proteinuria can be further divided into orthostatic subtype if the recumbent Pr/Cr is <0.2mg/mg but this rises to abnormal (>0.2mg/mg) after standing. One cause of orthostatic proteinuria is entrapment of the left renal vein, which is known as the Nutcracker Syndrome. Orthostatic proteinuria, isolated hematuria and pelvic congestion pain are the most common manifestations, however Nutcracker Syndrome is highly heterogeneous and frequently missed.

Case Description: We present an 18 year-old female with intermittent proteinuria, hematuria and occasional flank pain for nine years. The patient had proteinuria on dipstick at age eight. At age 15, she again was noted to have proteinuria on serial urinalyses with up to 500mg/dL protein. ANA, anti-dsDNA, C3, and C4 were normal. Renal ultrasound was performed with unremarkable kidneys and urinary bladder. For several years, proteinuria was mild and intermittently negative and no further workup was done. Split urine collection demonstrated minimal protein on first morning void but over 1g/g Pr/Cr by afternoon. We ordered renal ultrasound with Doppler, which demonstrated Doppler ultrasonography showed the left renal vein had significantly increased flow velocity and appeared to be compressed between the AO and SMA.

Discussion: Differential for etiology of orthostatic proteinuria should include Nutcracker Syndrome as this diagnosis requires a high degree of suspicion. Nutcracker Syndrome can involve proteinuria as well as hematuria but also pelvic pain, back pain, and pelvic congestion symptoms.



Elevated flow velocity in the LRV of 342 cm/s

PO2317

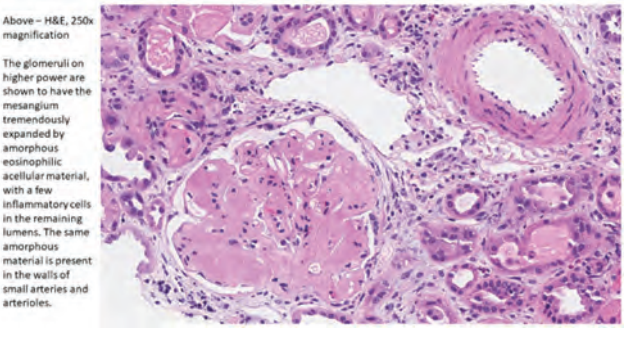
Rare Presentation of Nephrotic Syndrome in 10-Year-Old Male

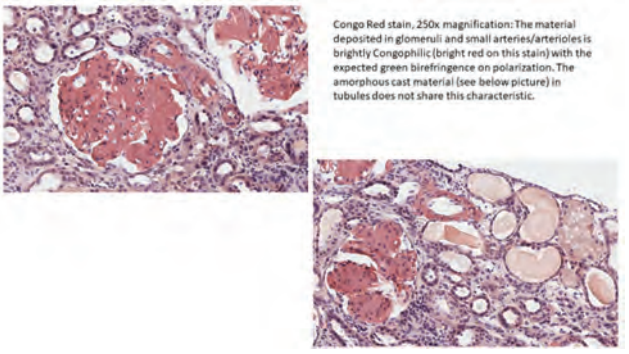
Ellen Cody, Katherine A. Vandenheuvel, Mark Mitsnefes. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Introduction: Review nephrotic syndrome 2/2 amyloidosis due to genetic mutation

Case Description: 10 year male w/ mild proteinuria, progressed to UPC of 4mg/mg over months, Cr 0.4, alb 2.5. Got strep, treated w/ amoxicillin & motrin, after 3 days developed periorbital edema, poor PO, fatigue, admitted. Labs Cr 4.1, alb 1.1, UPC 31 mg/mg, no blood. RUS b/l enlarged, echogenic kidneys. Biopsy w/ glomeruli expanded by amorphous, acellular proteinacous material in mesangium, walls of arteries and arterioles (Image 1), congophilic on Congo red stain (Image 2), apple green on light birefringence, & tubular injury, final read: amyloidosis and AIN. Completed 3 days of IV steroids for AIN, started colchicine for amyloidosis. Genetics w/ pathogenic Cys59Arg variant of TNFRSf1A, c/w TNF Receptor-Associated Periodic Syndrome (TRAPS). Started canakinumab, human monoclonal anti-IL-1 Ab. After 3 months, Cr baseline, no edema, still nephrotic range proteinuria, low alb. MOC w/ ESRD as teen, required dialysis, transplant. Later both kidney and liver failure, died at 31. Diagnosed w/ Familial Mediterranean Fever, as was MGF.

Discussion: Autoinflammatory disease usually presents as intermittent fever, abdominal & joint pain. Second most common is renal involvement, which starts w/ proteinuria, progresses to nephrotic syndrome, renal dysfunction. Diagnosis of amyloidosis based on amyloid fibrils in biopsy of involved tissue, stain positive w/ congo red, apple green birefringence to polarized light. No clear relationship between extent of amyloid deposition & severity of clinical manifestations of renal disease. TRAPS treated w/ directed therapy (IL-1 inhibitor), but difficult to track response to therapy as serum amyloid A not available. Use inflammatory markers (i.e. CRP) given autoinflammatory syndrome.





PO2318

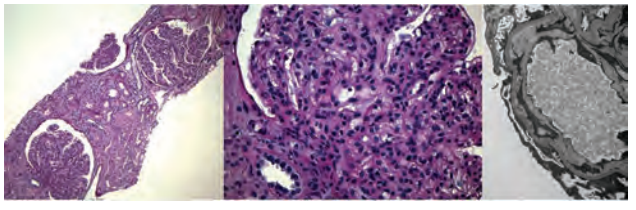
Cyanotic Nephropathy (CN) in Pre-Fontan Congenital Cyanotic Heart Disease (CCHD) with Solitary Kidney

Kimmy T. Vuong,[1,2] Katayoon Shayan,[1] Caitlin E. Carter.[1,2] *[1]Rady Children's Hospital San Diego, San Diego, CA; [2]University of California San Diego, La Jolla, CA.*

Introduction: CN is a glomerulopathy seen in patients with CCHD. Chronic hypoxia leads to proteinuria and reduced GFR through tubular and glomerular injury.

Case Description: 10 yo male with single kidney and pre-Fontan CCHD presented with hematuria and proteinuria on cardiac transplant evaluation. He had 6 months of symptomatic hypoxia requiring increased supplemental O2, but no other recent illness. Exam was notable for 3/6 pansystolic murmur, tachypnea with clear lung fields, hepatosplenomegaly, cyanotic nailbeds with marked clubbing, but no peripheral edema. 24 hour urine protein measured 4.1g (normal < 0.2g), 38% was albumin. Serum albumin was 3.5 g/L (normal) and eGFR by Cystatin C was 72 ml/min/1.73m^2. Hemoglobin was elevated at 20.1 (normal 12.5-16.1 g/dL). C3, C4, ANA, dsDNA, ANCA were normal. Ultrasound showed solitary left kidney with nephromegaly (12.5cm, 100th%ile) and dampened diastolic flow. MRI abdomen showed dilatation of the left renal vein and IVC. Renal biopsy showed marked glomerular enlargement, segmental mesangiolysis with erythrocytolysis, and irregular thickening of glomerular capillaries. EM showed widespread subendothelial widening and remodeling of basement membranes without immune deposits, consistent with CN (Figure 1).

Discussion: CN risk factors include duration of hypoxia, elevated hematocrit >40%, and thrombocytopenia. All were present in our patient. Solitary kidney and elevated venous pressure may have contributed. After heart transplantation, renal function improved with most recent eGFR by Cystatin C 121 ml/min/1.73m^2. Treatment and prevention of CN depend on correction of cyanosis. CN has become less common as most children with CCHD undergo Fontan in early childhood. There are limited data about medical management but proposed treatments include renin angiotensin system blockade, beta blocking drugs, diuretics, ivabradine, digoxin, and hydralazine/isosorbde dinitrate. Therapeutic phlebotomy has been reported. To our knowledge this is the first report of CN in a patient with solitary kidney. Low renal mass and baseline glomerular hyperfiltration may increase the risk of CN progression in this subset of patients.



PO2319

Lupus Vasculopathy Successfully Treated with Eculizumab and Rituximab in an 8-Year-Old Male

Elizabeth A. Black, Erica Winnicki. *University of California San Francisco, San Francisco, CA.*

Introduction: Lupus vasculopathy of the kidney is a rare form of vascular disease in patients with systemic lupus erythematosus characterized by non-inflammatory, necrotizing vessel wall changes. The pathogenesis may be related to immune-mediated vascular injury from accumulation of immunoglobulins and complement in the vascular wall. Lupus vasculopathy carries a poor renal prognosis, and no standardized treatment has been established.

Case Description: An 8-year-old previously healthy male presented to the emergency department with fever, fatigue, headache, diarrhea, nosebleeds, decreased urine output and lower extremity swelling. He was found to have hypertension, fluid overload, active urine sediment and severe acute kidney injury necessitating renal replacement therapy. He had thrombocytopenia and hemolytic anemia without presence of antiphospholipid antibodies or abnormal ADAMTS13 activity. He met criteria for systemic lupus erythematosus including hypocomplementemia, positive ANA and dsDNA antibodies. Renal biopsy showed class III lupus nephritis and multifocal arterial and arteriolar large intimal immune complex deposits with endothelial cell necrosis, consistent with a diagnosis of lupus vasculopathy. He received 6 sessions of plasmapheresis without improvement. Based on renal biopsy, he was treated with cyclophosphamide per Euro Lupus protocol. Eculizumab was started for treatment of lupus vasculopathy. His anemia, thrombocytopenia, and proteinuria improved after initiation of eculizumab, but he remained dialysis dependent. Eculizumab was discontinued after 6 weeks of therapy, but he again developed thrombocytopenia, hemolytic anemia, worsening proteinuria and hypertension. These improved after restarting eculizumab. Due to ongoing evidence of lupus activity, rituximab was given after completion of cyclophosphamide. Hemodialysis was discontinued one month after his first rituximab dose with B-cell depletion. He remains on eculizumab therapy and has stable chronic kidney disease stage 2 despite B-cell repopulation.

Discussion: Prior case reports have documented effective treatment of lupus vasculopathy with rituximab. To our knowledge, no data exists on eculizumab for treatment of lupus vasculopathy. Given our patient's clinical improvement with these therapies, we conclude that more research is needed to define their role in treatment of patients with lupus vasculopathy.

PO2320

Nephrotic Syndrome Relapse due to Bee Sting in Steroid-Resistant Nephrotic Syndrome

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Introduction: Initial and relapsing presentations of nephrotic syndrome are known to be commonly precipitated by acute illness such as upper respiratory infections and urinary tract infections. Rarely, bee stings can cause development of nephrotic syndrome, with reports of relapses secondary to insect stings being even more sparsely reported. Here we report a patient with steroid-resistant nephrotic syndrome who developed a nephrotic flare after being stung by a bee, and the clinical course to achieve remission.

Case Description: A 14 month old unvaccinated male presented with rapid weight gain, swelling and proteinuria, and was diagnosed with nephrotic syndrome, with renal biopsy consistent with minimal change syndrome. An initial 60mg/m^2 course of prednisolone failed to achieve remission. Mycophenolate mofetil (MMF) treatment was then initiated, which resulted in rapid remission. Two months after initial remission, patient sustained several bee stings, with initially minimal localized swelling. Several days later he was noted to have edema, proteinuria and weight gain, and was diagnosed with a relapse of his nephrotic syndrome. Spontaneous remission did not occur after 2 weeks of expectant management, and a subsequent increase in dosing of MMF also provided no clinical benefit. The patient ultimately achieved remission with a brief course of glucocorticoids, which was successfully tapered without incident. Patient has since been stably maintained on his prior effective dose of MMF, and has had no relapses since.

Discussion: To our knowledge, this is the first report of bee stings resulting in nephrotic relapse in a patient with steroid-resistant nephrotic syndrome treated with MMF. Notably, administration of glucocorticoids provided rapid resolution of this relapse, despite a prior lack of steroid efficacy in this patient. This case report highlights bee stings as a trigger for nephrotic syndrome relapses in patients. While not a common trigger, the prevalent exposure to bee and insect stings, in both the general and pediatric populations, argues for clinical awareness of this etiology for nephrotic syndrome presentation and relapse. This report also provides clinical insight into the management of nephrotic syndrome relapses caused by bee stings, and suggests the possibility that glucocorticoid use may be generally effective, irrespective of underlying nephrotic syndrome classifcation.

PO2321

Managing Pediatric Renal Cell Carcinoma in Jehovah's Witness Patient

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Introduction: Pediatric Renal Cell Carcinoma (pRCC) is rare in children and adolescents and only account for about 5% of all pediatric renal neoplasms. The driver mutation of the majority of these tumors is due to cytogenetic translations involving the MiT family of transcription factors. Surgical resection of the mass is the main treatment and depending on the advancement of the cancer, can result in a complete nephrectomy. Due to complexity of surgery and the risk of blood loss, treatment can be complicated by a patient's religion that decline blood product transfusions, such as Jehovah's Witness. This case describes an already rare cancer requiring a unique medical management due to a family's religious belief.

Case Description: A previously healthy 14-year-old male presented complaining of left flank pain. Patient was afebrile, tachycardic to the 120s, and initially hypertensisve to 133/81 that self resolved. Due to persistent pain with unknown etiology imaging was obtained and MRI showed 8 cm solid mass in the left kidney with a dilated and thrombosed left renal vein. The mass could not be differentiated between Wilms Tumor or pRCC, thus a complete nephrectomy was decided to be the best course of treatment. Due to family's religious background of Jehovah's Witness a multi-disciplinary approach was considered to reduce the need for blood transfusions. Patient received daily erythropoietin injections and iron supplementation about three weeks prior to nephrectomy to stimulate production of red blood cells and was continued post-operatively. Additionally, on the day of his procedure, interventional radiology (IR) first embolized the left renal artery leading to tumor followed immediately by a left radical nephrectomy. Patient tolerated the procedure well with minimal blood loss and only had mild anemia. He required no post-surgical transfusion. There was mild increase in creatinine levels with acute kidney injury status-post nephrectomy that has since improved. Pathology report came back and confirmed clear cell renal cell carcinoma. Cytogenetic screen showed a translocation of

the transcription factor E3 (TFE3) gene. Patient did well post-operatively with no signs of cancer on recent imaging and did not require any chemotherapeutics.

Discussion: This case adds to the field of pediatric renal cell carcinoma and highlights a treatment approach that incoroporates religious backgrounds into medical management.

PO2322

IgG4-Related Disease: Nephropathy and Bone Marrow Failure in a 2-Year-Old Child

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Introduction: IgG4 related disease (IgG4 RD) is a systemic immune-mediated disorder that can potentially affect every organ. It is characterized by fibro-inflammatory tissue damage, IgG4 positive plasma cells, and often by elevated serum IgG4. Renal involvement can include tubulointerstitial nephritis (TIN), membranous glomerulopathy (MGP), and retroperitoneal fibrosis. The disease is more frequent over 50 years of age and only a few cases of IgG4 RD are reported in children.

Case Description: A 2-year-old child was diagnosed with a trilinear bone marrow failure. Bone marrow biopsy showed poor and dyshomogeneus cellularity and lymphoplasmacytic infiltrate organized in follicular structures. Hematologic DNA analyses were negative. IgG subclass analysis showed elevated serum levels of IgG4 subclass (353 mg/dL). Kidney failure was also found (creatinine 1.3 mg/dL, microhematuria, proteinuria, and granular casts). A renal biopsy was performed. Light microscopy showed tubulointerstitial inflammatory infiltrate, thickening of the glomerular basement membranes, and subepithelial deposits C4d. IF showed subepithelial glomerular IgG deposits with granular pattern and tubular wall deposits; C3 glomerular deposits and focal tubular deposits. A diagnosis of MGP associated with TIN was made. IHC staining for IgG4 demonstrated plasma cells with overlapping positivity for IgG and IgG4. After the diagnosis of IgG4 RKD, a therapy with steroids was started, without clinical response. Thereafter the patient underwent to bone marrow transplant.

Discussion: IgG4 RKD in adults with simultaneous TIN and MGP has been reported in a few cases. This is the first documented case of IgG4 RKD with simultaneous TIN and MGP in a pediatric patient. IgG4 RD is an emerging systemic disease and it should be taken into account in the differential diagnosis in systemic autoimmune diseases, also in pediatrics.

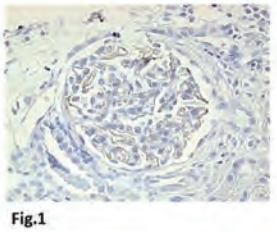

Fig.1

Fig. 1 *Hematoxylin stain + C4d IHC, original magnification X400.* **Fig. 2** *Periodic acid Schiff stain (PAS)+ IgG4 IHC original magnification X100.* **Fig. 3** *PAS + IgG4 IHC staining original magnification X400.*

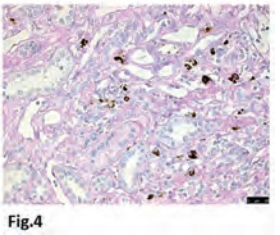

Fig.2

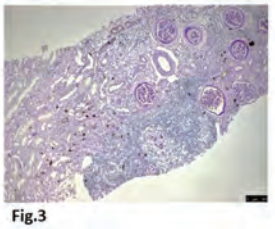

Fig.3

Fig.4

PO2323

Is a Single Static Cut Point Useful to Define Ambulatory Hypertension in Youth? The SHIP AHOY Study

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Background: Ambulatory blood pressure monitoring (ABPM) is increasingly utilized for the diagnosis of hypertension (HTN). While adult guidelines use absolute blood pressure (BP) cut points to define ambulatory HTN, current pediatric guidelines define ambulatory HTN based on a sex- and height-specific 95th percentile derived from limited pediatric normative data, in which many tall adolescents have a threshold for HTN higher than adult cut-points.

Methods: We compared absolute ABP values with sex- and height-specific ABP percentiles as predictors of left ventricular hypertrophy (LVH) in youth. We measured casual BP, ABPM, anthropometrics, and echo for LV mass index (LVMI) in 357 adolescents (mean age 15.5 ±1.7 years, 63% white, 59% male). ABPM was performed with Ontrak device (Spacelabs Inc., Snoqualmie, WA). ABP index was defined as mean ABP/sex- and height-specific 95th percentile. LVH was defined as LVMI ≥38.6 g/m2.7 (pediatric cut-point). Logistic regression was used to assess different ABP measures as predictors of LVH. Sensitivity and specificity of different ABP cut points as predictors of LVH were calculated.

Results: Seventy participants (19.6%) had LVH. Systolic 24-hour, wake and sleep mean BPs and indexes were all significantly associated with LVH. The C-statistics for absolute 24-hour (AUC 0.642 vs. 0.612, p=0.042) and wake (AUC 0.628 vs. 0.590, p=0.03) SBP predicted LVH better than SBP indexes of the same time periods. Absolute SBP cut points also had better balanced sensitivities and specificities in predicting LVH (24-hour SBP 120: 66% and 61%; wake SBP 125: 63% and 59%; sleep 110: 61% and 61%). There was no significant association between diastolic BP measures and LVH.

Conclusions: A single static cut-point using absolute ambulatory SBP is non-inferior to sex-and height- based SBP percentile in predicting LVH in youth. The cut-points for 24-hour and wake ABPM are lower than those for adults but may be used to define ambulatory HTN in this population.

Funding: Private Foundation Support

Table: AUC, sensitivities, and specificities of different ambulatory SBP measures in predicting LVH

Period	Cut-Point	Sensitivity	Specificity	AUC
24-hour	120 mmHg†	66.2%	60.9%	0.6416*
	125 mmHg‡	44.1%	75.8%	
	95th percentile	23.5%	83.3%	0.6121
Wake	125 mmHg†	62.9%	58.6%	0.6284*
	130 mmHg‡	42.9%	74.7%	
	95th percentile	24.3%	84.6%	0.5902
Sleep	110 mmHg†‡	61.4%	60.6%	0.6234
	95th percentile	24.3%	85.3%	0.5988

†Cut-point with best balance of sensitivity and specificity
‡Current adult cut-point for ambulatory HTN
*AUC of absolute BP significantly higher (p value <0.05) compared with BP index

PO2324

Proteinuria and Dipping on 24-Hour Ambulatory Blood Pressure Monitoring in Children

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Background: Absence of nocturnal blood pressure dipping is associated with adverse cardiovascular outcomes in adults. Risk factors for non-dipping in adults include obesity and proteinuria. In children, risk factors for non-dipping have not been well established.

Methods: We identified consecutive patients aged 5 to 19 years who underwent 24-hour ambulatory blood pressure monitoring (ABPM) at Rady Children's Hospital from August 2018 to January 2019 and had a spot urine protein to creatinine ratio (PCR) measurement within one year of their ABPM. Dipping was defined as ≥10% reduction in systolic and diastolic blood pressure from day to night. Multivariable logistic and linear regression models evaluated the association of proteinuria with dipping, employing backwards selection models to retain important confounders.

Results: Seventy-seven children had ABPM and urine PCR assessments during the study period, among whom 27 (35.1%) were non-dippers. Non-dippers had a higher left ventricular mass index as compared to dippers (mean difference 6.9 g/m$^{2.7}$, 95% CI 1.6 to 12.2). Doubling of urine PCR was associated with 38% higher odds of non-dipping in the multivariable model (**Table**). Doubling of urine PCR was also associated with a lower diastolic dipping percent by 1.33 (95% CI 0.31 to 2.34), after adjusting for age, body mass index, and estimated glomerular filtration rate.

Conclusions: Proteinuria is significantly associated with non-dipping in children. Pediatric patients with non-dipping should be evaluated with urine PCR, and conversely, those with proteinuria may benefit from a 24-hour ABPM.

Funding: NIDDK Support

Table. Association of Log_2 (PCR) with Non-Dipping.

	Unadjusted OR (95% CI)	Mutually Adjusted[a] OR (95% CI)	Backward Selection[b] OR (95% CI)
Log_2(PCR)	1.28 (0.97 -1.69)	1.37 (0.996 – 1.895)	1.38 (1.013 – 1.884)
p-value	0.086	0.053	0.041
BMI (per kg/m^2)	1.06 (0.99 – 1.14)	1.10 (0.999 – 1.221)	1.09 (1.004 – 1.180)
Age (years)	1.06 (0.92 – 1.22)	0.94 (0.782 – 1.137)	
Female	1.46 (0.55 – 3.86)	0.96 (0.325 – 2.808)	
eGFR (ml/min/1.73 m^2)	0.99 (0.98 – 1.01)	0.99 (0.976 – 1.007)	

Abbreviations: PCR, urine protein/creatinine; BMI, body mass index; eGFR, estimated glomerular filtration rate; CI, confidence interval; OR, odds ratio.
[a]Adjusted for all variables including BMI, age, gender, and Schwartz I or MDRD eGFR.
[b]Backward selection model leads to adjustment for BMI only.
P-values reported are for log_2(PCR) in the model.

PO2325

Association of Environmental Tobacco Exposure with Blood Pressure in US Children

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Background: Hypertension is a leading cause of cardiovascular and kidney disease in adults, and there is evidence that pathologic sequelae begin in childhood and young adulthood. Nicotine and other tobacco compounds have a variety of toxic effects, but to date their associations with chronic hypertension is unclear, especially in pediatric populations.

Methods: We examined the association between tobacco exposure and high blood pressure (HBP) in children who participated the National Health And Nutrition Examination Survey (NHANES) during 2008-2016. Children were classified as having tobacco exposure if they had blood cotinine levels >0.05ng/dL or reported living with a smoker or smoking themselves. High blood pressure was classified according to the 2017 AAP Clinical Practice Guidelines. Analysis was conducted by logistic regression with adjustment for baseline demographics, income and other possible confounders. Subgroup and sensitivity analyses were conducted.

Results: There was a positive association of high blood pressure with tobacco exposure in the study population. After adjustment for demographics, the odds of having high blood pressure was 1.39 (95% Confidence Interval (CI) 1.04, 1.87) for any tobacco exposure compared to no smoking exposure. The association was similar across participant subgroups. The association remained significant by sensitivity analysis using cotinine exposure as a continuous variable. Separately, the odds of having high blood pressure for passive smokers was 1.35 (CI 0.983, 1.85) while the odds for active smokers was 1.71 (CI 1.14, 2.54) compared to participants with no tobacco exposure.

Conclusions: Tobacco exposure is associated with high blood pressure in US children and adolescents.

Funding: Other NIH Support - 2T32DK007110-43

Association of Tobacco Exposure with High Blood Pressure

	Odds Ratio	Confidence Interval	p
Model 1 (Unadjusted)	1.66	1.27, 2.19	<0.001
Model 2 (Adjusted for age, sex, and race)	1.62	1.22, 2.15	0.001
Model 3 (Adjusted for age, sex, race, BMI category, poverty-income ratio category, and survey year)	1.39	1.04, 1.88	0.029

PO2326

Hypertension and CKD at 7 Years After Surgical Repair of Congenital Heart Disease in Children

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Background: We previously determined that children who require surgery for congenital heart disease (CHD) are at an increased risk for hypertension and CKD 5 years after cardiac surgery. This study assessed the long-term risk of hypertension and CKD after cardiac surgery and if these outcomes are sustained.

Methods: We prospectively enrolled children from 1 month to 18 years old, undergoing cardiopulmonary bypass at three centers. Children who survived their surgical hospitalization had blood pressure, urine albumin to creatinine ratio, and serum creatinine measured at two in-person follow-up visits (median 5.4 years and 7.4 years after surgery). Hypertension was defined using the American Academy of Pediatrics 2017 Hypertension guidelines. Estimated GFR (eGFR) was calculated using the CKiD equation. CKD was defined as the presence of low eGFR (<90 ml/min/1.73m^2) or microalbuminuria. We compared the risk of hypertension and CKD status at the 5 and 7-year visits using the McNemar test.

Results: Of 131 children with a follow-up visit 5 years after cardiac surgery, 88 (67%) children participated in the 7-year follow-up visit. The median age of the cohort at the 7-year follow-up was 10.7 [IQR: 7.8–13.0] years and 47% were female. 32 children had previously had a septal defect repair, 15 an inflow/outflow tract or valve procedure, 34 had a combined procedure, and 7 were not defined. Hypertension, microalbuminuria, eGFR<90, and eGFR<60 was 15%, 8%, 9%, and 1%, respectively, at the 5-year visit and 17%, 4%, 19%, and 1%, respectively, at the 7-year visit. CKD was present in 16% and 18% of children at the 5-year and 7-year visit, respectively, with no statistically significant change in risk at the two visits (p=0.35). Between the 5-year and 7-year visits, hypertension and CKD were sustained in 8 (62%) and 4 (29%) patients, respectively.

Conclusions: The long-term risk of hypertension and CKD were common at the 7-year visit. Compared to the five-year visit, hypertension was sustained in the majority of children. Although CKD was not sustained, there was an increased incidence of new children with GFR<90 at the 7-year visit. The risk factors for sustained hypertension and kidney disease should be further studied in children with congenital heart disease.

Funding: NIDDK Support

PO2327

Evaluating the Role of the Kidneys in Posterior Reversible Encephalopathy Syndrome in Pediatric Patients

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Background: Kidney disease is a known risk factor for posterior reversible encephalopathy syndrome (PRES), but the specific markers of kidney function that are relevant to PRES are undescribed. The objective was to investigate the associations of various markers of kidney function with PRES.

Methods: In a case-control study of high-risk children, we recorded most-recent blood urea nitrogen (BUN), documentation of acute kidney injury (AKI), serum creatinine, serum albumin, and hemoglobin level and calculated the estimated glomerular filtration rate (eGFR). PRES cases were confirmed clinically and radiologically. We applied multivariable regression models to estimate the associations of the exposures with PRES. We utilized directed acyclic graphs to inform the following model adjustments: 1) history of kidney disease and nephrotoxic medication exposure for the kidney function models; 2) history of kidney disease, eGFR, and albumin treatment for the serum albumin model; and 3) age, sex, history of kidney disease, eGFR, fluid overload, and nephrotoxic medication exposure for the hemoglobin model.

Results: The mean age of the study population was 9.5 years (±4.9) and 51% were female. Of that population, 29% had a history of kidney disease, 67% had exposure to nephrotoxic medications, and 29% had AKI prior to the onset of PRES. BUN [adjusted OR (aOR) 1.03 per 1 mg/dl increase, 95% CI 0.99-1.07, p=0.09] and AKI (aOR 3.78, 0.68-21.13, p=0.13) were modestly associated with PRES. eGFR (aOR 1.0 per 1 ml/min/1.73 m^2 increase, 0.98-1.01, p=0.55), albumin (aOR 1.7 per 1 g/dl increase, 0.73-3.93, p=0.22) and hemoglobin (aOR 1.12 per 1 g/dl increase, 0.81-1.56, p=0.48) were not associated with PRES.

Conclusions: In a case-control study of children at high risk for PRES, we demonstrated that among several markers of kidney function, BUN and AKI were modestly associated with PRES. Further prospective studies with larger sample sizes and higher power are necessary to fully evaluate the role of kidney function in the development of PRES.

Funding: Other NIH Support - Spectrum Stanford Center for Clinical and Translational Research and Education (NIH/NCATS TL1 TR001084), the Wake Forest Clinical and Translational Science Award (NIH/NCATS UL1 TR001420)

PO2328

Effect of Hypertension on Childhood-Onset Systemic Lupus Erythematous in a Tertiary Medical Center in Korea

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Background: Hypertension (HTN) is prevalent in childhood-onset systemic lupus erythematous (cSLE) and affected either by disease activity itself, cSLE medication or both. The purpose of this study is to evaluate the prevalence, clinical characteristics and long-term clinical effect of HTN in Korean cSLE patients treated in tertiary medical center in Korea.

Methods: The medical records of cSLE patients, diagnosed by 2019 SLE European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria, who visited Samsung Medical Center from January 2009 to May 2019 were reviewed retrospectively. The disease activity was evaluated by Modified Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and renal activity (renal SLEDAI) was measured by scores from SLDEA-2K. The long-term damage was evaluated by The Pediatric Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (Ped-SDI). The sex-, age- and height-blood pressure standards recommended by AAP 2017 guideline was used to define HTN. Left ventricular hypertrophy (LVH) was defined by sex, age specific left ventricular mass index (LVMI) ≥ 95th percentile.

Results: Total 32 patients were enrolled in this study. The median follow-up duration was 7.3 year and female was predominant. Median age at SLE and HTN diagnosis were 14.2 and 14.3 year, respectively. Initial renal involvement was detected in 12.5%. The biopsy proven LN was detected in 84.4% (n=28) and 37.5% of them were class IV (n=12). The prevalence of HTN, including 2 transient HTN, was 34.4% (n=11) and stage 2 HTN was prevalent (n=9). The median dose of steroids, converted to prednisolone, at diagnosis of SLE and HTN were 1.0mg/kg/day and 0.5mg/kg/day. Among cSLE patients with HTN, 2 patients had 3 episodes of posterior reversible encephalopathy syndrome. LVH was detected in 2 patients with HTN. In the cSLE patients with persistent HTN (n=9), lower eGFR (OR=0.9, p=0.031) and higher BMI (OR 1.4, p=0.047) were shown at the time of SLE diagnosis. Every patient with HTN - including transient HTN - in cSLE (n=11) showed lower eGFR at the time of SLE diagnosis (OR 0.9, p=0.029) and higher Ped-SDI (OR 1.8, p=0.047) at last visit.

Conclusions: In conclusion, HTN in cSLE is associated with BMI and renal function at SLE diagnosis. Also, HTN affect long term damage accumulation in cSLE.

PO2329

Hemodiafiltration Maintains a Sustained Improvement in BP Compared with Conventional Hemodialysis in Children: The HDF, Heart and Height (3H) Study

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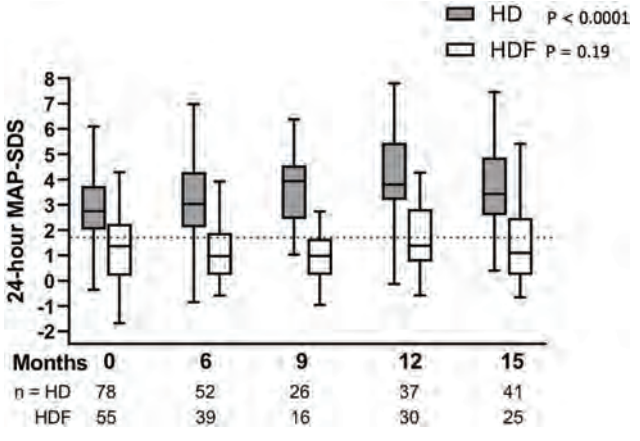
Background: Hypertension is prevalent in children on dialysis and associated with left ventricular hypertrophy, cardiovascular disease, and mortality. We studied the blood pressure (BP) trends as well as risk factors associated with the evolution of BP over 1-year in children on conventional hemodialysis (HD) vs hemodiafiltration (HDF)

Methods: This is a post-hoc analysis of the "3H - HDF-Hearts-Height" dataset, a multicenter, non-randomized, parallel-arm observational study. Mean arterial pressure (MAP) derived from 24-hour ambulatory BP monitoring was calculated and hypertension defined as 24-hour MAP standard deviation score (SDS) ≥95th percentile

Results: 78 children on HD and 55 on HDF who were followed-up for 1-year and had three ABPM measures were included. MAP-SDS was under-estimated by pre-dialysis systolic BP-SDS (mean difference -0.6; 95% LoA -4.9 to 3.8). At baseline 82% on HD and 44% on HDF were hypertensive, with uncontrolled hypertension (BP>95th centile on medications) in 88% vs 25% respectively; p<0.001. At 12-months children on HDF had lower MAP-SDS compared to those on HD in all age groups (p<0.001). Over the one-year follow-up, the HD group had a mean MAP-SDS increase of +0.98 (95%CI 0.77 to 1.20; p<0.0001), whereas the HDF group had a non-significant increase of +0.15 (95%CI -0.10 to 0.40; p=0.23). Significant and independent predictors of MAP-SDS were dialysis modality (β=0.83 [95%CI 0.51 to 1.15] SDS for HD vs HDF, p<0.0001) and higher IDWG% (β=0.13 [95%CI 0.06 to 0.19] p=0.0003)

Conclusions: Children on HD had a significant and sustained increase in BP over the 1-year study period compared to an attenuated and non-significant increase in HDF. Volume overload with higher IDWG%, but not anti-hypertensive medications, was associated with a higher MAP-SDS in both groups



PO2330

Novel Nephrin Protein/HLA Class II Complexes: A New Mechanism of Steroid-Sensitive Nephrotic Syndrome

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Background: We have recently identified the risk allele (HLA-DRB1*08:02) and the protective allele (HLA-DRB1*13:02) in the development of childhood steroid-sensitive nephrotic syndrome (SSNS) in a Japanese population (JASN 2018). HLA-DRB1*07:01-DQA1*02:01-DQB1*02:01 was also identified as a risk haplotype in other populations. In addition, we found that *NPHS1*, coding nephrin, which is a key component of podocytes, was associated with susceptibility to childhood SSNS (Kidney Int 2020). HLA class II genes are associated with susceptibility to many kinds of autoimmune diseases, with one of the mechanisms being misfolded protein/HLA class II complexes that are aberrantly transported to the cell surface inducing immune responses (Jin, Arase *et al.* PNAS 2014). Therefore, we investigated the relationship between each HLA allele and nephrin, based on the hypothesis that nephrin protein/HLA class II complexes might be involved in the development of SSNS.

Methods: Nephrin lacking the transmembrane domain (Neph^{mis}) was used as a model of misfolded protein that is not expressed on the cell surface. We co-transfected Neph^{mis} and HLA-DR to HEK293T cells and assessed the expression patterns by flow cytometry and immunoprecipitation.

Results: Neph^{mis} was detected on the cell surface in the presence of HLA-DR, which was more intense in the risk alleles than in the protective allele (DRB1*07:01>DRB1*08:02>DRB1*13:02). While Neph^{mis} coimmunoprecipitated with HLA-DR, Neph^{mis} was not detected in the absence of HLA-DR. [Discussion] Podocytes are sometimes considered as non-hematopoietic professional antigen presenting cells because they present antigens on the cell surface via HLA class II and stimulate immune signaling. We showed that the risk HLA DR allele tended to present Neph^{mis} stronger than the protective allele, suggesting that an immune response could be more easily induced in the risk alleles than in the protective allele. Although there are a variety of possible mechanisms by which HLA polymorphisms could be associated with SSNS, the binding of specific molecules, such as nephrin or Neph^{mis}, and their presentation may provide new insights into the pathogenesis of SSNS.

Conclusions: Our results suggest that nephrin protein/HLA classII complexes can be involved in the pathogenesis of childhood SSNS.

Funding: Government Support - Non-U.S.

PO2331

Efficacy and Safety of Ravulizumab in Pediatric Patients with Atypical Hemolytic Uremic Syndrome Previously Treated with Eculizumab: 26-Week and 1-Year Data

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Background: The complement C5 inhibitor eculizumab improves outcomes of atypical hemolytic uremic syndrome (aHUS) but must be administered every 2–3 weeks. Ravulizumab, engineered from eculizumab for a longer half–life, is efficacious and safe in adults with 8–week dosing intervals. This analysis was in eculizumab-treated children with aHUS.

Methods: ALXN1210-aHUS-312 (NCT03131219) is a phase 3, single–arm trial in complement inhibitor-naïve children (Cohort 1; reported separately) and children who were receiving treatment with eculizumab without thrombotic microangiopathy (TMA; Cohort 2; reported here). This analysis assessed TMA activity, and the pharmacodynamic measure serum free C5 levels after patients switched from eculizumab to ravulizumab treatment. Patients received loading doses then maintenance treatment with ravulizumab every 4 or 8 weeks, dependent on weight, for 26 weeks. An extension phase is ongoing; here we report data on efficacy through 1 year and safety from all available follow up (median 50.2 weeks).

Results: Ten patients (mean [SD] age 11 [5.0] years) were enrolled into Cohort 2; all completed the 26–week initial evaluation period and entered the extension. Mean eGFR, hematologic outcomes (platelet, lactate dehydrogenase and hemoglobin normalization), and fatigue measures remained stable during both trial periods. At 1-year, the mean (SD) changes from baseline were: eGFR, -3.9 (8.3) mL/min/1.75m^2; platelets, –17.8 (54.6) ×10^9/L; LDH –10.7 (19.2) U/L; hemoglobin +4.5 (7.1) g/L. All patients were in the same eGFR category at 1 year as recorded at baseline (eGFR mL/min/1.73m^2 ≥90, n=8; 60–89, n=1; 49–59, n=1). No patients required dialysis. Despite the increased dosing interval, serum free C5 levels were maintained below the threshold of 0.5 mg/mL. All patients experienced adverse events (AEs) but none discontinued the trial. No meningococcal infections occurred. One patient experienced serious AEs due to a respiratory tract infection.

Conclusions: Continued efficacy, no additional safety concerns and the benefit of reduced dosing frequency was demonstrated in pediatric patients with aHUS who were stable on eculizumab and switched to ravulizumab.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc., Government Support - Non-U.S.

PO2332

Typical Hemolytic Uremic Syndrome in Children: A Single-Center Experience

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Background: Typical hemolytic-uremic syndrome (HUS) associated with diarrhea can be a fatal disease in children. Diarrhea and blood-stained stools are early symptoms. Oliguria and renal failure can occur anywhere from 3-7 days after onset of diarrhea. Intravenous (iv) fluids in the initial timeline of disease presentation may decrease the need for dialysis. Oligo-anuria at admission and leukocytosis is associated with poor outcomes during hospitalization. After recovery, there is a risk of long-term renal complications such as hypertension, proteinuria, and chronic kidney disease (CKD).

Methods: We performed a retrospective analysis of 43 children admitted with diarrhea associated with HUS at our center in the last ten years. The 'late presentation' defined as serum creatinine>1 mg/dL, oliguria, or anuria at admission. The primary outcome was the presence of long-term renal sequelae. It included proteinuria, hypertension, or chronic kidney disease (CKD) (eGFR <75 ml/min/1.73m2) after one year of disease-onset. The Chi-square and correlation analysis performed on the SPSS platform.

Results: Overall, 32/43 presented late in the disease course, 30/43 required dialysis (median: 8 d), and 8/43 had a recent history of NSAID use. The administration of dextrose and saline containing iv fluids in the early presentation was associated with the decreased requirement of dialysis (p=0.042), but the effect was not significant with NSAID use (p=0.064). Peak white blood cell count (Wbc) had a strong correlation with days of hospitalization (p<0.001). 10/43 children were lost to follow up. 13/33 children showed renal sequelae (includes 3 with CKD and 1 with ESRD who required kidney transplant) after one year of disease onset. Wbc count >20000 cells/mm3 (at p=0.001) and duration of dialysis>14 days (at p=0.002) were associated significantly with the primary outcome. 6/43 children were un-immunized. There was no mortality.

Conclusions: High peak WBC count may be a useful prognostic marker to evaluate the risk of long-term renal complications. These children need monitoring periodically after disease recovery. Early diagnosis and iv fluids before the onset of renal failure may help to prevent dialysis-related morbidity at the time of admission. More awareness is needed to discourage the use of NSAIDs following initial symptoms of HUS.

PO2333

Targeting Bloody Diarrhea to Fight Shiga Toxin-Producing *Escherichia coli*-Hemolytic Uremic Syndrome in Children: The Experience of the ItalKid HUS Network

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Background: Bloody diarrhea (BD) is often the first distinctive sign of hemolytic uremic syndrome (eHUS), the leading cause of acute kidney injury in infants, caused by shiga toxin (Stx)-producing *Escherichia Coli* (STEC) infection. The few days prior the development of the renal complication, when bloody diarrhea is the only symptom, represent a window for better understanding, preventing or mitigating HUS. The present study aims at identifying patients at risk for HUS early and at evaluating the rate of BDs associated with STEC infection.

Methods: This multicenter case series study was performed between 2010 and 2019 in Pediatric emergency departments and clinics belonging to a network of 63 pediatric hospitals in Northern Italy (referral population: 12 million general population; 2.3 million children). 4767 children (<20 yo) presenting with BD were enrolled. Stool samples were centrally screened for the presence of *Stx* genes (1 and 2) using a Reverse Dot blot assays (Genotype EHEC - Arnika) until 2018 and Real Time PCR (RIDA Gene-Relab) thereafter. *Stx*-positive cases were further investigated for *E.coli* serogroups. Children positive for *Stx* genes were monitored for hemoglobinuria, blood tests to rule in or out the diagnosis of STEC-HUS were done if urine dipstick turned positive for hemoglobinuria.

Results: Out of the 4767 screened samples, 214 (4.5%) turned out to be positive for either Stx1 (n: 62; 29.0%) or Stx2 (n: 97; 45.3%) or both (n: 55; 25.7%). 34 patients out of the 214 positive for Stx (15.9%) developed eHUS (0.71% of BDs). Patients infected with STEC producing Stx2 alone were at higher risk for eHUS compared with Stx1+2 (23.7 vs. 12.7%) while Stx1 alone was only exceptionally associated with eHUS (1.1%). The most frequent serogroup found in patients with Stx+BD was the O157 while in patients with eHUS the O26 was the most (36.5% of cases), followed by O157 (20%).

Conclusions: STEC is all but a rare cause of BD in children thus the screening for Stx of BD is recommended. We also suggest to monitor patients carrying Stx2 closely with urine dipstick for hemoglobinuria every 12 hours for the early detection of eHUS together with providing them with generous fluid infusion.

PO2334

Hemoglobinuria for the Early Identification of STEC-HUS in High-Risk Children

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Background: Shigatoxin-producing *Escherichia coli* – associated hemolytic uremic syndrome (STEC-HUS) represents one of the main causes of acute kidney injury in children and can be associated with several extrarenal complications. Its management is entirely based on supportive care, which includes generous fluid infusions, since dehydrated patients have been described to have a worse outcome, compared to normo- and overhydrated patients. The present study aims at validating urine dipstick/urinalysis for hemoglobinuria as a early test to screen patients at high risk for the development of STEC-HUS (children with bloody diarrhea secondary to Shigatoxin – Stx - 2 or 1+2) for the early diagnosis of the disease.

Methods: Since 2010, a network 63 pediatric units (the ItalKid-HUS Network) has been developed in Northern Italy, with the aim of the early identification and management of STEC infections and STEC-HUS. Once a patient with bloody diarrhea (BD) is identified as Stx positive, he/she is rehydrated as appropriate and followed up with urine dipstick/urinalysis for hemoglobinuria until HUS develops or diarrhea resolves. We here reviewed all the urine dipstick/urinalysis results from pediatric patients with Stx positivity either with BD only (Group 1) or with ongoing HUS (Group 2) from 2010 to 2019.

Results: A total of 100 children were eligible for the study. In Group 1, 22/63 patients had or developed hemoglobinuria while the remaining 41/63 were and remained negative. In 15/22 positive cases, blood tests ruled in a ongoing HUS, while in the remaining 7 the diagnosis was excluded. Among the 41 negative patients no one developed HUS. As expected, the 37 children in Group 2 (already ongoing HUS) all had hemoglobinuria at admission.

Conclusions: Hemoglobinuria shows a sensitivity of 100% (95% CI 93-100%) and a specificity of 85% (95% CI 74-93%), with positive predictive value of 68% and negative predictive value of 100% in diagnosing ongoing HUS. Thus, urine dipstick or urinalysis for the detection of hemoglobinuria can be proposed as an easy, fast, inexpensive and repeatable test to screen patients at high risk for the development of STEC-HUS and to start supportive treatment as soon as possible.

PO2335

Hemoglobinuria for the Early Identification of Atypical Hemolytic Uremic Syndrome Relapse: Data from the ItalKId-HUS Network

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Background: Atypical hemolytic uremic syndrome (aHUS) is at risk of relapse any time, thus patients require lifelong monitoring. We suggested that patients could be monitored for relapses, with hemoglobinuria (twice weekly and during intercurrent diseases) based on the hypotesis that a thrombotic microangiopathy involving the glomerulus, cannot take place without hematuria. However this assumption has not been validated.

Methods: The aim of the study is to analyze our experience with the mentioned approach in patients with aHUS who have never been treated (group 1), on treatment (group 2) and who have discontinued C5 inhibition (group 3). The records of all aHUS patients managed or referred to our Center from January 2009 to March 2020 were included and the analysis for the presence of hemoglobinuria was restricted to the period following primary remission with the aim of validating this biomarker as a reliable one for the early identification of relapses. Patients with persistent hemoglobinuria, although in documented TMA remission, were excluded. A positive test was defined as hemoglobin ≥1+. Patients reporting positive urine dipstick were addressed to laboratory investigations to rule in or out, the diagnosis of aHUS relapse.

Results: 84 patients with aHUS (50% females) were included with 1517 determinations of hemoglobinuria during a cumulative observation period of 261 patient-year (Figure). Hemoglobinuria for the early diagnosis of ongoing aHUS relapse shows a sensitivity of 100% and a specificity of 87.4% with a PPV of 10.5% and NPV of 100 %.

Conclusions: Hemoglobinuria is a very sensitive and acceptably specific marker of aHUS relapse. This finding and its validation may have an important positive impact both on patient's quality of life and on the outcome of disease via an early diagnosis of relapses.

Funding: Private Foundation Support

	Group 1	Group 2	Group 3	Total
Patients	23	57	22	102
Gender, male (%)	19 (82.6)	27 (47.3)	10 (42.4)	56 (54.9)
Age, mean	22.1	21.7	20.7	22.6
Cumulative observation period, patient-year	247	257	238	742
Test performed	261	1113	143	1517
Positive test (% of tested)	20 (7.6)	165 (14.8)	24 (16.7)	209 (13.8)
True positive test (% of positive test)	8 (40.0)	0 (0)	13 (54.2)	21 (10.0)
Negative test (% of tested)	241 (92.4)	969 (85.2)	130 (83.3)	1308 (86.2)
False negative test (% of negative test)	0 (0)	0 (0)	0 (0)	0 (0)

PO2336

Extensive Complement Analysis in a C3 Glomerulopathy Cohort of Dutch Children with Benign Outcome

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Background: C3 glomerulopathy (C3G) is a rare renal disorder driven by dysregulation of the complement alternative pathway (AP) and characterized by predominant C3 depositions in the glomerulus. C3G can be subdivided in dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). Patient cohort studies including clinical features offer important data in rare renal diseases. Moreover, biomarkers are increasingly used to select patients for clinical trials with novel complement-targeted therapies. This retrospective study describes complement biomarker profiles and outcome of 29 Dutch children.

Methods: Patients with a C3G diagnosis from 5 Dutch university medical centers (1992- 2014) were included. Clinical, genetic, and laboratory findings were retrieved from patient files. Specialized biochemical assays were used to detect complement-directed autoantibodies and complement biomarkers.

Results: A total of 29 patients with DDD (n=19) and C3GN (n=10) were included. Median (IQR) follow-up was 51 months (26-90). Patients presented with proteinuria and hematuria (>90%) and low serum C3 levels (84%). Ten patients (35%; 8 DDD, 3 C3GN) presented with an impaired glomerulation filtration rate (GFR). DDD patients presented at younger age and with a lower GFR (P<0.05). C3 nephritic factors were found in 19 patients, and 3 patients carried rare genetic variants in AP genes. Elevated levels of the complement activation markers C3d, C3bBbP, and C5b-9, combined with lowered C3 and C5 levels, indicated AP activation in the acute phase. Taking longitudinal data into account, a linear mixed model showed that C3GN patients had higher C5b-9 and lower properdin levels than DDD patients (P<0.05). During follow-up, 13 (45%) patients experienced a relapse. No significant differences in clinical or laboratory features were observed between patients with and without a relapse and persistent renal sequelae. At last follow-up, only 4 patients (14%; all DDD) had a GFR below 60 ml/min/1.73m^2.

Conclusions: We present the extensive description of clinical, genetic, and biochemical complement features of a large pediatric C3G cohort. In most patients AP abnormalities were found. Overall, the outcome of the patients we described was relatively benign.

PO2337

Comparison of Clinicopathological Findings Between Childhood IgA Nephropathy and IgA Vasculitis Nephritis Using Oxford Classification

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Background: IgA nephropathy (IgAN) and IgA vasculitis nephritis (IgAVN) are nephritis with a common pathological feature of significant mesangial IgA deposition, but it remains controversial whether they are the same disease.

Methods: We compared clinical and pathological findings between 148 patients with IgAN and 100 patients with IgAVN who underwent renal biopsy from April 2000 to April 2019 to clarify the differences.

Results: Clinical findings showed significant differences in onset age (IgAVN vs IgAN, 7.4 vs 10.7 years, p<0.0001), episode of gross hematuria (8.0 vs 24.3%, p=0.0007), duration from onset to renal biopsy (1.7 vs 6.6 months, p<0.0001), and amount of proteinuria (1.8 vs 0.5 g/gCr, p<0.0001). Pathological findings by Oxford classification showed significant differences in the frequency of M1 (94.0 vs 59.2%, p<0.0001), S1 (21.0 vs 42.2%, p=0.0004), T present (28.0 vs 46.1%, p=0.004), C present (72.0 vs 58.1%, p=0.03) and G present (8.0 vs 19.1%, p=0.01), but no difference in that of E1 (52.8 vs 55.0%, p=0.75). Fluorescence findings showed significant difference in the frequency of fibrinogen deposition (93.3 vs 74.6%, p=0.0004) but not in that of glomerular peripheral capillary IgA deposition (9.5 vs 3.5%, p=0.10). Electron microscopic findings showed significant difference in the frequency of GBM lysis (35.2 vs 12.0%, p=0.0001). Degree of proteinuria is positively correlated with the frequency of M1 in IgAVN.

Conclusions: IgAVN has higher frequency of M1 lesion regardless of degree of proteinuria, lower frequency of chronic lesions such as S, T, and G, and higher frequency of acute lesions such as M and C compared with IgAN. Although IgAVN had some pathological similarities to that of IgAN, there seems to be differences which cannot be explained by the timing of renal biopsy.

PO2338

Race and Age at Onset of ESRD in Patients with Alport Syndrome

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Background: Angiotensin-converting enzyme (ACE) inhibitors have been shown to delay the onset of end-stage renal disease (ESRD) in both animal models and humans with Alport syndrome. In 2013, expert guidelines recommended the use of ACE inhibitors to delay the onset of ESRD. We examined temporal changes in the age at onset of end-stage renal disease (ESRD) and interaction between race and age at ESRD for patients with Alport syndrome.

Methods: We used the Scientific Registry of Transplant Recipients to identify all patients who received a kidney transplant in the United States for Alport syndrome between 1987 and 2017. We divided the study period into three equal eras (era 1, 1987-1997; era 2, 1998-2007; and era 3, 2008-2017) to assess changes in age at ESRD using a linear regression model adjusting for race and gender. Age at ESRD was defined as the earlier of the age at dialysis or the age at kidney transplant.

Results: Between 1987 and 2017, 4105 Alport patients received a kidney transplant in the United States. Of these patients 3,115 (75.9%) were male and 3176 (77.4%) were white. Pre-emptive transplants were performed in 962 (23.4%) patients. Table 1 demonstrates temporal changes in *median* age at ESRD, demographic and clinical characteristics for patients with Alport syndrome. After adjusting for race and gender, the age at ESRD increased by a mean of 2.7 years (SE 0.51, p <0.01) for era 2 and 4.4 years (SE 0.51, p <0.01) for era 3 compared with era 1. We also observed that age at ESRD was significantly lower for black (-9.3 years, p < 0.01), Hispanic (-9.4 years, p < 0.01), and other races (-6.9 years, p < 0.01) compared with the white race (Table 2).

Conclusions: The age at ESRD for patients with Alport syndrome has progressively increased over the last 30 years. White patients have delayed onset of ESRD compared with patients of other races.

Temporal changes in ESRD and transplant characteristics

Variables	1987-1997 N= 1461	1998-2007 N= 1299	2008-2017 N= 1345	p value
Age at ESRD (years) Median (range)	28.2 (73.1)	30.6 (73.2)	30.6 (71.3)	<0.001
Age at transplant (years) Median (range)	31.2 (70.9)	33.4 (75.1)	33.6 (72.5)	<0.001
Age at listing (years) Median (range)	31.0 (71.0)	32.0 (69.0)	32.0 (69.0)	0.05
Age at dialysis (years) Median (range)	27.9 (73.1)	29.5 (73.2)	29.7 (70.4)	0.007
Race n (%) White Black Hispanic Other	1218 (83.4) 111 (7.6) 103 (7.1) 29 (2.0)	1012 (77.9) 93 (7.2) 155 (11.9) 39 (3.0)	946 (70.3) 122 (9.1) 205 (15.2) 72 (5.3)	<0.001
Male n (%)	1134 (77.6)	964 (74.2)	1017 (75.6)	0.11

PO2339

Risk of Rituximab-Associated Severe Adverse Events Increases with Young Age in Children with Nephrotic Syndrome

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Background: Rituximab prevents relapse in steroid-dependent frequently relapsing nephrotic syndrome (SDFRNS). We aimed to assess the safety of rituximab in children with steroid-resistant nephrotic syndrome (SRNS) or SDFRNS.

Methods: This single-center retrospective study included all children with SRNS/SDFRNS treated with rituximab since 2007 at our institution. All information concerning adverse events (AE) were obtained from medical records. Severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events. We performed a survival analysis and log-rank tests or proportional hazards models to determine hazard ratios (HR) with 95% confidence intervals (CI) of risk factors associated with severe AE (SAE).

Results: Of the 38 children included in this study, most had a SDFRNS (n=36, 95%). Median age at diagnostic was 3.4 (interquartile range, 2.4-6.2) years and median age at rituximab initiation was 9.0 (6.8-13.6) years. Median [95% CI] time to relapse was 1.4 [1.16-2.27] years. Median follow-up time was 3.7 (2.2-4.9) years. No patient died during follow-up. Fourteen SAE occurred in 12 (32%) patients, including one case of *Pneumocystis jiroveci* pneumonia, 6 cases of severe neutropenia and 2 cases of inflammatory colitis. Rituximab initiation before 10 years of age was associated with a higher risk of SAE (HR [95%CI], 11.3 [1.44, 88.6], Figure 1) and all SAE occurred in children aged <10 years except for anaphylactic reactions. The occurrence of a SAE was not associated with an increased risk of relapse.

Conclusions: A young age at rituximab initiation for SRNS/SDFRNS is associated with an increased risk of SAE. Rituximab should be used with particular caution in children under 10 years old.

Funding: Government Support - Non-U.S.

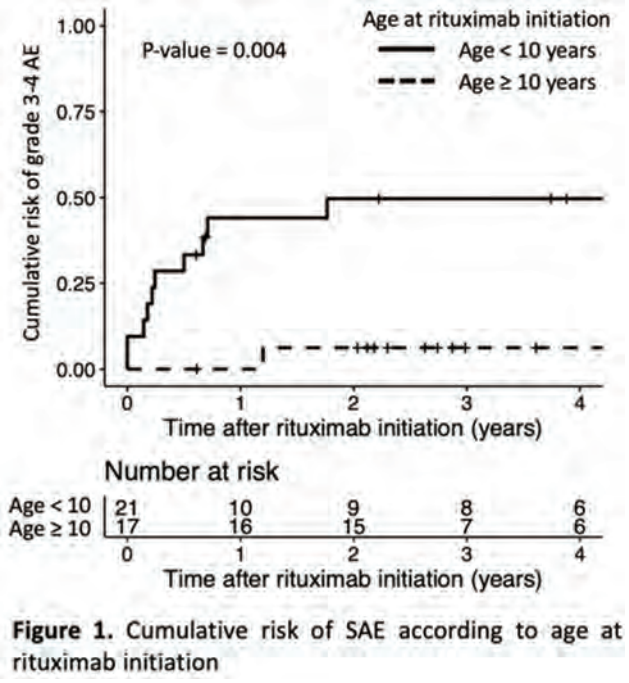

Figure 1. Cumulative risk of SAE according to age at rituximab initiation

PO2340

Evaluating Nephrotic Syndrome Response to Rituximab in Children

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Background: Nephrotic syndrome (NS) is the most common cause of glomerular disease in the pediatric population. In children, 80% of cases are steroid sensitive (SSNS) & 20% are steroid resistant (SRNS). Rituximab (RTX) has been identified as a steroid-sparing therapy with minimal nephrotoxic side effects. The determinants of clinical response to rituximab is not completely known.

Methods: A retrospective review of patients aged 0-21 years with idiopathic NS who received at least 2 doses of RTX therapy over 6 years. Data collected included gender, race, ethnicity, age at diagnosis, steroid response, number of RTX doses, CD20 levels post therapy & outcomes. Outcome was defined as complete remission, CR (urine protein to creatinine ratio mg/mg: UPCR ≤ 0.2), partial remission, PR (UPCR 0.3-1.9) & no response, NR (UPCR ≥ 2). Data were compared by Fisher's exact & Wilcoxon Rank Sum tests.

Results: 48 patients met the inclusion criteria for the study comprising of 23(48%) with SSNS & 25(52%) with SRNS. There was no difference in race or age of onset between the patients with SSNS & SRNS. 18/29(62%) of patients who had CD20 lymphocyte levels measured following treatment achieved therapeutic end point of CD20 lymphocyte depletion. There was no difference in the proportion of patients who achieved this therapeutic end point between the patients with SSNS & SRNS (46% vs 72%). Overall, 72% of patients achieved partial or complete remission. The remission rate was significantly higher in the SSNS group compared with the SRNS group (87% versus 58%, p=0.001); however, there was no difference in remission rate between patients who achieved the therapeutic end point of CD20 lymphocyte depletion & those who did not in the entire cohort (56% vs 55%, p=1.0) as well as in subgroup of patients with SSNS & SRNS.

Conclusions: Children with both SSNS & SRNS achieved the desired therapeutic effect of CD20 lymphocyte depletion following treatment with RTX; however, disease remission rate was higher in children with SSNS. This data suggests that RTX can be administered at any phase of the disease (relapse or remission) without jeopardizing clinical response.

PO2341

Clinical Course and Management in Children with Henoch Schönlein Purpura (HSP) Nephritis

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Background: HSP can lead to serious complications including HSP nephritis (HSPN). Controversy exists regarding outcomes of HSPN, varying between benign, self-limited disease and 2-19% risk of severe chronic kidney disease (CKD). Given this risk, treatment with immunosuppression may be warranted. Unfortunately, evidence-based guidelines for management of HSPN are lacking. The goals of this study were to identify children with HSP and describe the clinical course and management in those with HSPN using a large, multicenter electronic health record (EHR) database.

Methods: Children with HSP were identified using PEDSnet, a network of pediatric health systems with EHR data standardized in a common data model. In patients with HSP, contact with nephrology was used as an indicator of HSPN. Demographics and clinical data among those seen by nephrology were compared to those not seen by nephrology. Outcomes of hypertension, dialysis, and transplant were identified using standard terminologies (SNOMED and CPT4). Among those with HSPN, treatment and outcomes are described.

Results: From 2009 to 2020, 5,360 patients with HSP were identified, including 1,217 (23%) with HSPN. Average length of follow up was 2.7 years. Patients with HSPN were older (7.9 vs 6.2 years, p<0.001), with no difference in sex or race/ethnicity. Among those with HSPN, 128 (10%) had kidney biopsy. Treatment included renin-angiotensin system (RAS) blockade in 166 (14%), corticosteroids in 427 (35%), and other immunosuppressive agents (mostly azathioprine or mycophenolate mofetil) in 97 (8%). Hypertension was diagnosed in 224 (18%) within one year of HSP diagnosis. By the end of follow up, 26 (3%) had estimated glomerular filtration rate <60 mL/min/1.73m^2, including 11 (1%) requiring dialysis or kidney transplant.

Conclusions: In this large study of >5,000 children with HSP, 23% developed HSPN with the majority having mild disease. Management of HSPN by pediatric nephrologists most commonly included observation, steroids, and/or RAS blockade. Children with HSPN in this study had an excellent short-term prognosis, with only 3% with advanced CKD or end stage renal disease at last follow up.

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PO2342

Spectrum of Clinical Manifestations in Children with WT1 Mutation

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Background: Advances in genetic testing increases our ability to diagnose genetic causes of nephrotic syndrome (NS). The WT1 gene is a tumor suppressor gene necessary for kidney and gonadal development. Mutations in the WT1 gene are associated with NS and pose an increased risk of Wilms tumor and gonadoblastoma.

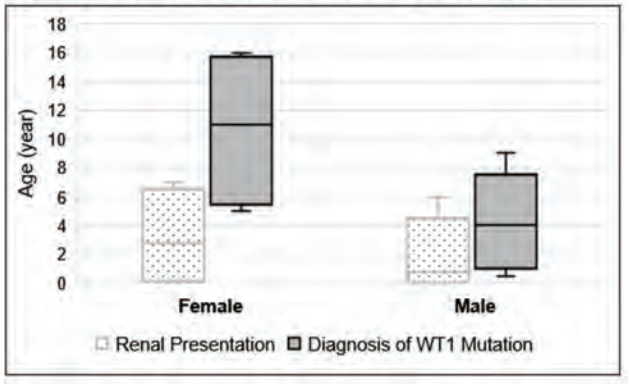
Methods: A retrospective chart review was performed in patients followed at the University of Miami from January 1990 to December 2019 with NS and WT1 gene mutation.

Results: WT1 mutations were identified in 9 children, included 5 Hispanic, 2 Caucasian, 1 Asian and 1 Middle Eastern. The mean age at renal presentation was 2.4 years (1 week to 7 years). Five presented with congenital NS (CNS). Three presented with steroid resistant NS (SRNS), at age 3 to 6 years, and received immunosuppressive treatments. One presented in advanced kidney failure at 7 years. Four had normal female external genitalia, and 5 had various abnormalities of male genitalia. Karyotype study showed XY in all. Two males developed Wilms tumor, found incidentally. All progressed to end stage kidney disease at a median age of 5 years (1 month to 14 years). Genetic diagnosis was delayed in 2 females and ultimately WT1 mutation was confirmed when they presented with primary amenorrhea. All phenotypic females underwent gonadectomy and required long term estrogen. Of two pubertal males, one had hypogonadism, and both were monitored for gonadal tumor. The median age from renal presentation to diagnosis of WT1 mutation was 7.6 years for females and 2.2 years for males ($p < 0.05$), (Figure).

Conclusions: Early recognition of NS associated with WT1 gene mutation is important for management which includes avoidance of immunosuppressive therapy, prevention of complications such as malignancy, and establishing long-term management of reproductive health. All females with infantile CNS or SRNS should get karyotype testing to identify WT1 gene mutation.

Funding: Clinical Revenue Support

Figure: Age at initial renal presentation and at diagnosis of WT1 mutation



PO2343

Caregiver Perspectives of Pre-Transplant Evaluation for Children

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Background: Pre-transplant evaluation is mandated by Centers for Medicare and Medicaid Services, but there is institutional variation in implementation. The family experience of this process also is incompletely understood. Current literature largely focuses on adult transplant recipients. Our interview study aims to fill the knowledge gap about family experience of the evaluation for children.

Methods: Interviews took place 07/2019 - 02/2020 with caregivers of children referred for kidney transplant at our center 07/2017 - 12/2018. The interview guide included closed- and open-ended questions; responses were audio-recorded and then transcribed for coding of themes. Respondents also completed a brief electronic questionnaire.

Results: Our team interviewed caregivers of 19 children; demographics in Fig. 1. Prominent themes included (1) the pre-transplant evaluation is overwhelming and emotional, (2) prior experiences and background knowledge are influential and (3) frustration with communication among teams was common. Fig. 2 highlights representative quotations from caregivers.

Conclusions: These findings are relevant to efforts by nephrologists to optimize delivery of information about transplant and other complex topics. The data highlight the importance of (1) acknowledging the scope of content and continually reevaluating accessibility of delivery (2) recognizing the influence of prior experiences and tailoring elements accordingly for increased family-centeredness and (3) making concerted efforts to define roles and set expectations, especially when multiple teams are involved in care.

Funding: NIDDK Support, Private Foundation Support

CHILD AND HOUSEHOLD DEMOGRAPHICS			
From chart review (n = 19)			
Transplant Status		**Etiology of CKD**	
Pre-transplant at time of interview	47%	CAKUT	47%
Post-transplant at time of interview	53%	Glomerular disease	11%
		Other (nephronophthisis, cortical necrosis, chronic interstitial nephritis, BK nephropathy, unknown)	42%
Lifetime Dialysis			
Currently on dialysis or on dialysis pre-transplant	74%		
No lifetime dialysis	26%		
From survey (n = 15)			
Travel Distance to Center		**Annual Household Income**	
Less than 20 miles	20%	Less than $20,000	7%
20 to 49 miles	27%	$20,0000 to $39,999	13%
50 to 99 miles	27%	$40,0000 to $79,999	13%
100 miles or more	27%	$80,0000 to $119,000	27%
		$120,000 or more	20%
		No response	13%
Weekly Commitments Outside Home		**Race**	
Less than 5 hours	20%	White	60%
5 to 14 hours	27%	Black	20%
15 to 24 hours	7%	Asian	10%
25 to 39 hours	7%	No response	10%
40 to 59 hours	40%		
60 hours or more	0%		

Fig. 1

Theme	Representative Quotations
Pre-transplant evaluation as overwhelming	"I think that process of the initial visits, those two days, that was extremely overwhelming. It was just so much information and I don't remember half of the people that we met with." "It was overwhelming no matter how you looked at it." "The first day we met the kidney transplant coordinator they told us a lot of different things and it was first very overwhelming."
Prior experiences and background knowledge as influential	"I don't think I realized that there was an approval process for him to have a transplant 'cause we had just been building this up for so long. We knew this was the outcome." "It's still new. It's only been like a year and a half [since diagnosis] but it only feels like two months to me 'cause, like I said, I just wanted to rush everything." "I read a lot on that so I kind of knew what to expect." "So I think that's why, when I got in there, probably what overwhelmed me at that point was that I knew nothing about a kidney transplant cause I didn't look it up."
Frustration with communication among teams	"The waiting for us was more on the donor side; that was the variable that was unknown." "Initially, when we got everything going and we were starting to go through donor testing, I think communication started out pretty good in the beginning and then communication has always been something that we've brought to the attention of many in general [as a problem]." "They're expecting sometimes for families to be the spokespeople in between like "make sure you tell them this or make sure you tell them that" and then when you're sitting there in those meetings, they're like "no I don't think that's all that important."

Fig. 2

PO2344

Treatment-Related Anxiety in Children After Kidney Transplant

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Background: An increasing number of children experience anxiety and pediatric kidney transplant recipients are particularly susceptible to mental health conditions given the impact of their complex chronic medical histories on their quality of life. We performed a retrospective study to assess the impact of anxiety on health-related quality of life (HRQoL) in pediatric kidney transplant recipients in order to design targeted interventions to improve HRQoL after transplant.

Methods: We retrospectively analyzed scores from the disease-specific PedsQL 3.0 ESRD and Transplant Modules in pediatric ESRD and transplant patients ages 2-18 years between 2014 and 2019 at Rady Children's Hospital. We used a linear mixed-effects model with a random intercept and ANOVA with Tukey *post-hoc* tests to analyze the effect of variables of interest on HRQOL in various groups.

Results: 180 modules were completed by pediatric patients who received dialysis and/or kidney transplantation. Transplant recipients had significantly better total HRQOL scores compared to dialysis patients ($p < 0.001$). Treatment-related Anxiety was the lowest (worst) scoring domain among kidney transplant patients ($p < 0.01$), especially among patients ages 5-7 years old ($p = 0.009$). Patients 13-18 years old had the lowest scores in the Transplant domain, which measures social isolation related to a patient's transplant ($p = 0.008$). Variables such as age at diagnosis, time on dialysis, diagnosis category, and time to transplant were not significant predictors of HRQoL.

Conclusions: These data suggest that children with kidney transplants have better HRQoL compared to children on dialysis. However, transplant recipients experience high rates of anxiety and social isolation. This may simply reflect the psychosocial stress surrounding medical care, but we may also be capturing more nuanced psychological issues in this population that requires further evaluation. Since transplant patients typically have frequent access to medical care, we have established a multi-disciplinary model in our clinic in part based on these data that utilizes psychologists to address acute and chronic psychological concerns simultaneous with their medical visits. This model may improve the HRQoL of transplant patients without increasing the overall burden of medical care and may have broader applicability to the general population of children with anxiety.

PO2345

Vaccination Status in Pediatric Kidney Transplants: An Integrated Pediatric Transplant Research Database Study

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Background: The American Society of Transplant recommends candidates be immunized before transplantation. However, there is limited data on pre/post-transplant vaccination status for children with kidney transplants. Our study evaluates vaccination rates & an approach to increasing vaccination in our kidney transplant program.

Methods: Pediatric kidney transplant recipients at Children's Hospital of Michigan from 2013-2019 were included. Official immunization records were obtained from the State of Michigan's Michigan Care Improvement Registry. During the pre-transplant period, age-based catch-up or accelerated immunization was performed at primary care provider's or at the in-house immunization center. Demographic, clinical & serology data were entered into an integrated database created through RedCap and analyzed with SPSS Version 26.

Results: Included were 58 children with mean age at transplant of 11.9±5.7 yrs, 66% Male, 52% African-American, 31% Caucasian, 76% deceased donor transplants & 10% re-transplants. Median duration of follow-up was 3 yrs. Pre-transplant vaccination rates of ≥95% were achieved for all vaccines, except PCV13 (69%), PCV23 (62%) & HPV4/9 (86%). Pre-transplant serology for HepA, HepB and Varicella showed immunogenicity of 95%, 93%, 88% respectively. Catch-up & accelerated immunization increased the vaccination rate to 100% from 53% (Varicella); 57% (HepA); 73% (MCV); 72% (MMR). Post transplant vaccination series was ≥ 95% complete for all vaccines except PCV23 (43%); HPV4/9 (37%); MCV (30%).

Conclusions: A systematic approach using catch-up & accelerated immunization improves vaccination rates. Regular monitoring of immunization record post-transplant is required to maintain up-to-date status.

Funding: Private Foundation Support

Pre & Post-transplant vaccination data (n=58)

Vaccination Series	Rate (%)	Dose # (range)	Routine vs. Catch-Up vs. Accelerated Vaccination (%)			Series Incomplete (%)
DTaP/Tdap Pre-transplant	100	3-7	96.6	3.4	0	3.3
DTaP/Tdap Post-transplant	21	0-1	20.7	0	0	3.4
HiB Pre-transplant	95	1-5	91.4	3.4	0	25.9
HiB Post-transplant	0	0	0	0	0	0
Polio Pre-transplant	100	2-3	96.6	3.4	0	6.9
Polio Post-transplant	9	0	8.5	0	0	1.7
MMR Pre-transplant	100	2-3	72.4	12.1	15.5	0
MMR Post-transplant	0	0	0	0	0	0
Varicella Pre-transplant	100	1-3	53.4	31.0	15.5	0
Varicella Post-transplant	0	0-1	0	0	0	0
Hep A Pre-transplant	100	1-3	56.9	41.4	1.7	3.4
Hep A Post-transplant	2	0-1	0	1.7	0	3.4
Hep B Pre-transplant	97	3-7	86.2	31.0	0	3.4
Hep B Post-transplant	0	0	0	0	0	3.4
PCV7/13 Pre-transplant	69	1-6	62.1	6.9	0	17.2
PCV7/13 Post-transplant	0	0	0	0	0	0
PCV23 Pre-transplant	62	1-3	27.6	34.5	0	37.9
PCV23 Post-transplant	2	1	1.7	0	0	56.9
MCV Pre-transplant (n = 37)	100	1-4	73.0	27.0	0	10.8
MCV Post-transplant (n = 30)	33	1-2	30.0	3.3	0	70.0
HPV 4/9 Pre-transplant (n = 37)	86	1-3	62.2	24.3	0	27.0
HPV 4/9 Post-transplant (n = 30)	32	1-2	20.0	12.0	0	63.3
Influenza Pre-transplant	98	1-6	98.3	0	0	3.5
Influenza Post-transplant	97	1-6	96.6	0	0	24.1

PO2346

Decreased CD28 Expression in Memory CD4⁺ T Cells in Children Awaiting Kidney Transplant Is Associated with Increased Expression of Senescence Markers

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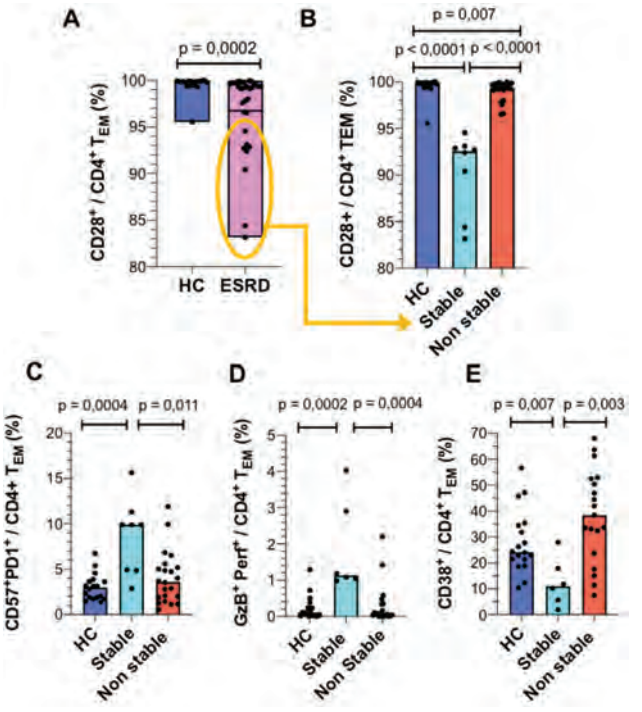
Background: Despite improved patient and graft outcomes with CD28-CD80/86 costimulation blockade, increased early acute rejection has hindered the widespread use of CTLA-4Ig (belatacept) for kidney transplant. Our group has previously reported lower pre-transplant frequencies of $CD28^+$ effector memory helper T cells ($CD4^+T_{EM}$ $CCR7^-$ $CD45RA^-$) with decreased functional capacity in adults that were subsequently free from early rejection on belatacept. We aimed to determine if a similar T cell phenotype is detectable in children awaiting kidney transplant.

Methods: We analyzed existing flow cytometry data of unstimulated blood cells collected from children on dialysis (n=30) or healthy children (n=18) and examined expression of markers of costimulation (CD28), senescence (CD57, PD1), activation (CD38) and cytotoxicity (Perforin, Granzyme B) on memory $CD4^+$ T cells.

Results: None of the children had $CD28^+CD4^+$ T_{EM} frequencies as low as those we have previously observed in adults that were rejection-free on belatacept. However, 8 children on dialysis (27%) had $CD28^+CD4^+T_{EM}$ frequencies below the minimum value observed in healthy children (Fig1A-B). Patients with this "stable-like" T cell phenotype had higher frequency of $CD4^+T_{EM}$ cells bearing senescence markers ($CD57^+PD1^+$ Fig 1C) and cytolytic effectors (Granzyme B, Perforin, Fig 1D) but decreased activation markers ($CD38^+$ Fig 1E).

Conclusions: Despite their young age and limited antigen experience, a subset of children on dialysis accumulate $CD4^+$ T_{EM} cells that have lost CD28 expression and bear markers suggestive of impaired function, a phenotype reminiscent of adults with decreased risk for early rejection on belatacept. The functional capacity of these cell populations in children needs further study.

Funding: NIDDK Support, Clinical Revenue Support



PO2347

Predicting Allograft Survival in Young Pediatric Kidney Transplant Recipients

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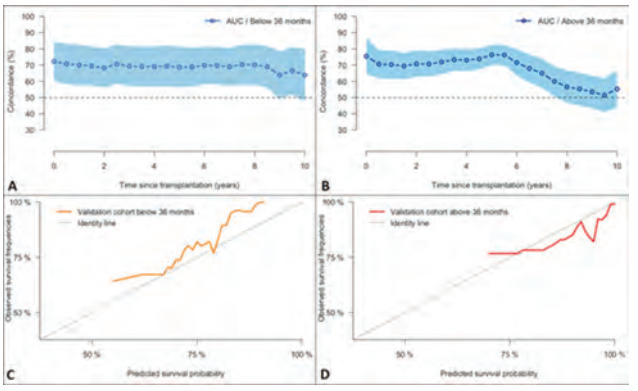
Background: Kidney transplantation (kTx) presents specific challenges in younger recipients. There are no predictive model of renal allograft loss in young pediatric recipients to inform donor selection. We aimed to develop and validate a predictive model of graft loss in an international cohort of young kTx recipients.

Methods: We included first-time kTX recipients under 5 years of age in the USA, Australia, New Zealand, UK and France between 2005 and 2018. A multivariate Cox regression was used to develop a predictive model of graft loss or death on the US cohort. Model discrimination (C-statistics) and calibration were assessed internally and externally on the non-US cohort.

Results: 2543 kTx in children <5 years old were included. 10-year overall graft survival rate was 80.0% [95% CI = 77.7% – 82.2%]. Given the interaction between some predictors and recipient's age, we developed two models stratified on recipient age (cut-off: 36 months) including donor/recipient body surface area ratio, ischemia time, donor weight and immunological matching. Immunological matching was a stronger predictor among older recipients, while morphological variables were stronger predictors in younger recipients. C-statistics on the training cohort were 0.63 (95% CI = 0.57 –0.68) and 0.65 (95% CI = 0.59 – 0.71) and the models were well calibrated. Figure 1 presents the discrimination of the models at different time horizons and the calibration at 10 years on the validation cohort.

Conclusions: We confirm the overall good renal allograft survival in children transplanted under the age of 5. We developed and validated predictive models of graft loss or death based on pre-transplant factors in this population that may be used to inform donor selection.



AUC and 95% CI at different horizons in the validation cohort and 10-year calibration plots in validation cohorts (A, C: ≤ 36 months old / B, D: > 36 months old)

PO2348

Safety and Efficacy of Low-Dose Rabbit Antithymocyte Globulin in Pediatric Renal Transplant Recipients

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Background: Currently there is no consensus among pediatric kidney transplant centers regarding the use and regimen for immunosuppressive induction therapy. The safety and effectiveness of reduced Rabbit Antithymocyte Globulin (ATG) ≤ 3.5 mg/kg cumulative dosing as induction therapy in low risk pediatric kidney transplant recipients is unknown.

Methods: Pediatric renal transplant recipients transplanted 1/1/2013-5/1/2018 were considered for inclusion. Recipients of deceased or living donor organs and with least 12-month follow-up were included. "High risk"was defined by a repeat transplant, preformed donor specific antibodies (DSAs), peak panel-reactive antibodies >20%, or African-American race. Maintenance immunosuppression protocol was tacrolimus and mycophenolate mofetil, steroid free unless high risk. Outcomes were de novo DSA (dnDSA) formation, graft survival, biopsy proved rejection (BPR) and EBV/CMV/BK viremia/infection during the first 12 months. DSAs were routinely screened at 3,6 and 12 months. Protocol biopsies were done at 6 and 12 months and graded with Banff criteria. Subclinical/borderline findings were included with or without treatment. Additional DSA testing and/or biopsies were done if there was a clinical concern. Group 1: low risk patients, ATG dose of ≤ 3.5 mg/kg, Group 2: low risk patients receiving dose of >3.5 mg/kg and Group 3: high risk patients

Results: A total of 181 patients met inclusion criteria. Age of patients was 11 years (11 mo-21 y),(median, range), 21% received a living donor transplant and 49% were female. Graft survival and dnDSA formation did not differ significantly between the three treatment groups. Graft loss at 12 months was a rare event with 99.5% graft survival and patient survival was 100%. Patients outcomes based on groups is shown in the table.

Conclusions: Reduced ATG dosing (≤ 3.5 mg/kg) when compared with higher dosing (>3.5 mg/kg) is safe and effective. Reduced ATG dose was associated with lower rates of BK viremia and BK nephropathy without increasing risk of dnDSA or BPR

Funding: Private Foundation Support

	Low risk ≤ 3.5 mg/kg	Low risk >3.5 mg/kg	High risk	P value
n	58	50	73	
dnDSAs n (%)	10(17.2)	5(10)	14(19.2)	ns
ATG dose (mean)	3.1	4.5	5.6	
EBV n (%)	10(17.2)	6(12)	13(17.8)	ns
CMV n (%)	13(22.4)	4(8)	11(15)	ns
BK n (%)	16(27.6)	19(38)	13(17.8)	0.01
BK nephropathy	0(0)	5(10)	1(1.4)	0.01
Acute Rejection	17(29.3)	14(28)	16(21.9)	ns
Graft loss	0	1 (BK nephropathy)	0	ns

PO2349

Pediatric-Specific Models Improve Prediction of Kidney Transplant Survival for Children Under 5 Years Old

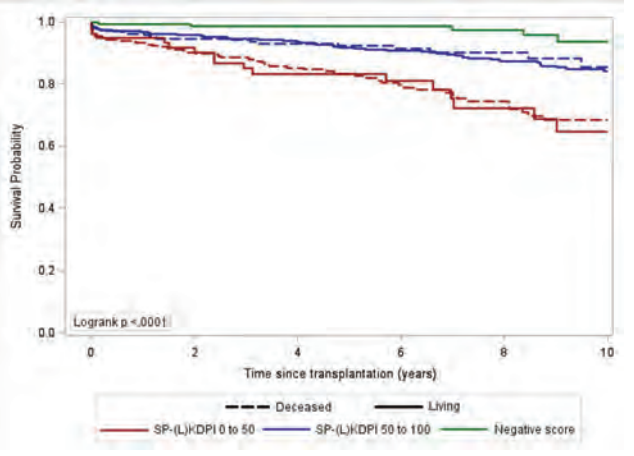
Florian Manca Barayre,[1] Larry A. Greenbaum,[1] Rouba Garro,[1] Pamela D. Winterberg,[1] Rachel E. Patzer,[1] Julien Hogan.[1,2] Emory Transplant Center [1]*Emory University, Atlanta, GA;* [2]*Robert-Debré Hospital, APHP, Paris, France.*

Background: The kidney allocation system directs high-quality kidneys to pediatric recipients, but the kidney donor profile index (KDPI) used to quantify donor quality may not accurately predict graft survival in small pediatric recipients. We aimed to determine if a pediatric-specific KDPI could improve the prediction of graft longevity for young recipients.

Methods: We evaluated first-time kidney transplantations in pediatric recipients between 1/2005 and 8/2018 in the U.S. (SRTR) and used a Cox model to assess KDPI accuracy for combined primary outcome of death or graft loss in young recipients. We developed an adapted KDPI score for recipients <5 years old of deceased (SP-KDPI) or living (SP-LDKPI) adult donor transplants using multivariate cox regression and scaled these models to allow comparison between living and deceased donors. Models' accuracies were validated internally by cross-validation.

Results: KDPI C-statistic was 0.52 (95% CI = 0.50 – 0.54) in recipients less than 5 years old. Ethnicity, age, body surface area, gender, cold ischemia time and number of HLA-B mismatches, were significant predictors for deceased donors (SP-KDPI model) while race, age, HLA-B mismatch and donor/recipient body surface area ratio were used in the living donor model (SP-LKDPI). C-statistics were 0.64 (95% CI = 0.57 – 0.70) for SP-KDPI and 0.65 (95% CI = 0.58 – 0.73) for SP-LKDPI. Figure 1 shows allograft survival by donor type and SP-(L)KDPI stratum. The SP-LKDPI model identified 16.8% of living donors with predicted graft survival superior to any deceased donor (denoted as SP-LKDPI <0).

Conclusions: Our adaptation of the KDPI demonstrated a higher accuracy to predict graft loss in young recipients of deceased donors. Furthermore, our SP-LKDPI model may allow direct comparison of living versus deceased donors offered to the youngest recipients.



Observed graft survivals by type of donor and SP-(L)KDPI

PO2350

Reduced 1-Year Allograft Function in Pediatric Renal Transplant Patients: Role of Subclinical Viral Replications

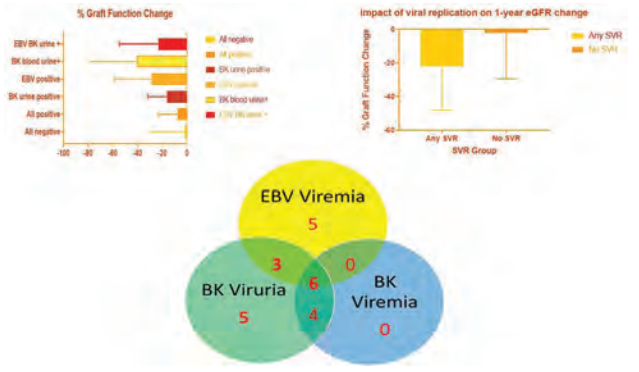
Raja Dandamudi, Stanley P. Hmiel, Vikas R. Dharnidharka. *Washington University in Saint Louis School of Medicine, Saint Louis, MO.*

Background: BK virus (BKV) and Epstein-Barr virus (EBV) subclinical viral replications (SVR) are common after renal transplant. The effects of SVR on the GF in pediatric kidney transplant (pKTx) recipients is not well defined and was the purpose of this study.

Methods: This retrospective study was done in our hospital from Jan 2012 to Dec 2018. 480 serum and urine samples from 39 pKTx were analyzed for viral load by quantitative PCR through the first post-transplantation year. Clinical characteristics, including GF by estimated glomerular filtration rate (eGFR) via bedside Schwartz formula were collected simultaneously. Analysis of differences between GF in patients with and without SVR was performed with t test and differences of $P < 0.05$ was significant.

Results: SVR occurred in 23/39(59%) of pKTx. EBV SVR occurred in 13/39(33%) pKTx at a mean (M) 95.8 days after transplantation (range(R) 14 to 220 days). M EBV level was 9188copies/ml (R 2K to190K copies/ml). BK viremia occurred in 10 pKTx at a M 132 days after transplantation (R 11 to 276 days) with a M level 49769 copies/ml (R 2K to 1,610K copies/ml). BK viruria occurred in 18 pKTx at a M 83 days after transplantation (R 11 to 230 days) with a M level 22,339,360 copies/ml (R 5K to 100,000K copies/ml). There was a significant difference in GF decline in patients with any SVR (M 21.97, SD 26.29) compared to patients with no SVR (M 2.1, SD 27.23), p 0.013. Patients with subclinical EBV/BK viremia and BK viruria experienced a M decrease of 28.9 (SD 29.78) and 40.72 (SD 38.06), and 16.53 (SD15.33) respectively, in GF during the 1-year period follow up. In patients with combined BK viremia, viruria and subclinical EBV RA experienced a M decrease in GF of 7.51 (SD 15.57) a year after transplantation.

Conclusions: BKV and EBV SVR significantly impacted the GF 1-year post transplant and therefore likely on long-term GF. Multicenter studies are required to study whether combined SVRs have more serious impact on GF than the corresponding mono SVR.



PO2351

The Creeping Creatinine in a Growing Child with a Kidney Transplant (KT): Using Absolute GFR Values to Separate Age Effects from Progressive Graft Dysfunction

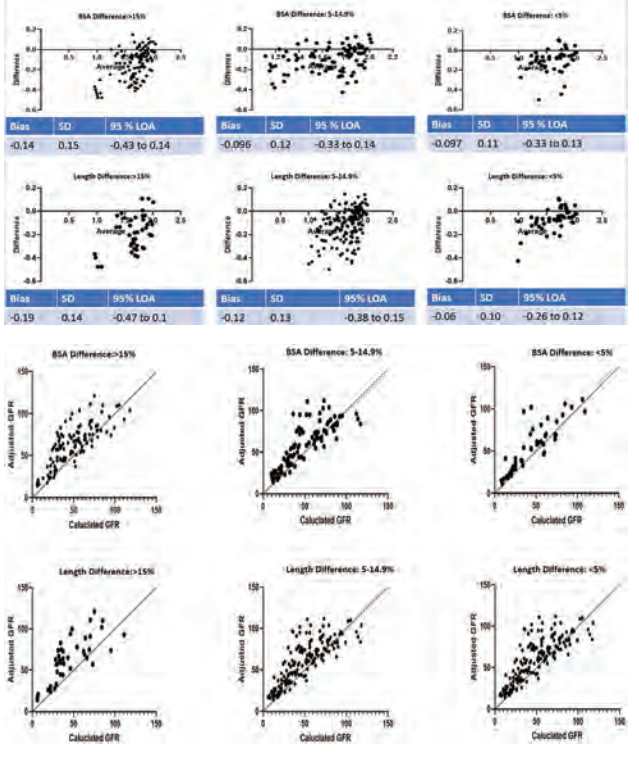
Raja Dandamudi, Stanley P. Hmiel, Vikas R. Dharnidharka. *Washington University in Saint Louis School of Medicine, Saint Louis, MO.*

Background: In very young KT recipients, the serum creatinine rises and glomerular filtration rate (GFR) decreases over the years. Without a biopsy, judging in a less invasive way whether this decline in GFR is due to linear body growth or progressive chronic allograft dysfunction is difficult. In measured glomerular filtration rate (mGFR) assays, the GFR is reported both as ml/min (ABS-GFR) and ml/min/1.73m2 (body surface area or BSA-GFR). We hypothesized that children who had rising serum creatinine predominantly due to linear growth would show a minimal change in ABS-GFR, with greater change in BSA-GFR.

Methods: This is retrospective cross-sectional study of 127 children who were aged < 15 years at time of transplant. We conducted analysis after stratifying basing on the height or BSA changes (< 5% change, 5-14.9% change and >15% change in linear height and BSA) between mGFR tests. Bland–Altman analyses were conducted to determine the agreement between log-ABS-GFR and log-BSA-GFR. We also performed correlation analysis with nonparametric Spearman's rank order correlation coefficient of BSA-GFR and ABS-GFR values.

Results: The bias between ABS-GFR and BSA-GFR increased as the percentage change in height and BSA increases (Figure). Spearman's rank order correlation demonstrated strong correlation when the BSA and length changes are<5% and the correlation weakened as the % changes increased.

Conclusions: We propose that in longitudinal follow up, it is important to use the ABS-GFR to avoid bias with the indexed GFR due to possible BSA change. A stable absolute GFR can be used to infer stable allograft function.



PO2352

Variability in Surveillance Monitoring and Management of Donor-Specific Antibodies Among Pediatric Transplant Programs Participating in the Improving Renal Outcomes Collaborative (IROC)

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Background: There have been few advancements in long-term outcome of pediatric kidney transplant (KT) recipients who develop rejection. Many centers perform surveillance monitoring for donor specific antibodies (DSA) to diagnose and treat subclinical rejection. Despite the existence of guidelines, there is variability in monitoring and management of DSA post-pediatric KT.

Methods: An IRB approved survey was distributed using REDCap among pediatric KT programs participating in IROC to evaluate practice patterns in monitoring and management of DSA post KT.

Results: Twenty-nine of 33 (88%) IROC centers completed the survey. Twenty-five of 29 (86%) centers perform surveillance DSA monitoring. Of those 25 centers, 20 (69%) check DSA twice or more in year one post KT. Nineteen (65%) check once in the second year and annually thereafter. Ten (35%) centers check DSA only by indication after year two post KT. Twenty-eight (97%) utilize MFI trend in interpreting DSA results and 10 (34%) centers use C1q complement fixing antibody assay to guide management. Management of patients with +DSA, stable creatinine and no evidence of antibody mediated rejection (AMR) on biopsy varies across centers from monitoring alone (10/29, 34%) to intensifying baseline immunosuppression (19/29, 66%). Very few centers reported giving IVIG alone (3/29, 10%) or IVIG and rituximab (3/29, 10%). Only 34% of centers (10/29) perform kidney biopsy if DSA develops with stable creatinine. When rituximab is used for treatment of DSA+ AMR, 11/29 (41%) centers use one dose and 13/29 (45%) use 2 doses with variable frequency. Of centers that use IVIG as monotherapy for treatment of DSA+ AMR, 12/20 (60%) use 1 g/kg/dose and 6/20 (30%) use 2 g/kg/dose. The frequency of IVIG dosing is monthly in 16/20 (80%). The number of IVIG doses is variable ranging from 1 to 6.

Conclusions: There is significant variability in surveillance monitoring and management of DSA post-KT across pediatric centers. Large, multicenter studies should be considered to evaluate the ideal post-KT surveillance DSA monitoring strategy and to determine the effect of different treatment approaches on long-term outcomes in pediatric KT recipients.

PO2353

Assessment of Pediatric Nephrology Programs' Readiness to Participate in Prospective Clinical Trials

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Background: Currently, there is a limited availability of effective, FDA-approved drugs for children with kidney disease in the United States; therefore, there is an increased need for clinical trials to evaluate drug effectiveness and safety for pediatric usage. Implementation and conduction of clinical trials is complex process, which requires a team approach, involves multiple inter-dependent steps, research infrastructure support, legal policies/procedures, equipment, and access to a regulatory oversight board. The conduct of clinical trials in small pediatric subspecialties (i.e. pediatric nephrology) may be hampered by provider clinical demands and small numbers of patients available for such studies. The goal of this survey was to assess the readiness to conduct clinical trials by pediatric nephrologists in institutions of different sizes. Assessment would also give consideration to the sites for prospective trials and educate the programs about steps needed in clinical research.

Methods: The survey was designed and tested by a small group of pediatric nephrology experts. Qualtrics Online Survey Platform and Statistical analysis were used. The survey was distributed to members of ASPN (60 sites in 30 U.S states and 2 Canadian Provinces). Respondents were asked to complete the survey on behalf of the institution/practice, not their individual preferences. There was a total of 17 survey questions, which assessed the respondent's institution's participation/interest in conduction of clinical research, availability of a clinical research coordinator/IRB, and access to equipment for trial execution (dry ice, centrifuges, freezers).

Results: Currently, we have recorded 68 survey responses. Two of the responding institutions had no interest in conducting clinical trials (2.9%). Notably, more respondents practiced at Academic Centers/Universities (91%) than in private practices (8.3%). We noted no major differences in access to clinical trial resources between large and small institutions.

Conclusions: Clinical trials remain vital to finding better treatments and cures for pediatric patients with renal diseases. Overall, pediatric nephrology programs have good infrastructure and readiness to conduct clinical trials independently of the size of the institution.

PO2354

Telemedicine During the COVID-19 Pandemic: Parents' Experience in a Pediatric Nephrology Clinic at the University of Florida

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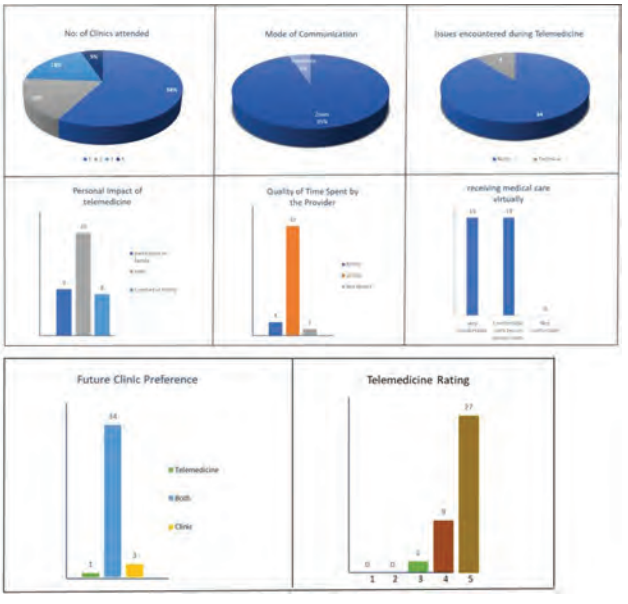
Background: In the setting of the COVID-19 pandemic, pediatric nephrology clinics at the University of Florida were switched to telemedicine. This transition occurred quickly without much education to either providers or families. There are some attempts to study the experience of providers, but there is no data regards to patients' and parents' experience with telemedicine.

Methods: We surveyed parents and patients (>18 years old) who had at least 1 telemedicine encounter via anonymous Qualtrics® survey sent to their email. Results were analyzed via qualitative analysis.

Results: Out of the 80 patents, 47.5% (38) completed the survey. 95% of the patients participated via Zoom and 5% used the telephone. 10.5% experienced technical issues. 100% reported that telemedicine had a positive impact on their family life. In response to the quality of time spent with physicians, 84% reported that telemedicine was similar to the clinic, and 10.5% reported it was better. In terms of receiving virtual medical care, 50% reported that they were very comfortable, 50% reported that they were comfortable but preferred some interim clinic visits. 71% rated telemedicine experience 5, 25% rated 4, and 5% rated 3 out of 5.

Conclusions: We observed that parents perceived the effect of telemedicine clinics as positive in respect to ease in the incorporation, quality of time spent by the physician, receiving virtual medical care, and the impact on the families. Though telemedicine seems to be effective in the current setting, it can only be served as adjunctive to in-person clinic visits in the future, since 90% of families preferred a mixture of clinic and telemedicine visits in our setting. Larger studies are needed to further evaluate the utility and efficacy of telemedicine in a pediatric setting.



PO2355

Prevalence and Determinants of Sickle Cell Nephropathy in Children Living in a Low-Resource Setting

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Background: Clinical and genetic factors have been reported to influence the development of sickle cell nephropathy (SCN). However, data on the association between these factors and SCN remain limited in the pediatric population, especially in sub-Saharan Africa. Our study aimed to: (i) determine the prevalence of the reported markers of SCN, including albuminuria, glomerular hyperfiltration and reduced kidney function in a pediatric sickle cell anemia (SCA) population from the Democratic Republic of Congo (DRC); (ii) examine the association between these SCN markers and some clinical and genetic factors.

Methods: Clinical parameters were collected. All participants were genotyped for Apolipoprotein-L1 (*APOL1*) G1 (rs73885319, rs60910145) and G2 (rs71785313) variants, and for Heme oxygenase 1 (*HMOX1*) GT dinucleotide repeats (rs3074372). *APOL1* high-risk genotype (HRG) was defined by the presence of 2 risk variants (G1/G1, G2/G2, and G1/G2) and low risk genotype (LRG) if 0 or 1 risk variants were present. *HMOX1* GT dinucleotide repeats were categorized into two allele classes (≤ 25 repeats as short and > 25 repeats as long). As the main outcomes, albuminuria was defined as albumin-to-creatinine ratio (ACR) ≥ 30mg/g, reduced kidney function (eGFR <60 ml/min per 1.73 m^2) and glomerular hyperfiltration (eGFR > 130 and 140 ml/min/1.73 m^2 for female and male, respectively).

Results: From 361 participants enrolled, 73 (20.2%) presented with albuminuria, 104 (28.8%) with hyperfiltration and 19 (5.26%) had reduced kidney function. Logistic regression analysis revealed that blood transfusions (> 9 per year) were significantly associated with albuminuria (P = 0.036); age (P = 0.015) and diastolic hypertension (P = 0.0099) were significantly associated with hyperfiltration. *APOL1* HRG emerged as the main genetic factor associated with both albuminuria (odds ratio [OR]: 3.70, 95% confidence interval [CI]: -0.0037—2.55; P = 0.041) and hyperfiltration (OR: 21.84, 95% CI: 1.51—5.20; P < 0.001), while no association was found with *HMOX1 GT* repeats.

Conclusions: Kidney disease is highly prevalent in children with SCA in the DRC. *APOL1* HRG is the main determinant associated with the risk of developing SCN.

Funding: Government Support - Non-U.S.

PO2356

Disparities in Kidney Failure Care for Children: A Global Survey

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Background: Globally, the capacity to access and deliver kidney replacement therapies (KRT - dialysis and transplantation) to children has never previously been described. The present study reports current disparities in access to kidney care between children and adults worldwide based on the results of the 2018 International Society of Nephrology Global Kidney Health Atlas (GKHA) survey.

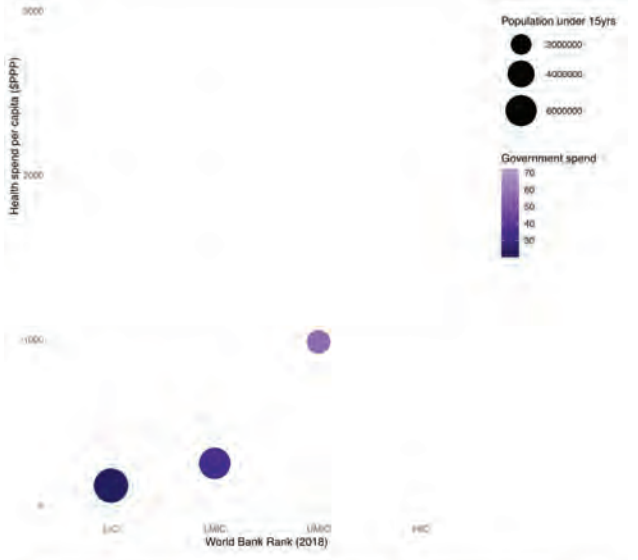
Methods: A mixed methods analysis of pediatric-specific data from the 2018 GKHA survey were used. Respondents were from countries categorized as low (LIC), lower-middle (LMIC), upper-middle (UMIC) or high income (HIC) according to 2018 World Bank income classification. Descriptive statistics were used for the population-based analysis of health expenditure across different world bank countries. Open text responses were thematically analyzed using HyperRESEARCH.

Results: Responses were received from 160 (88%) of 182 countries, including LIC (n=26, 16%), LMIC (n=36, 23%), UMIC (n=39, 24%) and HIC (n=59, 37%). Child access to end stage kidney disease care (ESKD) and KRT differed from adults in 29% and 23% of countries, respectively. Lower income countries were associated with graded increases in disparate access to ESKD (LIC 62%, LMIC 38%, UMIC 18%, HIC 19%) and KRT care (LIC 58%, LMIC 33%, UMIC 13%, HIC 9%). Five themes explained access disparities for children: inadequate resources for KRT; kidney failure care is expensive and incurs lifelong costs; priority and access based on a country's economic status; a lack of child-specific resources; and longer travel distances for children.

Conclusions: There are significant disparities worldwide in care for children with kidney failure when compared with adults, particularly in low resource settings. Future policy and advocacy efforts are needed to promote universal, equitable kidney care for children globally.

Funding: Government Support - Non-U.S.

Figure 1. Health care expenditure (per capita, $PPP) and government spend on kidney failure related care (as a % of the total cost of treatment) stratified by World Bank Income Groups (2018).



Note: the median pediatric population (under 15 years) per income group is directly proportional to the size of each bubble plotted. The color gradient of the bubble represents the mean percentage of the total cost of kidney failure related care covered by a government – the darker the color of the bubble, the more that is spent by the government.

PO2357

Clinical and Biopsy Characteristics in a Pediatric Cohort of C3 Glomerulopathy (C3G) and Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

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Background: C3G and IC-MPGN are rare diseases. The ability to identify and phenotype children with C3G and IC-MPGN using electronic health records (EHR) would aid description of natural history and prognosticate therapeutic response.

Methods: Using a computable phenotype algorithm, a pediatric cohort of children with glomerular disorders was identified in PEDSnet, a national network of pediatric health systems with aggregated EHR data, and refined using MPGN-specific SNOMED-CT codes to identify C3G and IC-MPGN patients at 6 centers. Discrete data elements were captured from electronic health records, and additional clinical data were extracted by standardized chart review. Biopsy diagnosis was classified as C3G or IC-MPGN by applying an automated algorithm to immunofluorescence data.

Results: Of 285 identified patients, 173 were true cases of C3G or IC-MPGN (Tables 1 and 2). Median C3 level at diagnosis was lower in C3G compared to IC-MPGN (p=0.005). There were no significant differences in light microscopic injury pattern or ultrastructure between C3G and IC-MPGN biopsies, but C3 intensity was higher in C3G compared to IC-MPGN (p = 0.006) (Table 3).

Conclusions: Patients with C3G and IC-MPGN can be identified and characterized by the use of a computable phenotype, allowing the creation of robust databases to define clinical predictors of treatment response. This may prove to be a vital asset for recruitment into clinical trials of complement-targeted agents likely beneficial to this patient population.

Funding: NIDDK Support, Commercial Support - Mallinckrodt Pharmaceuticals

Table 1. Patient Characteristics

	Total adjudicated MPGN cases	C3G	IC-MPGN
N	173	59	71
Age at diagnosis (years)			
0-4	7 (4.1%)	3 (5.1%)	2 (2.8%)
5-9	48 (28%)	17 (29%)	20 (28%)
10-14	68 (39%)	26 (44%)	18 (25%)
15-20	48 (28%)	12 (20%)	19 (27%)
20+	2 (1.2%)	1 (1.7%)	0
Follow-up time since diagnosis (years)	5.2 (2.6, 8.1)	5.8 (2.5, 8.1)	4.6 (2.7, 7.8)
# of nephrology visits (per person-year)	3.4 (1.8, 7.0)	3.1 (1.8, 5.7)	4.1 (2.7, 7.1)
Dialysis	16 (9.3%)	4 (6.8%)	3 (4.2%)
Kidney transplant	12 (6.9%)	3 (5.1%)	2 (2.8%)
Serum albumin (g/dL)	3.2 (2.4, 4.0)	3.0 (2.4, 4.0)	2.5 (2.1, 3.7)
Complement C3 (mg/dL)	42.1 (17, 89)	27.5 (12, 53.8)	42.5 (22, 102)

Table 2. Therapeutics

	Total adjudicated MPGN cases	C3G	IC-MPGN
ACE inhibition	121 (70%)	43 (73%)	42 (59%)
Angiotensin receptor blockade	54 (31%)	17 (29%)	22 (31%)
Immunosuppression/Immunomodulatory			
Corticosteroid	130 (75%)	44 (75%)	48 (68%)
Mycophenolate	74 (43%)	30 (51%)	23 (32%)
Calcineurin inhibitor	38 (22%)	9 (15%)	13 (18.3%)
Cyclophosphamide	2 (1.2%)	0	1 (1.4%)
Azathioprine	11 (6.4%)	5 (8.5%)	3 (4.2%)
Eculizumab	17 (9.8%)	10 (17%)	5 (7.0%)

Table 3. Biopsy Characteristics

	C3G	IC-MPGN
N	75	92
Light microscopy		
Membranoproliferative pattern	49 (66%)	69 (75%)
Mesangioproliferative pattern	28 (37%)	43 (47%)
Endocapillary proliferative pattern	18 (24%)	30 (33%)
Crescents	16 (22%)	26 (28%)
Globally sclerotic glomeruli	32 (43%)	29 (32%)
C3 Intensity on Immunofluorescence		
<2+	4 (5%)	19 (21%)
2+/2-3+	11 (15%)	21 (23%)
3+/3-4+	37 (49%)	34 (37%)
4+	23 (31%)	18 (20%)
Electron Microscopy		
Mesangial deposits	59 (81%)	64 (73%)
Subendothelial deposts	47 (64%)	63 (72%)
Intramembranous deposits	42 (58%)	44 (50%)
Subepithelial deposits	27 (37%)	31 (35%)

Data are reported as n (% of cohort), or median values with interquartile range where applicable.

PO2358

Efficacy and Safety of Ravulizumab in Pediatric Patients with Atypical Hemolytic Uremic Syndrome Naïve to Complement Inhibitor Treatment: 26-Week and 1-Year Data

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Background: Ravulizumab is a complement C5 inhibitor derived from eculizumab, with an increased half–life extending the maintenance dosing schedule from every 2–3 to every 4–8 weeks. We evaluated the efficacy and safety of ravulizumab to resolve active thrombotic microangiopathy (TMA) in children with atypical hemolytic uremic syndrome (aHUS) naïve to complement inhibitors.

Methods: ALXN1210-aHUS-312 (NCT03131219) is a phase 3, single–arm trial in children with TMA due to aHUS. Patients received ravulizumab every 4–8 weeks, depending on bodyweight. The primary endpoint was complete TMA response (platelet count and lactate dehydrogenase normalization and ≥25% improvement in serum creatinine from baseline at 2 visits ≥28 days apart) through 26 weeks. Key secondary endpoints included eGFR and dialysis requirement. Patients were then followed in an ongoing extension period. Here we report efficacy outcomes through 1 year and safety from all available follow–up (median 82.6 weeks).

Results: Eighteen patients (mean [SD] age 6.4 [4.5] years; 55.6% female) were enrolled; 14 (77.8%) achieved complete TMA response by 26 weeks, and 3 more patients (94.4%) by 50 weeks. Further improvements in TMA parameters occurred with longer-term treatment (Table). Mean (SD) increase in eGFR from baseline was 85.4 (54.3) mL/min/1.73m^2 at 26 weeks, and 94.1 (50.7) at 50 weeks. Of 6 patients on dialysis at baseline, 5 (83.3%) discontinued dialysis by week 26, and the last patient by week 50. Complete free C5 inhibition was sustained through the trial. No unexpected adverse events, deaths, or meningococcal infections occurred.

Conclusions: Ravulizumab administration every 4–8 weeks improved hematologic and renal outcomes in 94% of patients, with no unexpected safety concerns. Renal function improved with longer-term treatment.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

Complete TMA response components over time

Variable	Initial evaluation period (26 weeks) n=18	All available follow-up n=18
Complete TMA response	14 (77.8)	17 (94.4)
Platelet count normalization	17 (94.4)	17 (94.4)
LDH normalization	16 (88.9)	17 (94.4)
25% improvement in serum creatinine from baseline	15 (83.3)	17 (94.4)
Hematologic normalization	16 (88.9)	17 (94.4)

Data shown as n (%). LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

PO2359

A Pharmacologic "Stress Test" for Assessing Select Antioxidant Defenses in Patients with CKD

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Background: Oxidative stress is a hallmark and mediator of CKD. Diminished antioxidant defenses are thought to be partly responsible. However, there is currently no way to prospectively assess antioxidant defenses in humans. RBT-6 (stannous protoporphyrin; SnPP) induces mild, transient oxidant stress in animal models, triggering increased expression of select antioxidant proteins (eg, heme oxygenase 1 [HO-1], NAD[P]H dehydrogenase [quinone] 1 [NQO1], ferritin, p21). Hence, we tested the hypothesis that RBT-6 can also variably increase these proteins in humans and can thus serve as a pharmacologic "stress test" for gauging gene responsiveness and antioxidant reserves.

Methods: A total of 18 healthy volunteers and 24 participants with stage 3 CKD (n=12; eGFR 30–59 ml/min per 1.73m^2) or stage 4 CKD (n=12; eGFR 15–29 ml/min per 1.73m^2) received a single dose of RBT-6 at 9, 27, or 90 mg administered intravenously. Plasma and/or urinary antioxidant proteins were measured at baseline and for up to 4 days post-dosing. Kidney safety was assessed by serial measurements of BUN, creatinine, eGFR, albuminuria, and urinary AKI biomarkers (kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, cystatin C, and N-acetyl glucosaminidase).

Results: Plasma HO-1, ferritin, p21, and urine NQO1 were all elevated at baseline in CKD participants. Plasma HO-1 and urine NQO1 levels each inversely correlated with eGFR (r=-0.85 to -0.95). All four proteins manifested statistically significant dose- and time-dependent elevations after RBT-6 infusion. However, marked inter-subject differences were observed. p21 responses to high-dose RBT-6 and HO-1 responses to low-dose RBT-6 were significantly suppressed in participants with CKD versus healthy volunteers. RBT-6 was well tolerated by all participants, and no evidence of nephrotoxicity was observed.

Conclusions: RBT-6 can be safely administered and, after its infusion, the resulting changes in plasma HO-1, NQO1, ferritin, and p21 concentrations can provide information as to antioxidant gene responsiveness/reserves in subjects with and without kidney disease. Additionally, baseline values of these markers may also be indicative of oxidative stress at baseline, especially in patients in CKD.

Funding: Commercial Support - Renibus Therapeutics

PO2360

Prediction of Kidney Drug Clearance: A Comparison of Tubular Secretory Clearance and GFR

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Background: Tubular secretion is the primary mechanism of kidney drug elimination. Few studies have empirically evaluated the role of tubular secretion on the kidney elimination of administered drugs.

Methods: We evaluated 54 participants with and without chronic kidney disease. We administered a single dose of iohexol, furosemide, and famciclovir at the start of the study visit. We used LC-MS/MS to measure furosemide, penciclovir (the active form of famciclovir), and secretory solutes in sequential timed plasma samples and timed urine collections. We compared iohexol GFR (iGFR) with the kidney clearances of secretory solutes for predicting kidney drug clearance using mean absolute errors (MAE) derived from linear regression and leave-one-out cross-validation.

Results: Participants were characterized by a mean age of 55 years and a median iGFR of 73 ml/min/1.73m^2. Using iGFR as a single predictor, the MAE between model-predicted and measured furosemide and penciclovir clearance was 40.1 and 64.1 ml/min, respectively. The MAEs for models of individual secretory solute clearances were statistically similar to that of the iGFR model. The addition of kynurenic acid, pyridoxic acid, isovalerylglycine, and tiglylglycine clearances each individually improved the predictive accuracy of penciclovir clearance compared with the iGFR model.

Conclusions: The kidney clearance of secretory solutes and iGFR showed similar accuracy for predicting the clearances of furosemide and penciclovir, with some improvement from combining both measures. These findings provide cautious optimism that measurements of secretory clearance may improve kidney drug dosing.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

Accuracy of GFR and secretory solute clearances for predicting kidney clearance of furosemide and penciclovir

	Furosemide				Penciclovir			
	Secretory clearance as a single predictor		Secretory clearance plus iGFR as predictors		Secretory clearance as a single predictor		Secretory clearance plus iGFR as predictors	
	MAE between predicted and measured drug clearance, ml/min	Difference in MAE comparing iGFR to secretory clearance, ml/min (95% CI)[a]	MAE between predicted and measured drug clearance, ml/min	Difference in MAE comparing iGFR alone to iGFR plus individual secretory clearance, ml/min (95% CI)[a]	MAE between predicted and measured drug clearance, ml/min	Difference in MAE comparing iGFR to secretory clearance, ml/min (95% CI)[a]	MAE between predicted and measured drug clearance, ml/min	Difference in MAE comparing iGFR alone to iGFR plus individual secretory clearance, ml/min (95% CI)[a]
Pyridoxic acid	37.7	2.4 (-6.1, 9.7)	35.4	4.7 (-0.4, 10.5)	62.4	1.7 (-12.9, 16.2)	56.3	**7.8 (0.9, 16.2)**
Isovalerylglycine	40.6	-0.5 (-14.2, 10.8)	36.9	3.2 (-1.7, 14.1)	60.3	3.8 (-13.9, 21.7)	50.8	**13.3 (2.3, 27.4)**
Tiglylglycine	38.9	1.2 (-14.1, 12.8)	34.2	5.9 (-1.3, 16.3)	69.8	-5.7 (-22.3, 12.8)	54.8	**9.3 (0.9, 19.0)**
Kynurenic acid	37.4	2.7 (-8.7, 12.0)	33.3	6.8 (-0.4, 13.5)	70.7	-6.6 (-22.0, 14.6)	54.8	**9.3 (0.1, 21.1)**
Cinnamoylglycine	36.6	3.5 (-5.3, 11.2)	34.9	5.2 (-1.9, 11.8)	70.9	-6.8 (-23.1, 9.2)	61.3	2.8 (-2.3, 11.4)
Indoxyl sulfate	39.6	0.5 (-7.6, 9.1)	35.6	4.5 (-0.3, 10.6)	76.0	-11.9 (-25.3, 2.4)	61.7	2.4 (-1.5, 8.7)
p-cresol sulfate	38.9	1.2 (-6.6, 8.2)	37.2	2.9 (-0.6, 8.7)	61.9	2.2 (-12.1, 14.7)	57.6	6.5 (-0.4, 15.5)
Summary secretion score	31.0	9.1 (-1.7, 17.0)	31.6	8.5 (-0.2, 16.3)	53.2	10.9 (-2.9, 24.8)	52.3	**11.8 (3.8, 24.0)**

[a] Positive values indicate greater agreement for secretory clearances.

PO2361

Reduction in Proximal Tubular Secretion Precedes Reduction in Glomerular Filtration Rate in the Adenine-Induced CKD Model

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Background: Glomerular filtration rate (GFR) is frequently used to instruct dose levels of renally cleared drugs in patients with renal disease. This is based on the assumption that proximal tubule secretory clearance declines equally to GFR during disease progression. We tested this hypothesis in adenine-induced CKD mouse model.

Methods: C57BL/6 mice were fed either control or 0.2% adenine diet to induce progressive kidney damage. Body weight, urinary output, GFR and tubular secretion were monitored and histological analysis performed to assess disease progression at 1 and 3 weeks. Tubular secretion was estimated by measuring renal clearance of the endogenous secretory solutes indoxyl sulfate (IS), hippuric acid (HA) and cinnamoylglycine (CMG) using liquid chromatography couple to mass spectrometry. GFR was estimated by transcutaneous measurements.

Results: Mice on adenine diet developed kidney disease, indicated by progressive GFR decline. Histological assessment showed normal glomeruli throughout the study and a moderate tubular damage at 1 week which progressed to severe at 3 weeks. However, the maximum urinary albumin-creatinine ratio was reached already at 1 week of treatment, as was Kim-1, an early tubular injury marker, suggesting extensive early tubular injury and functional damage preceding structural damage. Likewise, when tubular secretion was assessed directly, a profound decrease in renal clearance of IS was detected already after 1 week on adenine diet with only a small further decrease by the 3rd week. Similar trends were observed for HA and CMG. In direct comparison, the decline in GFR versus tubular secretion over time revealed that at 1 week GFR was decreased by 30% whereas tubular secretion was decreased by >65%, suggesting earlier impact on the latter. Immunohistological analysis revealed a reduction in Oat1 transporter expression, to an extent not fully accounting for the reduction in secretion. This suggests a component of Oat1 inhibition and/or involvement of other transporters.

Conclusions: Our results indicate that tubular secretory function can be dissociated from glomerular filtration. Thus, assessment of tubular function based on GFR alone can be misleading, which has implications for dosing of renally excreted drugs to patients with kidney disease.

Funding: Commercial Support - AstraZeneca

PO2362

The Influence of Vitamin D Status and CKD on the CYP3A Metabolism Substrate Midazolam

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Background: Patients with chronic kidney disease (CKD) have a high prevalence of vitamin D (VitD) deficiency. Given its widespread use and knowledge of CYP gene induction, there is a paucity of data on how the pharmacokinetics (PK) of CYP3A substrates may be impacted by VitD in CKD. This study sought to investigate the role of VitD status (deficient vs. replete state) on CYP3A drug metabolism in CKD and healthy control (HC) subjects using midazolam (MDZ) as a prototypical probe substrate.

Methods: CKD (n=19) and HC (n=6) subjects with VitD deficiency (25(OH)D < 30ng/mL) were enrolled in a 2-phase study. In Phase 1, subjects were given one dose of oral cholecalciferol (D_3, 5000 IU) and oral MDZ (2 mg). In Phase 2, subjects received D_3 5000 IU daily for up to 14 weeks to repletion (25(OH)D >30 ng/mL) and were again given one dose of oral D_3 5000 IU and MDZ 2 mg. Blood was serially collected for up to 48 h at each phase. MDZ plasma concentrations were measured by LC-MS/MS. Population PK analysis was performed using Phoenix NLME (v.8.2, Certara®).

Results: A 2-compartment model with delayed absoprtion and a mixed ratio residual error model was fit to the observed MDZ plasma concentration data. Glomerular filtration rate (GFR) and study phase were included as covariates in the model. MDZ population parameter estimates (%RSE) were: central volume of distribution (Vc/F) 95.6 L (26.8%), clearance (CL/F) 31.1 L/h (25.0%), peripheral volume of distribution (Vp/F) 213 L (39.5%), inter-compartmental clearance (Q/F) 36.5 L/h (24.3%), and absorption rate constant (k_a) 16.4 h^{-1} (42%). Individual subject PK parameter estimates were determined from the population PK model (Table).

Conclusions: VitD status did not significantly influence the PK of MDZ in either HC or CKD subjects. There was a trend in CL/F being slower in CKD compared to HC regardless of phase, which may be due to decreased renal elimination or reduced ability for induction of CYP3A secondary to renal impairment. Future analyses will explore additional covariates to further reduce the error on MDZ PK parameters in order to discern differences between subjects in this small study.

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Table: Individual subject PK parameters from the population PK model

Parameter	CKD		HC		p-value
	Phase 1 (n =19)	Phase 2 (n = 13)	Phase 1 (n =6)	Phase 2 (n =5)	
Vc/F (L)	92.0 ± 45.5	104.8 ± 53.0	133.2 ± 69.4	126.8 ± 42.0	0.0890
CL/F (L/h)	34.7 ± 21.9	31.4 ± 16.3	42.4 ± 13.3	56.3 ± 22.8	0.1333
Vp/F (L)	237.3 ± 203.3	261.9 ± 227.2	264.6 ± 133.6	288.4 ± 131.9	0.5723
Q/F (L/h)	41.2 ± 25.2	44.2 ± 28.0	44.5 ± 19.1	47.7 ± 19.4	0.6240
k_a (h^{-1})	18.9 ± 9.5	16.5 ± 4.12	13.6 ± 5.5	16.8 ± 2.8	0.6951

Data reported as mean ± SD; p-values calculated using one-way ANOVA.

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Effect of Kidney Disease and Vitamin D Repletion on Drug Transporter Activity

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Background: CKD patients exhibit altered nonrenal drug clearance, which is reflected in numerous drug metabolism and transport pathways. Vitamin D (VitD) deficiency is common in CKD, and VitD-mediated regulation has been implicated in altering functional expression of renal and nonrenal transporters. This study aimed to elucidate the impact of VitD status (deficiency vs repletion) on drug transporter activity in CKD patients and healthy controls (HC).

Methods: VitD deficient ($25[OH]D_3$ < 30 ng/mL) subjects with CKD stage I-III (n=15), CKD stage IV-V (n=8) and HC (n=9) were enrolled. The phenotypic probe drugs fexofenadine (FEX) and olmesartan (OLM) were used to assess P-glycoprotein (P-gp), organic anion transporter (OAT) and organic anion-transporting polypeptide (OATP) function, and endogenous N-methylnicotinamide (NMN) was used to assess multidrug and toxin extrusion proteins 1 and 2K (MATE1/2K) activity. FEX 60 mg and OLM 10 mg were orally administered at baseline (VitD deficiency) and after 12 weeks of oral therapy with $VitD_3$ 5000 IU daily and confirmed repletion ($25[OH]D_3$ < 30 ng/mL). Serial blood and urine samples were collected for 48 hours. FEX, OLM, and NMN concentrations in plasma and urine were determined by LC/MS/MS and noncompartmental pharmacokinetic (PK) parameters were calculated.

Results: CKD IV-V subjects had 77% higher FEX systemic exposure (AUC, p=0.03), 37% lower clearance (p=0.03), and 68% longer half-life (p=0.0005) than HC at the time of VitD deficiency. In CKD I-III subjects, FEX AUC and C_{max} were increased 28% (p=0.03) and 52% (p=0.004), respectively, after VitD repletion. No differences in OLM PK were observed between VitD phases or subject groups. CKD IV-V subjects exhibited a doubling of AUC_{0-12} and 50% decrease in renal clearance of NMN after VitD repletion, but no differences were statistically significant.

Conclusions: The FEX data suggest that nonrenal transporter function (likely intestinal P-gp and/or hepatic OATP) is decreased in VitD deficient CKD patients and may be improved by VitD repletion. Reasons for unchanged OLM PK likely relate to overlapping substrate specificity with other transporters that are minimally effected by CKD or VitD status. Conversely, NMN results may suggest that MATE1/2-K function is decreased by VitD.

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PO2364

CYP3A and Drug Transporter Activity Changes in Thai Elderly with CKD Assessed Using a Microdose Cocktail

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Background: Chronic kidney disease (CKD) may influences cytochrome P450 (CYP) enzymes and drug transporters activity, resulting in the change of pharmacokinetics. This study investigated the effect of age and renal function on activity of CYP3A and various drug transporters in healthy Thai elderly and CKD patients using a validated microdose probe substrate cocktail.

Methods: Fifty three subjects were studied [healthy young subjects (Gr1, n=20), healthy elderly (Gr2, n=16) and elderly CKD patients (Gr3, n=17)]. Each subject was given a single dose of the microdose cocktail consisted of midazolam (M; for CYP3A), dabigatran etexilate (D; for gut P-gp), pitavastatin (P; for OATP1B), rosuvastatin (R; for BCRP, OATP, P-gp), and atorvastatin (A; for OATP, BCRP, P-gp, CYP3A). Plasma samples were collected at 0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after dosing. All plasma drug concentrations were measured using a fully validated LC/MS/MS. Area under the concentration-time curve (AUC) were calculated by the trapezoidal rule.

Results: No side effect was observed. Multivariate analysis, adjusted for body mass index, co-morbidity and liver functions) showed negative effects of ageing and CKD on drug transporters activity. AUC_{0-last} and maximum plasma drug concentration (C_{max}) were increased in Gr2 and 3 compared to those in Gr1 (AUC_{0-last} in Gr2 and 3, respectively: M 2.19 and 2.68 folds, D 1.65 and 4.43 folds, P 0.99 and 1.57 folds, R 1.43 and 1.83 folds, and A 2.19 and 4.20 folds; C_{max}: M 1.83 and 1.86 folds, D 1.23 and 1.61 folds, P 1.22 and 1.90 folds, R 1.12 and 1.59 folds, and A 2.28 and 4.22 folds). AUC_{0-last} of Gr3 were significantly increased when compared to Gr2 in D, P and A (2.69 ($p<0.001$), 1.59 ($p<0.001$) and 1.92 ($p=0.001$) folds, respectively). C_{max} were significantly increased only in P and A (1.70 ($p<0.001$) and 1.94 ($p<0.001$) folds, respectively).

Conclusions: Independent of ageing, CKD itself further reduces the activity of drug transporters, suggesting that this information has to be taken into account when drugs that pass through those transporters are prescribed to CKD patients.

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PO2365

Tacrolimus and Mycophenolic Acid Pharmacokinetics in Young, Middle-Aged, and Elderly Stable Renal Transplant Recipients

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Background: Tacrolimus (TAC) and mycophenolic acid (MPA) comprise a critical maintenance immunosuppressive regimen. Limited pharmacokinetic data are available comparing age-related differences of these immunosuppressive drugs which is an important fact considering the increase in renal transplants in older patients. This analysis compared TAC and MPA pharmacokinetics among young, middle age and elderly stable renal transplant recipients (RTR).

Methods: Twelve-hour TAC and MPA pharmacokinetic studies were conducted in 67 stable RTR at least 1-year post renal transplant. Tacrolimus dose regimens were adjusted to troughs (4 to 10 ng/ml) based upon time post-transplant. MPA regimens were adjusted using clinical responses only. Patients were categorized as: young: >21 & ≤ 40 years; middle age: >40 &≤ 60 years and elderly>60 years. Non-compartmental pharmacokinetic analysis determined area under the concentration-time curve 0-12hours (AUC0-12),

AUC4-12/AUC0-12 (to define MPA enterohepatic recirculation), apparent clearance (CL) normalized to BMI (CL/BMI) and 0 hour troughs. Univariate ANOVA was conducted using SAS V 9.4.

Results: Table 1 summarizes the results. No group differences were noted for estimated glomerular filtration rate, MPA and TAC doses. Enterohepatic recirculation and MPA troughs were reduced in elderly compared to young. For MPA target AUC0-12hr of 30 to 60 mg.hr/L, 34.3% of RTR achieved this range with 56.7% above this therapeutic exposure. There were 52.2% of RTR within the therapeutic tacrolimus AUC0-12hr target of 120-200 ng.hr/ml with 46.1% below this range with no age relationship. Reduced tacrolimus CL/BMI was noted in elderly compared to middle age.

Conclusions: Tacrolimus and mycophenolic acid pharmacokinetics demonstrates age-related differences with lower clearances or exposures in the elderly. Tacrolimus and mycophenolic acid immunosuppression may require age-adjusted individualization to achieve therapeutic exposure.

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Tacrolimus and Mycophenolic Acid Pharmacokinetics by Age

Endpoints (Mean[SD])	Young(N=16)	Middle Age(N=38)	Elderly(N=13)	P Value
MPA trough(mg/L)	5.8(3.6)	4.8(5.2)	3.3(3.6)	0.045*
MPA AUC4-12/AUC0-12	0.55(0.14)	0.51(0.15)	0.42(0.13)	0.047*
MPA CL/BMI	0.35(0.17)	0.38(0.19)	0.31(0.10)	0.539
TAC trough (ng/ml)	6.8(1.6)	6.9(1.9)	6.7(1.7)	0.948
TAC CL/BMI	1.01 (0.51)	1.01(0.51)	0.68(0.38)	0.055+

*: Significant

+: Trend toward significant

PO2366

A Single Time Point Plasma Concentration of Mycophenolic Acid Predicts Enteric-Coated Mycophenolate Sodium Exposure in Thai Renal Transplant Recipients

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Background: Enteric-coated mycophenolate sodium (EC-MPS) is a salt form of mycophenolate widely used in renal transplantation. The area under the concentration-time curve (AUC) of an active form of EC-MPS, mycophenolic acid (MPA) of ≥30 μg.h/L is highly associated with drug efficacy. However, this technique is impractical in clinical setting. Little is known regarding metabolites' AUC. This study determined the relationships of a single time point of plasma MPA level and the optimum MPA-AUC and assessed the cut off plasma levet of that single time point to predict AUC. The full profiles of active (7-O-MPA-glucuronide; MPAG) and inactive (acyl mycophenolic acid glucuronide; AcMPAG) metabolites, both free and total form are also measured and related to its AUC.

Methods: Twenty renal transplant recipients with EC-MPS were studied. On day 3 post transplantation, plasma samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, and 12 hours post dose. Total and free form levels of MPA and metabolites were measured using a fully validated LC-MS/MS. Receiver operating curve (ROC) was carried out.

Results: The AUC of the MPA total form moderately correlated with a single time point plasma MPA concentration at C_4 ($r^2 = 0.50$) with the concentration cut off 2.5 μg/ml (sensitivity 87%, specificity 80%, area ROC = 0.83). The AUC of the MPA free form poorly correlated with a single time point concentration. The AUCs of total and free forms of MPAG and AcMPAG highly correlated with a single time point concentration at C_6 ($r^2 = 0.97$) and C_8 ($r^2 = 0.95$) for MPAG and C_4 ($r^2 = 0.59$) and C_8 ($r^2 = 0.81$) for AcMPAG. high variability in metabolites concentrations were observed, suggesting inter-individual variability in drug metabolizing enzyme activity.

Conclusions: At the early stage post transplantation, in renal transplant recipients who received EC-MPS, a single time point of the total form plasma MPA concentration is best monitored at 4 hours post dose. The MPA level of 2.5 μg/ml at that time point predicts optimum AUC. Further studies required for the use of metabolites' AUCs to assess drug efficacy and to evaluate a single time point concentration that predicts drug exposure.

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PO2367

Preclinical Characterization of MAU868, a Novel Neutralizing Antibody Targeting BK Virus

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Background: Reactivation of BK virus (BKV) can cause significant kidney and bladder disease in immunocompromised patients. There are currently no effective or BKV-specific therapies. MAU868 is a novel human monoclonal IgG1 that binds to the BKV major capsid protein VP1. Its binding affinity, antiviral activity, and resistance profile were investigated *in vitro*.

Methods: Binding affinity was determined using a solution equilibrium titration assay. Neutralization of BKV infection in primary renal proximal tubule epithelial (RPTE) cells was evaluated by quantitating TAg-expressing cells using an immunofluorescence-based high content imaging assay. The emergence of BKV resistance-associated variants (RAVs) with reduced susceptibility to MAU868 was investigated in two long-term selection studies with BKV genotypes I and IV in RPTE and HEK-293 cells. Crystallographic studies were conducted using the MAU868 single-chain variable fragment bound to VP1 pentamers.

Results: MAU868 had pM binding affinity and sub-nM neutralizing activity against the 4 major BKV genotypes, with EC_{50} and EC_{90} values ranging from 0.009 to 0.093 μg/ml (0.062 to 0.645 nM) and 0.102 to 4.160 μg/ml (0.708 to 28.865 nM). No cytotoxicity observed up (highest concentration tested 500 μg/ml). MAU868 also potently neutralized BKV variants constructed to contain VP1 sequences from clinical isolates or highly prevalent VP1 polymorphisms, and JC virus, a related polyomavirus. No RAVs were identified following serial passage of BKV in the presence of MAU868 for up to 182 days. The crystal structure of MAU868 in complex with the VP1 pentamer at 2.66 Å resolution identified a conformational epitope including 3 contact residues in VP1 (Y169, R170, K172) that are strictly conserved across BKV isolates. BKV variants with double or triple alanine substitutions at residues Y169, R170, or K172 were non-viable.

Conclusions: The strict conservation of the contact residues within the conformational epitope of VP1 may explain the broad-spectrum antiviral activity of MAU868 and its high *in vitro* barrier-to-resistance, ideal characteristics for a potential first-in-class therapeutic agent for the treatment or prevention of BKV disease.

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PO2368

Pharmacokinetic Evaluation of Drug Interactions Between Vadadustat and HMG-CoA Reductase Inhibitors (Statins)

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Background: Cardiovascular disease is the most common cause of mortality in patients with chronic kidney disease (CKD). Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) in late-stage development for the treatment of anemia due to CKD. The prevalence of dyslipidemia in CKD is very high, and nearly 50% of patients have been prescribed statins to decrease cholesterol levels. The disposition of most statins is dependent on metabolic enzymes and transporters. This study evaluated the drug interaction potential for statins when co-administered with vadadustat.

Methods: In this 3-part study (NCT03801733), 108 healthy adults were enrolled for vadadustat-statin pharmacokinetic (PK) evaluation. Vadadustat (600 mg daily) was administered concomitantly with either rosuvastatin (20 mg; n=34), pravastatin (40 mg; n=26), atorvastatin (40 mg; n=24), or simvastatin (40 mg; n=24). PK evaluation of the statins was conducted following a single dose on Day 1 and after the washout period of a single dose when co-administered with steady state vadadustat. After treatment with a statin alone or a statin plus vadadustat, geometric mean ratios were calculated to determine the difference in the PK parameters area under the curve (AUC) and maximum concentration (C_{max}).

Results: Vadadustat was generally well tolerated by healthy subjects when taken alone or with statins. Exposure (AUC and C_{max}) to rosuvastatin, a BCRP and OATP1B1 substrate, increased 2- to 3-fold in the presence of vadadustat. No change in exposure to pravastatin (an OATP1B1 substrate) was observed. The AUC for atorvastatin (a BCRP and OATP1B1 substrate) increased 1.4-fold, although no change in C_{max} was noted; for simvastatin (a BCRP and OATP1B1 substrate), the AUC increased 2-fold and C_{max} increased 1.2-fold in the presence of vadadustat.

Conclusions: There were no clinically significant interactions with pravastatin or atorvastatin, suggesting that vadadustat has a low likelihood for OATP1B1-mediated drug interactions. Increases in exposures to rosuvastatin and simvastatin are possibly due to BCRP inhibition. In summary, these results provide information to aid in the management of concomitant administration of vadadustat with statins. Funded by: Akebia Therapeutics, Inc.

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PO2369

Impact of Renal Impairment and Dialysis on the Pharmacokinetics and Pharmacodynamics of Roxadustat

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Background: Roxadustat is an orally active hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of CKD anemia. The objective was to evaluate the pharmacokinetics (PK), metabolic profile, pharmacodynamics, and safety of roxadustat in patients (pts) with varying degrees of renal function (RF).

Methods: In this phase 1, open-label study (EudraCT: 2015-002565-28), pts were enrolled in one of four RF groups: normal (NRF; eGFR ≥90 mL/min/1.73 m^2); severely impaired (SIRF, not on dialysis; eGFR <30 mL/min/1.73 m^2); end-stage renal disease (ESRD) on continuous ambulatory or automated peritoneal dialysis (CAPD/APD); or ESRD on hemodialysis or hemodiafiltration (HD/HDF). Patients in the NRF, SIRF, and CAPD/APD groups received a single dose of 100-mg oral roxadustat on Day 1. Two treatment periods (P1/P2), separated by a washout period, were used for HD/HDF

pts; a single dose of 100-mg oral roxadustat occurred 2 hours after HD/HDF (P1) and 2 hours before HD/HDF, 2 days after the previous session (P2). The PK of roxadustat and its circulating metabolites (*O*-glucuronide-, *O*-glucoside-, and sulphate of hydroxy-roxadustat) were evaluated.

Results: Thirty-four pts were enrolled and received roxadustat (NRF, n=12; SIRF, n=9; CAPD/APD, n=1; HD/HDF, n=12). The geometric least-square mean ratio of AUC_{inf} relative to NRF pts was 223% (90% CI: 185, 268) and 195% (90% CI: 165, 229) in SIRF and HD/HDF, respectively. Roxadustat's C_{max} and $t_{1/2}$ were comparable between groups. The PK of roxadustat and its metabolites were not affected by HD/HDF. In NRF, the amount of unchanged roxadustat excreted in urine was <1%; urinary excretion and renal clearance of roxadustat and its metabolites decreased with lower baseline RF. Mean AUC_{inf} and $t_{1/2}$ for roxadustat's circulating metabolites were higher in SIRF and HD/HDF pts, compared to NRF. Metabolite:parent ratio of AUC_{inf} was <1% for *O*-glucuronide- and *O*-glucoside-roxadustat, and <10% for sulphate of hydroxy-roxadustat. Roxadustat was well tolerated in all groups.

Conclusions: The AUC for roxadustat and its metabolites was higher in SIRF and HD/HDF, compared to NRF. Roxadustat's C_{max} and $t_{1/2}$ were comparable among all groups. Roxadustat and its metabolites were not significantly cleared by HD/HDF.

Funding: Commercial Support - Astellas Pharma, Inc.

PO2370

A Genotype-Guided Antihypertensive Therapy and CKD Care Precision Health Initiative

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Background: A precision health initiative was implemented, wherein pharmacogenomic predictors of antihypertensive response and genomic predictors of chronic kidney disease (CKD) were provided to clinicians caring for nephrology patients.

Methods: This is a prospective cohort study of 580 individuals who presented to outpatient nephrology clinics. Subjects were genotyped for 60 antihypertensive response variants and chronic kidney disease (CKD) predictors. Predictors included variants of CYP2D6 for metoprolol dosing and CYP2C9 for angiotensin receptor blocker dosing. Variants in APOL1, UMOD, and SHROOM3 were markers of CKD risk prediction. Subjects were followed to ascertain utilization of the genetic information by nephrologists.

Results: The cohort was 46% female and 43% African-American. Actionable variants were found in 85% of subjects. These variants are known to affect metabolism of a drug or contribute to CKD progression. The prevalence of actionable genotypes was 66% for CYP2D6, and 36% for CYP2C9. In African American subjects, 23% of CKD patients had two APOL1 risk variants. Clinicians adapted treatment for 43% of individuals with actionable genotypes. The primary nephrologist was surveyed for each subject. In the 143 subjects who completed follow-up, nephrologists reported a change in diagnosis in 44% of their patients and a change in management in 28.0% based on genotype. Clinicians discussed the genetic testing results with their patients in 83.9% of cases.

Conclusions: Nephrologists utilized a genetic testing panel of up to 60 variants in the routine care of their CKD patients. Pharmacogenomics predictors of disease response may prove to be very valuable the care of patients with chronic kidney disease.

Funding: NIDDK Support

PO2371

KBP-5074, a Nonsteroidal Mineralocorticoid Receptor Antagonist, Reduces Urine Albumin-to-Creatinine Ratio and the Risk of Hyperkalemia in an Animal Model of CKD

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Background: KBP-5074 is a novel non-steroidal mineralocorticoid receptor antagonist (MRA) being developed for uncontrolled hypertension and advanced chronic kidney disease. The primary objective of this study was to evaluate KBP-5074 and eplerenone for renal protection against aldosterone-mediated renal disease in a uninephrectomized Sprague-Dawley (SD) rat model.

Methods: Uninephrectomized rats were maintained on a 6% high salt diet, and received aldosterone infusion for 27 days. Urinary albumin to creatinine ratio (UACR), urinary Na^+/K^+, and serum K^+ were assessed following 14 and 27 days of treatment. Blood samples were collected on days 1 and 26 to determine PK profiles. PK/PD analyses were performed on urinary Na^+/K^+ ratio, UACR, and serum K^+.

Results: KBP-5074 (1, 3, and 10 mg/kg/day) significantly reduced UACR by 77%, 96%, and 99% respectively on day 14, and 50%, 86% and 99% respectively on day 26 in a dose dependent manner, while eplerenone (100 and 900 mg/kg/day) reduced UACR by 40% and 99% respectively on day 26. PK/PD analysis of Urinary Na^+/K^+ ratio indicated that KBP-5074 was approximately 18-fold more efficacious than eplerenone. Analysis of UACR and serum K^+ indicated that the EC_{50} for serum K^+ increase and UACR reduction was 538 nM and 22.0 nM respectively for KBP-5074, and 666 nM and 1071 nM respectively for eplerenone, resulting in a therapeutic index (TI) against hyperkalemia of 24.24 for KBP-5074 vs 0.62 for eplerenone. Thus, the TI against hyperkalemia of KBP-5074 was 39-fold superior to that of eplerenone, suggesting that the non-steroidal MRA KBP-5074 may present an extended therapeutic window as compared to the steroidal MRA eplerenone.

Conclusions: KBP-5074 demonstrated a significant effect on UACR reduction with less risk for hyperkalemia compared to eplerenone in a rat model of nephropathy.

Funding: Commercial Support - KBP Biosciences USA Inc.

PO2372

Pharmacological Inhibition of Vanin 1 Is Not Protective in Models of Acute and Chronic Kidney Disease

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Background: Dysregulated oxidative stress handling is a hallmark of acute and chronic kidney diseases. The pantetheinase Vanin-1 is highly expressed in tubular cells and its reaction product cysteamine is described to negatively affect redox homeostasis by inhibiting the replenishment of cellular anti-oxidative glutathione stores. The aim of this study was to elucidate whether pharmacological inhibition of Vanin-1 protects mice from acute or chronic kidney injury.

Methods: C57Bl6 mice undergoing ischemia reperfusion injury and Col4α3-/- (Alport syndrome) mice were treated orally for 1d and 3wk, respectively, with a potent and selective Vanin-1 inhibitor or placebo. *In vitro* oxidative stress insult was mimicked in human renal proximal tubular epithelial cells either chemically or by hypoxia/reoxygenation. Kidney function was determined by serum and urinary creatinine as well as serum urea and urinary albumin. Furthermore, mRNA and protein expression, Vanin-1 activity, oxidative stress level and tubular apoptosis were monitored.

Results: Oxidative stress levels were elevated in all models. Treatment with the Vanin-1 inhibitor resulted in ample systemic compound exposure and full inhibition of Vanin-1 activity in kidney tissue *in vivo*. However, this did not translate to a relevant reduction of oxidative stress level. Moreover, kidney function (serum Crea, blood urea, albuminuria), fibrosis marker gene expression and tubular cell apoptosis were not improved by Vanin-1 inhibition.

Conclusions: Pharmacological inhibition of Vanin-1 is insufficient to protect kidneys from oxidative stress insults contributing to acute and chronic kidney injury. The biological relevance of pharmacological Vanin-1 inhibition for the treatment of kidney diseases remains to be proven.

Funding: Commercial Support - Bayer AG

PO2373

Evaluation of Veverimer Drug Interaction Potential

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Background: Veverimer is an orally administered HCl binder for treatment of metabolic acidosis in CKD. We assessed its potential for drug-drug interactions (DDIs) using a strategy based on its physicochemical characteristics. Since veverimer is a non-absorbed polymer, potential DDIs are limited to effects on absorption of other oral drugs via (1) direct binding or (2) increases in gastric pH resulting from HCl binding.

Methods: Features important for binding to veverimer were determined in vitro. A set of anionic probes and a panel of 16 drugs were used to define characteristics required for binding. Test drugs covered a broad range of size, charge, solubility and permeability characteristics across 14 drug classes. The magnitude and duration of veverimer's effect on gastric pH was determined in fed and fasting healthy subjects via 22-h monitoring with an intragastric pH probe. Results from binding and gastric pH studies informed selection of drugs for human DDI studies.

Results: In vitro studies showed the most important determinant for binding to veverimer is negative charge, with small size as a secondary determinant. Veverimer did not bind any positively charged, neutral or zwitterionic drugs. Negatively charged drugs >435 Da did not bind; the presence of chloride reduced or eliminated binding. The 2 drugs showing the most binding to veverimer in vitro (furosemide, aspirin) were chosen for human DDI studies. Veverimer increased gastric pH by ~3.0 (fasted) and 1.5 (fed) pH units. The gastric pH increase was transient, peaking by 1 h after dosing and returning to baseline after 1.5 (fasting) and 3 (fed) hours. Based on these results, 2 drugs with pH-dependent solubility (warfarin, dabigatran) were chosen for human DDI studies. In human DDI studies, no clinically meaningful changes in bioavailability were observed for furosemide, aspirin, dabigatran, or warfarin when coadministered with veverimer.

Conclusions: We observed: 1) no effect of veverimer on the bioavailability of drugs most susceptible to binding to the polymer; 2) modest, transient effects of veverimer on gastric pH; 3) no effect on bioavailability of drugs with pH-sensitive solubility. We conclude that there is a negligible risk of clinically significant veverimer DDIs.

Funding: Commercial Support - Tricida, Inc.

PO2374

Action of Veverimer on Gastrointestinal Acid Binding Is Not Affected by Omeprazole

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Background: Veverimer, an orally administered, non-absorbed polymer that selectively binds and removes hydrochloric acid (HCl) from the gastrointestinal tract, has been shown to correct metabolic acidosis in patients with CKD. Unlike proton pump inhibitors (PPIs), which do not affect systemic acid-base status, the removal of HCl

from the gastrointestinal tract by veverimer leads to a net increase in blood bicarbonate. Veverimer was designed to bind HCl across a wide range of intraluminal pH, but the effect of veverimer on acid binding in the presence of PPIs has not been previously described.

Methods: To evaluate the effect of veverimer on gastric pH, we conducted a Phase 1, open-label, 2-stage study in which subjects (N=46) were randomized 1:1:1:1 to receive 1 of 4 study drug treatments (water fasted; water fed; veverimer fasted; veverimer fed) in the presence and absence of a steady-state level of omeprazole. Gastric pH was measured continuously for 22 hours (hrs) using a microelectrode pH probe positioned in the gastric fundus.

Results: Ingestion of veverimer caused a modest, transient increase in gastric pH that peaked within 1 hr post-dose. In the absence and presence of food, the median (distribution-free 95% CI) times to peak pH after veverimer administration was 0.25 (0.17, 1.00) and 0.71 (0.25, 1.17) hrs, respectively. Peak pH after veverimer administration was ~3 and ~1.5 pH units greater than that observed after water control in the fasted and fed states, respectively. The magnitudes of these increases were in the same range in the presence of omeprazole. Gastric pH returned to baseline after ~1.5 hrs under fasting conditions and after ~3 hrs under fed conditions. In the presence of omeprazole, the veverimer-induced gastric pH increase dissipated by 4 hrs post-dose or shortly after initiation of the subsequent meal.

Conclusions: The effect of veverimer on gastric pH is transient and similar in the presence or absence of omeprazole. The magnitude of the individual effects of food, veverimer, and omeprazole on gastric pH were similar (increase of 2–4 pH units). These findings are consistent with prior studies in patients with CKD in which the magnitude of efficacy of veverimer was unaffected by use of H2-receptor antagonists and PPIs (Wesson et al. *Lancet*, 2019).

Funding: Commercial Support - Tricida, Inc.

PO2375

Clinical Pharmacology of Apixaban in Nephrotic Syndrome

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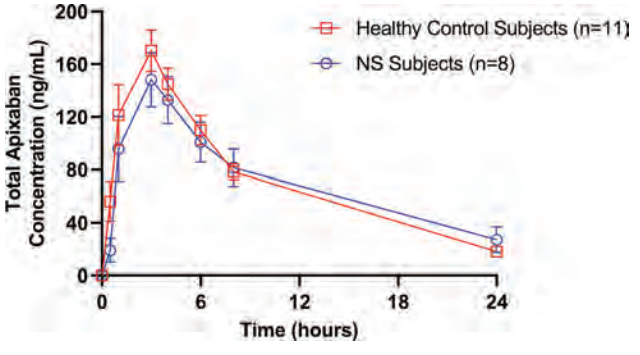
Background: Nephrotic syndrome (NS) confers high venous thromboembolism (VTE) risk, but no standard-of-care exists for thromboprophylaxis. Apixaban, an oral direct Factor Xa inhibitor, has favorable renal clearance but is highly protein bound and has not been studied in NS. We evaluated safety, pharmacokinetics (PK) and pharmacodynamics (PD) in NS subjects in a parallel-arm single-dose (apixaban 10mg) Phase 1 study.

Methods: NS subjects were included if: age 18-79 years; urine protein:creatinine >3.5 g/g or serum albumin <3.0 g/dL; non-diabetic NS. Blood was collected at 0, 0.5, 1, 3, 4, 6, 8, 24h for PK (total and free apixaban, anti-Xa levels) and at 0, 3, 6 and 24h for thrombin generation. Apixaban was quantified by liquid chromatography-tandem mass spectrometry, anti-Xa levels by a chromogenic assay, thrombin generation by a fluorescence assay, and D-dimer by ELISA. Non-compartmental analyses for PK utilized Phoenix 8.1, and linear regression models tested associations between PK and PD (SAS JMP 14.0).

Results: 8 NS and 11 healthy subjects completed the study. NS subjects had mean UPC ratio of 6.7 g/g and were older (mean age 28.0 v 42.7 years, P=0.01); other relevant baseline characteristics were similar. Anti-Xa levels and PK measures (C_{max}, T_{max}, AUC_{0-24}, Vd/F, $t_{1/2}$ and CL/F) for total (Figure) and free apixaban were similar between NS and healthy subjects. D-dimer was lower in healthy subjects at 24h (P=0.04). Peak thrombin generation did not differ over 24h. Correlations between free apixaban and peak thrombin generation at 3h were seen in healthy subjects (r^2=0.48, P=0.02 for C_{max}; r^2=0.38, P=0.04 for AUC_{0-24}) but not in NS. No adverse events occurred.

Conclusions: These preliminary data support prospective study of apixaban for thromboprophylaxis in NS. Additional multi-dose data will inform appropriate dosing for patients with proteinuria due to NS.

Funding: Other NIH Support - NCATS, NHLBI, Private Foundation Support



Total apixaban concentration over time in NS and healthy subjects

PO2376

Circulating Heparin and Its Relevance to Thrombin Generation Profile in ESRD Patients Undergoing Maintenance Hemodialysis

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Background: End stage renal disease (ESRD) is a complex pathophysiologic syndrome which results in vascular disorders and hemostatic disturbance. Despite the use of heparin during maintenance hemodialysis some of these patients exhibit hypercoagulable state. The purpose of this study was to characterize the thrombin generation (TG) profile in ESRD patients in relation to circulating heparin levels.

Methods: Citrated blood samples from 95 patients with ESRD undergoing maintenance hemodialysis were collected. NHP was prepared for referencing purposes. Individual samples were supplemented with heparinase. TG was assessed using a kinetic fluorogenic substrate method. TG parameters such as peak thrombin, lag time and area under the curve (AUC) were compiled. Circulating heparin levels were determined using activated partial thromboplastin time (aPTT) and chromogenic anti-Xa and IIa assays. The ESRD cohort was stratified into heparinized and heparin naïve groups.

Results: ESRD group showed decrease in peak thrombin (107.1 vs 168.3 nM) and AUC (589.8 vs 815.7 nM*min) with increase in lag time (2.9 vs 2.2 min) compared to NHP. Heparinase supplementation increase the lag time (3.4 min, p value <0.0001), while decrease the peak thrombin (100.0 nM, p value 0.0245) and AUC (503.4 nM*min, p value <0.0001). Such parameters as aPTT (43.2 vs 31.1 sec), anti Xa (0.21 vs 0.14 U/mL) and anti-IIa (0.27 vs 0.15 U/mL) decreased with heparinase treatment. Heparin naïve group showed decreased peak thrombin and AUC values whereas the lag time was increased. Simultaneously aPTT, anti-Xa and anti-IIa levels were decreased in this group. Heparinized patients did not show any difference in peak thrombin, decrease in AUC values and an increase in lag time. However, the aPTT, anti-Xa and anti-IIa were decreased in this group.

Conclusions: These studies showed that heparinase treatment of plasma samples from ESRD patients resulted in the decrease in the aPTT, anti-Xa and IIa levels suggesting the digestion of heparin. However, contrary to these results, TG parameters such as peak thrombin and AUC were decreased whereas lag time was increased suggesting that the depolymerized heparin fragments possessed thrombin generation inhibitory properties.

PO2377

Clinically Apparent AKI Secondary to Suspected Vancomycin Toxicity: A Cellular Kinetic Analysis

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Background: The use of antimicrobial therapies for treatment of hospitalized patients is abundant. While the usage rate of antibiotics has remained stable over the last decade, however, with the emergence of methicillin-resistant staphylococcus aureus, vancomycin usage has increased during that same time period. Although vancomycin induced AKI or vancomycin associated nephrotoxicity (VAN) has been a topic of debate since its generalized use approximately 50 years ago, the proposed mechanism of VAN is an on-going focus of research. The current study aims to answer whether proximal tubular creatinine secretion, which can account for upwards of 20% of creatinine clearance, is impacted by vancomycin dosing, and whether vancomycin trough levels seen in clinical practice alter this relationship.

Methods: For the cellular kinetic analysis, we took immortalized human proximal tubule epithelial cells, and after allowing them to epithelialize on a semi-permeable membrane, evaluated creatinine secretion in the presence of varying concentrations of both creatinine and vancomycin, while measuring eliminated levels for up to 24 hours. For the patient analysis, IRB approval was obtained to evaluate the cases of possible VAN on the renal consult service.

Results: Creatinine secretion through the cellular epithelium was not affected by vancomycin at levels up to 4X therapeutic, the upper limit of those seen on a cohort of patients in the renal consult service at the university of Colorado. This is consistent with other pharmacokinetic date, indicating that vancomycin is able to inhibit tranporters of creatinine, but at levels not seen in clinical practice. The patient cohort analysis identified thirteen patients who were deemed to have "possible VAN," and in all of these the rise in Cr did happen temporally related to vancomycin, and there were many other factors potentially confounding their AKI.

Conclusions: Proximal tubule dysfunction from vancomycin inhibition of cellular transporters does not cause creatinine elevation in concentrations used clinically. The cases of clinically apparent vancomycin associated nephrotoxicity are multifactorial. Therefore the nephrotoxocity associated with vancomycin administration does not seem to be the sole cause of creatinine elevation in patients with AKI.

PO2378

Systemic Absorption of Vancomycin from Sternal Slurry Contributing to Vancomycin Nephrotoxicity

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Introduction: Vancomycin has come a long way since its start as "Mississippi mud". It has been a valuable and safe agent in general. Adverse reactions include flushing and acute kidney injury. Clinicians are developing strategies to circumvent these problems. One strategy is the use of antibiotic slurry/paste applied to infected tissue. This has

traditionally not been associated with systemic vancomycin toxicity. We report here an incidence of vancomycin nephrotoxicity secondary to a sternal vancomycin slurry that required dialysis.

Case Description: A 62-year-old 91 kg man with Marfan's Syndrome and total aortic arch replacement presented with mediastinal abscess and recurrent sternal osteomyelitis. Exam revealed a fluctuant sternal lump and a trans-thoracic echo revealed a circumferential fluid collection around the aortic graft. He underwent a "redo" sternotomy, exploration and drainage. Plasma creatinine concentration (P_{cr}) on admission was 0.76 mg/dL, his known baseline. He received one dose of 1250 mg IV vancomycin prior to the operation. Intra-operatively 4 grams of vancomycin paste was applied to his sternum. That evening he received cefepime 2g IV and vancomycin 1250 mg IV (see figure), both scheduled to be repeated every 12 hours. P_{cr} and vancomycin troughs are detailed in the figure. On POD2 serum vancomycin trough was 42 mg/L. Intravenous vancomycin was discontinued after he had received 5 doses each of 1250 mg. By POD3 his P_{cr} had risen to 5.29 mg/dL, urine output dropped to 125 mL/day and the Nephrology Service was consulted. On POD4 the serum vancomycin was 48 mg/L and P_{cr} 6.45mg/dL. He was emergently dialyzed. After 5 rounds of dialysis, serum vancomycin concentration lowered to 8 mg/L and P_{cr} to 2.77 mg/dL. Urine output improved to 1200 mL/day. He was discharged on POD14 on daptomycin and ceftriaxone. On POD21 at follow-up, serum vancomycin was undetectable and P_{cr} was 1.08 mg/DL.

Discussion: There can be substantial unaccounted systemic absorption from vancomycin paste. The POD4 4 AM serum level was 48 mg/dL and he was dialyzed 14 hours later under operating conditions such that the level should be reduced by at least one-third. The post dialysis level was 47 mg/dL, so by conservative estimation his predialysis level was about 70 mg/L, suggesting that there was a substantial contribution of vancomycin to the serum level in that 17-hour interval from sternal slurry.

PO2379

Efficacy of the Recommended Ceftazidime/Avibactam Dose in Treating Carbapenem-Resistant Enterobacteriaceae in Critically Ill Patients Using Renal Replacement Therapies

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Background: Ceftazidime/avibactam (CEF/AVI) is a novel antibiotic used to treat Multi-drug Resistant (MDR) and gram-negative bacteria, including Carbapenem-Resistant Enterobacteriaceae (CRE). Data on CEF/AVI dosing and outcomes in patients with Chronic Kidney Disease stage-5 utilizing hemodialysis are scarce. The purpose of this study was to assess the efficacy of the recommended dose of CEF/AVI in patients utilizing renal replacement therapies.

Methods: A retrospective cohort study was conducted at our quaternary care institution between May 2015 and December 2019. All hospitalized adults who had CRE *Klebsiella Pneumoniae, E.coli*, or MDR *Pseudomonas Aeruginosa* related infections, and received CEF/AVI while utilizing either continuous venovenous hemofiltration (CVVH) or intermittent hemodialysis (IHD) or both were included

Results: Of the 24 patients who met the inclusion criteria, 70.8% were males, mean age was 66.0 ± 15.7 years. Eleven patients had bacteremia, 8 had pneumonia, 3 had urinary tract infection (UTI), and 2 had wound infections. Fourteen patients received CVVH while 10 received IHD during time on therapy. CEF/AVI dose while on CVVH was 1.25 g intravenous every 8 hours while the dose was 0.94 to 1.25 g daily in patients who were treated with IHD. Twenty-two of those patients were admitted to the critical care unit and required mechanical ventilation and 20 of them received vasopressors. A total of 13 patients had microbiological cure, and 10 patients were clinically cured. Nine patients with bacteremia had microbiological cure. Four patients with pneumonia had clinical cure during the follow up periods up to 3 months, recurrence/relapse occurred in 9 of the 24 patients. Eight patients deceased within 30 days of follow up and 4 more within 90 days. Only one patient did not have relapse or recurrence within the 90 days of follow up.

Conclusions: The CEF/AVI recommended dose could achieve uncertain clinical outcomes. Pharmacokinetics and pharmacodynamics studies are urgently needed to determine the adequacy of CEF/AVI dosing in this population

PO2380

Extracorporeal Removal of Valproic Acid in Overdose: A Case Report

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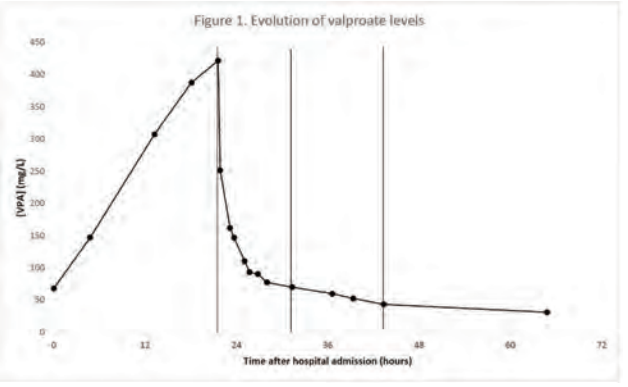
Introduction: Valproic acid (VPA) is considered not dialyzable at therapeutic concentration and dialyzable at supratherapeutic concentration because of saturable protein binding which increases its free fraction (from 10% to 90%).

Case Description: We report a case of a 53-year old 50kg woman admitted for suicidal polydrug intoxication. She had ingested 15g of VPA, 300mg of atorvastatin, 3g of quetiapine, and 750mg of naltrexone 3 hours prior to admission. Her vital signs were stable on admission and she was somnolent but arousable. Toxicology assays for ethanol, acetaminophen, and salicylates were negative. Biochemistry, blood gases, and complete blood count were unremarkable. She was initially treated with intravenous saline, naloxone, and intravenous carnitine. Despite these, she became progressively obtunded over 24 hours during which the serum VPA concentration rose from 69 to 422 mg/L (therapeutic concentration 50-125mg/L) and ammonia concentration rose from 17 to 56 mmol/L. Hemodialysis (HD) was initiated for 6h (GFS-210, Qb=400mL/min, Qd=750mL/min) via a right temporary femoral catheter because of concerns of coma-induced hyperammonemia and reduced access to VPA measurements. Her level of consciousness normalized during HD. No complications occurred during HD. VPA concentration and ammonia concentrations at the end of HD were 78 mg/L and 15 mmol/L, respectively, and did not re-increase thereafter (Figure 1). She was given three 50g doses of activated charcoal after HD and she eventually made a full recovery. VPA half-life was 3.0h during HD, 18.9h during multidose charcoal, and 44.9h without treatment. VPA was 48% unbound at the onset of HD. Instantaneous VPA clearance (calculated using simultaneous plasma and effluent VPA concentrations) decreased from 45 to 22mL/min during HD as protein binding increased.

Discussion: HD removed 1.4gm of VPA which would have been higher had HD been performed sooner after admission. This case illustrates that the dialyzability of VPA depends on its protein binding which itself depends on its serum concentration.



PO2381

Gabapentin Toxicity in Existing and Developing Renal Failure

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Introduction: Gabapentin is a medication used to treat partial onset seizures, neuropathic pain caused by diabetic neuropathy, postherpetic neuralgia, & central neuropathic pain. This medication is nearly completely excreted by the kidneys. It is recommended as one of a number of first-line medications for the treatment of pain.

Case Description: Here we report two cases of potential Gabapentin toxicity across the spectrum of renal insufficiency. The first case was a 48-year-old female with a history of ESRD (HD X 3 times/week), HCV, DM, HTN and spinal abscess presented with new onset seizure, body stiffening with head and eye deviation, confusion, fall and hypertensive emergency while awaiting for dialysis. She had a second seizure while in the ED and was started on anti-seizure medication Levetiracetam. Home medications included Gabapentin (800 mg TID). Head CT was unremarkable. The second case was a 69-year-old female patient with a history of DM, peripheral vascular disease, coronary artery disease & atrial fibrillation who presented with worsening of non-healing left heel ulcer. Home medications included Gabapentin (300 mg 3 times daily). The patient developed contrast-induced AKI due to a CT angiogram procedure on admission. Following the development of AKI, the patient became confused without evidence of significant azotemia (BUN 33). Both the cases were found to be arousable and GCS of 12/15, intact strength & sensation of both extremities, no ataxia, dysarthria, hemineglect or signs of pronator drift. In both cases, Gabapentin toxicity was suspected and the dosage of Gabapentin was reduced to 100 mg orally at night. There was a drastic improvement of confusion and other symptoms within 2 to 3 days post dosage adjustment in both patients.

Discussion: Renal insufficiency predisposes patients to increased risk of gabapentin induced toxicity due to reduced clearance. Advanced age and other comorbidities may further accelerate the risk. The range of Gabapentin toxicity across the spectrum of renal insufficiency is underrecognized. In this case report, the patient with AKI only was confused and the patient with ESRD had myoclonus and seizure in addition to confusion. There seems to be a graded increase in toxicity with the corresponding deterioration of renal function. Heightened awareness about medication toxicity developing in renal failure is important to prevent significant adverse effects.

PO2382

Gabapentin-Induced Edema Masquerading as Treatment-Resistant Heart Failure

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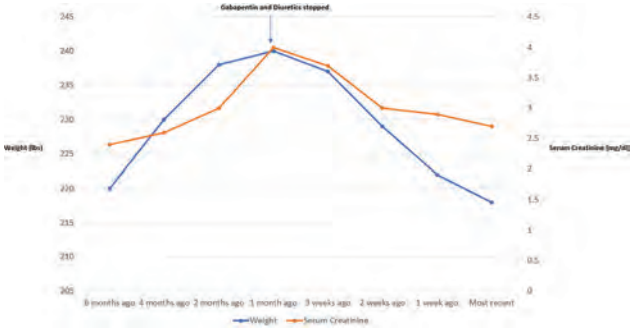
Introduction: Gabapentin is widely used in the management of neuropathic pain but has multiple well-known side effects but less recognized is edema. We describe a case of gabapentin induced edema, which was misdiagnosed as CHF exacerbation, resulting in significant diuretic use and stage 3 AKI.

Case Description: An 85-year-old male with a past medical history of stage 4 chronic kidney disease secondary to diabetic nephropathy (baseline serum creatinine 2-2.5mg/dl), Type 2 Diabetes Mellitus, diabetic neuropathy, and hypertension, presented to clinic for worsening of serum creatinine. Pertinent home medications included bumetanide 3 mg BID, metolazone 2.5 mg daily and gabapentin 600 mg TID. Bumetanide and metolazone were up titrated for worsening bilateral lower extremity edema over last 3 months with 20-pound weight gain. Exam was notable for 2+ LE edema. His serum creatinine progressively increased from 2.4 to 4 mg/dl in the setting of aggressive diuresis. A recent TTE showed only grade 1 diastolic dysfunction. The presumed diagnosis was heart failure with preserved ejection fraction. Urine sediment was bland. After identification of gabapentin as potential culprit agent for his edema, both gabapentin as well as his diuretics were discontinued with a resultant significant drop in his weight and serum creatinine to 218lbs and 2.7mg/dl respectively over next one month and complete resolution of his edema.

Discussion: Incidence of gabapentin induced edema varies from 2% to 8% and has been correlated to dosage. Exact mechanism is unknown but possibly related to loss of venoarteriolar reflex leading to increased capillary hydrostatic pressure and hence increased net capillary fluid filtration into the interstitium. Gabapentin induced edema, just like calcium channel blockers induced edema, is not associated with salt and water retention and hence diuretics are ineffective. Physicians, especially nephrologists, should be mindful of uncommon side effect of this commonly prescribed medication as distinguishing this early can prevent a lot of unnecessary work up and potentially prevent harm to the patient.



PO2383

Knowledge Deficits Are Barriers to Living Donor Kidney Transplantations

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Background: Living kidney donation is an underutilized treatment, and there is a paucity of educational interventions published in the literature describing efforts at increasing living donor kidney transplantation (LDKT); a systematic review of LDKT interventions documented only fifteen such interventions through 2017.[1] Transplant: A Family Journey is a two-hour educational session held prior to preemptive patients' initial transplant evaluation and includes members of patients' support network (e.g., significant other, family members, and/ or friends). Participants are encouraged to ask questions throughout the session, and can direct questions to the clinician and/or the speaker(s), typically a kidney recipient and/or a donor, about their experience with and knowledge of the transplant process.

Methods: Staff took verbatim notes of participants' questions during educational sessions and conducted qualitative thematic analysis on the content of the questions to derive patterns.

Results: There were 7 educational sessions for preemptive patients and their support network between December 2019 and March 2020; 57 patients and 89 family members and/or friends attended these sessions. 126 questions were asked that were classified into six main categories (see Figure 1).

Conclusions: There is still a large degree of confusion about transplantation among patients and their loves ones, specifically concerning LDKT. In addition to lack of familiarity of common terms (i.e., ESRD, preemptive, GFR) and a limited understanding of the waitlist process, patients and family members had questions about differential treatment outcomes. Continued efforts to increase patient understanding of transplantation and to involve their support networks early in the evaluation process are crucial to dispelling living donation misconceptions. 1. Sandal et al. (2019) doi:10.1097/TP.0000000000002715

Figure 1. Main Emerging Themes from Participants' Questions

PO2384

Glomerular Changes in Transplant Glomerulopathy

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Background: Transplant glomerulopathy (TG) affects 20% of transplanted kidneys 5 years post transplantation. It carries an important significance due to its correlation with decreased graft survival. Repeated endothelial cell injury by chronic active antibody mediated rejection (cAMR) leads to glomerular basement membrane (GBM) reduplication and thickening, the hallmark finding of TG. Based on our previous molecular mapping of the GBM, we aim to define the composition of the thickened GBM in TG using super-resolution microscopy.

Methods: Two super-resolution microscopy techniques, STORM (Stochastic optical reconstruction microscopy) and Airyscan, were used to image confirmed TG and control biopsies. For STORM, fresh frozen, 200 nm sections were imaged. While for Airyscan, 1-3 microns, formalin fixed paraffin embedded (FFPE) sections were used. Samples were labeled with antibodies for Laminin a5, Integrin a8, Myosin IIA, Vimentin, Synaptopodin, Integrin b1, Fibronectin, and several Collagen IV chains.

Results: STORM TG samples showed increased distance between Integrin b1 labeled membranes, indicating thickening of the GBM. Collagen a3a4a5(IV) did not change, while Collagen a1a1a2(IV) was increased at the GBM's endothelial aspect. There was an increase in Fibronectin, suggesting a role for the TGFb pathway. Airyscan TG images showed Vimentin- and Integrin a8-positive areas inside the GBM, indicating cellular protrusions extending into the GBM. Since these markers stain mesangial as well as endothelial cells, this suggests dedifferentiation of endothelial cells and transition to mesenchymal cells. We detected alternating Myosin IIA and Synaptopodin labeling in the form of "Sarcomere-like structures".

Conclusions: Our data revealed increased Collagen a1a1a2(IV) secreted from the endothelial side, while Collagen a3a4a5(IV) was unchanged. The increase in Fibronectin, cellular protrusions positive for mesenchymal markers, and sarcomere-like structures inside the diseased GBM suggest an endothelial to mesenchymal transition as culprit for increased Collagen IV rather than injury signals from podocytes.

PO2385

Calcineurin Inhibitor Cyclosporine A but Not Tacrolimus Induces Proapoptotic Endoplasmic Reticulum Stress in Kidney Epithelial Cells

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Background: Current immunosuppressive strategies in solid organ transplantation rely on the calcineurin inhibitors (CNI), cyclosporine A (CsA) or tacrolimus (Tac). Their nephrotoxicity is a major limitation for long-term usage. We hypothesized that CsA compared to Tac exerts more pronounced toxic side effects at the cellular level, with endoplasmic reticulum (ER)-stress and maladaptive unfolded protein response (UPR) as the most prominent landmarks.

Methods: To test this hypothesis we treated human embryonic kidney (HEK293) cells with CsA (10 μM) or Tac (10 μM) for 6h. The established ER stress-inducing agent, thapsigargin, served as positive control. To study the molecular mechanisms of CNI-induced cell toxicity we studied genetically-modified HEK293 cells lacking the crucial UPR elements, PERK or ATF6. Abundances of the ER-stress sensor IRE1a, adaptive transcription factor XBP1, and proapoptotic transcription factor CHOP were evaluated as endpoints.

Results: Treatment of native HEK293 cells with CsA or Tac equally increased phosphorylation of the known calcineurin substrate, NFAT, verifying the treatment protocols. CsA increased levels of activating IRE1a phosphorylation (pIREa) and stimulated both CHOP and spliced XBP1 (sXBP1) products. In contrast, Tac enhanced pIRE1a abundance only. CsA but not Tac significantly increased the number of cleaved caspase 3-positive cells suggesting enhanced apoptosis rate. Treatment with the chemical chaperone, TUDCA, partially abolished the CsA-induced increases of CHOP but did not affect sXBP1, suggesting alleviation of ER-stress. Knockdown of CsA binding partners, cyclophilin A and B, by siRNA reduced their expression approximately by half and increased CHOP expression suggesting that suppression of cyclophilins may contribute to CsA-induced cellular toxicity. PERK- or ATF6-deficiency blunted the increases of CHOP and sXBP1 in response to CsA, suggesting an implication of these pathways in CsA-induced ER-stress and UPR.

Conclusions: In summary, CsA but not Tac induces pronounced ER-stress and proapoptotic UPR. Pharmacological modulation of UPR bears the potential to alleviate CNI nephrotoxicity.

Funding: Government Support - Non-U.S.

PO2386

Tubular Cell Binding of β-Catenin to TCF1 or FoxO1 Associates with Chronic Fibrosis and Adverse Outcomes in Transplanted Kidneys

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Background: β-catenin is a key transcription factor via which multiple fibrogenic pathways converge. Importantly, it binds to multiple transcription co-factors mediating diverse signaling pathways. Its role in kidney transplantation is unknown.

Methods: A proximity ligation assay was used to assess binding of β-catenin within renal tubular epithelial cells to transcription factors, TCF1 and FoxO1, in 240 transplanted kidneys. Their correlation with pathological and clinical outcomes was evaluated.

Results: β-catenin-FoxO1 binding in 1-month protocol biopsies inversely correlated with contemporaneous chronic fibrosis, and subsequent inflammation and inflammatory fibrosis (P<0.001). The relative binding of β-catenin/TCF1 verus β-catenin/FoxO1 (TF ratio) was the optimal prognostic biomarker compared with individual components, and abnormal in a diverse range of fibrotic transplant diseases. A high 1-month TF ratio was followed by greater tubular atrophy and interstitial fibrosis scores, cortical inflammation, renal impairment, and proteinuria at one year (n=131, all P<0.001). TF ratio predicted reduced eGFR (AUC 0.817), mild fibrosis (AUC 0.717) and moderate fibrosis (AUC 0.769) using receiver-operating-characteristic analysis, exceeding conventional clinical and predictors including baseline fibrosis. An independent validation cohort (n=76) confirmed 1-month TF was associated with 12-month moderate fibrosis (15.8% versus 2.6%, P=0.047), but not with 10-year graft survival.

Conclusions: In conclusion, differential binding of β-catenin to TCF1 rather than FoxO1 is predictive of a fibrogenic response in transplanted kidneys.

Funding: Government Support - Non-U.S.

PO2387

Immunosuppression by Cyclosporine A Affects Proximal Tubular Homeostasis via Endoplasmic Reticulum Stress

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Background: Calcineurin inhibitors (CNI) such as cyclosporine A (CsA) or tacrolimus are first-line immunosuppressive drugs used after solid organ transplantation. However, renal side effects such as vascular and tubulo-interstitial malformations regularly occur in their long-term usage, especially in patients with renal allografts. Measures to reduce CNI nephrotoxicity by RAS inhibition or calcium antagonism had limited success. Dysfunctions in renal epithelial proteostasis suggested CNI-induced ER stress and malfunction of the unfolded protein response (UPR).

Methods: We have established a rat model for chronic CNI nephrotoxicity to test whether epithelial pathology and loss of functioning nephrons are related to ER stress and UPR dysfunction. Adult male Wistar rats received cyclosporin A (CsA, 25 to 40 mg/kg. b.w.) or vehicle via subcutaneously implanted minipumps. After three weeks, rats were sacrificed and organs removed for protein analysis or perfusion-fixed and kidneys analyzed for histopathology.

Results: Rats with CsA displayed a stimulated RAS and increased distal NaCl transporter activity along with decreased urine volume, GFR, FE_{Na}, and COX-2 expression. Pathological changes in vasculature and glomeruli were inconspicuous, whereas early proximal tubular segments (S1, S2) revealed large lysosomal vacuoles with granular content, their abundance correlating with epithelial dedifferentiation, basement membrane thickening, and subepithelial collagen I accumulation. Protein endocytosis was diminished. Changes in UPR included enhanced peIF2a, pPERK, CHOP, and BiP levels. Parallel studies in cultured cells indicated sensitivity to chemical chaperones ameliorating proteostasis.

Conclusions: These results suggest a so far unrecognized role of proximal tubular homeostasis in long term CsA-induced nephrotoxicity. Addressing UPR failure and restitution of proteostasis in proximal tubule may, therefore, have renoprotective potential.

Funding: Government Support - Non-U.S.

PO2388

Kidney-Intrinsic TLR/MyD88 Signaling Regulates the Susceptibility of Delayed Graft Function Following Kidney Transplantation

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Background: Delayed graft function (DGF) due to transplant ischemia/reperfusion injury (IRI) adversely affects up to 50% of deceased-donor kidney transplant (KTx) recipients. However, key factors contributing to the severity of IRI remain unclear. We hypothesize that kidney-intrinsic MyD88/Trif pathways could be a key determinant of DGF.

Methods: Kidneys from MyD88 knockout (KO) or MyD88 and Trif double knockout (DKO) mice were harvested and stored in a cold preservation solution (UW) for 4 hours, and then transplanted into bi-nephrectomized syngeneic or allogeneic recipients. Graft survival, renal function, histology change, phenotype analysis, and expression of involved genes, were observed and/or determined. Primary RTECs isolated from B6 and BALB/c mouse kidneys were stimulated by lipopolysaccharide (LPS) and cytokines in supernatant were measured.

Results: C57BL/6 (B6) kidneys were more susceptible to IRI following syngeneic transplant compared to BALB/c kidneys. Genetic ablation of MyD88 in B6 donors, but not BALB/c donors significantly reduced creatinine levels at post operation day (POD) 1-2, compared with wild-type (WT) kidneys. Moreover, compared with recipients of WT kidneys at POD 1-2, recipients of MyD88/Trif DKO kidney allografts showed improved graft function that was consistent with improved tissue integrity. Strikingly, MyD88/Trif DKO in the donor induced indefinite renal allograft survival and preserved intact renal allograft architecture at POD 100. In vitro study showed that levels of cytokines were increased by both B6 and BALB/c RTECs upon LPS (TLR4 agonist) stimulation, but BALB/c RTECs produced significantly higher levels of cytokines (including TNFα, IL-6, and IL-10) in a dose-dependent manner. Expression of KIM-1, a known biomarker for renal cell injury, were significantly increased by B6 RTECs as compared with that in BALB/c RTECs. These results suggest that kidney-intrinsic innate immunity, especially the TLR/Myd88 pathway, plays a critical role in the susceptibility to transplant IRI and DGF.

Conclusions: Kidney-intrinsic TLR/Myd88 signaling regulates the susceptibility of delayed graft function following kidney transplantation.

Funding: NIDDK Support

PO2389

Immunohistochemical and Molecular Characterization of Immune Cells in Pediatric Renal Allografts: Mononuclear Phagocytes Correlate with Rejection, Re-Transplantation, Graft Function, and Fibrosis

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Background: Standardized markers of immune cell infiltration may improve diagnostics in renal grafts. To date, no larger study investigating the role of immune cells in renal pediatric allografts exists and their impact on long-term outcome is poorly understood. Children are more prone to graft tolerance, have a more naive immune system and adaptive immune responses to allografts thus might differ from adults.

Methods: Renal graft samples (n=202) from 59 pediatric patients (63% male, mean age 10 years) transplanted 2000-2017 at our center were re-evaluated according to recent Banff criteria and stained for macrophages, dendritic cells, B cells and T cells (CD68, CD206, CD163L1, CD209, CD20, CD3). Quantification of immune cells was performed in whole slide images (WSI) using image analysis software (QuPath). Results were obtained separately for cortex, medulla and extrarenal tissue and displayed as percentages (%) of positively stained area. Additionally, RNA was isolated from paraffin tissue and used for quantification of >700 gene transcripts related to graft immunology (NanoString Human Organ Transplant Panel).

Results: In TCMR (T cell-mediated) and ABMR (antibody-mediated) rejection cortical macrophages were more frequent than in samples without rejection. B cells were most abundant in TCMR. In re-transplants a higher density of macrophages than in first allografts was observed. Protocol biopsies had lower macrophage numbers than indication biopsies. Infiltration of dendritic cells revealed higher densities in samples with i-IFTA. Macrophage numbers correlated negatively with kidney function (eGFR) and positively with fibrosis. Results obtained by NanoString technology confirmed high expression of macrophage-associated gene trancripts (e.g. CCL2, CXCL10) during graft rejection and stratified samples according to Banff morphological diagnosis.

Conclusions: Infiltrating immune cells, particularly mononuclear phagocytes, are highly abundant in pediatric renal transplants in rejection, re-transplantation and fibrosis and might influence long-term graft function. Gene expression analysis using the NanoString Human Organ Transplant Panel may supplement and confirm morphological diagnosis.

PO2390

IL-6- and IL-17-Mediated Inflammation Amplifier Loop in Chronic Antibody-Mediated Rejection

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Background: Renal fibrosis is a pathological condition associated with chronic inflammation that may result from a cellular injury and repair and result into late graft loss. In chronic inflammation, IL-6 combined with sIL-6R with gp130, together these complex activate the IL-6 trans signalling and control the transition from acute to chronic inflammation by the recruitment of MCP1 by activating NFkB and STAT3 signaling. We studied whether IL-17A and IL-6 mediated synergistic activation of inflammation amplifier loop is operational in CABMR.

Methods: CABMR patients were recruited according to revised Banff 2017 classification for the fibroblast culture from Renal Biopsy patients in vitro. Primary

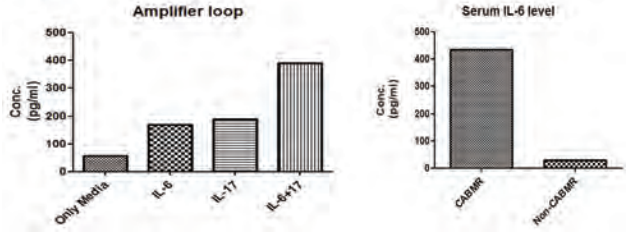
Fibroblast culture from CABMR patients were cultured to purity and to mimic this condition fibroblast were pre stimulated with IL-6 (20ng/µl), IL-17 (50ng/µl), IL-6 plus IL-17 for 24 hrs and culture supernatant were collected for IL-6 ELISA to see synergistic activation. Serum IL-6 levels of CABMR and Non-CABMR patients were measured by ELISA. mRNA expression of pro-fibrotic genes; COL1A1, FN1, ASMA1, and anti-fibrotic gene; MMP2/TIMP was analyzed with real-time PCR. Student's t-test was used for statistical analysis in SPSS 17 software.

Results: IL-6 in sera of CABMR patients was significantly higher ($p<0.001$) than non-rejection patients. In comparison to IL-6 and IL-17 alone these cytokines synergistically induced more IL-6 production from renal fibroblasts(Fig 1). Together IL+IL-17 signicantly increased the expression of COL1A1, ASMA1, Fibronectin and CCL2(MCP1) and reduced expression of MMP2 gene against GAPDH gene compared to alone IL-6, IL-17 and untreated fibroblasts.

Conclusions: CBMR is perpetuated by inflammation amplifier or synergistic induction of IL-6 and IL-17 which results in chronic inflammation and Allograft rejection. Anti-Il-6 may attenuate the CABMR related injury.

Funding: Government Support - Non-U.S.

Fig 1



Amplifier Loop in culture supernatent. Serum IL-6 con. in CABMR.

PO2391

B-Cell Maturation Phenotypes and Time Post-Transplant

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Background: Over the past decade, B cell participation in allograft response has been progressively elucidated. Beside the occurrence of DSA (donor-specific alloantibodies), different patterns of B cell phenotypes are also being related to graft outcome. Loss of naive B cells and appearance of memory B cells have been linked to chronic rejection and ultimately to graft loss. Here we show the impact of time post-transplant on phenotypic B cell changes, particularly regarding different distributions of naive B cells.

Methods: Single-center, observational cohort of 82 kidney transplant recipients (KTr), adults and clinically stable. Blood samples were collected between January 2015 and November 2018. Peripheral blood mononuclear cells (PBMCs) were isolated and analyzed on flow cytometry. B cells (CD19+) were stained for CD38 and IgD and classified according to Bm classification (IgD vs CD38).

Results: The median time post-transplant was 2.9 [0.9-9.89] years and the mean age was 54±13 years. 63% of the patients were males and mean eGFR was 49±17mL/min. B cells absolute counts were lower in later phases post-transplant (R -0.4, $p<0.01$). Among all B cell subtypes, Bm2 compartment (comprised mainly by naive B cells) had the most significant reduction in both absolute counts (R -0.62, $p<0.01$) and relative percentage (R -0.58, $p<0.01$) over time. On the opposite, mature B cells (both Bm5 and early Bm5 compartments) absolute counts did not differ over time (R -0.04 and 0.11 respectively, $p>0.05$) whereas the percentages of them were positively correlated with time post-transplant (R 0.40 and 0.56 respectively, $p<0.01$). Linear regression model showed that the absolute reduction in Bm2 cell compartment (i.e. naive B cells) was independent of age, sex, graft function and immunosuppression scheme.

Conclusions: Patients with longer time post-transplant have fewer circulating peripheral B cells. Phenotypic analysis of B cell subsets reveals that this reduction is due to an absolute decrease in naive B cells counts. Mature B cell absolute numbers, on the other hand, did not change significantly. Either exhaustion due to long-term immunosuppression or immunologic accommodation due to chronic alloantigen exposure could explain these observations.

PO2392

Donor Derived Cell-Free DNA in Renal Transplants, AlloSure vs. Prospera

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Background: The risk for allograft loss remains high due to rejection. Measuring donor cell free DNA has recently become an important noninvasive test for renal allograft injury and rejection. Two of the commercially available tests to measure dd -cfDNA, are Allosure(AS) and Prospera.

Methods: We measured dd -cFDNA in 44 post kidney transplants simultaneously using both tests. Patients were 3 to 50 months post kidney transplant and all samples were drawn for cause. Eleven of the 44 patients had allograft biopsies, see table. All patients had routine labs including trough CNI levels and in some cases DSA and/or BK PCR.

Results: 44 patients had side by side dd cf-DNA done using AS and Prospera for cause. There were 5 patients with either ACR 1a or 1b or AMR on biopsy. 6 patients had no rejection on biopsy. Please see image for statistical analysis.

Conclusions: There was no statistical difference between dd -cfDNA as measured by both commercial tests in all 44 patients, including 5 with ACR or AMR and 6 without rejection by biopsy. We acknowledge the number of patients who underwent biopsies were small. Prospera demonstated larger measurements of dd-cfDNA in comparison to AS, but this was not statistically significant p=0.27. Side by side analysis showed AS had marginally better AUC but no significant differences between diagnostic test characteristics observed. AS had better specificity, PPV, and NPV, but this did not reach statistical significance.

Cell Free DNA in Patients with biopsy

Sample	Prospera	Allosure	biopsy	creatinine	DSA
#3	1.07	0.96	NEG	1.37	NA
#10	0.06	0.19	NEG	2.32	NA
#12	5.86	4.6	AMR	1.5	A24,DR4,DR53
#16	0.66	0.35	1a	1.45	DQ6
#17	0.36	0.59	1a	1.53	DQ6
#19	1.21	0.92	NEG	2.32	NA
#23	3.69	2	NEG	1.27	DQ4
#24	1.2	1.2	AMR/FSGS	4.32	DQ2
#29	1.96	1.8	NEG	3.48	NA
#37	3.26	2.2	1B	1.8	NA
#43	1.84	1.6	NEG.	2.42	NA

(1) AUC ROC

Diagnostic Category	AlloSure	Prospera
AUC ROC [95% CI]	0.7200 [0.4248, 1.0000]	0.7000 [0.4086, 0.9914]

(2) Rejection threshold of 1.0%

Diagnostic Category	AlloSure	Prospera
Sensitivity [95% Exact CI]	0.6000 [0.1466, 0.9473]	0.6000 [0.1466, 0.9473]
Specificity [95% Exact CI]	0.7000 [0.3475, 0.9333]	0.5000 [0.1871, 0.8129]
PPV [95% Exact CI]	0.5000 [0.1181, 0.8819]	0.3750 [0.0852, 0.7551]
NPV [95% Exact CI]	0.7778 [0.3999, 0.9719]	0.7143 [0.2904, 0.9633]

AUC ROC and Rejection threshold of !%

PO2393

Donor-Derived Cell-Free DNA Kinetics After Kidney Transplant Biopsy

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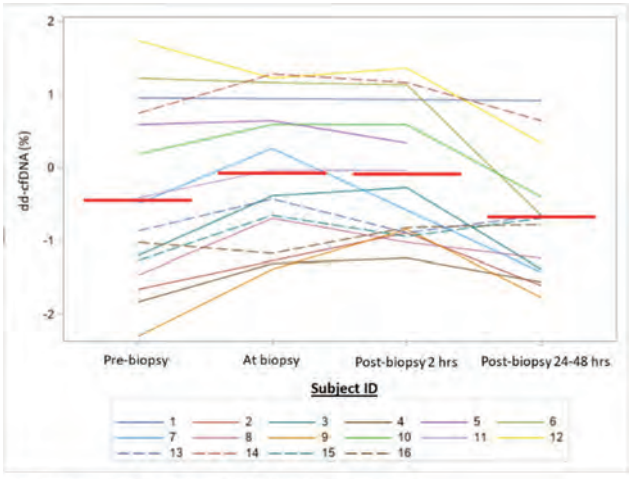
Background: Donor-derived cell-free DNA (dd-cfDNA) has generated interest as a potential biomarker for kidney transplant (KT) rejection. It is possible that the KT biopsy procedure itself can cause the release of dd-cfDNA in the blood stream, therefore affecting the reliability of this assay in the post biopsy period. In this study we evaluated the effect of KT biopsy on the level dd-cfDNA and assessed the magnitude and duration of this effect.

Methods: We conducted a single arm prospective study. Samples were collected from 16 adult KT recipients undergoing renal allograft biopsy. All participants had samples drawn within eight hours prior to the biopsy (pre-biopsy), within 20 minutes (hour 0), 2 hours after (hour 2), and 24-48 hours (hours 24-48) after the biopsy.

Results: Mean age at the time of biopsy was 50.6 ± 7.02 years. Most participants were men and Caucasian. Mean serum creatinine at the time of biopsy was 2.24 +/- 0.42 mg/dL. The most common reason for obtaining biopsy was rise in serum creatinine, while 4 patients had the biopsy due to elevation in dd-cfDNA. The pre-biopsy time point was compared against all remaining time points. At hour 0 and hour 2, there was a significantly larger log dd-cfDNA mean scores compared to pre-biopsy time point (0.37 vs -0.44, p=0.006), (0.35 vs -0.44, p=0.03) respectively. By 24-28 hours post biopsy there was no significant difference in log dd-cfDNA mean score compared to the pre-biopsy score.

Conclusions: KT biopsy leads to an increase in dd-cfDNA percentage after the procedure, however, this rise is transient and resolves by 24-48 hour after the biopsy. Providers can obtain dd-cfDNA level as soon as 48 hours post biopsy with high confidence that the levels have not been affected by the biopsy.

Funding: Commercial Support - This study was an investigator initiated study supported by CareDx, Inc., Brisbane, CA.



Note: The horizontal red lines denote the LS Means for each time point.

Observed longitudinal Log-Transformed AlloSure Measurements by Assessment Time Point

PO2394

Development and Clinical Experience with a Cell-Free DNA Monitoring Algorithm for Kidney Re-Transplants

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Background: The presence of donor-derived cell-free DNA (dd-cfDNA) in blood samples from kidney transplant recipients can be utilized as a biomarker for transplant rejection.[1] Failure of the original allograft due to rejection, infection, or recurrent disease leads to retransplants, observed in up to 10% of all kidney transplant patients.[2,3] In these cases, the original transplanted kidney is generally left in-situ. A rapid, accurate, and noninvasive diagnostic test assessing dd-cfDNA using single nucleotide polymorphism (SNP) based massively multiplexed PCR (mmPCR) test (Prospera™) may be utilized to detect allograft rejection.[1] Among retransplant patients, this test can detect both donor fractions in the plasma, when both the new and previously transplanted kidneys are releasing cfDNA. **Objective:** To present the clinical performance of the SNP-based mmPCR test analysis algorithm on samples from patients with kidney retransplants in which allografts are present from two genetically distinct donors.

Methods: Plasma samples from a cohort of second transplant patients were collected and processed as described previously.[1,4] The SNP-based mmPCR test algorithm is designed to detect all donor fractions in the plasma, when both the newly transplanted kidney as well as previously transplanted kidney(s) may be releasing cfDNA into the plasma. This algorithm estimates the total fraction of DNA due to all donor fractions combined.

Results: We present the clinical performance of patients with a second kidney transplant by this retransplant algorithm. In our dataset to date, no significant difference in dd-cfDNA levels compared to single allograft recipients was observed, suggesting limited cfDNA shedding from the initial kidney transplanted. Our results confirm the ability of this assay to analyze and quantify dd-cfDNA levels in kidney retransplant patients.

Conclusions: Our results indicate that performance of this SNP-based mmPCR test is preserved in repeat transplant recipients. Non-invasive assessment of dd-cfDNA in retransplant patients may be used to detect the presence of injury or rejection of the transplanted organ at an early stage, facilitating physician management around change of anti-rejection therapy.

Funding: Commercial Support - Natera, Inc

PO2395

Correlation of Donor-Derived Cell-Free DNA with Histology and Molecular Diagnoses of Kidney Transplant Biopsies

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Background: Circulating donor-derived cell free DNA (ddcfDNA;CareDx, Brisbane, USA), a non-invasive test that could detect rejection in kidney transplants, was validated using histologic diagnoses. The interpretation of these findings could be difficult due to variable inter- and intra-observer agreement with regards to histologic diagnoses and evolving classifications overtime. The centralized Molecular Microscope(MMDx; Edmonton, CA) tissue gene expression platform may provide increased precision to traditional histology

Methods: In this single-center prospective study of 208 biopsies, we present novel data on calibration of cfDNA using simultaneous assessments of all 'for-cause' and surveillance biopsies with histology(Hx) and MMDx. AUC curves were calculated using the previously published ddcfDNA cut-offs of < 0.21% to rule-out rejection and >1% to rule-in rejection

Results: Of 208 biopsies done at a median of 5.8 months post-transplant, 108(52%) were done for allograft dysfunction; 74(36%) for surveillance (due to DSA) and 26(12%) for post-rejection treatment surveillance. There were significant discrepancies between Hx and MMDx; with MMDx(92; 44%) identifying a higher number of rejection cases vs Hx(79; 38%). While MMDx identified a higher number of antibody-mediated rejection cases(65; 31%) than Hx(43; 21%); the opposite was true for T-cell mediated rejection[TCMR; Hx:27(13%) vs MMDx: 13 (6%)]. AUC Curves for cfDNA concentration and prediction of rejection were more robustly correlated with MMDx(AUC=0.830; p<0.001) than with Hx(AUC=0.75; p<0.001). The median cfDNA levels decreased significantly in responders to rejection treatment(median 0.94 to 0.20; p=0.015) vs non-responders(0.76 to 0.82; p=0.25)

Conclusions: In this single-center study, for the first time we describe the calibration of ddcfDNA with simultaneous assessment of kidney transplant biopsy with traditional histology and MMDx. We confirmed and expanded on the data from the DART study where a cut-off≥1% was highly sensitive and specific for ruling-in rejection. We report the correlation of cfDNA with response to rejection therapy. We propose that the combination of tissue gene expression using the molecular microscope and blood-based ddcfDNA may add precision to traditional histology and could change future practice and treatment paradigms

PO2396

Elevated Donor-Derived Cell-Free DNA (dd-cfDNA) Attributed to Angiotensin II Type 1 Receptor Antibodies (AT1R-Ab) in Renal Re-Transplantation

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Introduction: Complications of renal transplants include graft rejection and failure. Noninvasive dd-cfDNA values greater than 1% detect renal allograft injury and rejection, prior to changes in creatinine. Although antibody mediated rejection (AMR) typically involves donor specific antibodies (DSA) to human leukocyte antigens (HLA), non-HLA antibodies may also impact allograft outcomes. This series of re-transplantation patients with graft injury from AT1R-Ab (>10 U/mL) shows improvement in dd-cfDNA levels with initiation of an ARB, Losartan.

Case Description: Case #1: 23 year-old man with history of CKD IV due to hypoplastic kidneys. First transplant living unrelated donor failed due to renal vein thrombosis. Received a 2nd deceased donor transplant (DDRT) with thymoglobulin induction. Combined panel reactive antibodies (cPRA) was 99%, with no DSA. Post-transplant allograft function was excellent with nadir creat of 1.0mg/dL. Non-invasive allograft surveillance was initiated with initial dd-cfDNA (ALLOSURE, CareDx, Brisbane, CA) elevated at 1.8%. Antibody assessment was negative for DSA but positive for AT1R-Ab at 28 U/mL. Losartan was initiated with a sustained decrease in dd-cfDNA to <0.3% and stable creatinine levels. Case #2: 63 year-old woman with ESRD from hypertension. Prior living donor transplant failed due to chronic allograft nephropathy. Received 2nd DDRT with thymoglobulin induction given cPRA of 98%, with no DSA. Post-transplant allograft function was excellent with nadir creatinine of 0.8 mg/dL. Non-invasive allograft injury surveillance showed an acute rise in dd-cfDNA to 3.9% on post-operative week 5. Despite stable creatinine, a renal biopsy showed C4D-negative, mild antibody mediated rejection with peritubular capillaritis (ptc 2) and glomerulitis (g1). Antibody assessment showed no DSA but positive AT1R at 16 U/mL. Following Losartan initiation, dd-cfDNA decreased to <1%, with continued excellent graft function.

Discussion: AT1R-Ab may be more prevalent in the re-transplant population and is a causative factor for accelerated allograft injury, chronic fibrosis, and graft loss. Early detection of kidney injury via dd-cfDNA, prompt assessment of AT1R-Ab, and initiation of ARB therapy may lead to preserved allograft function, particularly in high immunologic risk patients.

PO2397

Class II Donor-Specific Anti-HLA Antibody Level Is the Major Determinant of Elevated Donor-Derived Cell-Free DNA in Renal Allograft Recipients

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Background: Dd-cfDNA is a biomarker of allograft injury used for rejection risk monitoring. We sought to analyze the relationship between dd-cfDNA and DSA.

Methods: We included all kidney transplant recipients (n=171) who underwent DSA and dd-cfDNA testing as part of their clinical care between 9/17-12/19 at our center. We aimed to identify independent predictors of high dd-cfDNA (at a cut-off of 1%).

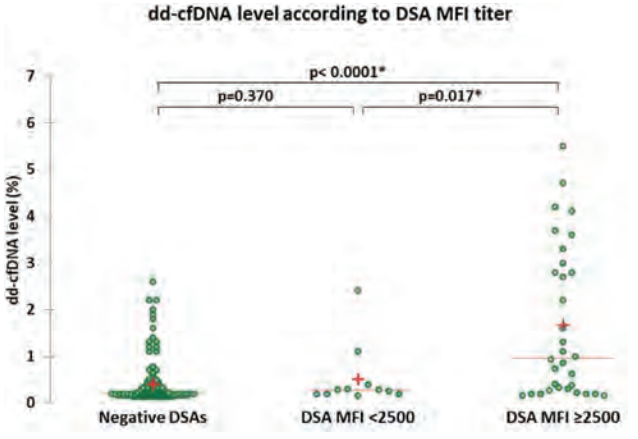
Results: Table 1 outlines clinical characteristics. There was a strong association between absolute dd-cfDNA level and DSA MFI category (Figure 1). In multivariate logistic regression analysis, DSA MFI was an independent predictor of high dd-cfDNA (Figure 2).

Conclusions: Dd-cfDNA is strongly associated with class II DSAs and MFI level. Variability observed identifies dd-cfDNA as a potential biomarker for monitoring allograft injury status in patients with DSA.

Funding: Commercial Support - CareDx Inc, Clinical Revenue Support

Clinical Characteristics

	Low dd-cfDNA <1%	High dd-cfDNA >1%	p value
Number of subjects	139	32	
Creatinine (mg/dl)	1.54±0.52	1.41±0.51	0.18
No DSA	114 (82%)	14(44%)	<0.001
Class I DSA	4(3%)	1(3%)	
Class II DSA	20(14.4%)	15(46.9%)	
Class I+II DSA	1(0.7%)	2(6.2%)	
DSA MFI(median)	2900	13200	



Donor-derived cell-free DNA level by presence and titer of DSAs

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age (for each 1 y)	0.98 (0.96-1.01)	0.22	0.99 (0.96-1.02)	0.65
Gender (female vs. male)	1.9 (0.87-4.14)	0.1	2.99 (1.14-7.83)	0.02
Ethnicity (other vs. Caucasian)	1.02 (0.47-2.22)	0.95	0.53 (0.19-1.45)	0.22
Type of transplant (cadaveric vs. living)	0.66 (0.29-1.51)	0.33	1.19 (0.39-3.57)	0.75
Time from Tx to dd-cfDNA measurement (for each 1 year)	1.03 (0.97-1.1)	0.28	-	-
Serum creatinine (for each 1 mg/dl)	0.57 (0.25-1.29)	0.18	0.58 (0.24-1.39)	0.22
Urine protein/creatinine ratio (for each 1 g/g)	1.2 (0.9-1.6)	0.2	-	-
Calculated Panel Reactive Antibody (>50%vs. <20%)	0.84 (0.26-2.67)	0.77	0.32 (0.07-1.36)	0.12
DSA category (vs. negative DSAs)	-	-	-	-
DSA MFI <2500	1.81 (0.35-9.23)	0.47	1.78 (0.28-11.14)	0.53
DSA MFI ≥2500-10000	8.14 (3.35-19.78)	<0.001	11.8 (4.11-33.8)	<0.001
Induction IS (ATG vs. Basiliximab)	1.3 (0.35-4.82)	0.68	-	-
FK level (for each 1 ng/ml)	0.99 (0.87-1.11)	0.87	-	-
Mycophenolate dose (for each 1 mg)	1.00 (0.99-1.001)	0.59	-	-

Binary logistic regression analysis regarding variables associated with a high dd-cfDNA level (>1%)

PO2398

Case Series: Systemic Infection Alters Background Cell-Free DNA and Influences Results of Donor-Derived Cell-Free DNA Transplant Rejection Assays

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Introduction: Donor-derived cell-free DNA (dd-cfDNA), a biomarker for kidney transplant rejection (1,2) is reported as a percentage of background cfDNA. Various factors affect total cfDNA levels (3,4). We present 3 cases with elevated background cfDNA where dd-cfDNA was assayed for rejection assessment.

Case Description: 1: A 78 year old man with end-stage renal disease (ESRD) underwent a kidney transplant. A biopsy at +6 months (m, all time points relative transplant date) due to an elevated creatinine level indicated an acute T cell-mediated rejection (TCMR). At +7m, the patient tested positive for BK viremia, and was treated. He was admitted for nephrectomy of his native kidney at +14m and tested positive for herpetic and cytomegalovirus (CMV) esophagitis and treated. A cfDNA analysis was negative for rejection with background cfDNA = 10,326 Arbitrary units (AU)/mL (~21X median cfDNA).) Banff chronic active cellular rejection was confirmed from a subsequent biopsy. **2**: A 62 year old woman with ESRD who underwent a kidney transplant had a cfDNA assay +3 years, that was reported as a negative result. However, the background was elevated at 3,466 AU/mL (~7X median). She had a biopsy that showed BK virus-associated nephropathy and TCMR. **3**: A 53 year old woman with ESRD had a kidney transplant from an ABO incompatible donor. A month later, she was diagnosed with dengue fever followed by acute allograft dysfunction. A biopsy at +6m showed active antibody-mediated rejection (ABMR). On a cfDNA assay at +7m indicated a negative result; however with an elevated background (6344 AU/mL, ~13X median). A biopsy showed resolution of ABMR and borderline acute cellular rejection.

Discussion: In all 3 cases, active viral infections may have caused elevated background cfDNA leading to false negative results in 2 cases. A cfDNA-based rejection assay only reporting a percentage of the total cfDNA may be inaccurate, particularly in patients with viral infections. Dd-cfDNA rejection assays should account for the variable background cfDNA when reporting results. 1. Bloom RD et al. *J Am Soc Nephrol.* 2017; 28(7):2221–32; 2. Sigdel TK et a. *J Clin Med.* 2019;8,19; 3. Sherwood K, Weimer ET. *J Immunol Methods*. 2018; 463:27–38; 4. Fleischhacker M, Schmidt B. *Biochem Biophys Acta.* 2007;1775:181–232

PO2399

Donor-Derived Cell-Free DNA Identifies Patients with Antibody-Mediated Rejection and Strongly Correlates Histologically with Microvascular Inflammation

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Background: Accurate and timely detection of rejection is central to improving long-term kidney transplant outcomes. We sought to characterize the association of dd-cfDNA level with rejection status and histological lesions.

Methods: We included all patients (n=54) that underwent a kidney transplant biopsy for suspicion of rejection at our center between 9/17-12/19. Concurrent dd-cfDNA and DSA testing was obtained. Rejection type (Banff 2017) and histological lesions were tested for association with dd-cfDNA level.

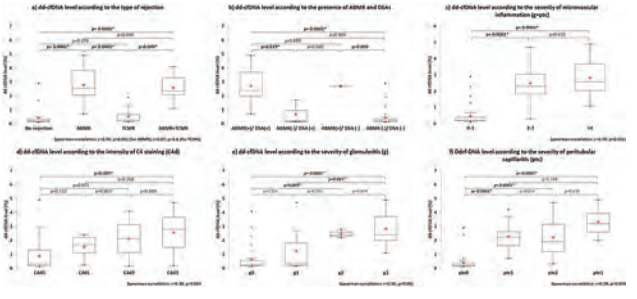
Results: 18 patients had ABMR (6 mixed ABMR/TCMR), while 12 patients had TCMR alone. Of those with ABMR, 94.4% had a dd-cfDNA level >1%, compared to 16.6% of those with TCMR alone (p<0.001). Of those with a high dd-cfDNA (>1%), 76.2% had both DSAs and ABMR. In multivariate logistic regression analysis, a high dd-cfDNA was a more important predictor of ABMR than a DSA MFI level over 2500 (Fig1). A high dd-cfDNA accurately discriminates ABMR (AUC=0.96; 95%CI, 0.92 to 1.00; p<0.001), with a positive and negative predictive value of 80.9% and 96.9%, respectively. Dd-cfDNA level showed a strong correlation with microvascular inflammation (Fig2), but not with tubulitis or interstitial inflammation.

Conclusions: Our study confirms the high diagnostic accuracy of dd-cfDNA for ABMR, while the strong association with elementary lesions of microvascular inflammation supports the specificity of this test for antibody-mediated allograft injury.

Funding: Commercial Support - CareDx, Clinical Revenue Support

Variable	Multivariate analysis* (Model A)		Multivariate analysis* (Model B)	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Recipient age (for each 1 y)	1.01 (0.92-1.08)	0.98	1.05 (0.97-1.13)	0.22
Type of transplant (cadaveric vs. living)	0.3 (0.015-5.95)	0.43	0.43 (0.02-7.46)	0.56
Time from Tx to dd-cfDNA measurement (for each 1 year)	1.51 (0.96-2.39)	0.07	1.37 (0.95-1.98)	0.08
Serum creatinine (for each 1 mg/dl)	0.14 (0.003-6.53)	0.31	0.17 (0.01-3.32)	0.24
dd-cfDNA level (high vs. low)	**118 (5.52-2551)**	**0.002**	-	-
DSA category (DSA MFI ≥ 2500vs. negative DSAs)	-	-	**59.4 (4.67-755)**	**0.002**
FK level (for each 1 ng/ml)	0.57 (0.26-1.23)	0.15	0.6 (0.29-1.22)	0.15

Binary logistic regression analysis regarding variables associated with antibody-mediated rejection



The absolute level of dd-cfDNA and its correlation with rejection type and individual pathological lesions

PO2400

Impact of Body Mass Index on Baseline Donor-Derived Cell-Free DNA in Kidney Transplant Recipients

Harsha Aramada, Bhavna Chopra, Kalathil K. Sureshkumar. *Allegheny Health Network, Pittsburgh, PA.*

Background: Donor derived cell free DNA (dd-cfDNA) is useful in predicting acute rejection in renal allografts. The technology uses next generation sequencing and does not require donor genotyping. dd-cfDNA is expressed as a percentage of the total (including self and non-self) circulating DNA fragments. Since self-portion of cell free DNA can vary according to body size, we aimed to test the hypothesis that expressed percent of baseline dd-cfDNA can vary by the recipient's body mass index (BMI).

Methods: Our center has been doing for-cause as well as surveillance (for high immunologic risk) dd-cfDNA in kidney transplant recipients (KTRs) using AlloSure (CareDx, Brisbane, CA). We identified patients who underwent kidney transplantation between September 2017 and June 2019 and had serial dd-cfDNA levels. A dd-cfDNA value ≥ 1% prompted allograft biopsy. KTR with biopsy evidence for rejection or other injuries were excluded from the analysis. Study subjects were divided into BMI (kg/m^2) groups as follow: <25, 25-29.9, ≥30. Baseline dd-cfDNA values were compared between BMI groups.

Results: There were 88 (81 first-time and 7 repeat) KTRs during the study period who had dd-cfDNA measurements and available BMI. We excluded 16 first-time and 3 repeat KTRs from the analysis due to biopsy evidence of rejection. The remaining 69 patients had 227 dd-cfDNA levels available for analysis. Patients were divided based on BMI categories with stratification of baseline dd-cfDNA values as shown in table 1. There were no significant differences in baseline dd-cfDNA values for BMI groups <25 vs. 25-29.9 (0.63 ± 0.63% vs. 0.41±0.27%, p=0.16) and BMI groups 25-29.9 vs. ≥30 (0.41±0.27% vs. 0.33±0.16%, p= 0.22). However, there was a trend towards significantly higher baseline dd-cfDNA values in BMI group <25 vs. ≥30 (0.63±0.63% vs. 0.33±0.16%, p=0.06).

Conclusions: Our study showed a trend towards significant differences in dd-cfDNA values between extremes of BMI groups. These differences could become significant with larger study subjects. Our findings point towards the need for normalization of dd-cfDNA values with respect to body size for reporting purposes.

Table 1. BMI and dd-cfDNA

BMI (kg/m2) categories	<25	25 -29.9	≥30
Number of patients	19	29	21
Number of dd-cfDNA tests	67	96	64
dd-cfDNA % mean± SD	0.63±0.63	0.41±0.27	0.33±0.16

PO2401

Protocol-Based Donor-Derived Cell-Free DNA Surveillance in Kidney Transplant Recipients: A Single-Center Experience

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Background: Kidney biopsy is invasive and has limited utility when used as a surveillance test post-transplant. Donor-derived cell-free DNA (dd-cfDNA) surveillance testing has never been studied in comparison with other routinely performed surveillance tests.

Methods: Our transplant center implemented the dd-cfDNA (Allosure ®) surveillance protocol (1,2,3,4,6 months and then quarterly post-op) in kidney transplant recipients starting July 2018, in addition to our existing protocol measurements of serum Cr, proteinuria and DSA. We retrospectively reviewed all kidney alone transplant recipients transplanted between July 2018- April 2020. Data collection was done at time of dd-cfDNA surveillance and included: dd-cfDNA (positive if >1% dd-cfDNA), elevated Cr (≥0.3mg /dL from Baseline), elevated proteinuria (≥0.3 mg/dL from baseline), DSA (if available).

Results: 366 screening dd-cfDNA test results were reviewed from 84 patients. There were 13/366 positive dd-cfDNA tests in 8/84 patients. 5 of the 8 patients underwent a kidney biopsy which showed: 4 rejections (2 humoral, 2 cellular) (for 1 patient who had cellular rejection, dd-cfDNA test was the only surveillance test that was positive) and 1 ATN (dd-cfDNA test was borderline positive at 1.0%). The remaining 3 patients did not undergo a biopsy and repeat dd-cfDNA testing improved without intervention. In the 353/366 negative dd-cfDNA tests in 76 patients: 8 patients underwent a biopsy: 2 patients who had increased Cr showed borderline acute cellular rejection, 3 had recurrent disease (MPGN, DM, IgAN) and 3 showed ATN/Vascular disease/IFTA. In the 2 patients with borderline acute cellular rejection dd-cfDNA was <0.7%.

Conclusions: We found that the addition of surveillance dd-cfDNA testing to current testing algorithm was able to identify rejection in 1 patient, when others surveillance tests were negative. A negative result may obviate the need for biopsy, including protocol biopsies in centers who perform them.

Funding: Commercial Support - CareDx

	No biopsy performed	Biopsy Performed	
		Rejection	No rejection
dd-cfDNA positive	8	4	1
dd-cfDNA negative	343	2 (borderline ACR)	8
Total	351	15	
Standard protocol positive	33	5	6
Standard protocol negative	318	1	3
Total	351	15	

PO2402

Successful Transplantation Outcomes Using Deceased Donors with AKI

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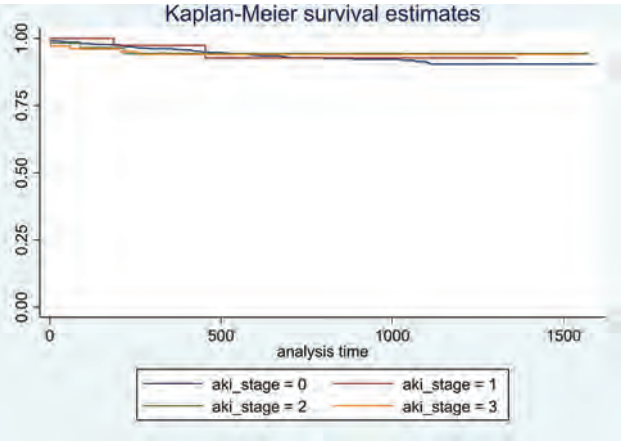
Background: Kidneys from deceased donors with acute kidney injury (AKI) are discarded at a higher rate than those without AKI, exacerbating the organ shortage. This paper reviews outcomes of kidneys from deceased donors with AKI over a four-year period at a single transplant center.

Methods: We analyzed 1119 consecutive deceased donor kidney adult recipients transplanted from 2016 through 2019 at our center. Donors were classified using AKIN criteria for AKI based on increase of terminal serum creatinine (SCr) over initial SCr. Death-censored graft survival and eGFR (MDRD) were compared.

Results: 911 recipients received kidneys from donors with no AKI (Stage 0). 208 (18.6%) received kidneys from donors with AKI. 45 (4.02%) had Stage 1 AKI, 59 (5.27%) had Stage 2 AKI, and 104 (9.29%) had Stage 3 AKI. There were no significant differences between the AKI and non-AKI groups in recipient age, gender, ethnicity, or Estimated Post-Transplant Survival score. Using a Cox Proportional Hazards Model, death-censored graft survival at 1 year was not distinguishable between recipients whose donor had any stage of AKI versus donors without AKI (HR 0.94, p=0.854) nor among AKI stages (Figure 1). Mean eGFR by MDRD formula for recipients alive and with followup at 1 year was 60.0 (SD 23.2) in recipients with non-AKI donors and 61.9 (SD 26.1) in recipients with AKI donors, which was of no statistical significance (p=0.4384). The rate of delayed graft function was significantly higher in recipients from AKI donors (62.0%) versus non-AKI donors (31.5%), p<0.0001.

Conclusions: Recipients of AKI donors did not yield inferior outcomes to those of non-AKI donors at 1 year. Increased DGF can be anticipated, but does not appear to have any lasting impact on graft survival or renal function. As such, transplant centers should consider expanding the use of these kidneys for any waitlisted candidate.

Funding: Clinical Revenue Support



PO2403

Combined Impact of Presensitization and Delayed Graft Function on Allograft Outcome in Deceased Donor Kidney Transplantation: Nationwide Cohort Study

Byung ha Chung,[1] Hanbi Lee,[1] Yohan Park,[1] Tae Hyun Ban,[2] Sang Heon Song,[3] Jaeseok Yang,[4] Curie Ahn,[4] Chul Woo Yang.[1] Korean Organ Transplantation Registry Study group *[1]Seoul Saint Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; [2]Eunpyeong St. Mary's hospital, Seoul, Republic of Korea; [3]Pusan National University Hospital, Busan, Republic of Korea; [4]Seoul National University College of Medicine Department of Internal Medicine, Seoul, Seoul, Republic of Korea.*

Background: Pre-sensitization to HLA has detrimental effect on allograft rejection, worse allograft function and survival. Delayed graft function (DGF) is associated with poor allograft outcome by ischemia-reperfusion injury. We undertook analysis to determine combined association of pre-sensitization to HLA and DGF on allograft outcome in deceased donor kidney transplantation (DDKT) and whether there is a synergistic effect.

Methods: In our prospective cohort study, between May 2014 and June 2019, 1370 deceased donor kidney transplants were assigned into 2 groups; pre-sensitized and non-pre-sensitized. Each group was divided into 2 subgroups according to DGF. Pre-sensitization was defined as the presence of donor specific antibodies (DSA) or the presence of panel-reactive antibody (PRA), combination with crossmatch positive. DGF was defined as the need for dialysis before discharge. We compared the clinical outcomes including allograft rejection, the change of allograft function, infectious and cardiovascular complication and allograft survival.

Results: Pre-sensitization group were 137 (10.0%) patients and others (n=1233, 90.0%) belonged to non-sensitized group. Pre-sensitization-DGF subgroup was 21 (15.3%) and pre-sensitization-non-DGF group was 116 (84.7%). Non-pre-sensitization-DGF subgroup was 133 (9.7%) and non-pre-sensitization-non-DGF group was 1100 (80.3%). In both pre-sensitization and non-pre-sensitization groups, allograft function using eGFR by CKD-EPI equation (mL/min/1.73m^2) was lower in DGF subgroup than non-DGF subgroup. In contrast, allograft rejection rate showed no significant difference between DGF and non-DGF subgroup within non-pre-sensitization group (15.0% vs 12.9%, *p*=0.493). There was no significant difference between DGF and non-DGF subgroups in both groups in regard to allograft survival and patient survival.

Conclusions: DGF combined with pre-sensitization had much worse effect on allograft outcome in terms of allograft rejection. Therefore, we suggest more careful monitoring or surveillance for allograft rejection when DGF occurred in DDKT with pre-sensitization to HLA.

PO2404

The Clinical Significance of Preformed C1q-Binding Donor-Specific HLA Antibodies in Kidney Transplantation

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Background: The anti-human leukocyte antigen (HLA) antibodies are well known for risk factor of rejection or allograft loss in kidney transplantation (KT). De novo complement component 1q-binding donor-specific anti-HLA antibodies (C1q-binding DSAs) are already reported to be associated with an increased risk of acute allograft rejection in KT. This study investigated the clinical significance of identification of preformed C1q-binding DSAs for predicting graft outcomes in KT.

Methods: From December 2016 to December 2018, 323 recipients underwent KT at Seoul St. Mary's Hospital. If the results of panel reactive antibodies (PRA) were positive in the pre-transplant examination, DSAs and C1q-binding DSAs were performed using Luminex Single Antigen Bead Assay (SAB) at the same time. Graft outcomes in term as Chronic Kidney Disease-Epidemiology Collaboration estimated Glomerular Filtration Rate, biopsy proven acute rejection and graft survival were compared between recipients with preformed C1q-binding DSAs and recipients without preformed C1q-binding DSAs.

Results: Eighty-two of 323 recipients (25.4%) were evaluated DSAs and C1q-binding DSAs before transplantation. Among them, 40 recipients (48.8%) had preformed DSAs and 8 recipients (9.9%) had preformed C1q-binding DSAs. The higher MFI values of DSAs had higher prevalence of C1q-binding DSAs (9263.9 ± 3670.3 vs. 5955.3 ± 5245.5; p = 0.050). There was a strong correlation between the presence of DSAs against Class II and C1q-binding DSAs (p = 0.007; CI 95%, OR 9.333). Five of 21 patients (23.8%) with positive at least one of complement-dependent cytotoxicity (CDC) or flow cytometry crossmatch (FCXM) had preformed C1q-binding DSAs. There was a correlation between positivity of crossmatch and preformed C1q-binding DSAs (p = 0.024; CI 95%, OR 6.042). Four of 8 recipients (50%) in C1q-binding DSAs(+) group were confirmed acute antibody mediated rejection. C1q-binding DSAs(+) group had higher incidence of acute antibody mediated rejection than C1q-binding DSAs(-) group (p=0.044; CI 95%, OR 4.286).

Conclusions: The identification of preformed C1q-binding DSAs may be important in predicting acute antibody mediated rejection. Therefore, the surveillance such as protocol allograft biopsy is required for early detection of acute antibody mediated rejection after transplantation in patients with preformed C1q-binding DSAs.

PO2405

Potential Combined Use of Kidney Donor Profile Index (KDPI) and Estimated Post-Transplant Survival (EPTS) Scales to Predict eGFR Decline in Deceased Donor Kidneys

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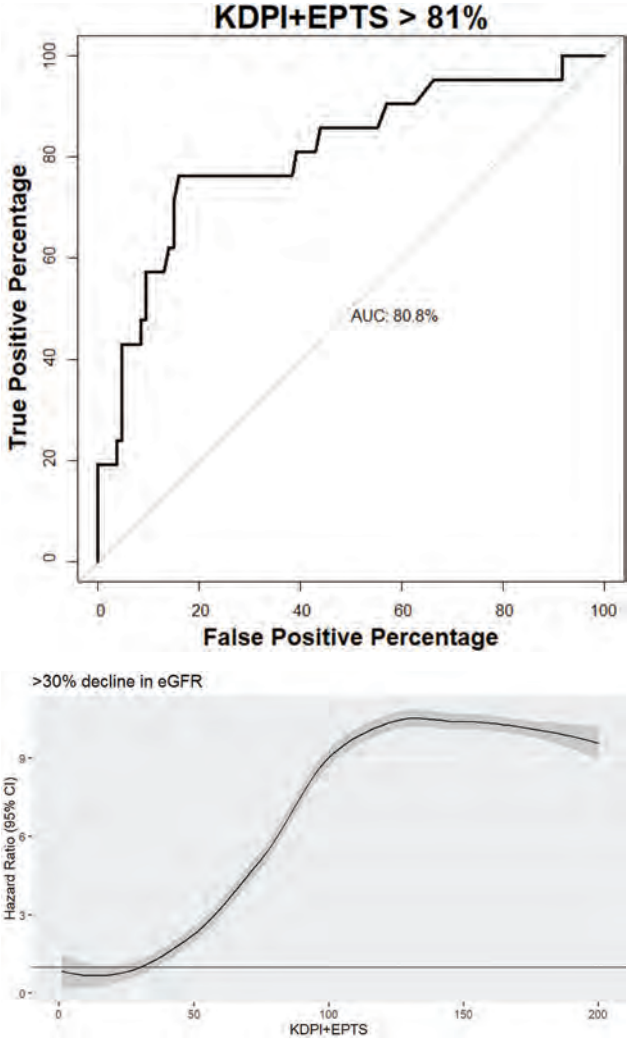
Background: Utility of the sum of EPTS and KDPI scales to predict the decline of eGFR in patients who received a cadaveric donor transplant. Assess the reproducibility of the Organ Assignment System of the USA in our country.

Methods: 128 deceased-donor kidney transplant recipients at two National Mexican Hospitals between 2015 – 2017, retrospective, observational cohort study over 36 months following transplant. We include age, gender, primary renal disease, sensitization events, peak panel-reactive antibody, cold ischemia time, dialysis type and vintage, KDPI and EPTS, DGF, PTDM, Acute rejection, eGFR and cause of graft failure P. outcome: Relationship between a decrease >30% eGFR and the different combined scores of the KDPI and EPTS scales.

Results: The sum of the scores of the EPTS and KDPI scales >81% had a sens. 76% and a spec. 84% to predict a >30% decline in eGFR. AUC 80.8% (95% [CI] 0.002 to 0.005, p < 0.001). Multivariable Cox proportional hazard model: the sum of EPTS and KDPI scores >81% was associated with a 9.9-fold increase in losing more than 30% eGFR over the 36-months follow-up ([adjHR] 9.9; 95% [CI] 1.85 to 53.6, p = 0.007). Acute rejection was associated with a 3.1-fold increase in losing more than 30% eGFR ([adjHR] 3.1; 95% [CI] 1.15 to 8.72, p = 0.02).

Conclusions: Observing **the donor and the recipient as a sum can be an new tool** that helps us to predict the decline eGFR in Deceased Donor Kidneys transplants



PO2406

Vasopressin Use After Deceased Donor Kidney Transplant (DDKT): Patient Characteristics, Graft Function, and Clinical Outcomes

Muhammad Y. Jan, William Goggins, Muhammad S. Yaqub, Tim E. Taber, Dennis P. Mishler, Sharon M. Moe, Ranjani N. Moorthi, Michael T. Eadon, Jeanne Chen, Asif A. Sharfuddin. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Vasopressin (AVP) is used for maintenance of volume status and hemodynamics due to its vasopressor activity with less arrhythmogenic and ischemic potential. It has catecholamine sparing effect. AVP has been shown to improve rates of deceased organ donation. We studied AVP use post DDKT for improving hemodynamics with resultant effect on graft function and clinical course.

Methods: A retrospective chart review was done on patients >18 years of age who required AVP post operatively after a DDKT over 5 years (2012-2017). Recipient, donor characteristics, intraoperative parameters, hospital/ICU stay, graft failure, patient survival, and hyponatremia during first 48 hours were reviewed.

Results: A total of 43 patients fulfilled inclusion criteria. Refer to Table for summary. Total of 5 patients (11.6%) required dialysis, 3 of whom received donation of kidney after cardiac death. There were 3 deaths during the first 12 months (6.9%). Mean cold and warm ischemia time were 32.5±12.9 hours and 39.2 ±10.2 minutes, respectively. Mean time to start AVP was 6.8 hours post operatively and mean duration of AVP use was 43.2 with a median of 30 hours. 72.1% of patient also required dopamine. Mean hospital stay was 14.5 days and length of ICU stay was 5.4 days. Mean creatinine at day 7 was 4.0 ± 4.2 mg/dl. There was no incidence of hyponatremia during the first 48 hours. Graft survival was 72% at median follow up time of 7.2 years.

Conclusions: Patient requiring AVP post DDKT have unique characteristics - fewer anti-HTN medications and longer time on dialysis prior to transplant. A longer than median hospital length of stay was noted. To our knowledge this is the first study reviewing AVP use post DDKT. Future studies are needed to compare characteristics and outcomes with patients' who did not require AVP post DDKT.

Recipient Characteristics and Intraoperative BP (n=43)

Gender: Male 51.2% Female 48.8%	Age: Mean 58.6 Years (± 12.3)
Race: Caucasian 60.5% African American 39.5%	BMI: Mean 30.2 kg/m2 (± 5.3)
Atrial Fibrillation*: 14%	Ejection Fraction*: Mean 60.2% (± 8.4)
Diastolic Heart Failure*: 26.2%	Pulmonary hypertension*: 27.9%
Anti-Hypertensive medication: Median 1.0 (0-6)	Midodrine pre-transplant: 18.6%
Time on dialysis: Mean 6.7 Years (± 4.12)	Dialysis Modality: HD 83.7%, PD 14%
Etiology of ESRD: Glomerulonephritis: (30.2%) Hypertension: (27.9%) Diabetes Mellitus: (25.5%)	Mean Systolic Max/Min BP in OR: 138.8 ± 22.4/ 91.7 ± 16 Mean Diastolic Max/ Min BP in OR: 69.6 ±13.7/ 42.8 ± 9.5

*prior to DDKT. OR=operating room.

PO2407

Differences in Urinary Inflammatory Profiles in Donor-Recipient Pairs

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Background: Renal transplant is the most common type of transplant performed in the US. Immunosuppressants are used in transplant recipients to prevent rejection. Kidney transplant recipients are at a higher risk for infection in the pre- and post-transplant state. Urine inflammatory profiles may lend insight to this balance between infection and rejection. Since donor and recipient urine is generated by genetically identical kidneys, it represents an ideal biosample for paired analysis.

Methods: Urine samples were obtained from stable children > 2 months post-transplant along with their donors (n=6) and another 8 recipient donor-recipient pairs (adult and children) that were collected for longitudinal samples; of which a pretransplant sample has been obtained. Using the V_PLEX Human CytoKine Panel (Mesoscale Discovery, Rockville MD) urine inflammatory mediators were quantified. The paired T-test or Wilcoxon test for parametric and nonparametric data respectively

Results: Interleukin (IL)7, IL15, Monocyte chemoattractant protein-1 (MCP-1) and Granulocyte-macrophage colony-stimulating factor (GM-CSF) were higher in the pediatric post-transplant recipients compared to their donors P values of 0.017, 0.037, 0.046 and 0.031 respectively. IL-9 was higher in recipient urine in pre-transplant patients (p=0.004) compared to donors.

Conclusions: Transplant patients have an elevated urine inflammatory mediator profile. Pretransplant patients have elevated IL-9 compared to their donors. Reasons for this altered inflammatory profile include immunologic, hemodynamic or physiologic changes intrinsic to the transplant procedure versus medications used to manage transplant patients.

Funding: NIDDK Support

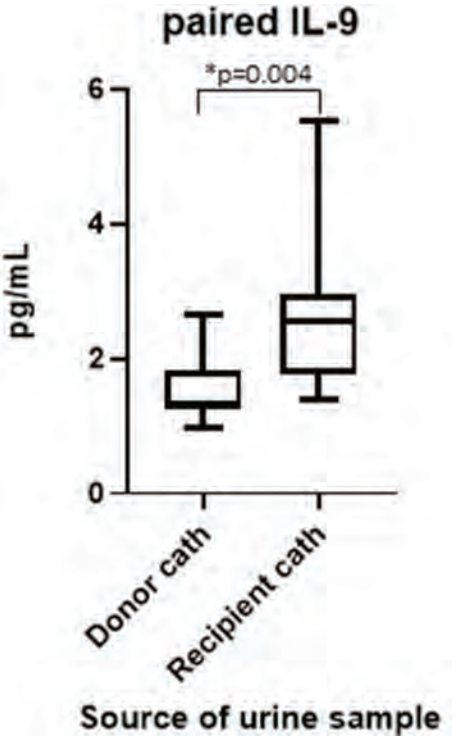

Figure 1. Catheterized urine samples from recipients at time of transplant have higher levels of IL-9 than their donors

PO2408

LIMS1 Gene Mismatching and Risk of Rejection in Kidney Transplant Recipients

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Background: Recent advances in precision medicine have provided new insights into the pathogenesis of kidney transplant (KTx) rejection such as the potential role of genetic risk variants in LIM Zinc Finger Domain Containing 1 (*LIMS1*). We aimed to evaluate the relationship between donor and recipient *LIMS1* genotype matching status and allograft rejection and survival.

Methods: We genotyped 41 prevalent living KTx recipient [24 (59%) males; mean age 34±13 years] and donor [15 (37%) males; mean age 47±13 years] pairs for *LIMS1* rs893403 variant by Sanger sequencing in order to assess their impact on rejection and graft failure. The recipients homozygous for *LIMS1* rs893403 GG genotype which tags a common 1.5-kb deletion (CNVR915.1) received a transplant from a nonhomozygous donor were defined as risk mismatched. CNVR915.1 deletion is confirmed by PCR in recipients with rs893043-AG and GG genotypes. Rejections were defined as T-cell mediated (TCMR) or antibody mediated rejection (ABMR) defined by Banff 2013 criteria. Outcomes were abstracted by review of medical records.

Results: There were no differences between recipients with risk *LIMS1* mismatching (n=5) and recipients without risk *LIMS1* mismatching (n=36) regarding demographic factors, duration of dialysis, pretransplant PRA, HLA mismatching, immunosuppressive protocols and follow up time. After a median post-KTx follow up of 10.5 (IQR 8.7-12.6) years recipients with risk *LIMS1* mismatching had significantly higher risk of allograft rejection (60%; median 1 month) compared to recipients without risk *LIMS1* mismatching (13.9%; median 72 months) (HR=4.32, 95CI% 1.46-12.76, p=0.015). TCMR was higher in recipients with risk *LIMS1* mismatching (40%) compared to recipients without risk *LIMS1* mismatching (11.1%) (p=0.087). There were no significant differences found between patients with and without risk *LIMS1* mismatching regarding risk of post-KTx DSA, ABMR and allograft failure. The mean eGFR levels at last follow up were also similar among recipients with and without risk *LIMS1* mismatching.

Conclusions: Genomic mismatching at *LIMS1* gene appears to impact risk of TCMR. *LIMS1* may be a potential minor histocompatibility antigen and pre-transplant genetic testing may have clinical implications for the prediction and clinical management of KTx rejection.

Funding: Private Foundation Support

PO2409

Monitoring of Gene Expression in Tacrolimus-Treated De Novo Renal Allograft Recipients Facilitates Individualized Immunosuppression: Results of the IMAGEN Study

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Background: The expression of nuclear factor of activated T-cells (NFAT)-regulated genes in the peripheral blood has been suggested as a potentially useful immune monitoring tool to individualize tacrolimus (Tac) therapy. The aim of the present study was to characterize the possibility and clinical utility of monitoring of residual NFAT-regulated gene expression in renal allograft recipients in a multicenter approach.

Methods: The IMAGEN study enrolled 64 de novo renal transplant recipients from three European centers. All patients were treated with Tac, mycophenolic acid, and corticosteroids. NFAT-regulated gene expression (NFAT-RGE; IL-2, IFN-g, GM-CSF) was evaluated by quantitative real-time PCR in whole blood samples at day 7, month 1, 2, 3, and 6 after transplantation.

Results: Altogether, 60 patients could be evaluated. Tac concentrations (C0 and C1.5) correlated inversely with gene expression ($p<0.001$). NFAT-RGE showed a high interindividual variability (1 to 61%). RGE increased in the first two months from 16±9% to 34±21%. Patients (n=20) with high residual gene expression (NFAT-RGE≥30%) were at the increased risk of acute rejection in the following months (35% vs 5%, $p=0.002$), whereas patients (n=40) with low residual gene expression (NFAT-RGE<30%) showed a higher incidence of viral complications, especially cytomegalovirus and BK virus replication (52.5% vs 10%, $p=0.001$).

Conclusions: NFAT-RGE was confirmed as a potential non-invasive early predictive pharmacodynamic marker in the immediate post-transplant period for the risk of acute rejection and infectious complications in Tac-treated renal allograft recipients. Monitoring of NFAT-RGE may provide additional useful information for physicians to achieve individualized treatment adjustments based on the immunomodulatory effect of Tac, thus preventing serious clinical events. The method of NFAT-RGE measurements can be applied in trials with multicenter approach.

PO2410

The Role and Inducers of Nonclassical HLA-G in Renal Transplanted Allografts

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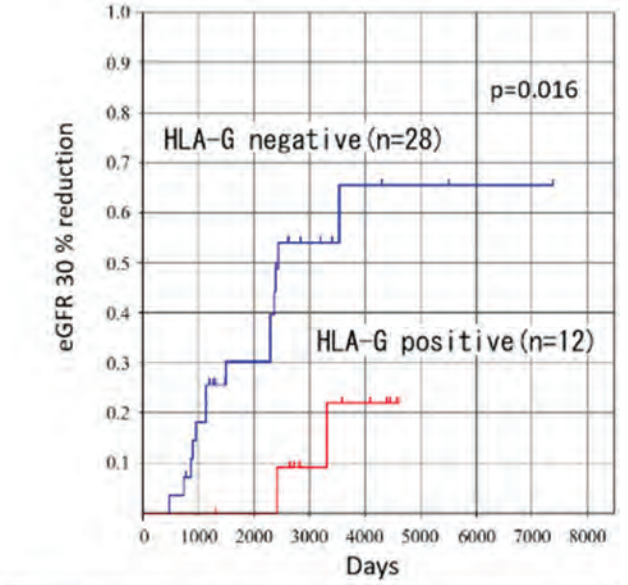
Background: Non-classical class I molecule HLA-G has a high potential to modulate immune response. However, the mechanism of HLA-G induction was still unknown. In this study, the expression of HLA-G on proximal tubular epithelial cells (pTECs) and the inducer of HLA-G were investigated.

Methods: Our subjects comprised 40 adult Japanese subjects whose allograft had survived for at least 1 year (35 patients from a living donor, 5 patients from a deceased donor). They were evaluated for HLA-G1/5 expression using an immunofluorescence method. We investigated inducer of HLA-G using primary cultured human pTECs treated with cytokines and immunosuppressants.

Results: In renal biopsy tissues, 2 to 4 weeks or 1 year following the transplantation, HLA-G expression was noted in the perinuclear region or on the basement membrane side of pTECs in 12 of 40 cases (30 %). Further, for median 8.8 years, the time taken for a 30 % reduction in eGFR was longer in the HLA-G-positive group than in the HLA-G-negative group ($p=0.016$, Figure). HLA-G1/5 expression on pTECs was also found to be an independent predictor of the improvement in renal allograft function by Cox's proportional hazard model ($p=0.030$). *In vitro* study, interferon-beta (IFN-β) was the strongest inducer of HLA-G expression, while immunosuppressants (everolimus, tacrolimus, cyclosporin, and dexamethasone) did not induce expression.

Conclusions: The study showed that HLA-G1/5 expression on pTECs was an independent improving predictor of renal allografts. Furthermore, the strongest HLA-G1/5 inducer was IFN-β, but not the immunosuppressive agents. These results suggested the possibility that acquired expression of HLA-G exhibits a long-term renal preservation effect, different from the effect of immunosuppressants.



Number at risk	0	1000	2000	3000	4000	5000	6000	7000	8000
Positive	12	12	12	10	6	6	6	6	6
Negative	28	22	15	9	3	3	3	3	3

PO2411

The Clinical Impact of Preformed HLA-DQ Donor-Specific Antibodies on Graft Outcomes in Kidney Transplantation

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Background: De-novo HLA-DQ donor-specific antibody (DSA) has been identified as a risk factor for graft rejection and loss in kidney transplantation (KT). Recently, the impact of preformed HLA-DQ DSA has been discussed. This study aimed to investigate the clinical impact of preformed HLA-DQ DSA on graft outcomes.

Methods: We evaluated 990 recipients who underwent kideny transplantation at Seoul St. Mary's Hospital from January 2010 to July 2019. According to the result of DSA using luminex single antigen bead assay, recipients were classified as no DSA, only DQ, non-DQ, and DQ + non-DQ. Primary outcomes were the incidence of biopsy-proven acute rejection and the rate of death-censored graft loss.

Results: In total cohort, 611 recipients (61.7%) and 379 recipients (38.3%) underwent living-donor KT and deceased-donor KT, respectively. Recipients were classified as no DSA (909 recipients, 91.8%), only DQ (18 recipients, 1.8 %), non-DQ (57 recipients, 6.3%), and DQ + non-DQ (6 recipients, 0.7%). The overall incidence of acute rejection and acute antibody-mediated rejection (AMR) were 20.3% and 7.5%. Only DQ, non-DQ, and DQ + non-DQ group had significantly higher the incidence of acute AMR compared to no DSA group ($p < 0.05$, respectively). There was no significant difference in the incidence of acute AMR between sensitized groups. There was no difference in the rate of death-censored graft loss between groups. In univariate Cox regression analysis, all of 3 groups with DSA were associated with high risk of acute AMR (Only DQ: HR 5.051; CI 95%, $p = 0.002$, non-DQ: HR 6.005; CI 95%, $p < 0.001$, DQ + non-DQ: HR 7.748; CI 95%, $p = 0.005$, respectively). HLA-DQ DSA and other DSAs (HLA-A, HLA-B, HLA-DR) had a tendency to interact with acute AMR, although no statistical significance ($p = 0.055$).

Conclusions: Preformed HLA-DQ DSA is associated with the development of acute rejection, especially acute AMR. Therefore, the identification of preformed HLA-DQ DSA may be necessary to improve graft outcomes.

PO2412

Outcomes of High Kidney Donor Profile Index Kidneys at a Large Center

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Background: Kidneys from donors with high Kidney Donor Profile Index (KDPI) are often discarded due to concerns about outcomes. Despite decreased survival, the survival benefit of receiving a transplant and avoiding time on dialysis is beneficial, especially for selected patients.

Methods: We increased use of high KDPI (KDPI>85) deceased donor kidneys (DDKT) over several years. We performed a single-center analysis of 1119 consecutive adult DDKT from 2016-2019. Our endpoints were Kaplan-Meier death-censored

graft survival (HR calculated by the Cox Proportional Hazards model) and eGFR by MDRD equation at 3, 6, and 12 months post-transplant. Mean eGFR was compared for significance using a t-test.

Results: 1119 patients were transplanted: 205 (18.3%) received a kidney from a donor with KDPI > 85% vs. 914 (81.7%) from a donor with a KDPI of <=85%. As expected, the high KDPI group had a higher mean age (66.5 vs. 53.6 ($p < 0.0001$) and a higher mean EPTS (74.7 vs. 50.4 ($p<0.0001$), reflecting deliberate selection. Death-censored graft survival at 1yr was 91.9% (CI: 86.9-95.0) in the high KDPI group vs 96.7% (CI: 95.3-97.7) in other recipients. High KDPI was a significant risk factor for death-censored graft survival (HR: 1.91; p=0.017). 1-yr mean eGFR by MDRD equation in patients alive with followup was 49.0 ml/min/1.73m2 in the high KDPI group vs 62.3 ml/min/1.73m2 in the < 85% KDPI group ($p<0.0001$). Box-and-whiskers plots of 3, 6, and 12-year eGFR are shown (figure 1).

Conclusions: Despite reduced graft survival, high KDPI kidneys offered renal function to 91.9% of surviving patients at 1 year. eGFR was also consistently lower, but provided good function to those recipients. Utilizing high KDPI kidneys in well-selected recipients is an important aspect of reducing waiting time and morbidity and mortality of dialysis.

Funding: Clinical Revenue Support

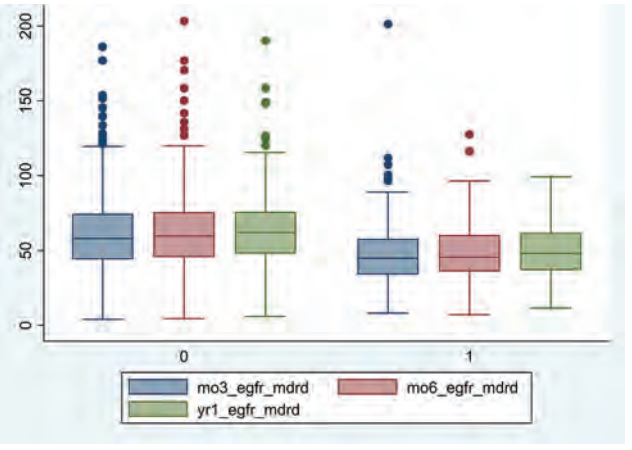

Figure 1. eGFR by MDRD at 3, 6, and 12 months for recipients of KDPI <= 85 (0) vs. KDPI > 85 (1)

PO2413

Could Individually Measured Creatinine Clearances Decrease the Discard Rate of High Kidney Donor Profile Index (86-100) Deceased Donor Kidneys?

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Background: The Kidney Donor Profile Index (KDPI) guides center acceptance and allocation of deceased donor kidneys (DDKs). It uses donor factors such as serum creatinine (sCr), diabetes mellitus and hypertension to predict organ quality and corresponsing longivity. Due to this higher KDPI kidneys are often discarded. KDPI offers "only moderate predictability" of long-term transplant function with a *c statistic* of 0.6.

Methods: As an unexplored, but direct measure of deceased donor kidney quality, we determined pre-recovery creatinine clearances (CrCls) in 260 deceased donor candidates (1/2015 -12/2018) using ICU urine collections (Ucolls) and pre- and post- collection serum creatinine (sCr) values. We used CrCl > 80 ml/min as the threshold of interest, as that defines acceptable kidney function for living kidney donor candidates. Donor creatinine production rates were calculated to assess the veracity of CrCls. Organ match sequence was reviewed for all denials and UNOS denial codes and corresponding reasons for denial were reviewed.

Results: Of the 134 kidneys available from 67 high KDPI donors, 32/67 donors had both kidneys transplanted, 7/67 donors had one kidney transplanted and 28/67 donors were not transplanted. Reviewing the 35/67 donors in whom either one or both kidneys were not transplanted; 10 of them had CrCl > 80. This amounts to about 28.6 % (10/35) of the non-transplanted donors with high KDPI; having a CrCl >80 ml/min. In the high KDPI group 28/67 candidates (~42%) had measured CrCl >80 ml/min. In the KDPI 21-85 group, 97/155 (63%) of donors had CrCls that >80 ml/min; while 42/50 (84%) in the KDPI 0-20 group had measured CrCls > 80 ml/min. Lower CrCls did not correlate with higher KDPIs within each subcohort. Donor creatinine production rates were 17.9 +/- 9.1 mg/kg/day, within population expectations. UNOS denial codes for high KDPI organ offers were mostly 830 - donor age or quality or 837 - organ specific donor issue

Conclusions: Our data suggests that about 28.6% of the non-transplanted high KDPI donors had CrCl >80 and these kidneys could have been potentially used and not discarded. Direct measurement of CrCl in deceased kidney donors is not difficult and deserves further study, as it may improve estimates of donor kidney quality and reduce inappropriate discards in a heterogeneous group.

Funding: Clinical Revenue Support

PO2414

Glomerular Blood Flow in Living Donor Kidney Transplant Recipients

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Background: Renal graft hemodynamics may be a valuable predictor of graft survival and long-term outcomes. Although several studies have reported that renal blood flow was correlated with graft function and decreased remarkably during acute rejection episode, the glomerular hemodynamic changes during kidney transplantation are lacking because there is no method of measuring nephron number in vivo. In this study, we calculate glomerular blood flow (GBF) by estimating the nephron number and investigate changes in GBF after kidney transplantation and their clinicopathological relationship.

Methods: We performed a retrospective analysis of 42 patients who underwent living donor kidney transplantation. The number of glomeruli (Nglom) was calculated as the cortical volume of both kidneys as assessed on computed tomography times the 1-hour posttransplant renal biopsy-determined glomerular density. Effective renal plasma flow (ERPF) was assessed as 99mTc-MAG3 clearance. GBF was calculated as follows: GBF (nl/min) = ERPF/Nglom/(1-hematocrit/100) $x10^6$. We analyzed the GBF before and during a 1-month observation period after transplantation. The GBF ratio as a marker of change in GBF was calculated as follows: (GBF one-month post-transplantation) / (GBF before transplantation in donors).

Results: Prior to transplantation, the GBF in donors was 559.7±257.3 nl/min, whereas the GBF in recipients on day 2 post-transplantation was decreased to 502.6±317.4 nl/min. After successful transplantation, the GBF one-month post-transplantation has settled down to 491.9±291.1 nl/min, while the eGFR progressively rose (48.7±18.4 ml/min/1.73m²) together with the hematocrit (31.1±3.9 %). The GBF at one month was positively associated with eGFR at one month ($p<0.05$). Of note, the GBF ratio was correlated with the eGFR and urinary protein execration at one month and urinary protein execration at 1 year but was not correlated with eGFR at 1 yr.

Conclusions: We first reported the GBF in kidney transplant recipients before and after kidney transplantation. Our findings suggest that abnormal change in GBF may be considered predictive indices for short-term allograft outcomes.

PO2415

Characteristics of Anonymous Living Donors and Their Recipients and Outcomes: Appropriate Use of a Rare and Valuable Gift

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Background: Anonymous Living Donors are a special select set of donors. We review the trends and the characteristics and utilization of such donors nationally.

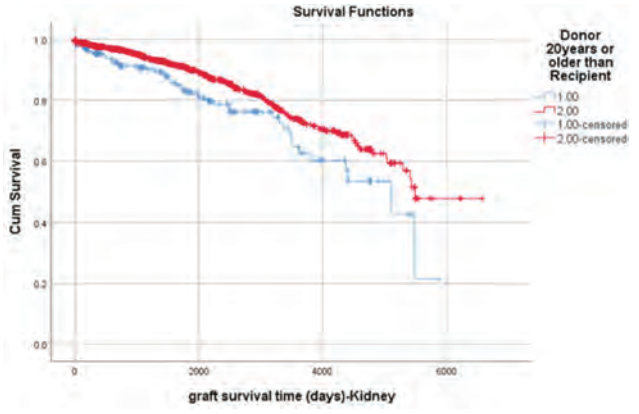
Methods: All Living Donors (code=10 "Anonymous") and their recipients who were recorded in the UNOS database from Oct 1997 through Sep 2017 were reviewed for demographics and recipient outcomes.

Results: There were a total of 2286 such donors during the study period. There was an increasing trend of the donors over the time period. Demographics and Outcomes are shown in the Table. DCGS was significantly superior when donor was 20 years or more younger than the Recipient (p=0.019) and significantly inferior when the 20 years older than the recipient (p=0.0005). There was no difference in cumulative graft survival between adult and pediatric graft survival (p=0.055), although DCGS was superior in the adults (p=0.021).

Conclusions: To our knowledge, this is the first comprehensive report on the characteristics of Anonymous Living Kidney Donors and their Recipients and outcomes. Better characteristics matching in a minority of such transplants may improve further longevity from such donors.

Donor, Recipient and Transplant Characteristics

Donor Mean Age / Median (range)	43.6±12.1/ 44 (18-76) yrs
Donor Race (W/AA/H) // Gender (M/F) %	96.3/2.4/2.7 // 56.5/43.3
Mean / Median (range) Donor BMI // h/o HTN (%)	25.6±3.9 / 25.3(15-42) // 1.9%
Recipient Mean Age / Median (range)	47.4±15.3 / 50 (1-79)
Recipient Race (W/AA/H) // Gender (M/F) %	67.3/15.7/8.7 // 59.3/40.7
Re-Transplants / Pre-emptive / PVD / DM %-// Median Time Wait list	12.2/ 23.3/ 4.8/ 27.1 // 462 days
Donor Nephrectomy Side (%)	Left 87.3 / Right 12.7
1 yr Rejection / DGF (%)	7.9 / 4.9
ABO MisMatch (%)	Identical 89.3/Compatible 9.8/ Incompatible 0.8
HLA 0 MM / DR 0 MM	1% / 9%
Age Mismatch Mean / Median (range)	3.8±17 / 3.0 (-51 to 51)
BMI Mismatch (Recap-Donor) Mean/ Median (range) / >10 unit Difference (%)	1.8±6.7/ 1.8 (-25 to 31) / 2.1%
Recipient Age > 20 yrs Older Than Donor (%)	18.1
Donor Age > 20 yrs Than Recipient (%)	2.9
1 yr Rejection / DGF (%)	7.9 / 4.9



PO2416

Outcomes of Delayed Graft Function: A Systematic Review and Meta-Analysis

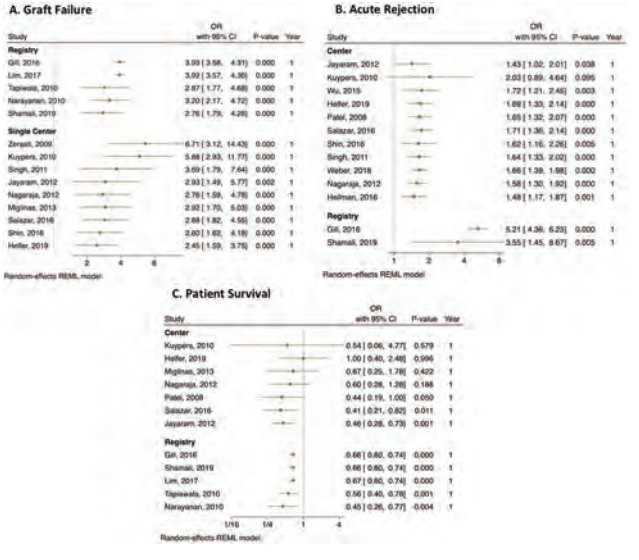
Vanessa Sandra,[1] Navin Sanichar,[1] Emily Daniel,[1] Miah T. Li,[1] Kristen L. King,[1] Jacob Stevens,[1] Syed A. Husain,[1] Tracy J. Mayne,[2] Sumit Mohan.[1] [1]*Columbia University, New York, NY;* [2]*Angion BioMedica, San Fransisco, CA.*

Background: Delayed Graft Function (DGF) is a frequent complication of kidney transplantation, but its impact on long and short-term outcomes remain uncertain.

Methods: We conducted a literature search for studies investigating the association of DGF on subsequent outcomes from 2007-2020. Outcomes were abstracted and used to create cumulative forest plots with pooled odds ratios, stratifying our analysis between center-studies and registry-studies and follow-up time where possible. The outcomes analyzed were graft failure (GF), acute rejection (AR), patient survival, and renal function.

Results: Of the 1464 articles reviewed, 27 were included. In single center-studies, DGF patients experienced higher GF at 1 year (OR 2.45, 95% CI 1.79-4.29, p<0.001), 3 years (OR 1.70, 95% CI 1.01-2.86, p<0.001), increased AR 1-year post-transplant (OR 1.48, 95% CI 1.79-4.28, p=0.001), and decreased 1-year patient survival (OR 0.46, 95% CI 0.28-0.73, p<0.001). Registry-studies showed a similar significant association with GF at 1 year (OR 2.76, 95% CI 1.79-4.28, p<0.001) and 3 years (OR 1.70, 95% CI 1.01-2.86, p=0.046), with AR within 1 year (OR 1.48, 95% CI 1.45-8.67, p=0.005) and 3-years (OR 0.54, 95% CI 0.41-0.72, p<0.001), and 1-year survival (OR 0.45, 95% CI 0.26, 0.77, p<0.001). Qualitative analysis showed that DGF had significant effect on eGFR and creatinine levels, though studies conflict on timeframe. Few studies investigated outcomes stratifying DGF severity or KDPI.

Conclusions: DGF was associated with increased risk of GF, AR, and mortality, although effects were largest within 1 year post-transplant. Our analysis indicated a need for a standardized method to measure DGF severity and further studies on DGF outcomes on varying KDPI. These results should inform the selection process, treatment, and monitoring of transplanted kidneys at high risk for DGF.



PO2417

Duration of Delayed Graft Function Predicts Kidney Allograft Function and Survival

Sanjana Kapoor, Nawras Alshoubaki, Chethan M. Puttarajappa, Sundaram Hariharan. *University of Pittsburgh Medical Center, Pittsburgh, PA.*

Background: The current study evaluated the duration of DGF as a measure of severity of ischemic injury to kidney transplant outcome.

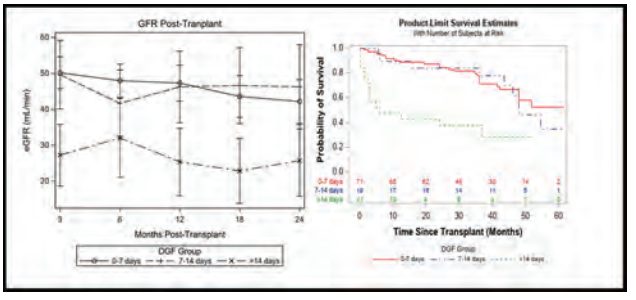
Methods: This single center study evaluated DD kidney transplant recipients with DGF between Jan 2014 and Dec 2019. DGF was defined as the need for dialysis within 7 days post-transplant & were divided into three groups according to post transplant dialysis duration. Group I: dialysis ≤7 days, Group II: dialysis 8-14 days and Group III: dialysis >14 days. All primary & repeat adult kidney recipients of DD transplants were included. We excluded multiorgan recipients and pediatric en-bloc kidneys. We calculated eGFR over time using CKD EPI formula. Statistical analysis was performed to identify differences in variables, Linear Mixed Model for eGFR over time. Log-rank test was used to evaluate differences in graft & patient survival & composite end point (graft loss, patient loss & GFR, 20ml/min) for all 3 subgroups.

Results: A total of 132 DD KT recipients with DGF were identified: Group I: n=84 (64%), Group II: n=24 (18%) & Group III: n=24 (18%). The recipient/donor demographics and Donor (KDPI) & Transplant variables were similar across groups.**Figure 1 (left)** shows significantly lower eGFR values over time using linear mixed model among patients who needed dialysis for >14 days (Gr III vs I&II, P=0.006). **Table 1** shows the incidence of Isolated Graft Loss, Patient death and combination of graft loss & patient death among 3 groups. **Figure 1 (right)** shows significantly lower composite end point (combination of patient loss, graft loss and impending graft loss) for among patients who needed dialysis for >14 days (P=0002).

Conclusions: In conclusion, we found a strong association between prolonged DGF>14 days with lower GFR values and survival outcomes. No differences in eGFR and survival rates were noted among patients with DGF patients < 7 days vs.7-14 days.

Funding: Clinical Revenue Support

	Group I: Dialysis <7days	Group II: Dialysis 7-14 days	Group III: Dialysis >14 days	p-value
Graft loss, n(%)	13 (15.5%)	2 (8.3%)	9 (37.5%)	0.028
Patient death, n(%)	11 (13.1%)	5 (20.8%)	8 (33.3%)	0.07
Graft & patient loss, n(%)	23 (27.4%)	9 (37.5%)	14 (58.3%)	0.019



PO2418

Design of the Graft Improvement Following Transplant (GIFT) Trial, a Phase 3 Study of ANG-3777 in Kidney Transplantation Patients with Delayed Graft Function

Flavio Vincenti,[1] Tracy J. Mayne,[2] Deb Gouveia,[2] John F. Neylan.[2] [1]*University of California San Francisco, San Francisco, CA;* [2]*Angion Biomedica, San Francisco, CA.*

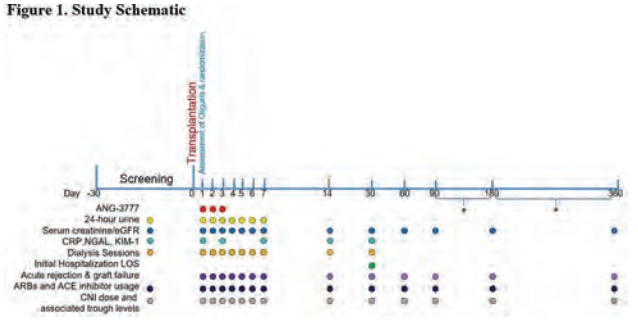
Background: Patients after kidney transplantation can experience acute kidney injury (AKI) resulting in delayed graft function (DGF). The Food and Drug Administration has prioritized the development of new treatments for DGF. A Phase 2 trial demonstrated that treatment with ANG-3777, a hepatocyte growth factor (HGF) mimetic, improved renal function up to 12-months in patients with signs of DGF.

Methods: Objective: To describe the GIFT trial (Study 001-15), designed to evaluate the efficacy and safety of ANG-3777 in renal transplantation patients with signs of DGF

Results: GIFT is a Phase 3, multicenter, prospective, randomized, placebo-controlled, study enrolling patients who have undergone a kidney transplantation with a deceased donor kidney who exhibit signs of DGF (producing a mean of <50cc urine per hour over 8 hours in the first 24-hours post-transplantation). Patients are randomized 1:1 to ANG-3777 (2 mg/kg) or placebo administered intravenously once daily for 3 consecutive days starting within 30 hours after transplantation. The primary endpoint is estimated glomerular filtration rate (eGFR) at 12 months. Secondary endpoints include proportion of subjects with eGFR > 30 mL/min/1.73m^2 at days 30, 90, 180 and 360; proportion of subjects whose graft function is slow, delayed or primary non-function; length of hospitalization; duration of dialysis through day 30. A study schematic is shown in Figure 1. Adverse events are being assessed throughout the study.

Conclusions: No pharmacologic intervention has been demonstrated in a rigorous trial to be effective preventing or improving the outcome of DGF. The GIFT study will generate data that are critical to advancing the treatment of DGF.

Figure 1. Study Schematic



PO2419

Clinical Outcomes of Kidney Transplant Recipients Living Away from Their Home Country

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Background: Many people leave their home country looking for better job opportunities and among those are kidney transplant recipients. However, taking care of such recipients might be challenging especially when information regarding induction immunosuppression, donor HLA typing, donor-specific antibodies, crossmatch and/or infections are not available. The aim of this study was to compare clinical outcomes of kidney recipients transplanted in their home conutry with kidney recepients transplanted locally.

Methods: In this retrospective cohort, we included all adult recipients transplanted between 2005 and 2016 and followed at our transplant clinics within their first year of transplant. Patients were categorized into two groups; local group including recipients transplanted at our center and abroad group including recipients transplanted in their home country.

Results: There were 111 patients in local group and 110 patients in abroad group. The mean age at transplant in local and abroad groups were 48 and 42 year-old, respectively. 63% of receipients in local group were from the Middle East, while 53% of patients transplanted abroad were from South Asia. Deceased donation was higher in local group (41% vs. 4%; p<0.0001). There was no difference in recipient sex, native kidney disease, preexisting diabetes mellitus or preemptive transplants. Most patients were on CNI and steroid immunosuppression (n=209; 95%). The mean follow up post transplantation was 6.3 years. The risk of acute cellular rejection was statistically significant in abroad group (13% vs 3%; p=0.005). However, the risk of ABMR or borderline rejections were similar. The incidence of post-transplant diabetes and malignancies was similar in both groups. There was no difference in 1-,3- and 5-year creatinine and proteinuria between both groups. Patient and graft survival rates were excellent in both groups and 5-year patient and death-censored graft survival rates in local and abroad groups were 100% vs. 93% and 95.2% vs. 96.6%, respectively.

Conclusions: Transition of care between countries carry its risks as it may be related to drug disruption or incomplete medical record. Kidney recipients transplanted abroad are at increased risk of acute cellular rejection; however, patient and graft survival rates remain excellent.

PO2420

Factors Associated with the Use of Hypothermic Machine Perfusion in Kidney Transplant Recipients

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Background: Delayed graft function (DGF) is associated with an increased risk of graft loss. The use of cold hypothermic machine perfusion (HMP) has been shown to reduce the incidence of DGF in kidney transplant recipients (KTRs), especially when extended-criteria donors (ECDs) are used. However, there is a paucity of data on the determinants of HMP use in real-life setting.

Methods: We aimed to determine the factors associated with the use of HMP in a cohort of donors and KTRs. We collected data on consecutive brain-dead donors admitted to an organ procurement organization and their KTRs between June 2013 and December 2018 in 5 adult transplant centers in Canada. There is no standardized protocol for the use of HMP in the province of Quebec. The use of HMP is left at the discretion of the surgeon recovering organs. However, a HMP device was available for every organ recovered at the organ procurement organization. Generalized estimating equations were used to predict the use of HMP.

Results: The cohort included 159 deceased donors and their 281 KTRs. Thirty-three percent of donors were ECDs, and 59% of KTRs received organs placed on HMP. The median cold ischemia time (CIT) was 12.4 (IQR 7.9-16.2) hours. There were no differences in use of HMP over time. In univariate analysis, none of the donors' characteristics were associated with the use of HMP. The use of HMP was similar in ECD and standard criteria donors (33% vs 34%, p=0.82). For KTRs, in univariate analysis, race (non-Caucasian), cold ischemia time, use of basiliximab/alemtuzumab, and KTR center were associated with the use of HMP. In multivariate analysis, CIT (odds ratio [OR] 1.09, 95% confidence interval [CI] 1.03-1.16) and KTR center were significantly associated with use of HMP.

Conclusions: We found that use of HMP was strongly associated with the transplant center where the surgeons practiced, suggesting that surgeon preference/training plays an important role in determining the use of HMP. The presence of ECD did not influence the use of HMP. The reasons underlying the differences in practice between centers should be explored in further studies.

Funding: Government Support - Non-U.S.

PO2421

Microvascular Inflammation Is the Main Determinant of Elevated Donor-Derived Cell-Free DNA in Kidney Transplantation

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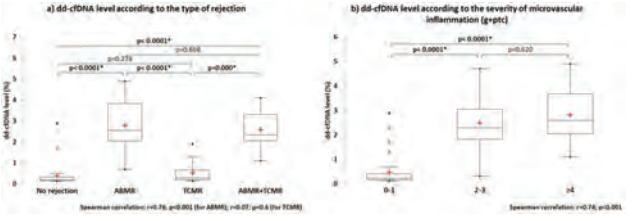
Background: Microvascular inflammation (Mi) is the main histological lesion for ABMR. Mi may occur separate from other ABMR criteria, early in the injury process, and may not be captured by the current Banff criteria. Donor-derived cell-free DNA (dd-cfDNA) has the potential to identify early allograft injury and supplement the current diagnostic criteria for rejection.

Methods: We included all patients(n=54) who underwent a kidney transplant biopsy for suspicion of rejection at our center from 9/17-12/19. Determinants of a biopsy were renal dysfunction, elevated dd-cfDNA, or presence of DSAs.

Results: Dd-cfDNA correlated strongly with the presence of ABMR, Class II DSA>2500, and histological lesions of ABMR. The strongest association was with Mi lesions (OR 192,95%CI: 18.6, 1984, p<0.001). Of the 18 patients with Mi, 2 did not meet the criteria for ABMR and had a dd-cfDNA level of 0.32% and 1.9%. All patients with Mi that met the criteria for ABMR had a dd-cfDNA over 1%. There was no association with renal function or histological lesions of tubulitis or interstitial inflammation (Fig 2).

Conclusions: Dd-cfDNA has the potential to identify early allograft injury and allow for early and less aggressive interventions that can beneficially alter long term outcomes of kidney transplant recipients.

Funding: Commercial Support - CareDx, Clinical Revenue Support



The absolute level of dd-cfDNA and its correlation with rejection type and microvascular inflammation

Variable	Univariate analysis		Multivariate analysis*	
	Odds ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Recipient age (for each 1 y)	0.98 (0.94-1.01)	0.29	-	-
Recipient gender (female vs. male)	2.53 (0.81-7.85)	0.1	-	-
Recipient race (other vs. Caucasian)	1.16 (0.39-3.49)	0.78	-	-
Type of transplant (cadaveric vs. living)	0.35 (0.096-1.33)	0.12	-	-
Time from Tx to dd-cfDNA measurement (for each 1 year)	1.19 (0.98-1.43)	0.06	-	-
Serum creatinine (for each 1 mg/dl)	0.14 (0.039-0.516)	0.003	-	-
Urine protein/creatinine ratio (for each 1 g/g)	1.05 (0.78-1.43)	0.71	-	-
DSA category (DSA MFI ≥2500vs. negative DSAs)	40 (7.95-201)	<0.001	**109 (8.67-1382)**	**<0.001**
Calculated Panel Reactive Antibody (>50%vs. <20%)	1.57 (0.2-12.17)	0.66	1.16 (0.12-11.2)	0.89
Induction IS (ATG vs. Basiliximab)	1.13 (0.23-5.38)	0.87	-	-
FK level (for each 1 ng/ml)	0.82 (0.65-1.04)	0.11	-	-
Presence of ABMR	136 (14.06-1314)	<0.001	**146 (12.19-1786)**	**<0.001**
Presence of TCMR	1.41 (0.44-4.47)	0.55	1.31 (0.35-4.81)	0.6
Microvascular inflammation (g+ptc≥2 vs. <2)	192 (18.57-1984)	<0.001	-	-
Presence of transplant glomerulopathy	24 (2.74-210)	0.004	-	-
Cd4 staining ≥ 1	6.59 (1.7-25.45)	0.006	**9.12 (1.83-45.4)**	**0.007**
Glomerulitis (g) ≥ 1	14.4 (3.77-54.89)	<0.001	**25.4 (4.26-151)**	**<0.001**
Peritubular capillaritis (ptc) ≥ 1	147 (19.1-1134)	<0.001	**294 (24.9-3472)**	**<0.001**
Presence of arteritis	1.63 (0.21-12.56)	0.63	1.67 (0.14-19.2)	0.6
Tubulitis (t) ≥ 2	0.61 (0.14-2.71)	0.52	1.02 (0.19-5.52)	0.9
Interstitial inflammation (i) ≥ 2	2.58 (0.39-16.94)	0.32	5.4 (0.5-57.4)	0.15
Tubular atrophy (ct) ≥ 2	1.2 (0.24-6.03)	0.81	0.87 (0.13-5.68)	0.8
Interstitial fibrosis (ci) ≥ 2	0.93 (0.19-4.39)	0.93	0.62 (0.1-3.84)	0.6
Arteriosclerosis (cv) ≥ 2	2.9 (0.7-11.88)	0.13	3.73 (0.61-22.77)	0.15

*After multivariate adjustment for age, race, gender, type of transplant and FK level (Backward Wald final step).

Binary logistic regression analysis regarding variables associated with a high dd-cfDNA level (>1%)

PO2422

Point-of-Care Creatinine Self-Testing in Renal Transplant Patients: An Assessment of Accuracy, Precision, and Patient Experience

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Background: During the Covid-19 pandemic it has become increasingly important to provide virtual care for patients with CKD. Point-of-Care testing of capillary creatinine (POC-Cr) is now available and has demonstrated validity, ease of use, improved efficiency and cost-efficiency. We aimed to determine patients' desire to self-monitoring of POC-Cr and their characteristics.

Methods: Renal transplant patients were shown how to perform self-POC-Cr testing with a NovaBio StatSensor®Xpress device, then undertook a test independently and answered survey questions about their attitude to self-testing of POC-Cr.

Results: All patients (N=189; Median age 52 years (IQR 40,64) ; 44 (23%) English as a second language; 128 (68%) male; Median eGFR 49 mls/min/1.73m^2 (IQR 34,64) successfully performed a POC-Cr test and 110/120 (91%) of patients who completed the survey reported they would like to self-monitor POC-Cr. Most patients wished to reduce their clinic attendance and the majority were willing to have telephone consultations. Characteristics of the cohort are described in Table 1.

Conclusions: All transplant patients successfully performed a POC-Cr test with written instructions and a demonstration. Most patients would like to self-monitor POC-Cr and reduce clinic attendance. Limitations include the single-centre design, number of participants and language barrier. Virtual care including patient self-monitoring using POC-Cr should be explored.

Characteristics of patients who would and would not like to self-monitor POC-Cr at home

Characteristics	Would like to self-monitor POC-Cr at home N=110	Would not like to perform testing at home N=10
Male, n (%)	76 (69%)	5 (50%)
Age (Years Median (IQR))	54 (41, 64)	35 (40, 61)
English as Second Language	40 / 109 (37%)	2 (20%)
Educational level n (%) Primary School Secondary School Higher education	5 / 77 (6%) 25 / 77 (32%) 47 / 77 (61%)	1 / 9 (11%) 3 / 9 (33%) 5 / 9 (56%)
First Year post transplant	41 (37%)	5 (50%)
Ethnicity White Black Asian Other	40 (36%) 16 (14%) 38 (34%) 16 (14%)	1 (10%) 1 (10%) 7 (70%)* 1 (10%)
eGFR (mls/min/1.73m2 Median (IQR))	50 (38, 63)	50 (24, 72)
After single test in clinic felt able to perform at home	104 /108 (96%)	6 (60%)†*
Able to check blood pressure at home	99 /107 (93%)	9 /9 (100%)
Access to an email address	100 (91%)	7 (70%)
Access to a smartphone or a computer	105 (95%)	7 (70%)‡
Has Remote Access to Laboratory Results	96 (87%)	5 (50%)‖¶
Would like to reduce attendance at clinic	85 /106 (80%)	7 (70%)
Would be willing to have telephone consultations	104 (95%)	7 (70%)§
Would be willing to have video consultations	82 (75%)	5 (50%)

PO2423

Short-Term Variability in Graft Function Is Associated with Long-Term Mortality but Not Allograft Survival in Kidney Transplant Recipients

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Background: It is critical to identify kidney transplant recipients (KTR) at highest risk of graft failure and death to focus on monitoring and interventions to improve long-term outcomes. Variability in native kidney function is associated with the risk of mortality and hospitalization in chronic kidney disease, but it remains uncertain whether such associations exist in KTR. We examined the hypothesis that short-term graft function variability is associated with long-term outcomes in KTRs.

Methods: Using the Wisconsin Allograft Recipient Database (WisARD), we identified 2919 KTRs who had a functioning allograft at least 2 years after transplantation and at least 3 outpatient estimated glomerular filtration rate (eGFR) measurements from 1 to 2 years post-transplant. Graft function variability was defined for each patient as the coefficient of variation based on a linear regression of eGFR from 1 to 2 years. Associations between eGFR variability and total graft loss, death and graft failure were estimated in competing risk models

Results: Patients with greater variability were more likely to be female, have more comorbidities, and have more prior hospitalization events at baseline. Compared to the lowest quartile, the highest quartile of eGFR variability was associated with a higher risk of total graft loss (adjusted HR 1.51, 95% CI: 1.11-2.06) and a higher risk of death (adjusted HR 1.85, 95% CI: 1.23-2.76), but not with a higher risk of graft failure (subHR 1.08, 95% CI: 0.64-1.83 in competing risk analysis), independent of eGFR and slope of eGFR. The associations remained consistent across strata of acute rejection, diabetes, peripheral arterial disease, baseline eGFR, history of cardiovascular disease, baseline hospitalization, and with all variability indicators and modeling approaches.

Conclusions: Short-term eGFR variability is associated with long-term death but not graft failure. Variability in eGFR provides independent prognostic information on transplantation outcomes and may be an indicator to differentiate the risk of death and graft failure.

PO2424

Defining a Minimal Clinically Meaningful Difference (MCMD) in Estimated Glomerular Filtration Rate (eGFR) for Kidney Transplantation

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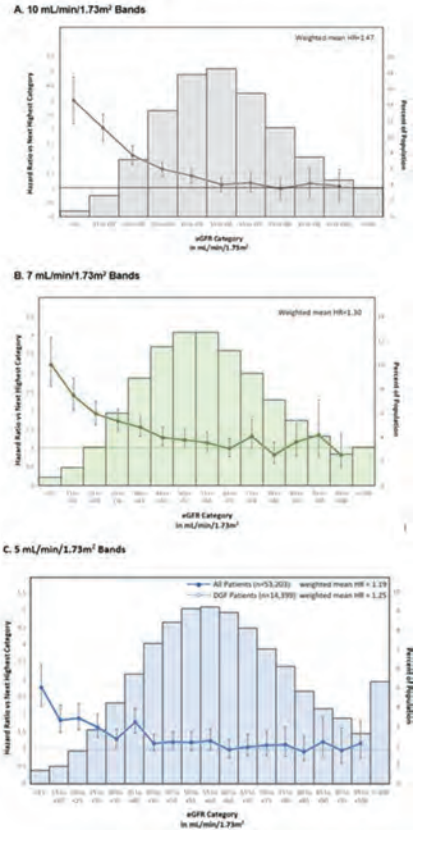
Background: eGFR is an established measure of renal function & predicts clinical outcomes. A MCMD for eGFR has never been clearly defined.

Methods: Data source: United Network for Organ Sharing (OPTN) database Study population: Adults (≥18 years of age); received deceased donor kidney 01/01/2013 to 12/31/2018; multi-organ & non-incident transplants were excluded. Analysis: Cox proportional hazards regression Primary outcome: Death-censored graft survival starting 12-months post-transplantation. Predictors: Recipient (gender, age, race, diabetes, body mass index, panel reactive antibodies); Donor (age, diabetes, hypertension, proteinuria); Transplantation (cold ischemia time, pump, DR locus mismatch, delayed graft function); 12-month eGFR (CKD-EPI). Analysis. eGFR was stratified by bands of 5, 7 or 10 mL/min/1.73m^2. Regressions compared each band to the next sequential band. A weighted mean hazard ratio was calculated using OPTN population eGFR distribution.

Results: The relationship between 12-month eGFR & graft failure is non-linear: HR=~3 to 4 at eGFR <15 mL/min/1.73m^2; HR=~1.1 at eGFRs ≥ 55. Mean HR=1.47 for 10 mL/min/1.73m^2 bands; 1.30 at 7 mL; 1.19 at 5 mL.

Conclusions: Controlling for multiple factors, 12-month eGFR is a strong predictor of death-censored graft survival. Mean HR (1.19) is consistent with an effect size considered significant, clinically meaningful, & supporting of regulatory approval (eg, angiotensin receptor blockers; statins). This supports 5 mL/min/1.73m^2 as the eGFR MCMD in kidney transplantation. **DISCLAIMER**. The interpretation & reporting of these data are the responsibility of the authors & in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

Figure 1: Hazard Ratio for Death-Censored Graft Failure by eGFR Band by Percent of Population within Each eGFR Band



PO2425

Composite Events Associated with Increased Expected Post-Transplant Survival Scores

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Background: Kidney transplant candidates on the waiting list are assigned an expected post transplant survival (EPTS) score. This score is used to determine allocation of kidneys in the kidney allocation system (KAS). The outcomes of candidates with an EPTS >95% at the time of listing is limited.

Methods: UCLA kidney Transplant Program data of waiting list with EPTS > 80% from January 2015 – December 2018 were included. Median follow up time of waiting list was 845 days. The outcomes included kidney transplant rate, 3 year death censored graft survival and patient survival in candidates with EPTS ≥ 95% compared with EPTS < 95%.

Results: A total of 124 patients were identified with an EPTS score > 95% at the time of listing during the study period. Of these patients 23 received a kidney transplant during the specified time frame (transplant rate of 16.9%). Recipients of kidney transplant had a longer dialysis vintage (2368.6 days vs. 9881 days, P< 0.0001) and were more sensitized at the time of listing (34.8% vs. 11.8%, p=0.018). Compared to a group with an EPTS between 80-94% at time of listing (n=170) there were no differences in mortality (4.35% vs. 4.55%, p=0.969), graft failure (14.3% vs. 6.4%, p=0.254), or 3 year death censored graft survival (70.0% vs. 84.5%, p=0.517). The EPTS > 95% group was older, had a longer dialysis vintage, had a higher proportion of candidates with diabetes as a cause of ESRD, and was less likely to undergo transplantation. Candidates with an EPTS >95% who did not receive a transplant had a mortality rate of 7.9% and waitlist removal rate 16.9%.

Conclusions: Kidney transplantation in candidates with an EPTS > 95% provides comparable outcomes to candidates with an EPTS between 80-94%, which was superior to remaining on dialysis. Despite this benefit, the transplantation rate of this group was low and a quarter of those not transplanted either died or are removed from the waitlist. Strategies are needed to improve transplantation rates in this population.

PO2426

Transition of Renal Transplant Care from Pediatrics to Adolescence and Young Adulthood: Retrospective Study Comparing Serum Creatinine-Based GFR Estimating Equations

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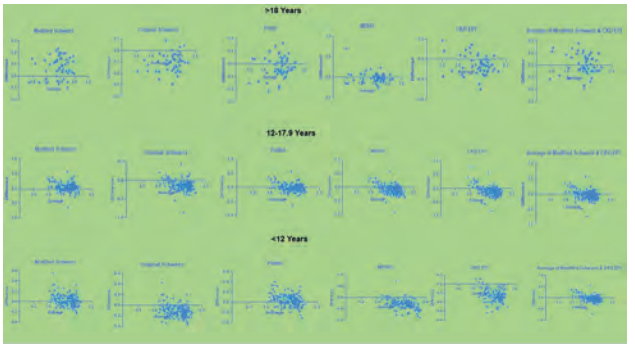
Background: The evaluation of graft function is vital in the management of pediatric kidney transplant (pKTx) recipients. Measured GFR (mGFR) using exogenous markers, is very accurate, but not suitable for daily use. Estimated glomerular filtration rate (eGFR) using Serum creatinine (Scr) is the easiest way and equations are categorized as either pediatric or adult specific. None of the equations were formally compared in adolescents and young adults with renal transplants. The aim of study was to assess the performance of creatinine-based formulas in a cohort of pKTx in pediatric, adolescents and young adult age groups.

Methods: This retrospective study was conducted at our hospital from January 2000 to March 2019 from 125 pKTx recipients. We compared 415 mGFR values to 5 different Scr-based eGFR formulae (original Schwartz(OS), BS, Pottel, Modification of Diet in Renal Disease (MDRD), CKD-EPI, and average of BS and CKD EPI. Basing on the age at which the GFR was measured we divided the cohort in to 3 categories (children <12 ys, Adolescents (12.1-17.9 ys and young adults >18-21 ys. We used Bland-Altman analysis to evaluate the bias, precision and accuracy between eGFR and mGFR.

Results: Pottel and BS performed well across pediatric and adolescent age groups with high 30% accuracy(figure). MDRD and CKD EPI performance improved in young adults >18 years. Average of BS and CKD EPI outperformed all other equations with minimal bias (0.006 ml/min/1.732 m^2) and 90% accuracy in young adults.

Conclusions: Height independent Pottel and height dependent BS formulae had low bias and high accuracy in children and adolescents. Average of BS and CKD EPI outperformed other equations in young adults and provides an overall unbiased estimate of GFR.



PO2427

A Comparison of the Associations of Urine Markers with the Rate of Decline in Kidney Allograft Function

Yoshitsugu Obi,[1,2] Naotsugu Ichimaru,[3,4] Yoshitaka Isaka,[3] Takayuki Hamano.[3,5] The CANDLE-KIT Trial Inverstigators *[1]Obi Clinic, Osaka, Japan; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]Osaka Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Suita, Japan; [4]Ippan Zaidan Hojin Sumitomo Byoin, Osaka, Japan; [5]Nagoya Shiritsu Daigaku Daigakuin Igaku Kenkyuka Igakubu, Nagoya, Japan.*

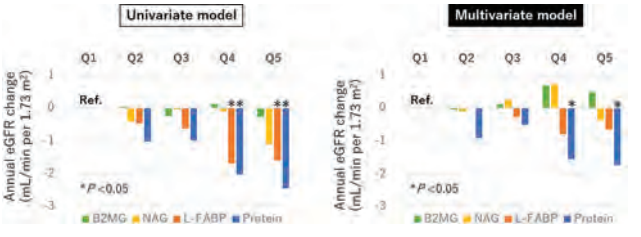
Background: Various urine markers are proposed to predict renal outcomes. However, there are few head-to-head comparison studies comparing their clinical relevance among kidney transplant recipients (KTRs).

Methods: In a prospective clinical trial, we enrolled 153 KTRs with anemia and >1-year history of transplantation across 23 facilities and followed them for 2 years. The annual change in eGFR was estimated based on mixed effects model. We then selected 102 patients who had baseline urine data on total protein, beta 2-microglobulin (β2MG), N-acetyl-beta-D-glucosaminidase (NAG), and L-type fatty acid binding protein (L-FABP). Total protein, NAG, and L-FABP were standardized according to urine creatinine concentration. We then compared the associations of the quintiles of each urine marker with annual decline in eGFR using univariate and multivariable linear regression models.

Results: Patients were 51±12 years-old and 54% were male. The median (IQR) of transplant vintage was 8 (5, 12) years, and the baseline eGFR levels were 31±11 mL/min per 1.73 m^2. The annual eGFR change was -1.6±2.0 mL/min per 1.73 m^2/ year. The median (IQR) urine levels of total protein, β2MG, NAG, and L-FABP at baseline were 0.3 (0.1-1.1) g/g Cr, 1535 (238-4780) μg/L, 0.06 (0.04-0.12) IU/L, and 16.7 (4.2-42.1) μg/g Cr, respectively. The higher levels of L-FABP and total protein were significantly associated with more rapid annual eGFR decline (*P* for trend <0.001 for both; **Figure**) while there was no significant association for β2MG or NAG. R^2 was 0.10 (*P*=0.03) and 0.18 (*P*=0.001) for L-FABP and total protein, respectively. After adjustment for age, gender, mean arterial blood pressure, and baseline eGFR, the association remained significant for total protein but not for L-FABP (**Figure**).

Conclusions: Among urine markers of total protein, L-FABP, NAG, and β2MG, total protein appears to have greatest predictive value for eGFR decline among KTRs.

Funding: Commercial Support - Chugai, Kissei, Roche Diagnostic K.K.



Associations of the quintiles of urinary markers with annual eGFR decline in the unadjusted models (left) and the multivariable adjusted models (right)

PO2428

Chronic Graft vs. Host Disease in Pancreas After Kidney Transplant Recipient: An Unrecognized Entity

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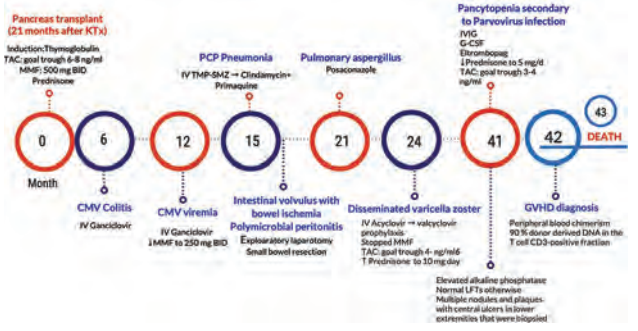
Introduction: Graft-versus-host disease (GVHD), a common complication after allogenic bone marrow transplantation is rarely seen after solid organ transplants (SOT). Reports of acute GVHD (maculopapular rash, diarrhea and cholestatic liver disease) described after SOT invariably happened in the early post-transplant period (days to months). In contrast, reports of SOT recipients with clinical features more consistent with chronic GVHD (cGVHD) (resembling autoimmune disease with chronic inflammation/ fibrosis) are lacking. We present a case of cGVHD in pancreas after kidney transplant (PAK) recipient diagnosed at 42 months post transplant.

Case Description: A 43 year old man received a HLA 5/6 mismatch, CMV mismatch (donor positive, recipient negative) deceased donor pancreas transplant two years after receiving a HLA 5/6 mismatch living unrelated kidney transplant. Anti-thymocyte

globulin induction was given along with a maintenance immunosuppression - tacrolimus, mycophenolate mofetil and prednisone. Post-transplant course was complicated by multiple opportunistic infections (Figure 1) leading to immunosuppression reduction. At 42 months post transplant, he developed dry eyes, arthralgia, anorexia, elevated alkaline phosphatase, dyspnea on exertion, lichen simplex chronicus dermatitis, and severe pancytopenia. GVHD was suspected which lead to peripheral blood chimerism testing revealing 90% pancreas donor-derived DNA in CD3-positive fraction of T cells. Patient passed away.

Discussion: The infections may have represented the immune dysfunction associated with cGVHD. De-escalation of immunosuppression could have led to an unopposed activation of donor cytotoxic T-lymphocytes resulting in worsening GVHD. Donor-derived T lymphocytes received during pancreas transplant may have targeted the bone marrow, causing severe pancytopenia, hence compounding the dysregulated immune state. Transplant professionals should be aware of the possibility of the rare but challenging diagnosis of cGVHD in PAK recipients and hence identify it appropriately.



PO2429

Graft vs. Host Disease Following Simultaneous Liver-Kidney Transplant

Bushra Syed, Mohamed Hassanein, Saul Nurko. *Cleveland Clinic, Cleveland, OH.*

Introduction: Solid organ transplant associated GVHD is uncommon with an incidence of 0.5 to 2%. Risk factors include donor HLA homozygosity, younger donor, recipient age >50 years and sex mismatch. We present a case of GVHD following a simultaneous liver kidney transplant (SLK).

Case Description: A 64-year-old female with NASH cirrhosis and CKD due to diabetic nephropathy underwent SLK from a 38-year-old male deceased donor. The pair had 3 HLA AB mismatches and 1 DR mismatch. A total of 3.5mg/kg of thymoglobulin (ATG) was used for induction. Renal and liver parameters were stable at discharge on a maintenance tacrolimus, mycophenolate and prednisone. She was readmitted after 1-month with diarrhea and fever. Infectious work up was unrevealing. She developed a maculopapular rash, mucositis and pancytopenia. Skin biopsy showed grade 2 acute GVHD. Donor lymphocyte chimerism in peripheral blood confirmed diagnosis of GVHD with 65% donor T cells, 10% donor CD8 cells and 42% donor natural killer (NK) cells. Treatment with high dose steroids and ATG was ineffective with worsening in CD8 and NK cell donor chimerism to 91% and 52% respectively. Weekly infliximab (INX) was introduced complicated by development of enterococcal bacteremia. Clinical improvement was seen after three doses INX, however there was a lag of several weeks before an improvement in donor chimerism. Six months later her hematological, renal and liver parameters remained stable, chimerism study showed <5% T cells, CD8 cells and NK cells and a protocol renal biopsy showed no evidence of GVHD associated denovo glomerulonephritis.

Discussion: The non-specific presentation of GVHD with rash, cytopenias and diarrhea leads to delayed diagnosis and high mortality. Detection of donor chimerism through short tandem repeat sequences is used to establish diagnosis and monitor response to treatment. Treatment options include high dose steroids with ATG, TNF a inhibitors or IL-2 antagonists. Adequate immunosuppression has to be balanced with risk of infection and timely use of empiric antibiotics and antifungals is recommended. Despite treatment, rapid progression to marrow aplasia, sepsis and multisystem failure ensues with an estimated mortality of >75%. Further studies are required to better understand this rare complication and explore novel treatments to improve outcomes.

PO2430

Kidney After Intestinal Transplantation, a Comparison with Combined Kidney with Intestinal Transplant: A UNOS Database Analysis

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Background: There is limited data on outcomes for patients receiving a isolated kidney transplant (KAIT) after any prior Multi-organ or Isolated Intestinal transplant (IT). We compared the outcomes of such transplants with Combined Intestinal-Kidney Transplants (CIKT).

Methods: The KT database from 1992 through Sep 2017 was cross-linked with the IT database for all kidney transplants performed. Data was analyzed for incidence, demographics, risk factors and outcomes after KT.

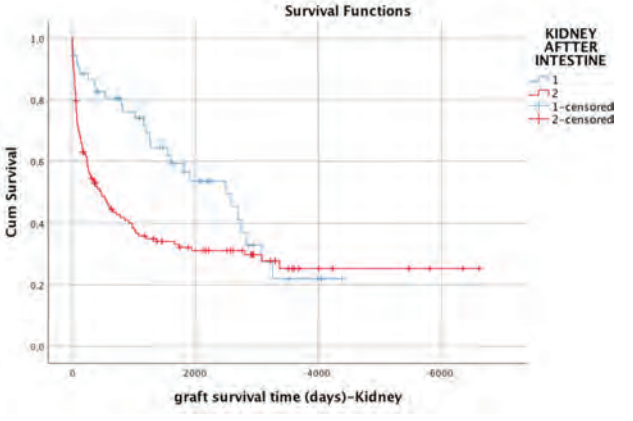
Results: There were a total of 2,886 IT recorded from 1990 through Sep 2017. There were a total of 190 (6.6%) Kidney transplants recorded of which 54 (28.4%) were KAIT while the remaining 136 (71.6%) where Combined (CIKT). The Median Duration from Intestinal Transplant to Kidney transplant was 5.6 years (Range 0.47 to 18.9). One year KAIT graft survival was 87% as compared to CIKT 52%. 5 year graft survival was 74% vs 36%. Death censored KAIT graft survival at 1 year was 98% vs 87% and 5 years 83% vs 74%.overall unadjusted kidney graft survival was significantly lower in CIKT as compared to KAIT p=0.009.

Conclusions: Our data shows that isolated kidney transplant after any prior Multi-organ or isolated Intestinal transplant has higher graft survival as compared to combined Intestinal Kidney Transplant. Higher CNI tough levels may be one common factor leading to lower graft survival.

Variable	Total N=190	KAIT 54	CIKT 136
Adult/Peds (%)	62.1/37.9	57.4/42.6	64/36
Recipient age at Transplant	32 +/-21	34+/-20.7	31+/-22.1
Kidney transplant adult/peds (%)	66.9/33.1	74.1/25.9	
Wait time	158+/-279	268+/-361	117 +/-230
Females	48.4 %	57.1%	47.1%
whites	78.4%	79.6%	77.9%
Kidney rejectin within 1 year	7.4%	11.1%	5.9%

NEW ERA 2007-2017 UNDAJUSTED GRAFT OVERALL SURVIVAL

	1YR	3YR	5YR	10YR
KAIT N=30	93%	85%	64%	64%
CIKT N=95	56%	40%	34%	34%



PO2431

Association of the Rate of Kidney Transplant Function Decline with the Risk of Death After Graft Loss

Everly Ramos, Laura Binari, Peter E. Thorne, Guneet S. Kochar, Saed Shawar, Thomas G. Stewart, Heather L. Prigmore, Rachel C. Forbes, Khaled Abdel-Kader, Beatrice P. Concepcion. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Patients with failed kidney transplants are at increased risk of death after graft loss compared to transplant-naïve counterparts. We hypothesized that in this high risk population, a faster decline in eGFR in the 2y prior to graft loss is associated with death after graft loss.

Methods: We retrospectively reviewed all patients with death censored graft loss (DCGL) from 1995-2018 at a single center. We collected demographic, clinical and transplant characteristics at time of transplant and graft loss. Rate of eGFR decline was expressed as eGFR slope, calculated from all SCr values obtained within 2y prior to graft loss. Cox proportional hazards regression was used to determine the association between rate of eGFR decline and death while adjusting for age, gender, race, cause of ESKD, cause of graft loss, dialysis access at graft loss, and nephrectomy after graft loss.

Results: 333 patients with DCGL were included. Baseline characteristics were: median age 45y (IQR 35,57), 59% male, 43% black; 19% DM as cause of ESKD. CAN (65%) and acute rejection (29%) were the top causes of graft loss at a median time from transplant of 4.9y (IQR 2.5,7.9). Rate of eGFR decline (in ml/min/1.73m^2/y) was -14.49 ± 13.24 (mean±SD) and -11.73 (-18.72,-6.19) (median, IQR). At time of DCGL, 46% had a history of acute rejection and 34% had a permanent dialysis access. Of the 251 patients without missing data, 97 (40%) died and 68 (27%) underwent a nephrectomy after graft loss. Median time from graft loss to death was 3.1y (IQR 1.4,7.3). In multivariable analysis, there was a 0.6% increase risk in death for every 1 ml/min/1.73m^2/y increase in rate of eGFR decline though not statistically significant (HR 1.006, 95% CI 1.00-1.01). Exploratory analysis with non-linear modeling of eGFR slope showed that the risk of

death increases up to a rate of decline of 10 ml/min/1.73m²/y. DM as cause of ESKD was associated with an almost 2-fold increase in risk of death after graft loss compared to non-DM (HR 1.95, 95% CI 1.27-2.96).

Conclusions: In this single-center cohort of kidney transplant recipients with DCGL, a faster rate of eGFR decline in the 2y prior to graft loss was not associated with a higher risk of death after graft loss after adjustment for important clinical variables.

PO2432

Renal Recovery After Liver Transplantation Alone in Patients with Liver Cirrhosis and Severe CKD with Normal Kidney Size

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Background: Most guidelines recommend simultaneous liver-kidney transplantation (SLKT) in patients with liver cirrhosis (LC) and severe chronic kidney disease (CKD) over liver transplantation alone (LTA). CKD, however, is not irreversible. This study evaluates the reversibility of kidney disease after LTA based on kidney size.

Methods: In this single-center retrospective study, we classified 90 patients with LC and severe CKD into 3 groups: normal kidney-LTA (NK-LTA, n=39), small kidney [both <9cm]-LTA (SK-LTA, n=40), and small kidney-SLKT (SK-SLKT, n=11). Baseline characteristics and renal recovery and survival outcomes were compared among 3 groups.

Results: The NK-LTA group had a lower percentage of hepatocellular carcinoma, a higher pre-LT eGFR, and a shorter duration of eGFR at <60 ml/min and pre-LT dialysis. This group, however, was older, received livers from a higher percentage of deceased donors and had a higher Child-Pugh score. Renal recovery, defined as no hemodialysis (HD) after LT, was found in 79% of those in the NK-LTA group, which was higher than 7.5% of those in the SK-LTA group. Renal survival, defined as patient survival without progression to HD or kidney transplant was found in 56% of patients in the NK-LTA group, which was higher than 2.5% of those of the SK-LTA group.

Conclusions: Patients with LC and severe CKD with normal kidney size may experience reversible kidney disease after LTA. Therefore, kidney after liver transplantation is recommended over SLKT for these patients.

Funding: Private Foundation Support

Table 1. Comparison of outcomes after LT among the 3 groups

	NK-LTA n=39	SK-LTA n=40	SK-SLKT n=11	p-value
Duration of follow-up (months)	27 (1–178)	29.5 (1–135)	135 (19–180)	0.001
Mortality				
1-year mortality	7 (18%)	6 (15%)	0 (0%)	0.32
Total mortality	9 (23%)	8 (20%)	2 (22%)	0.92
Duration until total mortality (months)	7 (1-22)	8 (1-102)	98.5 (19-178)	0.001
Cause of total mortality				0.54
LT graft failure	4 (10%)	3 (7.5%)	0 (0%)	
Duration until graft failure	5.5 (1-7)	2 (1-14)		
HCC recurrence	0 (0%)	2 (5%)	1 (11%)	
Duration until recurrence		15.5 (9-22)	19	
Sepsis	4 (10%)	2 (5%)	1 (11%)	
Duration until sepsis	12.5 (4-22)	6 (4-8)	178	
Others	1 (3%)	1 (2.5%)	0 (0%)	
Duration until event	10	102		
Renal outcome				0.001
No renal recovery	6 (21%)	37 (92.5%)	0 (0%)	
Renal recovery	31 (79%)	3 (7.5%)	11 (100%)	
→Renal survival	22 (56%)	1 (2.5%)	9 (82%)	0.001
→No renal survival	9 (23%)	2 (5%)	2 (18%)	0.068
Time until renal recovery (weeks) †	2 (0-13)	3 (0-3)	0 (0-0)	0.001
Duration of renal survival (months) ‡	34.5 (12-103)	29	135 (56–180)	0.001
eGFR at final FU §	39.4±18.1	64	66.7±20.8	0.002

† Comparison between no renal recovery and renal recovery, ‡ For patients with renal recovery, § For patients with renal survival
NK-LTA = Normal kidney-liver transplantation alone, SK-LTA = Small kidney-liver transplantation alone, SK-SLKT = Small kidney-simultaneous liver-kidney transplantation, eGFR = Estimated glomerular filtration rate, HCC = Hepatocellular carcinoma, LT = Liver transplantation, FU = Follow-up

PO2433

Immediate Allograft Function After Liver Transplant (LT) Modifies the Effect of Pre-LT Renal Dysfunction (RD) on Post-LT Survival

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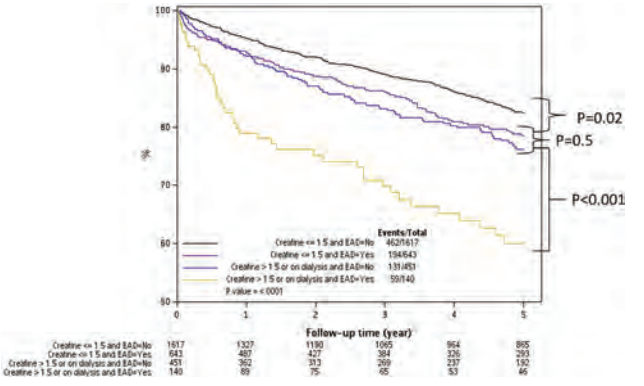
Background: Pre-LT RD is associated with higher post-LT mortality. It is unclear if immediate liver allograft function modifies this risk.

Methods: We retrospectively reviewed data on 2,856 primary LT performed in our center from 1998 to 2018. Pre-LT RD was defined as Cr >1.5 mg/dl or on dialysis at LT. Immediate liver allograft function was defined using the validated early allograft dysfunction (EAD) criteria (bilirubin≥10 mg/dl, INR ≥1.6 or ALT/AST ≥2000IU/mL on POD 7). Pre-LT RD was present in 591(21%), of these 429 patients had Cr >1.5 and 165 were on dialysis. EAD developed in 784 (27%). The cohort was divided into 4 groups according to pre-LT RD and EAD. Group 1 (n=1,617): No RD and no EAD, Group 2 (n=643): No RD but had EAD, Group 3 (n=451): had RD and no EAD, Group 4 (n=140): had both RD and EAD. The unadjusted and adjusted post-LT survival was compared between the 4 groups.

Results: Results are presented in Figure 1. Group 1 had the best outcome with 1,3 and 5 year survival of 95%, 89% and 82%, respectively, and group 4 had the worst outcome with 1, 3 and 5 year survival of 79%, 70% and 60%, respectively, P <0.0001. Group 2 and 3 had intermediate and comparable (P=0.5 between group 2&3) outcomes. Survival was better in group 2&3 compared to those in group 4 (P<0.001) but was worse than group 1 (P=0.02). After adjusting for recipient age, female gender, DM, MELD score, cause of ESLD and DRI, group 4 had the highest risk of death (aHR 2.33, CI:1.69-3.21, P<0.001). Patients in group 2 (aHR 1.16, CI:0.95-1.41, P=0.1) and group 3 (aHR 1.23; CI: 0.96-1.58, P=0.09) had comparable adjusted risk of death to group 1 patients.

Conclusions: LT recipients with pre-LT RD who enjoy immediate liver allograft function have comparable adjusted survival to those with normal renal function at LT. Our results indicate that livers at higher risk of EAD should be avoided in LT recipients with RD.



Kaplan-Meier analysis of post-LT patient survival according to pre-LT RD and post-LT EAD

PO2434

Sex and Equity in Pediatric Kidney Transplantation

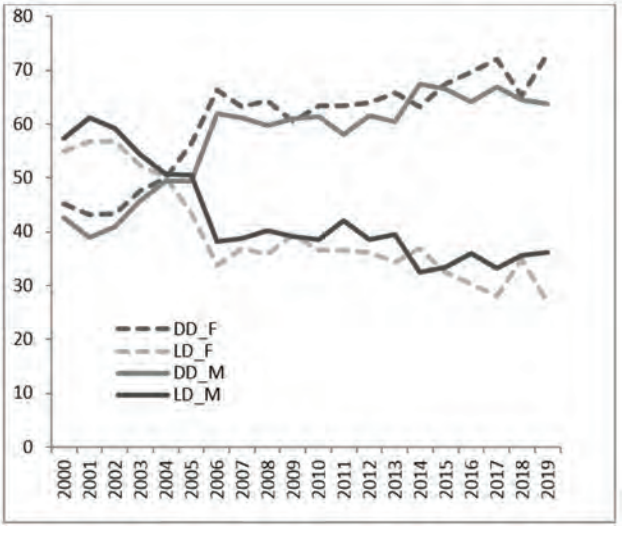
Rita L. McGill, Nevin Murthy, Lainie F. Ross. *University of Chicago, Chicago, IL.*

Background: Mortality in pediatric kidney failure (ESRD) is higher in girls than in boys, in contrast to the general population. In a recent report, correcting for access to transplantation partially ameliorated this risk, prompting an examination of equity in pediatric kidney transplantation.

Methods: USRDS files were used to examine incidence of pediatric ESRD (age≤18) and initial Rx modalities from 2000-15. UNOS data were used to evaluate pediatric kidney recipients between 2000-2019. Logistic regression was used to calculate an odds ratio (OR) for receiving a living donor kidney (LD). Hazard ratios (HR) of death, graft failure and death-censored graft failure (dcGF) were obtained in Cox models stratified for LD/deceased-donor (DD). Models were adjusted for age, sex, and year of transplant and reported with 95% CI.

Results: Among 17,366 incident pediatric ESRD patients in USRDS, 42.8% were female. Mean and median age did not differ. Initial kidney treatment was transplantation in 17.9% of girls and 23.8% of boys, with more hemodialysis in girls (46.0 vs 40.5%, P<0.001). Among 16,811 UNOS recipients, 41.0% were female. Changes in allocation policy were associated with a shift from parental donors to deceased-donors, which was more marked in female recipients (figure). 42.8% of boys and 39.7% of girls received LD (P<0.001); adjusted OR of receiving LD was 0.91 (0.85, 0.98, P=0.007) for girls. Compared to boys, girls had inferior outcomes with DD, with HRs: death 1.51 [1.30, 1.76], graft failure 1.31 [1.21, 1.40], and dcGF 1.30 [1.20,1.40, P<0.001 for all]. LD outcomes did not differ by sex.

Conclusions: Female children have fewer early transplants and higher odds of receiving DD kidney transplants that are associated with inferior outcomes than their male counterparts. Attention to sex-specific disparities may improve ESRD outcomes in girls.



Living (LD) & Deceased-donors (DD) in male (M) and female (F) recipients

PO2435

Outcomes of Emergency Department Visits of Children After Kidney Transplantation

Christian Hanna,[1] Ashish Shah,[2] Mark G. Roback,[4] Priya S. Verghese,[5] Ronald A. Furnival.[3] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]University of Minnesota, Minneapolis, MN; [4]University of Colorado, Denver, CO; [5]Northwestern University - Chicago, Chicago, IL.*

Background: Systematic data evaluating the postoperative Emergency Department (ED) care and outcomes of Pediatric Kidney Transplant (PKTx) recipients is limited. Our study objective is to identify the risk factors, disposition, and outcomes of PKTs recipients presenting to the ED.

Methods: We retrospectively reviewed the medical records of PKTx patients (<18 years of age) who presented to our University Children's Hospital ED from 04/01/2011 to 06/30/2015. Data pertaining to patient demographics, chief complaint, evaluation, interventions, results, length of stay (LOS) and disposition were abstracted. Multiple logistic regression analysis was used to study the associations between admission, the presence of bacteremia, and multiple risk factors.

Results: During the study period, 60 of the 85 PKTx recipients (71%) presented to the ED for acute care (total of 210 visits, range 1-20; mean 3.5 per recipient). The majority (148/210; 70%) of the visits occurred in the first year following transplant. Fever (44%) and gastrointestinal complaints (27%) were the most frequent presentations. Mean ED LOS was 3.5 hours (range 0.22-10.8 hours). Most (109/210; 52%) visits resulted in hospital admission, for a mean inpatient LOS of 4 days (range 1-55 days). After adjusting for age and sex, the following risk factors were significantly predictive of hospital admission: shorter time since transplant (p=0.003), presence of fever (p<0.001), higher heart rate (p<0.001), higher white blood cell count (p=0.004), and presence of Systemic Inflammatory Response Status (SIRS) (p<0.001). Age adjusted systolic and diastolic blood pressure, type of transplant (deceased vs living donor), underlying primary kidney disease, the presence of a central line, or the number of immunosuppressant drugs were not predictive of hospital admission. Multivariate analysis of all significant risk factors found that shorter time since transplant and presence of SIRS were the only factors significantly associated with hospital admission (p<0.05). Only presence of SIRS was significantly associated with positive blood cultures (p=0.03).

Conclusions: Nearly three-quarters of all PKTx recipients presented to ED most frequently in the first postoperative year, with over half requiring hospital admission. Shorter time since transplant and presence of SIRS were significantly predictive of hospital admission.

PO2436

The First Increase in Live Kidney Donation in the United States in 15 Years

Fawaz Al Ammary, Allan Massie, Deidra C. Crews, Dorry L. Segev, Abimereki Muzaale. *Johns Hopkins University School of Medicine, Baltimore, MD.*

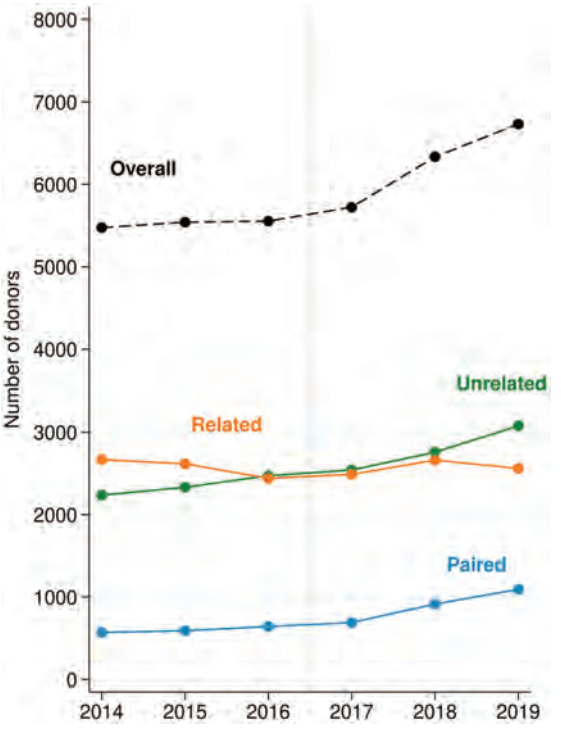
Background: After more than a decade of decline, the first sustained increase in live kidney donation was observed in the US from 2017 to 2019. Understanding these trends in donation may provide opportunities to effectively sustain or even enhance this recent increase in donors.

Methods: We conducted a national registry study of 35,900 donors (70.3% white, 14.5% Hispanic, 9.3% black, 4.4% Asian) to understand the increase in 2017-2019 vs. 2014-2016 using Poisson regression stratified by donor–recipient relationship (biologically related, unrelated, and kidney paired donors).

Results: Among biologically related donors aged <35, 35-49, and ≥50 years, the number of donors did not change across race/ethnicity but increased by 38% and 29% for Hispanic and black ≥50. Among unrelated donors <35, 35-49, and ≥50, white donors increased by 18%, 14%, and 27%; Hispanic donors <35 did not change but increased by 22% and 35% for 35-49 and ≥50; black donors <35 declined by 23% and did not change for 35-49 and ≥50; Asian donors did not change. Among kidney paired donors <35, 35-49, and ≥50, white donors increased by 42%, 50%, and 68%; Hispanic donors <35 and 35-49 increased by 36% and 55% and did not change for ≥50; black donors did not change; Asian donors <35 did not change but increased by 107% and 82% for 35-49 and ≥50.

Conclusions: The increase in live kidney donation was driven predominantly by unrelated and paired white donors. Donation among unrelated black individuals should be promoted.

Funding: NIDDK Support, Clinical Revenue Support



Annual number of live kidney donors in the US from 2014 to 2019, stratified by donor type

PO2437

Safety and Effect of Alkali Therapy on Vascular Function in Kidney Transplant Recipients: A Pilot Study

Rachel R. Bohling, Monica Grafals, Zhiying You, Jessica B. Kendrick. *University of Colorado Denver School of Medicine, Aurora, CO.*

Background: Acid retention is a common feature of kidney transplant recipients (KTR). Studies have found that lower bicarbonate levels in KTRs are associated with an increased risk of mortality and cardiovascular disease. We tested the hypothesis that alkali therapy was safe and feasible in KTRs and would improve vascular function.

Methods: We performed an 18-week, randomized, double-blind, placebo-controlled crossover safety and feasibility pilot study of the use of sodium bicarbonate therapy in 16 KTRs. We recruited KTRs at least one year from transplant with an eGFR ≥ 45 ml/min per 1.73m^2 and a serum bicarbonate level of 16-24 mEq/L. Patients received study drug therapy (sodium bicarbonate and placebo) at 0.5 mEq/kg/lean body weight for the entire 8-week treatment period. Each treatment period was 8 weeks in duration with a 2-week washout period between treatments. All patients had to be on stable immunosuppression and antihypertensive regimen for at least one month prior to randomization. Each patient served as his or her own control. During each treatment period, patients were assessed at 4 and 8 weeks for adverse events, weight, blood pressure, gastrointestinal symptoms and pill compliance. Brachial artery flow-mediated dilation (FMD) was obtained at beginning and end of each treatment period.

Results: The mean (SD) age, eGFR, and serum bicarbonate levels were 52 (19) years, 71 (21) ml/min/1.73 m^2, and 23 (2) mEq/L, respectively. Serum bicarbonate levels increased by 0.4 mEq/L during treatment. Sodium bicarbonate therapy was not associated with worsening blood pressure, weight gain, or hypokalemia. 46% of patients experienced nausea and/or bloating on sodium bicarbonate therapy compared to 40% while on placebo. The study was not powered to detect differences in FMD, but there was a trend towards improved FMD in the sodium bicarbonate group compared to the control (mean difference 1.6%; 95% confidence interval, -0.39 to 3.6; p=0.1). Additionally, a trend towards decreased 24-hour urine net acid excretion (mean (SD) change -9.0 (17.1) mEq/d, p=0.07) and ammonium excretion (mean (SD) change -6.0 (12.1) mEq/d, p=0.08) was observed.

Conclusions: Sodium bicarbonate therapy is safe and feasible in KTRs. There was a trend towards improvement in FMD, strengthening the need for a larger randomized controlled trial.

PO2438

Demographic Variability of Kidney Function in Live Donors: A Single-Centre Analysis

Tina Thomson, Andreas Kousios, Rawya Charif, Honeylet Orr, Harvinder K. Dulku, Marina Loucaidou. *Imperial College London Department of Medicine, London, United Kingdom.*

Background: Live donation is encouraged as better outcomes in kidney transplant recipients. Donor assessment requires thorough evaluation but kidney function varies with demographics. We compre mGFR with the performance of eGFR formulas and creatinine clearances

Methods: Analysis of 997 live donors between February1995 and October2019. Using pre-donation measured GFR(Tc EDTA-GFR) as the gold standard, we compared the performance of CKD-MDRD,CKD –EPI(ml/min/1.73m^2),24hour creatinine clearance(Cr Cl) and Creatinine clearance by Cockcroft Gault(CrCl C-G)(ml/min) between age, ethnicity, and gender. We also calculated the relative bias(mGFR-eGFR/mGFR), root mean square error and the accuracy(P30)(eGFR between+-30%mGFR)of different eGFR equations

Results: 422(42.32%)male donors. 616(62%) Caucasian, 228(23%) South Asian, 114(11%) Afro Caribbean and39(4%) of other ethnic groups(Arabic, oriental and mixed ethnicity)**(Graph1).**Mean mGFR was 100.08(SD 10.87). Mean mGFR for males and females were 105.77 vs 96.27, respectively(p=0.05).63(6%) donors were >65 years. Mean mGFR comparing young and >65 years old donors were 103.44 vs 82.27, respectively(p= 0.0028). As predicted, there is a linear decline in mGFR with increasing age. Cr Cl C-G has a tendency towards underestimating function in healthy living donors over 65 years old .GFR calculated by CKD-EPI formula was comparable to mGFR amongst all age groups, genders and ethnically diverse living donors .CKD-EPI performed better in terms of least bias and highest accuracy compared to MDRD for all donor subgroups**(Table1).**

Conclusions: mGFR declines with age and healthy older donors have significantly lower mGFR compared to younger donors. Cr Cl overestimates kidney function and should be used with caution.eGFR by CKD EPI comes closest compared to mGFR in all groups. It could be reliably used as first screening tool for assessing function of living donors pre donation, irrespective of age, gender or ethnicity.

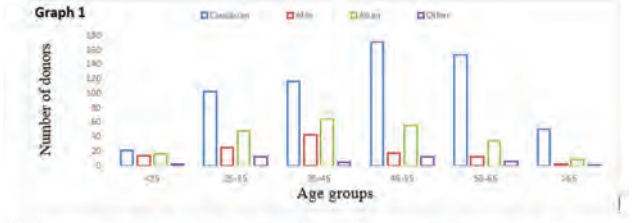


Table 1	mGFR	MDRD	EPI	CrCl	CrCl CG	R Bias MDRD	R Bias EPI	P30 MDRD N (%)	P30 EPI N (%)	RMSE MDRD	RMSE EPI
All Donors	100.08	83.15	93.11	113.98	105.47	0.14	0.04	790(79)	834(84)	2.82	0.51
Caucasian	102.25	79.54	88.08	117.9	109.68	0.22	0.14	151(63)	485(79)	15.74	8.98
AfroCaribbean	106.45	90.5	102.79	121.66	107.34	0.15	0.03	41(79)	97(88)	26.52	9.16
South Asian	96.83	84.95	94.74	104.18	105.12	0.12	0.02	65(83)	206(90)	7.87	2.52
Other	99.75	88.15	101.11	112.86	108.2	0.12	-0.01	16(84)	41(93)	23.53	5.71
<65 yrs	103.44	88.37	99.64	121.73	113.79	0.15	0.04	714(76)	770(82)	2.36	0.59
>65yrs	82.27	78.65	79.82	98.49	66.64	0.04	0.02	58(92)	60(95)	1.49	0.86
Males	105.77	93.77	99.69	128.22	112.59	0.15	0.11	299(71)	365(87)	9.85	6.61
Females	96.27	77.79	93.67	100.08	102.58	0.13	0.07	479(83)	505(88)	13.58	3.96

Demographics & Comparitive performances

PO2439

Assessment of Kidney Function at 3 and 6 Months in Kidney Donors with Cardio-Metabolic Risk Factors

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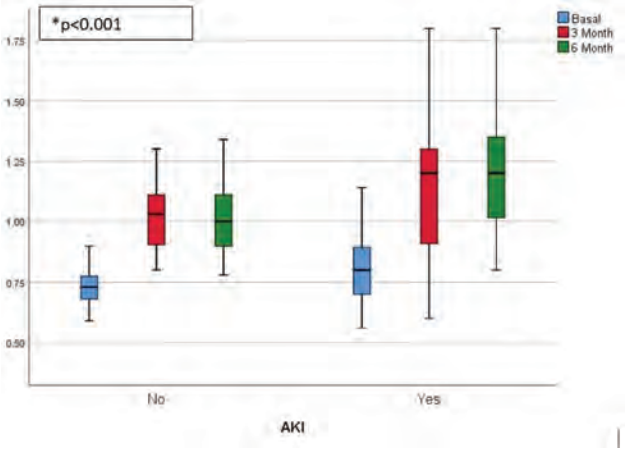
Background: Cardio-metabolic risk factors (CRFs) in kidney donors contribute to further deterioration of kidney function after donation, increase their post-donation cardiovascular risk. Objective: To assess the renal function of kidney donors with CRFs at 3 and 6 months after donation.

Methods: Cross-sectional, descriptive study, which included kidney donors who were admitted to the National Medical Center "Dr. Antonio Fraga Mouret" during the period from 2015 to 2019. Descriptive statistics were made, ANOVA with a 95% CI and a value of p <0.05. The CRFs dyslipidemia, hypertension, hyperglycemia, body mass index (BMI) and hyperuricemia were evaluated.

Results: 153 donors were admitted, 34% without social security, 59% women, with a mean age of 42.7 ± 10.7 years. The clinical and biochemical characteristics at hospital admission were: mean SBP / DBP was 106 ± 6.02 /72.9=5.4, BMI, 26.3 ± 3.2, proteinuria 126.4 ± 13.4, hematocrit 44.6 ± 4.9, albumin 4.1 ± 0.4, K 4.1 ± 0.4, Ca 9.2 ± 0.6, Uric acid 5.4 ± 1.2, Total cholesterol 185.6 ± 34.4, triglycerides 156.5 ± 91.7, fasting glucose 91.6 ± 15.2, Creatinine 0.78 ± 0.14. The mean bleeding during surgery was 263.66 ± 447 ml, creatinine after surgery was 1.21 ± 1.8, upon release from hospital it was 1.13 ± 0.27. 72% of donors presented acute kidney injury (AKI) after surgery, with an average of 1.56 ± 1.8 days with AKI, 56% of donors released from hospital with AKI. More than 25% of kidney donors had 2, 3 and 4 CRFs. Figure 1 presents the comparison between groups (AKI vs No AKI) of creatinines at baseline, 3 months and 6 months.

Conclusions: A higher presence of CRFs is associated with higher AKI events after kidney donation. AKI patients during renal donation show a further deterioration of renal function at 3 and 6 months of follow-up. Timely interventions prior to donation could improve the evolution of this group of patients.



PO2440

Direct Acting Antiviral Prophylaxis to Prevent Virus Transmission from Hepatitis C Viremic Donors to Hepatitis C-Negative Kidney Transplant Recipients

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Background: Studies have described a 12-week course of direct-acting anti-viral drugs (DAA) for HCV transmission from infected donors to negative kidney transplant recipients. This strategy is limited by high cost and access to DAA. A prophylactic strategy may be safer and cost-effective. We recently reported the results of our experience where a 2-4 day peri-operative DAA prophylaxis using sofosbuvir/velpatasvir (SOF/VEL) for D+/R- transplants prevented HCV transmission in a majority (88%) of cases. We report our entire experience based upon an adaptive iterative trial design where prophylaxis with SOF/VEL was initially extended to 7 days, and ezetimibe was added for a second cohort.

Methods: Wait listed patients were eligible if they met the following: (absence of living donor; panel reactive antibody≤50%; ≤1 prior transplant; absence of liver disease). The primary outcome was HCV transmission, defined as 2 consecutive positive HCV nucleic acid tests tested at Day 7 and 14-21 post-transplant. Confirmed HCV viremia triggered a12-week course of DAA.

Results: 100 patients (mean age=56 years) received D+/R- transplants from November 2017 to April 2020. Mean wait time to transplant from enrollment was 34 days and the mean KDPI was 67%. At a median follow-up of 10 months (IQR: 1-30months), graft survival was 99% and patient survival was 98% with no cases of liver dysfunction. In Group 1, 10 patients received one dose SOF/VEL immediately pre-transplant and a second dose on post-transplant Day 1. Viral transmission was 30% [3/10]. In Group 2, 42 patients received two additional doses of SOF/VEL on Days 2 and 3 post-transplant. Viral transmission rate dropped down to 9.5% (4/42). All patients then achieved SVR with full DAA therapy in groups 1 and 2. In Group 3 (N=28), prophylaxis was extended to 7 days with further reduction in transmission to 3.5% (1/28). In group 4, 19 patients received ezetimibe and SOF/VEL for 7 days. Viral transmission was 5% (1/19).

Conclusions: A 7-day DAA prophylaxis is effective in preventing donor-derived HCV transmission, can result in significant cost-savings and increase access to transplants. Adding ezetimibe to SOF/VEL did not provide an additional benefit in preventing viral transmission.

PO2441

Donor Hepatitis C Antibody Positivity Misclassifies Kidney Donor Profile Index in Non-Hepatitis C-Infected Donors: Time to Revise the Kidney Donor Profile Index

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Background: Kidneys from donors with hepatitis C(HCV) infection are traditionally considered to be at risk for poorer graft outcomes, as reflected in the Kidney Donor Profile Index(KDPI). The KDPI defines an HCV positive donor based on HCV antibody(Ab) testing and/or nucleic acid amplification test(NAT), so not actively infected donor is also

considered as HCV positive. The outcome of kidneys from HCVAb positive but NAT negative donors are unknown.

Methods: A national-registry-based retrospective cohort study was conducted using the SRTR data set. We identified all HCV negative recipients between April 1st, 2015 and March 2nd, 2018, who received kidney transplant from HCV Ab positive and NAT negative (D-HCVAb(+)/NAT(-) n=116) and HCV Ab negative and NAT negative (D-HCVAb(-)/NAT(-); n=25,574) donor kidneys. We then compared recipients' estimated glomerular filtration rate(eGFR) at 6 months in matched cohorts, using combined exact matching (based on KDPI) and propensity score matching. We created two separate matched cohorts to examine differences in outcomes based on how HCV positive status is defined: for the first cohort, we used the allocation KDPI (where HCV is considered positive in D-HCVAb(+)/NAT(-)patients), while for the second cohort we used a modified KDPI, where the HCV component of KDPI was considered negative in D-HCVAb(+)/NAT(-)patients.

Results: The mean±SD age of the allocation KDPI matched cohort at baseline was 59±10 years, 69% were male, 61% and 30% of the patients were white and African American, respectively. The baseline characteristics of the recipients were well-balanced in both matched cohorts. Recipients' eGFR at 6 months after transplantation was significantly higher in the D-HCVAb(+)/NAT (-) group compared to the D-HCVAb(-)/NAT (-) group (61.1±17.9 versus 55.6±18.8 mL/min/1.73m^2, p=0.011) in the allocation KDPI matched cohort, while it was similar (61.8±19.5 vs. 62.1±20.1 mL/min/1.73m^2, p=0.9) in the modified KDPI matched cohort.

Conclusions: Recipients who received HCVAb positive, but NAT negative donor kidneys did not experience worse 6-month eGFR than correctly matched D-HCVAb (-)/NAT (-) recipients. HCVAb positive, but NAT negative donor kidneys should not be allocated as HCV positive kidneys.

PO2442

Transplantation of Kidneys from Hepatitis C-Infected Donors to Hepatitis C-Negative Recipients: 1-Year Renal Allograft Outcomes

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Background: Transplant centers in United States are increasingly willing to transplant kidneys from hepatitis C (HCV) infected donors to hepatitis C negative recipients. Long-term renal outcome data of a non-prophylactic HCV treatment approach outside clinical trials is missing.

Methods: We examined 65 HCV negative recipients who received a HCV infected kidney transplant (HCV+) and 59 HCV negative recipients who received a HCV non-infected kidney transplant (HCV-) during 2018 in a single transplant center. We compared estimated glomerular filtration rate (eGFR), cumulative results of per-cause and surveillance protocol biopsies, development of de novo donor specific antibodies (DSAs), co-infection rates and patient and graft outcomes up to 1 year post-transplant between HCV+ versus HCV- groups.

Results: The mean±SD age of recipients was 52±11 years, 43% were female, 19% and 80% of recipients were Caucasian and African-American, respectively. Baseline characteristics were similar between the HCV+ and HCV- groups. The delayed graft function rate, estimated GFRs at post-transplant 3, 6, 9 and 12 months, cumulative rejection rate, development of de novo DSAs and co-infection rates were not statistically significantly different between the HCV+ and HCV- groups (Table).

Conclusions: Recipients of HCV-viremic kidneys have similar renal allograft function, incidence of rejection in the first year after transplantation compared to those who received HCV-non-viremic kidneys.

Renal graft and patient outcome of all kidney transplant recipients

	Entire Cohort	HCV+	HCV-	p-value
Observations (n)	124	65	59	N/A
Delayed Graft Function, N, (%)	12 (10%)	5 (12%)	7 (8%)	0.43
Estimated GFR at 3 months after transplantation (ml/min/1.73m2), mean (SD)	63 (20)	63 (18)	64 (21)	0.85
Estimated GFR at 6 months after transplantation (ml/min/1.73m2), mean (SD)	66 (19)	66 (18)	66 (21)	0.96
Estimated GFR at 9 months after transplantation (ml/min/1.73m2), mean (SD)	67 (18)	66 (15)	67 (20)	0.62
Estimated GFR at 12 months after transplantation (ml/min/1.73m2), mean (SD)	66 (19)	64 (16)	66 (22)	0.69
ACR/ABMR (N of patient / N of patients with biopsy result (%))	26/113 (23%)	13/54 (24%)	13/59 (22%)	0.80
De novo DSA (N of patient / N of patients with DSA result (%))	26/94 (28%)	20/64 (31%)	6/30 (20%)	0.26
BK viremia (> 10,000 copies) (N (%))	19 (16%)	12 (18%)	7 (13%)	0.42
CMV viremia (>1,000 copies) (N (%))	15 (12%)	11 (17%)	4 (7%)	0.10
Death (N (%))	4 (3%)	1 (2%)	3 (5%)	0.26
Graft Loss (including death) (N (%))	7 (6%)	1 (2%)	6 (10%)	0.04

PO2443

Hepatitis C NAT-Positive Kidney Transplant into Hepatitis C-Negative Recipients: A Single-Center Experience

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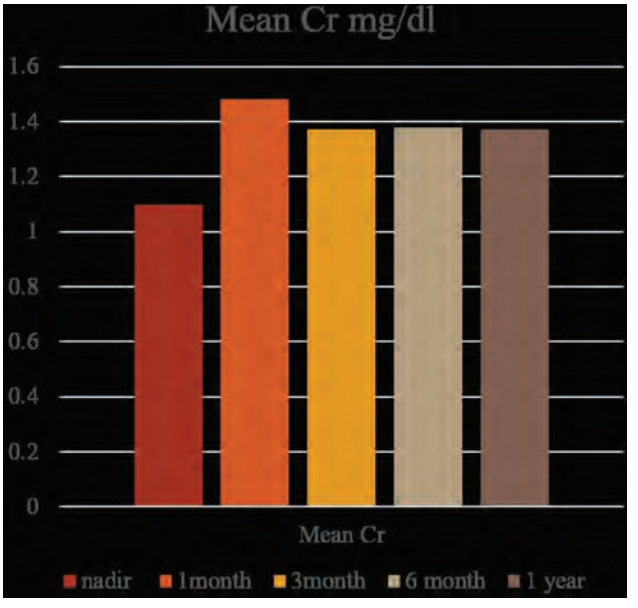
Background: Direct-acting antivirals (DAA) for Hepatitis (Hep) C have a 96-100% sustained viral remission (SVR) rate. This makes transplant of Hep C nucleic acid amplification testing (NAT)+ kidneys and treatment post-transplant feasible. We performed a prospective IRB approved trial at our center to validate the use and challenges of this approach.

Methods: Informed consent from eligible patients was obtained. Patients with chronic liver disease, dual organ transplants, HIV and active Hep B infection were excluded. Post-transplant, viral load was tested on day 3-5 and 7-10 and weekly thereafter until viremia was confirmed. All pts. were treated by hepatologist based genotype and insurance company preference. Standard of care immunosuppression protocols was used.

Results: 51 pts. got Hep C NAT+ kidney. The median age of the recipients was 58 years (range 29-72) and the mean wait time was 802 days (range 68-3073). Mean KDPI was 58.8 (range 27-94) with a median donor age of 38 years (range 21-56). Out of 16 implant biopsies, 13/16 (81%) had <5 %of sclerotic glomeruli, 14/16 (88%) had minimal interstitial fibrosis, and 15/16 (94%) had no arteriosclerosis. There was a 100 % transmission rate of Hep C. As of now, 46/51 (90%) have completed a 12-week course of DAA, and 45/46 (98%) have become RNA negative with 34/46 (74%) achieving SVR. So far, there had been no insurance denials of DAA coverage. Among 18 for cause allograft biopsies, 1 showed tubuloreticular inclusion thought to be Hep C related and another showed recurrent C3GN thought to be triggered by Hep C and Hep B

Conclusions: Transplantation of HepC NAT+ kidneys to Hep C negative recipients followed by treatment with DAA is a feasible option as a standard of care outside trials. Recipients should be monitored for Hep C related complications



PO2444

Human Herpesvirus 8-Associated Kaposi Sarcoma Developing in a Kidney Allograft from a Hepatitis C-Positive Donor

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Introduction: Kaposi Sarcoma (KS) is an endothelial malignancy caused by the oncogenic virus Human Herpesvirus-8 (HHV-8) and transmission during kidney transplantation can occur. We describe two cases of donor-to-recipient transmission of HHV-8, with one recipient developing KS in the kidney allograft causing acute kidney injury (AKI).

Case Description: Donor: The donor died from complications of IV drug use and had known hepatitis C (HCV) at the time of organ donation. Recipient 1: 64-year-old male with ESRD, induction with basiliximab. He tested positive for HCV on post-transplant day 2 and was treated with sofosbuvir/velpatasvir for 12 weeks. Two months post-transplant, he developed encephalopathy and was found to have HHV-8 viremia during his workup. Immunosuppression was decreased, HHV-8 PCR levels were monitored and eventually were undetectable. He did not develop KS. Recipient 2: 71-year-old male with ESRD, induction with anti-thymocyte globulin. He was treated pre-emptively for HCV with glecaprevir/pibrentsvir. Five months post-transplant he was admitted for rising creatinine. Initial allograft biopsy was of poor quality but was suggestive of Banff IIA

rejection; IV methylprednisone and anti-thymocyte globulin were administered. Repeat biopsy demonstrated extensive replacement of the allograft tissue with KS. PET scan revealed metastatic KS. Immunosuppression was discontinued and he underwent allograft nephrectomy. He died at home 2 months later. Retroactive testing of samples prior to transplantation revealed the donor was HHV-8 PCR positive at the time of death and both recipients were HHV-8 antibody and PCR negative.

Discussion: We describe donor-to-recipient transmission of HHV-8 during kidney transplantation. HHV-8 associated post-transplant KS is well described but rare in the US. Post-transplant KS typically presents with classic skin lesions and kidney allograft involvement with KS is rare, with only 7 previously reported cases. Public Health Service (PHS) increased risk donors may represent a subset of donors at especially high risk for HHV-8 transmission. Future investigation is needed into this population to determine if post-transplant HHV-8 PCR monitoring or adjustments in immunosuppression are needed for kidney transplant recipients of PHS increased risk organs.

PO2445

John Cunningham Virus (JCV) in Renal Allograft Recipients (RAR)

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Introduction: Both JCV and BK virus belong to Polyoma virus (PV) family and can lead to opportunistic infection in RAR. BK nephritis in RAR is well described in literature (incidence 1- 10 %) in contrast to JCV nephropathy (JCVN) which is a rare entity. Here we describe two cases of JCV in RARs.

Case Description: Case 1: 44-year-old woman with PMH of HTN and ESRD received her first renal transplant in 2009 followed by antibody mediated rejection (AMR) resulting in graft dysfunction. She received a preemptive second renal transplant in 12/2015 followed by multiple RA biopsies within first few months due to elevated serum creatinine (s.cr). The biopsies showed borderline CMRs, acute AMRs and eventually chronic active AMR. Treatment regimen included steroids, rituximab, IVIG and plasmapheresis. Despite repeated treatments, her s.cr remained elevated leading to another biopsy in 6/2016 showing viral cytopathic changes suspicious for PVN. SV40 stain was negative as was serum BK titer. Immunosuppression (IS) was reduced and a biopsy was repeated in 8/2016 that stained positive for SV40. Given repeatedly negative serum BK, serum JCV titer was sent, which was positive and peaked at 350659 copies/ml on 9/2016. Titer improved to 66153 after 2 doses of Cidofovir however, later deteriorated to 334240. She had no neurological involvement. Despite Cidofovir, her renal function deteriorated rapidly requiring bilateral RA nephrectomies with pathology showing JCVN. IS was discontinued following which JCV titer became undetectable. Case 2: 59-year-old man with PMH of HTN and ESRD who received renal transplant in 4/2013 followed by baseline s.cr of 1.6 mg/dl. He was on Myfortic, Sirolimus and Prednisone for IS. He presented with rising s.cr in 9/2019 (2.1mg/dl). He underwent RA biopsy in 11/2019 showing viral cytopathic changes, positive SV40 consistent with PVN. BK by PCR resulted negative x 2 but JCV titer returned at 3896 copies/ml. Myfortic was discontinued. Repeat JCV titer trended down to 2603 in 3/2020. Further follow up was delayed due to COVID-19 pandemic.

Discussion: The diagnosis of JCVN is challenging and easy to miss. Index of suspicion should be high with positive viral cytopathic changes (+/- SV40 stain) on allograft biopsy and negative serum BK. Currently there is no definitive therapy for JCV. Early diagnosis and reduction in IS are critical. Cidofovir may be of utility.

PO2446

Disseminated Adenovirus Treated with Brincidofovir in a Kidney Transplant Recipient

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Introduction: Adenovirus is a common viral infection, with which immunocompromised patients have an increased risk of disseminated disease. It is less frequently described in solid organ transplant recipients and the optimal therapy for disseminated disease is unknown. We present a case of disseminated adenovirus in a kidney transplant recipient who was treated successfully with brincidofovir.

Case Description: A 56 year old female with ESRD of unclear etiology received her second kidney transplant from a deceased donor 2 years ago with thymoglobulin induction. She presented with one day of gross hematuria and right flank pain, as well as 2 weeks of malaise and 5 days of fever, cough, sore throat, nausea and vomiting. She had acute kidney injury with creatinine of 1.75 mg/dl from a baseline of 0.8 mg/dl. She was found to have adenovirus in urine (>2million) and serum. Other infectious etiologies were ruled out. Initial treatment consisted of reduced immunosuppression with discontinuation of mycophenolate mofetil and tacrolimus and increased prednisone from 5mg to 10mg daily due to leukopenia. Given disseminated symptoms, adjunctive treatment was also initiated with cidofovir 1mg/kg IV q48hr alternating with IVIG 500mg/kg q48 hr. She received 4 doses of cidofovir and IVIG, with resolution of hematuria and decreased adenovirus level in urine. Although she received hydration before and after cidofovir, creatinine rose to 2.04 mg/dl. With 2 additional cidofovir doses, she continued to have AKI (peak 3.1 mg/dl), before brincidofovir was started at a dose of 100mg twice weekly. Creatinine was 2.73 mg/dl when initiated on brincidofovir which decreased and stabilized to 2.2 mg/dl. Brincidofovir was discontinued when adenovirus was undetected in serum and <500 copies/ml in urine.

Discussion: The most commonly used adjunctive treatment to reduced immunosuppression in the treatment of adenovirus infection is cidofovir. However, cidofovir is nephrotoxic and renally cleared. This may limit its use, particularly in kidney transplant patients. Brincidofovir is less nephrotoxic due to decreased accumulation in proximal tubules, and may be better tolerated in kidney transplant recipients. We report a case of well tolerated brincidofovir treatment of disseminated adenovirus infection in a kidney transplant recipient who demonstrated clearance of infection and improvement in kidney function.

PO2447

Early Ganciclovir-Resistant Cytomegalovirus Infection in a Kidney Transplant Recipient: Could We Avoid It?

Kaushik Ivaturi, Ekamol Tantisattamo. *University of California Irvine, Irvine, CA.*

Introduction: Although uncommon, ganciclovir-resistant cytomegalovirus (GR-CMV) can lead to a therapeutic challenge given drug nephrotoxicity. Here we report a case of GR-CMV infection during early post-kidney transplant (KT).

Case Description: A 41-year-old woman with ESRD received the second KT in February 2019 with rATG induction. She also received rituximab one dose for pre-KT donor specific HLA antibodies. Maintenance immunosuppression are tacrolimus, mycophenolate sodium (MPS), and prednisone. Serum creatinine slowly trended down to the baseline of 1.3mg/dL at 3 month post-KT. CMV IgG serostatus was D+/R-. She received a 6-month CMV prophylaxis with a renally-adjusted dose of valganciclovir 450 mg twice weekly for 1 month, which was increased to 450 mg twice daily for 5 more months. 4 months after the CMV prophylaxis was completed, she developed asymptomatic CMV viremia with a titer up to peak of 47,643 IU/ml. Valganciclovir 900 mg twice daily was started and MPS was decreased. CMV PCR slowly decreased to 440 IU/ml after 1 month of therapy. Despite continuation of valganciclovir, CMV PCR became rapidly increased to 3,349 IU/ml [Figure]. A CMV genetic resistance test revealed a UL97, but not UL54 gene mutation. Foscarnet was started and CMV PCR was decreased. Allograft function has been at the baseline.

Discussion: Our patient has several risk factors for GR-CMV including high-risk CMV serostatus, prolonged exposure to low-dose oral valganciclovir prophylaxis, and intensified immunosuppression including rituximab. Given current treatment for GR-CMV remains limited with drug toxicity, adequate dose of CMV prophylaxis is critical to avoid GR-CMV. Pattern of CMV PCR after initiation of therapy should also raise a suspicion for GR-CMV and genetic CMV resistance testing is of paramount in early diagnosis. Novel preventive and therapeutic options may mitigate the risk of GR-CMV and drug-induced renal allograft toxicity.

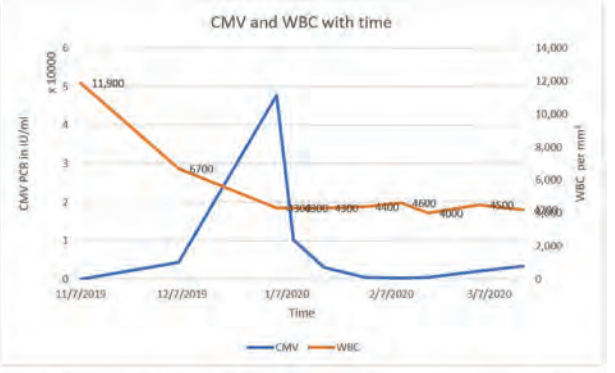

Figure: Clinical course of cytomegalovirus viremia correlated with low-normal white blood cell count from 8 months to 13 months post-kidney transplantation.
CMV, cytomegalovirus, WBC, white blood cell count

PO2448

A Case of Cytomegalovirus Infection with Splenic Infarction in a Renal Transplant Patient

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Introduction: Cytomegalovirus (CMV) infection is common after kidney transplant (KT) but it is not known to be associated with splenic infarction.

Case Description: A 67-year-old female living-related KT recipient for end stage renal disease from systemic lupus erythematosus presented with acute fever, left flank pain, and diarrhea. Her medications included tacrolimus, mycophenolate mofetil (MMF), and prednisone. Examination was significant for fever (101.8°F) and abdominal tenderness. Labs revealed normal blood counts, metabolic profile (creatinine 0.9 mg/dL) and urinalysis. Stool study was negative for *Clostridium difficile*. Quantitative CMV DNA PCR was elevated at 126,000 IU/ml. Sigmoidoscopy with biopsy also showed CMV colitis. CT abdomen and pelvis with contrast (Fig 1A) showed multiple wedge-shaped hypodense foci in the spleen consistent with splenic infarction and a splenic artery that was widely patent. Further investigations including Doppler ultrasound of the lower extremities, lung VQ scan and hypercoagulable studies were all negative. CMV was suspected to be the cause of the splenic infarct. Thus, the patient was started on ganciclovir and anticoagulation and MMF was discontinued. On her 3-month follow-up, she was found to have improved symptoms, undetectable consecutive CMV titers and with interval radiographic resolution of her splenic infarctions (Fig 1B).

Discussion: By inciting an inflammatory response due to direct cytotoxic endothelial cell damage, CMV infection may cause a procoagulant state. This can lead to potentially life-threatening end-organ infarction such as splenic infarction. To our knowledge, this is the first reported case of CMV infection in a KT recipient presenting with splenic infarction. A high index of suspicion for this association is warranted for early recognition and treatment of these potentially reversible conditions.

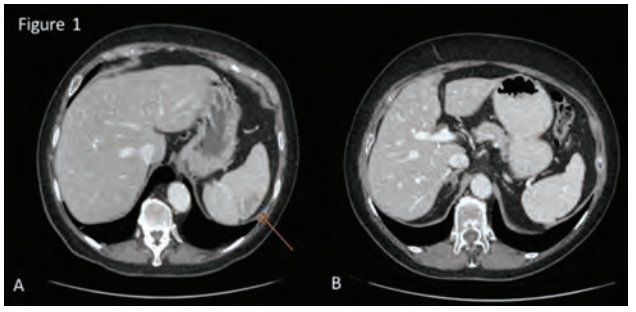

Figure 1: CT image (A) showing splenic infarction with radiologic improvement (B) after CMV treatment.

PO2449

BK Polyomavirus Nephropathy After Kidney Transplantation from HCV-Infected Donor to HCV-Uninfected Recipient

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Introduction: BK polyomavirus (BKPyV) is an important cause of renal allograft dysfunction. We previously published the potential association of an increased risk of BKPyV DNAemia/nephropathy in kidney transplant recipients receiving Hepatitis C (HCV) infected donor transplantation. Here, we report severe BKPyV DNAemia/nephropathy in a recipient who received HCV infected donor transplantation, which was temporally associated with initial HCV treatment failure.

Case Description: 62-year-old HCV negative African American male received a cadaveric kidney transplant from a HCV infected donor in January 2019, with immediate graft function. Laboratory results 4 weeks later indicated HCV PCR of 9,310,000 IU/mL, serum creatinine 1.62 mg/dL, and BKPyV DNAemia was negative. He received glecaprevir and pibrentasvir (March 2019) for a total of 12 wk. At completion of treatment, HCV PCR was negative. Evaluation 4 weeks later revealed HCV PCR level of 482,446 IU/mL, indicating initial treatment failure. While waiting for insurance approval for coverage of secondary direct acting antiviral (DAA) regimen, he developed acute kidney injury 6 wk after HCV viremia, with serum creatinine peaking at 3.3 mg/dL along with a rapidly rising BKPyV DNAemia to >5,000,000 copies/mL. His immunosuppressive regimen was decreased. Allograft biopsy showed BKPyV nephropathy and proliferative glomerulonephritis (GN) with monoclonal IgG deposits. He was started on cidofovir, levofloxacin and intravenous immunoglobulin, followed by a course of sofosbuvir/velpatasvir/voxilaprevir and ribavirin for a total of 12 wk, achieving SVR at 12 wk. His BKPyV DNAemia slowly responded with 1,257,789 copies/mL at 6 weeks of DAA treatment and 7,378 copies/mL at 12 wk. Serum creatinine gradually improved to 2.04 mg/dL. His 1 year protocol biopsy still showed tubulointerstitial inflammation, rare positive SV40 staining, proliferative GN with improving monoclonal IgG deposits, indicating Banff borderline acute cellular rejection. His immunosuppressive regimen was intensified and graft function has remained stable.

Discussion: Our case report with close proximity of HCV treatment failure and severe BKPyV DNAemia/nephropathy supports the previous finding that transplantation from HCV infected donor kidneys to uninfected recipients may be a risk factor of BKPyV DNAemia/nephropathy.

PO2450

Cytomegalovirus Nephropathy in a Renal Transplant Patient

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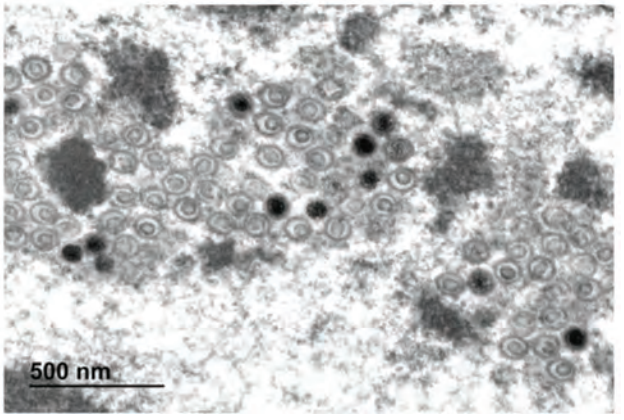
Introduction: Human cytomegalovirus (CMV), a DNA virus in the human herpesviridae family, is a frequent opportunistic infection following renal transplant. It can present as viremia without end organ damage and can affect the GI tract, liver, and lungs. CMV nephropathy is an uncommon complication of systemic CMV infection, occurring in < 1% of infected patients. Here we present a case of a renal transplant patient with CMV viremia was found to have evidence of CMV infection in the kidney.

Case Description: The patient was a 57 year old woman who had undergone deceased donor renal transplant 5 months prior to presentation due to ANCA vasculitis. Pre-transplant serologies were CMV D+/R- and induction was alemtuzumab. Her immune suppressive regime was tacrolimus, mycophenolic acid, and prednisone. She presented to the hospital with progressive fatigue, shortness of breath with new 4 L oxygen requirement, and decreased oral intake for several weeks. Her post-transplant creatinine nadir was 1.2 mg/dl, up to 3.1 mg/dl on admission and uptrended to 5.1 mg/dl, briefly requiring CRRT. She was found to have multiple infections including CMV viremia (peak > 3.9 M copy/mL) and pneumonitis, pseudomonas pneumonia, JC in her CSF and serum, and eventually bacteroides bacteremia due to bowel perforation. She underwent kidney biopsy which showed acute tubular necrosis, scattered glomerular epithelial cells and rare peritubular capillary endothelial cells positive for CMV by immunostaining (negative for BK/JC and rejection). She was treated with ganciclovir with resolution of her CMV viremia and improvement in her renal function, however, unfortunately passed due to her multiple infections.

Discussion: There are several possible manifestations of CMV nephropathy including interstitial nephritis, positive staining for CMV inclusions in glomerular cells, and collapsing focal segmental glomerulosclerosis. CMV nephropathy is an uncommon complication of CMV viremia following renal transplant but should be considered in the differential diagnosis of patients with CMV viremia and AKI.



PO2451

Cytomegalovirus-Associated Collapsing Glomerulopathy in a Renal Transplant Recipient

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Introduction: Collapsing focal segmental glomerulosclerosis also known as collapsing glomerulopathy (CG) is a glomerular disease presenting with nephrotic syndrome and acute kidney injury (AKI), and showing collapse and sclerosis of glomerular capillaries with hypertrophic and injured podocytes on kidney biopsy. CG is most often seen in association with HIV infection and APOL1 nephropathy; however, CG can be associated with non-HIV viral infections. We describe a case of CMV-associated CG in a renal transplant patient.

Case Description: A 73 year old Caucasian male with history of ESRD due to biopsy-proven arterionephrosclerosis, status post deceased donor kidney transplantation (African-American donor) with baseline serum creatinine of 1.6 – 2 mg/dl presented with one day of explosive diarrhea. Lab revealed AKI with serum creatinine of 6.12 mg/dl. The patient was treated with IV fluids for AKI presumably due to volume depletion; however, serum creatinine and renal function failed to improve. Urinalysis was positive for blood and protein, and urine protein/creatinine ratio was 25 g/g cr with serum albumin of 1.6 g/dL. Testing for complements, serum and urine protein electrophoresis, serum free light chains, hepatitis panel, HIV and polyomavirus virus was negative. Serum cytomegalovirus NAAT was positive and the patient was started on IV Valganciclovir (vGCV). Renal allograft biopsy showed CG, including retraction/collapse of the glomerular tuft and podocyte hypertrophy with accumulation of protein reabsorption droplets. CMV immunostain showed positive staining of few glomerular endothelial cells in glomeruli with collapsing features. Electron microscopy demonstrated extensive foot process effacement without immune complex deposition. Immunosuppression was reduced. Patient was treated with cVGC for 10 weeks and a low dose lisinopril; serum creatinine and UPC improved to 1.69 mg/dl and 0.9 g/ g cr respectively without requiring renal replacement therapy. APOL1 genotyping demonstrated that the allograft kidney was heterozygous for the G1[GA1] risk allele, but homozygosity or compound heterozygosity was not present.

Discussion: Collapsing glomerulopathy can occur with non-HIV infection, such as CMV in renal transplant recipients. Allograft function may be preserved with appropriate therapy.

PO2452

Early Increase in Urinary Exosomal BK Virus MicroRNA as a Predictive Marker of BK Virus Nephropathy: A Prospective Kidney Transplantation Cohort

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Background: Urinary exosomal bkv-miR-B1-5p was associated with BK virus (BKV) nephropathy (BKVN) in a cross-sectional study. However, its time-dependent post-transplantation changes and predictive value for BKVN have not been investigated.

Methods: We carried out a multicenter prospective cohort from which 83 kidney transplant recipients (KRTs) in South Korea (biopsy-proven BKVN [n=10], presumptive BKVN [n=12], and non-BKVN patients [n=61]) were selected for the measurement of urinary exosomal bkv-miR-B1-5p levels at 0.5, 3, 6, and 12 months posttransplant.

Results: At 2 weeks posttransplant, urinary exosomal bkv-miR-B1-5p levels showed an increasing trend (non-BKVN < presumptive BKVN < biopsy-proven BKVN), while plasma BKV DNA levels were undetectable in all groups. Thereafter, both urinary exosomal bkv-miR-B1-5p and plasma BKV DNA levels peaked at 3 months posttransplant and then decreased. Multivariable-adjusted Cox regression showed that urinary exosomal bkv-miR-B1-5p levels at 2 weeks and 3 months posttransplant independently predicted biopsy-proven BKVN development. In particular, the early increase in urinary exosomal bkv-miR-B1-5p makes its predictive ability for biopsy-proven BKVN superior to that of plasma BKV DNA at 2 weeks posttransplant.

Conclusions: Our results suggest that urinary exosomal bkv-miR-B1-5p can be used to identify the KRTs at high risk for BKVN at earlier time than plasma BKV DNA loads, enabling earlier intervention.

Table 1. Baseline characteristics of the study population

	Biopsy-proven BKVN (n = 10)	Presumptive BKVN (n = 12)	Non-BKVN (n = 61)	*P*
Age (years)	50.6 ± 9.8	48.8 ± 14.0	49.1 ± 11.1	0.918
Male gender	8 (80.0)	6 (50.0)	36 (59.0)	0.338
Body mass index (kg/m^2)	21.9 ± 3.0	22.3 ± 2.5	23.4 ± 3.4	0.220
Diabetes mellitus	2 (20.0)	2 (18.2)	25 (42.4)	0.174
Hypertension	9 (90.0)	10 (83.3)	54 (88.5)	0.855
ABO incompatible KT	3 (30.0)	3 (25.0)	12 (19.7)	0.625
HLA mismatch number	4.4 ± 1.6	3.1 ± 2.2	3.4 ± 1.6	0.146
Induction immunosuppression				
ATG	2 (20.0)	3 (25.0)	17 (27.9)	0.923
Basiliximab	8 (80.0)	9 (75.0)	44 (72.1)	0.923
Maintenance immunosuppression				
Steroid	10 (100.0)	11 (91.7)	60 (98.4)	0.462
Tacrolimus	9 (90.0)	11 (91.7)	60 (98.4)	0.170
Mycophenolic acid	8 (80.0)	11 (91.7)	60 (98.4)	0.033
Desensitization				
Rituximab	3 (30.0)	4 (33.3)	21 (34.4)	1.000
Intravenous immunoglobulin	2 (20.0)	3 (25.0)	19 (31.1)	0.855
Plasmapheresis	2 (20.0)	3 (25.0)	21 (34.4)	0.636
Donor				
Donor age (years)	50.8 ± 10.9	51.5 ± 9.9	46.7 ± 11.3	0.135
Male donor	5 (50.0)	7 (58.3)	27 (44.3)	0.658
Deceased donor	5 (50.0)	2 (16.7)	7 (11.5)	0.016

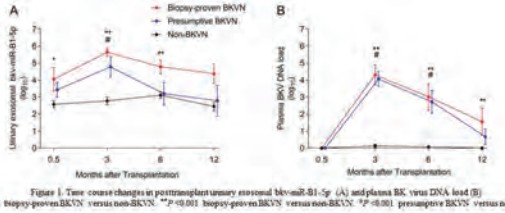

Figure 1. Time course changes in posttransplant urinary exosomal bkv-miR-B1-5p (A) and plasma BK virus DNA load (B)
*P <0.01 biopsy-proven BKVN versus non-BKVN. **P <0.001 biopsy-proven BKVN versus non-BKVN. #P <0.001 presumptive BKVN versus non-BKVN.

Model	urine exosomal bkv-miR-B1-5p at 2 weeks			urine exosomal bkv-miR-B1-5p at 3 months		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted	1.88	1.19 to 2.97	0.007	4.03	1.73 to 9.43	0.001
Model 1	2.01	1.16 to 3.50	0.013	4.10	1.68 to 10.01	0.002
Model 2	1.91	1.05 to 3.48	0.035	8.71	1.27 to 59.59	0.027

Table 2. Cox proportional hazards models for development of biopsy-proven BKVN

Model 1 is adjusted for recipient factors including age, gender, body mass index, diabetes, and the use of ATG (versus basiliximab).

Model 2 is adjusted for covariates in model 1 plus donor age and deceased donor (versus living donor).

PO2453

Polyomavirus Nephropathy with Crescent Formation

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Introduction: Polyomavirus reactivation in an immunosuppressed transplant patient may cause polyomavirus nephropathy (PVN). Classically seen as a pleomorphic tubulointerstitial inflammatory reaction to the virally infected tubular epithelial cells, there are few reports of glomerular viral tropism. We present unique histopathologic findings of PVN including crescent formation with ultrastructural and immunohistochemical evidence of viral infection of glomerular epithelial cells in a kidney transplant recipient with acute kidney injury.

Case Description: A 52 y/o man s/p DDKT with well-controlled HIV presented with 2 weeks of worsening cough. He was diagnosed with multifocal pneumonia and disseminated CMV and VZV infection. His serum creatinine (SCr) and BK virus PCR were elevated to 3mg/dl (baseline 1.4-2.0 mg/dL) and 3.8M copy/mL respectively. He received ganciclovir and his immunosuppression was reduced. His pneumonia improved, but his BK PCR increased to 13.6M copy/mL and SCr remained elevated at 2.4 mg/dL. A renal biopsy showed a diffuse plasma cell-rich pleomorphic interstitial inflammatory infiltrate, tubulitis, and acute tubular injury. Viral cytopathic effect was evident and an SV40 immunostain was positive in 60-70% tubular profiles, as well as parietal and visceral epithelial cells. EM revealed viral particles measuring 30 nm in diameter in tubular epithelial cells and a parietal epithelial cell. In addition, 7 of 21 total glomeruli had crescent formation with no GBM breaks or fibrinoid necrosis. There was no evidence of concomitant cellular or antibody-mediated rejection or CMV infection. These findings were indicative of PVN, with the rare finding of frequent crescents with glomerular epithelial cell infection.

Discussion: PVN is rarely described as having crescentic glomerular lesions, and if present, only one glomerulus per biopsy was affected. There are no reported cases of rapidly progressive glomerulonephritis in PVN. In our case, we found crescent formation more frequently in 33% of glomeruli. Additionally, viral cytopathic changes uncommonly affect glomeruli, typically only involving parietal epithelial cells when present. We demonstrated viral infection of both parietal and visceral epithelial cells. Our case highlights a pattern of kidney injury not commonly seen in PVN and supports that crescent formation can be caused by viral infection of the parietal epithelial cells.

PO2454

Risk Factors for Detrimental Progression in Kidney Transplant Recipients with BK Viremia

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Background: The only effective management for BK viremia (BKV) among kidney transplant recipients (KTR) is regular monitoring and adjustment of immunosuppression. With this strategy, the majority of patients will clear BK or have low-level persistent BKV (Group A). However, few will transition toward over-immunosuppression [BKV level > 5 $\log_{10}$ copies/ml or BK nephropathy (BKN) (Group B)], or under-immunosuppression [de novo DSA (dnDSA) or acute rejection (AR) (Group C)]. In this study, we sought to find the characteristics of patients who progress to group B or group C.

Methods: It was a prospective study among KTR transplanted at our University hospital between 01/2015 and 12/2017. All KTR who developed BKV (> 3 $\log_{10}$ copies/ml) within 2 years of transplant were included in the study. Patients were followed up to 2 years of transplant and were divided into 3 groups as above, based on the BK levels or other outcomes. Those patients with progression of BK >5 $\log_{10}$ copies/ml or BKN along with dnDSA or AR, were assigned to the Group B or Group C, whichever event occurred first.

Results: A total of 224 KTR fulfilled our selection criteria, of which 118 (53%) remained in group A, while 64 (28%) and 42 (19%) transitioned to groups B and C, respectively. Compared to group A, in multivariate analysis, female (HR 2.05, 95% CI: 1.08-3.90, p=.02), rejection before BKV (HR 2.90, 95% CI: 1.04-8.12, p=.04) and interval from transplant to first BKV (HR 0.81, 95% CI: 0.72-0.90, p=<0.001) were associated with transition to group B. Conversely, basiliximab induction (HR 2.06, 95% CI: 1.03-4.11, p=.03), HLA mismatch > 3 (HR 2.27, 95% CI: 1.01-5.06, p=.04) and DGF (HR 4.14, 95% CI: 1.12-15.3, p=.03), were associated with progression to group C. At 2 years, graft failure rates were similar between the groups. However, among those with functional graft, group A had significantly better graft function with eGFR of 62 ml/min compared to 46 for group B and 50 for group C.

Conclusions: Our study suggests that in KTR with BK viremia, nearly 50% progress unfavorably toward a state of under-immunosuppression (AR) or over-immunosuppression (worsening BK). Modifiable risk factors including history of rejection, induction therapy, HLA mismatch, and DGF could help preventing untoward disease progression.

PO2455

A First-in-Human Study of MAU868, a Novel Neutralizing Antibody Against BK Virus

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Background: Reactivation of BK virus (BKV) infection can cause significant kidney and bladder disease in immunocompromised patients. BKV nephropathy is a leading cause of allograft loss in kidney transplant recipients. There are currently no effective or BKV-specific therapies. MAU868 is a novel monoclonal human IgG1 that binds to the BKV major capsid protein (VP1) with potent *in vitro* neutralizing activity against the 4 major BKV genotypes (EC_{50}s ranging from 0.009 to 0.093 μg/ml).

Methods: MAU868 was administered i.v. (1, 3, 10, 30, and 100 mg/kg) or s.c. (3 mg/kg) to healthy adults in a randomized, placebo-controlled, blinded, single ascending dose design. Each i.v. cohort was 5 subjects (4 MAU868:1 placebo); the s.c. cohort was 8 subjects (6 MAU868:2 placebo). Subjects were observed for 24 h and followed for 106 d with routine safety monitoring and PK assessments. *Ex vivo* neutralizing activity of serum was measured before and 4 w after dosing. The range of doses included and exceeded the predicted clinically efficacious dose.

Results: 33 subjects completed the study. Adverse events were mild and infrequent; those occurring in more than 1 subject included nasal congestion (3, 9.1%), oropharyngeal pain (3, 9.1%), and injection site hemorrhage (ecchymosis after s.c. injection; 2, 6.1%). There were no infusion reactions. No subject discontinued the study due to an adverse event or developed anti-drug antibodies. MAU868 PK was typical of a human IgG with a half-life of 23 to 30 d. AUC and Cmax were dose-proportional, ranging from 9880 to 1060000 μg*hr/mL and 24.7 to 2740 μg/mL (ie, no evidence of FcRn saturation). Day 29 plasma MAU868 concentrations, adjusted for extravascular distribution to estimate parenchymal exposure, were approximately 7- to 751-fold higher than the highest *in vitro* EC_{50} (0.093 μg/mL). Maximum *ex vivo* neutralizing activity of serum was achieved for doses >10 mg/kg. Bioavailability after s.c. injection was 57.6%.

Conclusions: MAU868 was safe and well tolerated with PK typical for a human IgG. The *ex vivo* neutralizing activity suggests where the therapeutic range may be for the treatment or prevention of BKV disease. These results warrant further clinical investigation of MAU868 in patients with or at risk for BKV disease.

Funding: Commercial Support - Novartis

PO2456

Induction with Alemtuzumab and Thymoglobulin in Kidney Transplant and the Risks of Leukopenia, Cytomegalovirus Infection, and BK Virus Nephropathy

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Background: Induction immunosuppressive therapy at the time of kidney transplantation reduces the risk of allograft rejection and improves graft outcomes. We compared the association between induction with thymoglobulin and alemtuzumab on the risks of leukopenia, CMV infection, and BK virus nephropathy.

Methods: We used TriNetX, a global federated research network that provides access to statistics on the electronic medical record (EMR). The Penn State Health TriNetX searchable database allows the analysis of approximately 1.7 million Penn State Health patient observations dating back to 1997. We analyzed the EMR of 1070 adult patients who had undergone kidney transplant between 1997 and May 10, 2020 (mean age: 60 ± 17; Male: 63%; White: 81%; Hispanic or Latino: 8%). We created two cohorts based on induction with either thymoglobulin or alemtuzumab. We compared the rates of leukopenia, CMV infection and BK virus nephropathy between the two cohorts. We calculated the relative risk (RR) and the 95% confidence interval (CI) for each outcome in the thymoglobulin group compared with the alemtuzumab group. Analyses were done in the TriNetX "analytics" network using the browser-based real-time analytics features.

Results: Study cohorts included 220 patients (mean age: 57 ± 15) in the thymoglobulin group, and 160 patients (mean age: 54 ± 19) in the alemtuzumab group. Leukopenia occurred in 50 patients in the thymoglobulin group and in 70 patients in the alemtuzumab group (RR: 0.52; CI: 0.39 to 0.70; p<0.0001). CMV infection occurred in 40 patients in the thymoglobulin group and in 20 patients in the alemtuzumab induction group (RR: 1.45; CI: 0.89 to 2.39; p = 0.14). BK virus nephropathy occurred in 20 patients in the thymoglobulin group and in 20 patients in the alemtuzumab group (RR: 0.72; CI: 0.41 to 1.31; p = 0.29).

Conclusions: Induction therapy with thymoglobulin is associated with a lower risk of leukopenia compared with alemtuzumab induction. The risks of CMV infection and BK virus nephropathy are not statistically different in the two induction therapies.

PO2457

Effects of Early Conversion to mTOR Inhibitors on Viral Infections in Renal Transplant Recipients: Eight-Year Single-Center Experience

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Background: Mammalian target of rapamycin inhibitors (mTORis) may decrease cytomegalovirus (CMV) and BK infection in renal transplant recipient. long-term effect on rejection rate deserves follow up.

Methods: This is a retrospective analysis of all patients who underwent living unrelated donor kidney transplant at Nasr city Insurance and Nile Badrawy Hospitals from 2011 to 2018, panel reactive antibody zero and no donor specific antibody. Uni- and multi-variate analysis were done to compare between mTORis based regimen and cyclosporin inhibitors (CNI)-based regimen.

Results: We identified 1458 patients who underwent living unrelated kidney transplant with intermediate risk for CMV. All patients received Induction with anti-thymocyte globulin then were maintained on mycophenolate mofetil (MMF)-CNI-prednisone for at least 6 months. They were classified into two groups: *Group I: 658 patients on mTORis (sirolimus or everolimus), who were shifted from CNI to mTOR-I due to different causes. Group II: 800 patients on CNI (cyclosporin or tacrolimus). The overall incidence of CMV infection and BK infection (Table 1) were statistically significant lower in mTORis group compared to CNI group with no statistical differences in incidence of rejections in the first 36 month but late higher rate of BPAR (Table 2).

Conclusions: mTORis/MMF is associated with low incidence of CMV and BK infection with no significant difference in rejection rate in the first 36 months. However, further regiment modification is required to reduce late rejections.

Comparison between m.TOR-I and CNI in the complications rather than rejection: Table (1)

Overall time	Group one mTOR	Group two CNI	P value
	N=658	N=800	
proteinuria	217(33%)	15(1.9%)	*<0.001**
CV	15(2.2%)	60(12.5%)	*<0.001**
Polyomavirus	8(1.2%)	50(16%)	*0.012**
Other malignancies	4(0.6%)	51(6.3%)	*0.001**

- *Chi square test for qualitative data between the two groups*
- **: Significant level at P value < 0.05*

Table (2) comparison between M TOR and CNI in the incidence of BPAR

Year	mTOR		CNI		P value
	Total number	(BPAR) Rejection N(%)	Total number	(BPAR) Rejection N(%)	
2011	50	1(2%)	98	8(8.2%)	*0.138*
2012	64	4(6.3%)	122	12(9.8%)	*0.407*
2013	65	10(15.4%)	120	14(11.7%)	*0.473*
2014	50	18(36%)	100	10(10%)	*<0.001**
2015	100	45(45%)	103	15(14.6%)	*<0.001**
2016	98	45(45.9%)	67	13(19.4%)	*0.001**
2017	124	76(61.3%)	79	12(15.2%)	*<0.001**
2018	107	76(71%)	111	5(4.5%)	*<0.001**
Overall time	658	275(41.8)	800	89(11.1%)	*<0.001**

- *Chi square test for qualitative data between the two groups*
- **: Significant level at P value < 0.05*

PO2458

The Utility of Procalcitonin in the Management of Kidney and Pancreas Transplant Recipients with Suspected Infection

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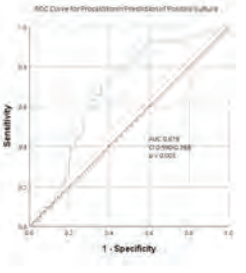
Background: Procalcitonin is used to differentiate between bacterial and viral infections to guide judicious use of antibiotics. It has not, however, been well studied in renal and pancreas transplant recipients. These patients are frequently exposed to antibiotics and are at risk for developing resistant infections. Thus, there is a need for reliable markers of bacterial infection. The purpose of this study was to compare procalcitonin levels in patients with and without bacterial infection to determine whether procalcitonin is a reliable marker of bacterial infection in the transplant population.

Methods: Serum procalcitonin levels were measured on admission on all patients admitted to the Transplant Nephrology service with suspected infection as determined clinically by the on-call physician. We obtained all study data via chart review.

Results: Procalcitonin was measured in 154 patients. Demographics are included in the table. Forty-two patients (27%) had a positive bacterial culture. Mean procalcitonin for those with positive cultures was 5.36 ng/ml vs. 3.35 ng/ml in those without positive cultures, however this was not statistically significant (t=0.642, p=0.522). Patients with positive cultures were more likely to have procalcitonin levels >0.5 mg/ml (p=0.003). Procalcitonin had a modest but significant correlation with WBC count (r=0.249, p=0.002). Receiver operating characteristic analysis demonstrated an area under the curve (AUC) of 0.679 (95% confidence interval: 0.590-0.768, p=0.001) for predicting positive cultures with procalcitonin compared with an AUC of 0.584 (95% confidence interval: 0.474-0.694, p=0.110) for WBC count.

Conclusions: In this cohort of hospitalized kidney and pancreas transplant recipients, serum procalcitonin concentration was associated with bacterial infection and was found to be a better predictor than WBC count. More information is needed to determine the utility of procalcitonin measurements in clinical decision making in this patient population.

Demographics	
Age (years)	46.5
Sex (% male)	49.0%
Time from transplant (years)	4.8
Pancreas or kidney pancreas transplant	17
Race – % (no.)	
White or Caucasian	75.1% (115)
Native Hawaiian or Pacific Islander	4.5% (7)
Other	14.3% (22)
Ethnicity	
Hispanic/Latino - % (no)	20.3% (31)
BMI (kg/m^2)	27.3
Weight (kg)	79.4
Height (cm)	169.4
Serum creatinine (mg/dl)	2.34



PO2459

Infection Rate at 1 Year of Deceased Donor Kidney Transplant in the Elderly

Wina Yousman, Nicole Low, Wei Xiang Wong, Venkatesh Kumar Ariyamuthu, Bekir Tanriover. *The University of Arizona, Tucson, AZ.*

Background: There is limited publications about infection incidence rate in deceased donor kidney transplant (DDKT) recipients older than 65. The objective of this study is to examine our center specific infection incidence rate within one year of DDKT.

Methods: Retrospective chart review of DDKT (N=176) from July 2016 to December 2019 at Banner Medical Center in Tucson, AZ. Primary outcome was the infection incidence rate among recipients older than 65 year-old, including Cytomegalovirus (CMV) viremia and BK viremia (screened by monthly plasma PCR testing), or urinary tract infection (UTI) (diagnosed with positive urine culture and urinary symptoms within first year of transplant). We also fitted a multivariable logistic regression for the outcomes variables adjusted for demographics, KDPI, CIT, EPTS, and cPRA.

Results: The characteristics of the study cohort was shown in Table 1. Out of 176 patients, 63 patients (35.8%) were older than 65 year-old. There was no significant difference in the incidence rate of total infection, CMV viremia, BK viremia, and UTI in the elderly versus non-elderly patient (63.5% vs 51.3% p=0.11, 20.6% vs 11.5% p=0.10, 15.9% vs 11.5% p=0.41, 32.3% vs 28.3%, p=0.59). The multivariable logistic regression analysis (adjusted for ethnicity, KDPI, EPTS, cPRA, and CMV mismatch) did not show increased odds of all type of infections among older recipients.

Conclusions: The infection rate of elderly versus non-elderly who received DDKT were similar.

Variables		Elderly (n=63, 35.8%)	Non-Elderly (n=113, 64.2%)	p Value
Ethnicity	African American	2 (3.2%)	8 (7.1%)	0.01
	American Indian	0 (0%)	13 (11.5%)	
	Asian	3 (4.8%)	6 (5.3%)	
	Caucasian	32 (50.8%)	34 (30.1%)	
	Hispanic	26 (41.3%)	44 (38.9%)	
	Middle Eastern India	0 (0%)	3 (2.7%)	
	Pacific Islander	0 (0%)	1 (0.9%)	
Age	Mean	71±4.9	49.3±11.8	0.00
Induction	rATG	15 (23.8%)	39 (35.5%)	0.11
	Basiliximab	48 (76.2%)	71 (64.5%)	
KDPI	> 85	16 (27.1%)	9 (8.7%)	0.00
	Mean	71.08 ± 20.61	54.89 ± 24.03	0.04
EPTS	Mean	80.61 ± 17.17	43.70±27.44	0.00
cPRA	Mean	15.84 ± 31.00	23.7±38.02	0.01
CIT	Mean	29.9 ± 12.81	23.75 ± 12.90	0.70
CMV Donor	Positive	39 (62.9%)	73 (64.6%)	0.82
CMV Recipient	Indeterminate	0 (0%)	1 (0.9%)	0.04
	Positive	40 (63.5%)	90 (79.6%)	
CMV Mismatch	Yes	14 (22.2%)	15 (13.3%)	0.13
EBV Donor	Positive	54 (93.1)	85 (84.2%)	0.08
EBV Recipient	Positive	62 (98.4%)	111 (98.2%)	0.92
Toxoplasma Recipient	Positive	11 (18.3%)	11 (10.1%)	0.13
Coccidioidomycosis Recipient	Indeterminate	3 (4.8%)	9 (8.1%)	0.65
	Positive	4 (6.5%)	9 (8.1%)	
PHS High Risk	Yes	9 (18.4%)	15 (17.9%)	0.95
DGF	Yes	27 (48.2%)	45 (42.1%)	0.45
Rejection	Yes	9 (14.5%)	19 (16.8%)	0.69
Infection	Yes	40 (63.5%)	58 (51.3%)	0.11
CMV	Yes	13 (20.6%)	12 (11.5%)	0.10
BK viremia	Yes	10 (15.9%)	13 (11.5%)	0.41
BK urine	Yes	18 (28.6%)	22 (19.5%)	0.17
UTI	Yes	20 (32.3%)	32 (28.3%)	0.59
Logistic Regression (adjusted for Ethnicity, KDPI, EPTS, cPRA, CMV Mismatch)				
Outcome		Odd Ratio for elderly		p Value
CMV		1.03		0.97
BK viremia		0.89		0.88
UTI		1.15		0.80

Table 1: Baseline Characteristics and Outcomes of Elderly vs. Non-eldery

PO2460

Two Deaths of Acute Transplant Patients from Strongyloides Hyperinfection Syndrome (SHS): Can We Prevent Harm with Screening and Prophylaxis at the Time of Transplantation?

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Background: A 59 year old Vietnamese man presented with non-specific abdominal pain 8 weeks after a deceased donor kidney transplant. He was thoroughly investigated and no cause for the pain identified. On day three of the admission he became febrile and hypoxic. He died with multi-organ failure. Within three months a patient of Congolese origin presented nine weeks post transplant with abdominal pain. He became febrile with gram positive bacteraemia and was admitted to the ICU with type 1 respiratory failure where he unfortunately died. Autopsy findings revealed SHS. These cases were patients at a transplant centre in a non-endemic area albeit with an ethnically diverse population. A survey of other UK transplant centres showed that none did pre-transplant screening for strongyloides infection.

Methods: As a result of these cases we implemented and evaluated a program to screen for and prophylactically treat Strongyloides infection: Live donor patients were screened with Strongyloides serology in advance of transplantation. All recipients of deceased donor transplants were screened on admission for their transplant unless they had never travelled to an endemic area. At induction recipients received a weight adjusted dose of Ivermectin pending serology results. If positive a second prophylactic dose was administered at day 14. Travel histories and demographic data were recorded.

Results: Between July 2019 and March 2020; 135 patients were transplanted at our unit. Of those 125 had strongyloides serology testing; eight were positive at time of transplant with an additional two patients reported as "borderline". One further patient tested positive on a previous admission for a transplant which was cancelled; but was negative on the admission of the successful transplant. This indicates that at least 8% of our transplant listed patients are positive for strongyloides infection. By May 2020 there were no recorded deaths due to SHS, or morbidity associated with strongyloides infection in this group.

Conclusions: We have demonstrated that there is a significant level of sero-positivity within our pre-transplant population and that a relatively low-cost strategy may help prevent the potentially fatal Strongyloides Hyperinfection Syndrome.

PO2461

Infectious Complications and Malignancy After Kidney Transplant in the Elderly Population

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Background: Kidney transplantation improves quality of life and survival in all patients regardless of age. However, older patients are prone to development of side effects related to immunosuppressive medications including infections and malignancy. We aim to evaluate clinical outcomes in recipients >65 years of age.

Methods: We retrospectively reviewed all patients over the age of 18 who received an isolated renal transplant at our center from January 2013 to June 2017. We compared clinical outcomes including allograft and patient survival, as well as the development of infections and malignancy in patients > 65 compared to younger patients.

Results: Of 624 patients analyzed, 148 (24%) were > 65 years of age. There was no difference in terms of gender, race, immunosuppressive or induction therapy between the two groups. Older patients were more likely to receive a deceased donor kidney transplant (92% vs. 81%, p=0.009). During a median 48 months (28, 70) of follow-up, as expected mortality was higher in older patients (16% vs. 6.5%, p=0.0001) but there was

no difference in terms of death-censored graft loss (10.8% to 9%, p=0.52) compared to younger patients. Detailed analysis of infections revealed that there was no difference in terms of BKV and CMV viremia, pneumonia, bacteremia, influenza and c. diff between the two groups. However, older patients had more fungal and urinary tract infections and malignancy. The most common infection in the elderly was PJP pneumonia (4%), candidemia (3%), and cryptococcal infection (2%). The most common malignancy in the elderly was skin cancer (6%) followed by prostate (2%), lung (1%), and colon (1%).

Conclusions: Recipients older than 65 had similar graft survival compared to younger patients, but had a higher incidence of fungal and urinary tract infections and malignancies.

Clinical outcomes	Patients age > 65	Patients age =< 65	p-value
BKV	22%	19%	0.43
CMV	12%	9%	0.25
Influenza	8%	10%	0.47
Pneumonia	23.7%	20%	0.38
Bacteremia	20%	18%	0.55
C diff colitis	8%	4.5%	0.07
Urinary tract infections	49%	31%	< 0.0001
Fungal infections	10.5%	5.1%	0.02
Malignancy	16%	5%	< 0.0001

PO2462

Risk of Active Tuberculosis Infection in Kidney Transplantation Recipients: A Matched Comparative Nationwide Cohort Study

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Background: Although the risk of *mycobacterium tuberculosis* (TB) infection is high in both kidney transplantation (KT) recipients and dialysis patients, a large-scale evidence comparing the risk between the two groups in a nation with moderate or higher TB prevalence was rare.

Methods: We performed a nationwide retrospective cohort study based on the claims database of South Korea where moderate TB prevalence is reported. We included incident KT recipients from 2011 to 2015 and compared their active-TB risks with matched controls. The 1:1 matched general population group was matched for age, sex, and era, while the dialysis group was matched for age, sex, era, underlying hypertension, and diabetes. We excluded the matched pairs with age < 20 years old, a previous TB history, and those matched to a multi-organ transplantation case. The incident active-TB risk was assessed by the multivariable Cox regression analysis. Within KT group, associations between active-TB, as a time-dependent variable, and post-transplant death or death-censored graft failure was investigated.

Results: The number of matched 7,462 subjects (total 22,386) were included to each of the study groups. During median 3.57 years of follow-up duration, the incidence rate for active-TB was 3.92/1,000, 4.38/1,000, and 0.67/1,000 person-years in the KT, dialysis, and general population groups, respectively. The KT group showed a significantly higher risk of active-TB than the general population group [adjusted HR 3.39 (1.88-6.12)] but a similar to the dialysis group [adjusted HR 0.98 (0.73-1.31)]. Active-TB was a significant risk factor for death [adjusted HR 2.24 (1.19-4.42)] or death-censored graft failure [adjusted HR 2.21 (1.36-3.58)] in the KT patients.

Conclusions: In Korea with moderate TB prevalence and active surveillance strategies, KT patients may not have to burden additional risk of active-TB when compared to dialysis patients. Still, clinical attention for active-TB complication should not be overlooked in end-stage kidney disease patients, particularly for KT patients as active-TB was associated with worse post-transplant prognosis.

PO2463

Hydroxychloroquine as an Alternative or Adjunctive Antimetabolite in Kidney Transplant Recipients: Analysis of Linked US Registry and Claims Data

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Background: Hydroxychloroquine (HCQ) is an antimalarial drug with immunomodulatory effects in patients with systemic lupus erythematosus (SLE) and scleroderma. The potential anti-viral effects of HCQ have raised attention in the context of the COVID-19 pandemic, although safety is controversial.

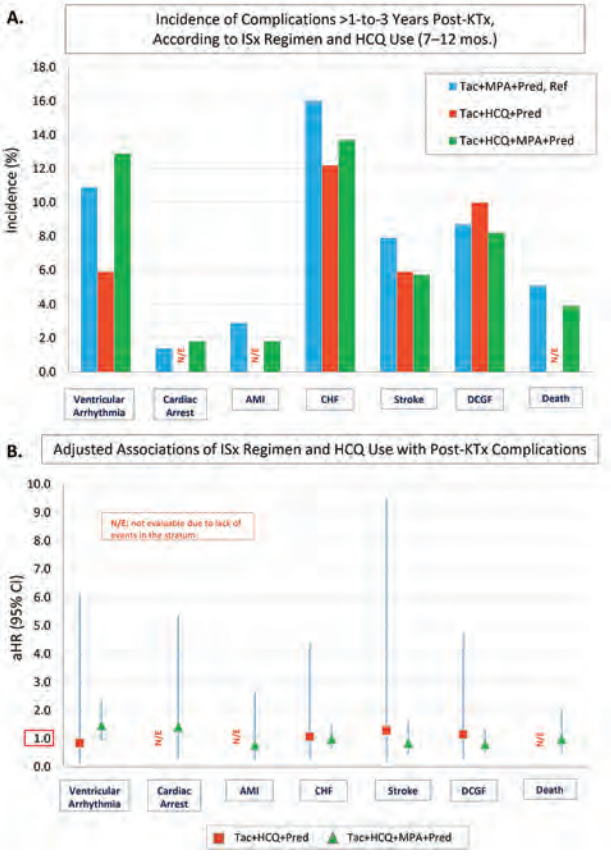
Methods: We examined a novel database linking national transplant registry identifiers for kidney transplant recipients (KTx) to records from a large U.S. pharmaceutical claims warehouse (2008–2017) and Medicare claims to study HCQ use among Medicare beneficiaries with kidney failure due to SLE or scleroderma (N=2,550). We compared 3 groups based on immunosuppressive regimen 7–12 mos. post-KTx: 1) **tacrolimus (Tac) + mycophenolic acid (MPA) + prednisone (Pred) – Reference**; 2) **Tac+HCQ+Pred**; or 3) **Tac+HCQ+MPA+Pred**. Associations of regimen with graft failure, death and clinical cardiovascular complications captured in Medicare claims >1-to-3 yrs post-KTx were examined with multivariate Cox regression, adjusted for baseline factors in the registry.

Results: Among the study sample, 18.3% received Tac+HCQ+MPA+Pred 7–12 mos. post-KTx, while 1.7% received Tac+HCQ+Pred. Use of HCQ containing regimens was more common in women (*vs* men), and Black and Hispanic (*vs* white) recipients; use of Tac+HCQ+MPA+Pred was more common in younger patients (*vs* older) patients (**Table**). The unadjusted incidence of adverse events did not differ across the 3 groups (**Fig A**); risks also did not differ with covariate adjustment (**Fig B**).

Conclusions: HCQ is an inexpensive immunomodulatory agent that may be used safely in selected KTx recipients as an alternative or adjunct to standard immunosuppression.

HCQ & Immunosuppression Regimen use, According to Demographic Traits

*P<0.05 vs Ref	Tac+MPA+Pred, Ref n = 2,125	Tac+HCQ+Pred n = 36	Tac+HCQ+MPA+Pred n = 389
Age			*
18-30	79.7 %	1.1 %	**19.1 %**
31-44	82.4 %	1.9 %	15.7 %
45-59	85.8 %	1.1 %	13.1 %
>=60	88.7 %	0.9 %	10.4 %
Gender			*
Male	89.8 %	0.7 %	9.5 %
Female	81.9 %	**1.6 %**	**16.5 %**
Race			*
White	88.3 %	0.7 %	11.1 %
Black	80.7 %	**2.0 %**	**17.3 %**
Hispanic	82.1 %	**1.7 %**	**16.2 %**
Other	82.4 %	0.5 %	17.1 %



HCQ / Immunosuppressive Regimen Use, & Outcomes

PO2464

Bacillary Angiomatosis in a Kidney Transplant Recipient

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Introduction: Bacillary angiomatosis (BA) is a vascular proliferative manifestation of *Bartonella henselae* (BH) or *Bartonella quintana* (BQ) that usually affects immunocompromised hosts. It usually involves the skin but may affect other organs. Few cases of BA in kidney transplant (KT) recipients have been reported, with most cases presenting years after KT. We describe a case of BA in a KT recipient that occurred early post-transplant.

Case Description: A 67-year-old male KT recipient from a deceased donor developed fevers, night sweats, and fatigue 1-month post-KT. He received antithymocyte

globulin induction, and maintenance tacrolimus, mycophenolate, and prednisone. Two months later, he presented with diffuse violaceous papules (Figure 1A). Biopsy of a papule with Warthin-Starry stain showed clusters of bacteria suggestive for BA (Figure 1B). Diagnosis was confirmed with a positive serum Bartonella polymerase chain reaction (PCR). He was treated with doxycycline with resolution of symptoms. BH and BQ Immunoglobulin G (IgG) were equivocal. A few weeks later, IgG for BH was 1:256 (reference range <1:128). Echocardiogram, abdominal computed tomography, and kidney biopsy were unremarkable. Recipient Bartonella PCR and antibodies on the day of transplant were negative. Donor Bartonella PCR and BH IgG were negative. Donor BQ IgG was equivocal. The recipient had a cat 8 years prior to KT without recent exposure. Allograft function remains intact, and the rash completely resolved. Bartonella PCR 6 months on treatment was negative.

Discussion: Our patient developed signs of BA with positive seroconversion within the first 3 months of KT which is rare. BA should be considered in the differential diagnosis of fever and cutaneous angioma-like lesions in KT recipients, even in the absence of exposures. Combined serology and molecular testing (PCR) is useful in diagnosing BA as serology alone may be unreliable. Early empiric treatment should be considered in transplant recipients while waiting for confirmatory results.

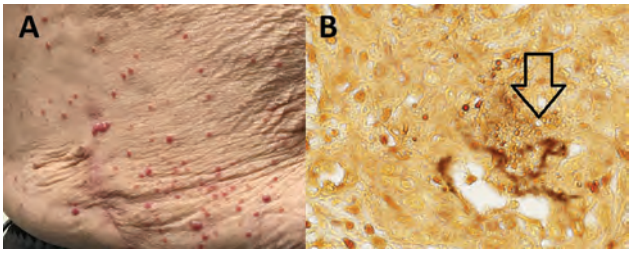

Figure 1. (A) Violaceous papules on the trunk. (B) Warthin–Starry stain showing bacteria (arrow).

PO2465

Isavuconazole as Consolidation Therapy for Disseminated Histoplasmosis in a Kidney Transplant Recipient

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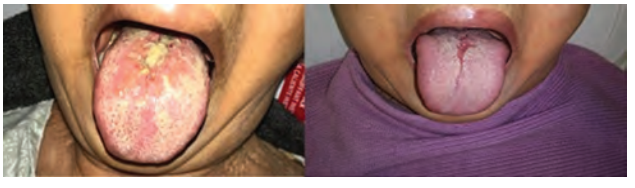
Introduction: The diagnosis of systemic fungal infection may be elusive and requires a high index of suspicion with prompt evaluation, directed laboratory and radiological work-up and if necessary, histological examination. To our knowledge, this is the first case report of isavuconazole use as consolidation therapy for disseminated fungal infection in a kidney transplant recipient.

Case Description: A 76-year-old female with polycystic kidney disease presented 8 years post kidney transplantation with a painful tongue ulcer, anorexia, weight loss, progressive anemia and severe de-conditioning. She was on maintenance mycophenolate, prednisone and tacrolimus. A midline fissure on the dorsal tongue surface (image 1- left). and two non tender nodular masses in the left forearm and right buttock were noted. A diagnosis of disseminated histoplasmosis was made by biopsy of the tongue ulcer, and cultures of blood, tongue tissue and forearm nodule aspirate. Blood and urine histoplasma antigens were positive. The patient was treated with amphotericin for two weeks before transitioning to itraconazole then to Isavuconazole due to QT prolongation. Mycophenolate was stopped. An outstanding clinical response with healing of the tongue ulcer (image 1 - right), shrinking of the subcutaneous lesions, and substantial functional progress to prior independence was seen within 3 months. Histoplasma urinary and plasma antigen levels declined to undetectable levels. Isavuconazole was continued for a year with no adverse side effects reported.

Discussion: Infections with Histoplasma capsulatum are largely asymptomatic but progressive disseminated mycosis can occur in the immunocompromised. There is no specified agent selectively approved for second line maintenance therapy when itraconazole is not tolerated or is ineffective. Limited experience has been reported with other azoles, and even less so with isavuconazole. This case demonstrates an excellent outcome of treating disseminated histoplasmosis with isavuconazole in a kidney transplant recipient.



Ulcerated median sulcus of the tongue, before (left) and 8 months after (right) starting antifungal therapy

PO2466

The Diagnostic Dilemma of Diffuse Lymphadenopathy in a Kidney Transplant Recipient

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Introduction: Immunological balance is critical for transplant recipients. An optimum amount of immunosuppression prevents rejection while avoiding infection and cancers. Constitutional symptoms and lymphadenopathy could be present in both scenarios and could pose a diagnostic challenge.

Case Description: A 36-year-old male immigrant from India (ten years ago) with PMH of ESRD secondary to IgAN received a DDKT (9/2019, EBV D+/R+, on tacrolimus and myfortic). He was admitted with extensive retroperitoneal and mesenteric lymphadenopathy and a hypodense structure in the left upper abdomen (3.8 x 5.1 cm) on CT scan along with constitutional symptoms of fevers, constipation, and abdominal pain for ten days duration three months after transplant. Vital signs and physical examination were unremarkable except for low-grade fever. Aside from mild anemia (Hb 10 mg/dL), laboratory analysis was normal. PET scan revealed hypermetabolic lymphadenopathy in the neck, abdomen, and pelvis and consolidative changes in the left lung base and a right-sided loculated pleural effusion. Extensive workup - CMV PCR, pan-culture, fungal infections, and flow cytometry – was negative. CT-guided retroperitoneal lymph node biopsy, incisional biopsy of the mesenteric mass, and an endobronchial ultrasound-guided transbronchial needle aspiration of subcarinal LN were non-diagnostic. Finally, exploratory laparotomy and resection of the mesenteric mass revealed granuloma formation with multinucleated giant cells concerning for TB. The AFB culture grew mycobacterium tuberculosis on day 24. He is currently on antitubercular treatment.

Discussion: Our case highlights the importance of a high degree of clinical suspicion for infectious etiology in transplant recipients, especially those from countries with a high prevalence of TB. Our patient bore a distant immigration history and a negative tuberculin test and did not have a history of exposure. Still, he was at increased risk of activation of latent TB due to his immunocompromised state. Extra-abdominal TB, like abdominal TB, poses a diagnostic challenge as the presentation can be non-specific and the AFB stain and culture can be non-diagnostic. Thus, a tissue biopsy becomes key to diagnosis. PTLD was high on differential given the PET-avid LAP. PET-avid lesions imply a hypermetabolic state which can happen in both malignancies and infections.

PO2467

Post-Transplant Lymphoproliferative Disorder: Recurrence at an Unusual Site

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Introduction: PTLD includes a spectrum of clinical presentations due to lymphoid proliferation ranging from benign hyperplasia to aggressive lymphomas that occur after either a SOT or HSCT. PTLD can involve extra nodal sites like graft tissue, GI tract, and lungs. Skin and soft tissue involvement is very rare. We report a patient with PTLD who had relapsed with axillary lymphadenopathy and a soft tissue mass on the arm.

Case Description: A 59-year-old male was diagnosed with EBV negative PTLD involving retroperitoneal, mediastinal and supraclavicular lymph node, one year after renal transplant. He was treated R-CEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone). After 6 cycles of chemotherapy repeat PET scan confirmed complete resolution. 3 months later, he presented with LUE pain and swelling. Labs were significant for high LDH and Beta-2 microglobulin. CT LUE revealed 4.8 cm mass over left anterior arm and left axillary adenopathy. Biopsy and flow cytometry of axillary lymph node and left arm mass confirmed relapse. Immunohistochemical stains showed tumor cells positive for CD20, PAX5, BCL2, MUM1, BCL6 with Ki67 of 80-90%. Patient developed compartment syndrome and had to undergo fasciotomy. Patient was started on modified regimen with Rituximab, Gemcitabine and Oxaliplatin (R-GEMOX) for poor performance status.

Discussion: The incidence of PTLD ranges from 1 to 25% with 90% of cases being EBV-associated, CD 20 positive, B cell neoplasms. EBV negative PTLD occurs only in 5-10% cases, appears late with worse prognosis than EBV positive PTLD. EBV negative PTLD is assumed to be related to Tp53 mutation caused by immunosuppressive agents like azathioprine or tacrolimus. Skin and subcutaneous lesions are extremely rare as sites of extra nodal presentation and may take the form of solitary or multiple papules, nodules, plaques with ulceration, comedo-like lesions, follicular keratotic papules, or localized alopecia. Our patient is interesting as he had a relapse of EBV negative PTLD in the form of a soft tissue fibro-adipose mass in the upper extremity. To the best of our knowledge, there have been three cases of PTLD presenting as soft tissue masses on head reported in the literature. Biopsy remains the gold standard for diagnosis. Treatment is includes reduction of immunosuppression and rituximab with additional chemotherapy.

PO2468

Post-Transplant Lymphoproliferative Disorder (PTLD) Presenting as Solitary CNS Lymphoma: A Rare Occurrence

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Introduction: PTLD associated lymphoma is the second most common malignancy in patients receiving SOT or HSCT with an incidence rate of 1%-3%. PCNS-PTLD occurs in 7%-15% of all PTLD cases. We present a case of isolated PCNS lymphoma two years after renal transplant.

Case Description: A 57 year old woman with PMH of ESRD s/p kidney transplant (D/EBV -,R/ EBV +) with chronic CrCl of 30-40% presented with paresthesia and numbness over the right side of her body with mild ataxia 2 years post transplant. Physical exam revealed only numbness over the right side of body. MRI with contrast revealed a left thalamic lesion with moderate vasogenic edema, and MR spectroscopy confirmed high grade neoplasm involving left thalamus. Stereotactic biopsy showed polymorphic CD-20 and EBV positive PTLD. EBV PCR were elevated. Further evaluation ruled out systemic PTLD. Myfortic was stopped and oral steroids started with mild improvement in symptoms. Choice of systemic chemotherapy was limited due to reduced CrCl and risks of graft failure. She received modified regimen with renally adjusted high dose Methotrexate, Vincristine and Rituximab for 6 cycles with partial remission and then Temozolomide for 7 cycles with complete remission.

Discussion: The incidence of PTLD ranges from 1 to 25% with 90% of cases being EBV-associated, CD20 positive, B cell neoplasms. PCNS-PTLD has a higher incidence in renal SOT, occurs late and is usually monomorphic unlike our patient. Median time of occurrence is 4-5 years after transplant. Risk factors include age, intensity of immunosuppression, time to transplant and EBV status of donor and recipient. Common presenting features include neurological deficits, seizure, and raised intracranial pressure. MRI is the preferred imaging and shows multifocal, ill defined, ring enhancing lesions usually in supratentorial and lobar regions. Positive CSF EBV PCR is highly suggestive but biopsy remains the gold standard for diagnosis. Treatment modalities include reduction of immunosuppression, rituximab, high dose methotrexate, cytarabine and cranial radiotherapy. Use of high dose methotrexate has shown improved outcomes with median survival of 26-47 months. Lack of response to first line therapy is considered the dominant prognostic factor. Early recognition and diagnosis remain crucial for improving outcome.

PO2469

National Trends in Kidney Transplantation Among Patients with ESKD from Plasma Cell Dyscrasias

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Background: Due to relapses and kidney involvement, plasma cell dyscrasias have been a relative contraindication for kidney transplantation. With newer medications and improved prognosis of plasma cell dyscrasias, kidney transplantation in this population is becoming more common. We aimed to describe national trends in the proportion of kidney transplants among recipients who had ESKD from plasma cell dyscrasias (multiple myeloma, amyloidosis, and monoclonal gammopathy of renal significance).

Methods: We used data from the United Network for Organ Sharing/ Organ Procurement and Transplantation Network (UNOS/OPTN) database. Patients 18 years or older, BMI >15 or <45 kg/m^2, received a first kidney transplant between January 1, 2006 to December 31, 2017 were eligible. Recipients of more than one organ transplant were excluded.

Results: A total of 160,966 patients received a first kidney transplant. Among these, 487 (0.3%) had ESKD from plasma cell dyscrasia, 45,570 (28.3%) from diabetes mellitus, and 114,909 (71.4%) from other diagnoses. Clinical characteristics of the plasma cell dyscrasia group are as follows: median age 59.0 (IQR 50.0 - 65.0) years, 294 (60.4%) men, 379 (77.8%) White, 19 (3.9%) with diabetes mellitus, median BMI 26.4 (IQR 23.1-29.0) and 53 (10.9 %) pre-emptive transplant. **Table 1** shows the national trends of kidney transplants among first time recipients and those with plasma cell dyscrasia. Time series analysis shows an increase of 0.1% (95% CI 0.1 - 0.1) over 12 years in the proportion of kidney transplantation for recipients with ESKD from plasma cell dyscrasias.

Conclusions: Despite improvement in the treatment of plasma cell dyscrasias, national trends show only a small rise in the proportion of kidney transplantation for patients with ESKD from plasma cell dyscrasias. Additional analyses are needed to assess the outcomes of these kidney transplant recipients.

Table 1. National trends in kidney transplantation among recipients who had end-stage kidney disease from plasma cell dyscracias (multiple myeloma, amyloidosis, and monoclonal gammopathy of renal significance).

Year	Total transplants (N)	Total plasma cell dyscrasia (%)	Multiple myeloma (%)	Amyloidosis (%)	MGRS (%)
2006	12311	39 (0.32)	4 (0.03)	29 (0.24)	6 (0.05)
2007	12344	33 (0.27)	6 (0.05)	24 (0.19)	3 (0.02)
2008	12635	28 (0.22)	7 (0.06)	19 (0.15)	2 (0.02)
2009	12799	38 (0.30)	6 (0.05)	29 (0.23)	3 (0.02)
2010	13090	33 (0.25)	8 (0.06)	25 (0.19)	0 (0.00)
2011	13175	35 (0.27)	14 (0.11)	21 (0.16)	0 (0.00)
2012	12811	40 (0.31)	9 (0.07)	29 (0.23)	2 (0.02)
2013	13280	31 (0.23)	8 (0.06)	20 (0.15)	3 (0.02)
2014	13551	39 (0.29)	10 (0.07)	29 (0.21)	0 (0.00)
2015	14010	60 (0.43)	16 (0.11)	39 (0.28)	5 (0.04)
2016	15059	58 (0.39)	15 (0.10)	40 (0.27)	3 (0.02)
2017	15901	53 (0.33)	14 (0.09)	37 (0.23)	2 (0.01)

MGRS: Monoclonal gammopathy of renal significance

PO2470

A Retroperitoneal Cyst of Pancreatic Origin in a Renal Transplant Recipient: Expect the Unexpected

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Introduction: The immunosuppression required to maintain a renal allograft function puts the recipient at a higher risk of malignancy. We report a rare case that presented a diagnostic challenge when a retroperitoneal hemorrhagic cystic mass turned out to be an adenocarcinoma of pancreaticobiliary origin.

Case Description: 43-year-old female with a history of End Stage Renal Disease due to IgA Nephropathy and two renal transplantations, first in 1999 from her sister and second in 2005 from a deceased donor, presented with complaint of left sided abdominal pain and distention for one month. Her graft function was stable with creatinine of 1.8mg/dl on immunosuppression with tacrolimus, mycophenolic acid, and prednisone. The CT scan showed a large 12 x 13 x 16 cm well-defined septated cystic mass. She subsequently underwent exploratory laparotomy which revealed a retroperitoneal 1.7L cystic hematoma with no association to native or transplant kidneys. The histopathology showed adenocarcinoma with mucinous and enteric features. Based on the morphology and immunoprofile, the differential diagnosis included an ovarian, gastrointestinal or peritoneal primary. Tumor markers showed elevated CA19-9, but normal CEA and CA-125. Given the positivity for both CK 7 and CK 20, colonic origin was unlikely but could not be completely excluded. Negative EGD and colonoscopy ruled out GI Primary. PET scan was unremarkable. Molecular analysis predicted 90% probability of pancreaticobiliary adenocarcinoma. Subsequently patient was started on adjuvant chemotherapy with Gemcitabine. She failed first and second lines of chemotherapy with progression of cancer. Then she received PD-L1 inhibitor, Nivolumab which could not prevent progression of disease but resulted in renal graft failure. Per last reports, patient was on palliative chemotherapy and in terminal phase of her life.

Discussion: Post-transplant malignancy is one of the most feared complications. It is the third leading cause of mortality and accounts for 8-10% of all deaths in United States and 30% in Australia in kidney transplant recipients. Compared with general population, the risk is increased 2-3 folds and mortality rates are higher. The occurrence of pancreatic cancer is high too. But finding a pancreaticobiliary cancer from a retroperitoneal cyst with negative pancreas imaging is rare.

PO2471

Secondary Malignancy in Kidney Transplant Recipients: University of Southern California Experience

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Background: Kidney transplant recipients (KTR) on immunosuppressive therapy are at higher risk of developing secondary malignancy (SM). Although previous studies have demonstrated this increased risk, much remains to be elucidated regarding the spectrum of SM and the contributing factors to morbidity and mortality.

Methods: We conducted a retrospective review of all KTR from April 2005 to December 2017 at our institution. We then selected only those patients with SM, and collected demographics, variables related to kidney transplant, malignancy, and outcomes.

Results: Among 1414 KTR, 84 patients (pts) had post-tx SM. Forty-five percent of pts were Hispanic, 33% Caucasian, 11% Asian and 6% African American. Twenty four pts (28%),11 pts (13%), and 51 pts (59%) developed cutaneous malignancy, hematological malignancy and solid organ malignancy (SOM) respectively. One patient developed both a secondary cutaneous and SOM, while another pt developed 2 different SOM. 46 (55%) pts were deceased by 1/1/20: 25 pts died from malignancy and 9 pts died from infection. Among those 46 pt, 37 pts (80%) had intact graft function at death. Eleven pts (13%) had malignancy prior to tx. The induction was rATG (36%) and basiliximab (41%). 20 pts had biopsy-proven acute rejection; of these 75% was prior to and 25% was post cancer diagnosis. 18 pts were switched to mTOR inhibitor from tacrolimus and cellcept was stopped in 22 pts.

Conclusions: We describe a wide range of SM among a diverse population of KTR, with nearly half of our patients being Hispanic. This highlights the need for further investigation of the impact of ethnicity on SM. Among our KTR, SM was the cause of death for 25 pts and infection was for 9 pts. Regardless of etiology, the majority of pts (80%) had intact graft function at death. Our findings illustrate the need for vigilant cancer screening and additional strategies to decrease cancer risk and death in KTR.

Type of cancer	N = 86	%
GU	16	19
Thoracic	14	16
GYN	2	2
GI	14	16
Sarcoma	3	4
Hematological	11	13
Skin	24	28
Primary unknown	2	2

PO2472

Spectrum and Consistency of Cancer Outcomes in Randomized Trials in Kidney Transplant Recipients: A Systematic Review

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Background: Cancer is an important cause of morbidity and mortality in kidney transplant recipients. Despite being established as a critically important outcome by patients, caregivers and health professionals, inconsistency in how cancer outcomes are defined and reported in trials of kidney transplant recipients may limit decision-making. The aim of this study was to assess the spectrum and consistency of cancer outcomes in trials involving kidney transplant recipients.

Methods: ClinicialTrials.gov was searched from inception to October 2019 to identify all randomized controlled trials (RCTs) in adult kidney transplants recipients which included cancer as a pre-defined outcome. We extracted the details of all primary and secondary cancer outcomes, including type, timepoint and definition of cancer (histology, grade and stage).

Results: Among the 71 RCTs included, there was a total of 87 cancer outcomes. The majority of trials (n = 61, 86%) included cancer as a secondary outcome only, with 8 trials (11%) including cancer as a primary outcome and 2 (3%) including cancer as part of a composite primary outcome measure. The most common descriptions of cancer in these outcome measures was "malignancy" without specific reference to diagnostic criteria, histology, grade or cancer stage (40, 46%) or "cancer" without specific clarification (8, 9%). Some trials included mention of specific cancer types, with post-transplant lymphoproliferative disorder (13, 15%), non-melanoma skin cancer (10, 11%) and skin cancer (in general) (5, 6%) being the most common, but these were not defined. A range of timepoints were used, with a single timepoint at the end of the primary trial being the most frequent (38, 44%); 13 studies included measurement at several timepoints during the trial (15%). A range of metrics for measuring cancer outcomes were used, including cancer incidence (53, 61%), proportion with cancer (9, 10%), and time-to-event (5, 6%). No measurement metric was specified in 18 (21%) cancer outcome measures.

Conclusions: Cancer is one of the most important outcomes for patients post-transplantation, but cancer outcomes are very poorly defined and highly variable in RCTs. A core outcome for cancer for all trials in kidney transplant recipients should be developed that is consistent and meaningful to patients and clinicians.

Funding: Government Support - Non-U.S.

PO2473

Acute Rejection and Graft Failure in a Kidney Transplant Recipient with Malignant Melanoma and Treated with Pembrolizumab: A Case Report

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Introduction: Malignancy treatment with immunotherapy in renal transplant recipients is complicated by a very high risk of rejection. Immunochemotherapy increases immune recognition and destruction of immune-evading cancer cells. This can lead to an overly robust immune response leading to allograft injury and failure. Here we present a case of graft failure due to rejection within a week of starting immunochemotherapy.

Case Description: 73-year-old female with a history of end-stage renal disease attributed to hypertensive nephrosclerosis underwent live unrelated kidney donor transplant and presented 6 months post-transplant with a right foot lesion and was diagnosed with stage IIIC malignant melanoma. Her maintenance immunosuppression was decreased from tacrolimus/prednisone to prednisone monotherapy and the lesion was excised. 14 months later, disease surveillance via PET scan revealed metastatic disease. After carefully weighing the risks of mortality without treatment versus graft rejection, pembrolizumab, a programmed cell death one (PD-1) -inhibitor, was initiated. 5 days after administration of the first dose, the patient presented emergently with acute kidney injury with Cr of 4.3 mg/dL, increased from baseline Cr of 0.9-1.0 mg/dL. Ultrasound of her graft demonstrated significant edema and graft thrombosis. Allograft biopsy was consistent with 95% cortical necrosis with thrombotic microangiopathy and grade III acute cellular and antibody mediated rejection. Transplant nephrectomy was performed on day 7 and HD was re-initiated.

Discussion: Immune checkpoint inhibitors have been shown to be effective treatments for certain malignancies (melanoma, renal cell carcinoma namely); however, they can cause acute rejection and graft loss in transplant recipients. Though PD-1 inhibition has been a major scientific breakthrough in late-stage cancer treatment, its risks should be carefully considered in organ transplant recipients due to high risk of graft rejection. Prevention and management of rejection in a transplant recipient with an aggressive melanoma such as ours is not clear.

PO2474

Renal Transplant Recipients Suffer Significantly More Complications After Breast Cancer Surgery but Benefit from Treatment at Transplant Centers

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Background: Breast Carcinoma has the highest incidence of any cancer in adult females. The impact of kidney transplant (KT) on breast cancer surgery has not been examined. Our objective was to evaluate the influence of a previous KT on the short-term outcomes of mastectomy or lumpectomy.

Methods: A retrospective analysis was conducted using Nationwide Inpatient Sample (NIS) data between 2005 and 2014. Population included adult females with kidney transplant surgically treated for breast malignancy. Weighted multivariate regression models were employed to compare outcomes at transplant and non-transplant centers.

Results: 398 women met the inclusion criteria. There was a greater proportion of African-American (p<0.001), and Hispanic women (p=0.01) compared to the cohort. KT recipients had more comorbidities and higher Elixhauser Comorbidity Index scores (p<0.001). We noted longer length of stay (p<0.001), higher expenditure (p=0.001), and complications (p<0.001). Specifically, rates of hematomas (p=0.041), acute renal failure (p<0.001), blood transfusion (p<0.001), fresh frozen plasma transfusion (p<0.001), cardiovascular (p<001), and other complications (p=0.012) were increased. There was no mortality among transplant recipients. Weighted multivariate analyses highlight that rates of complication (p=0.040), and length of stay (p<0.001) are lower at transplant centers.

Conclusions: History of kidney transplant has a significant impact on the outcomes of mastectomy or lumpectomy. These patients suffer more post-operative adverse events. However, KT recipients experience superior outcomes at transplant centers.

Demographics			
Characteristics	**No KT (N=736,619)**	**KT (N=398)**	**P-value**
Age >65 years	37.20%	24.70%	<0.001
African American	10.1%	21.0%	<0.001
Hispanic	6.6%	9.8%	0.01
Elixhauser Comorbidity Index, Median (IQR)	0 (-1.0 to 1.0)	6 (5.0-10.0)	<0.001
Outcomes After Breast Cancer			
Patient Outcomes	**No KT (N=736,619)**	**KT (N=398)**	**P-value**
Any complication	8.2%	16.5%	<0.001
Cardiovascular	0.5%	2.6	<0.001
Hematomas	3.2%	5.1%	0.041
Acute Renal Failure	0.6%	2.5%	<0.001
Fresh Frozen Plasma Transfusion	0.2%	1.4%	<0.001
pRBC Transfusion	3.3%	7.4%	<0.001
Total Charges, Median	$43,005	$50,670	<0.001
Weighted Multivariate Adjusted Outcomes for Kidney Transplant Recipients Treated at Transplant Centers			
Characteristics	**Adjusted Odds Ratio**		**P-value**
Any complication	0.579		0.040
Characteristics	**Co-efficient**		**P-value**
Length of stay	-0.010		<0.001

Table 1. Patient Demographics, Outcomes, and Adjusted Outcomes for Kidney Transplant Recipients Treated at Transplant Centers.

PO2475

Local Renal Graft Irradiation as Salvage Treatment for Rejection Secondary to Checkpoint Inhibitor: A Case Report

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Introduction: Graft rejection after treatment for malignancies with checkpoint inhibitors targeting the CTLA-4 and the PD-L1 pathways has been a growing interest in recent years since the rates of graft rejection are high as 33.3% with a median time to rejection of 8 days. To the best of our knowledge, there are no prior case reports of a renal transplant patient with stage IV gastric adenocarcinoma treated with pembrolizumab (a PD-1 inhibitor) who developed graft rejection and required local irradiation.

Case Description: This is a 65-year-old male with history of ESRD secondary to IgA nephropathy, chronic Hepatitis B and related donor kidney transplant who was diagnosed with gastric malignancy with peritoneal carcinomatosis and outlet obstructionafter 12 years of transplantation. Gastric adenocarcinoma was HER2 equivocal, FISH negative, MMR deficient, PDL1 positive. Initial therapy includede discontinuation of Tacrolimus, steroid monotherapy. Initial chemotherapy included 2 cycles of FLOT followed by ramucirumab. After finding disease progression at 6 months, he received a salvage chemotherapy with pembrolizumab. Two weeks after, presented to the ED with anuric AKI. A Mag-3 scan demonstrated good perfusion and a kidney biopsy showed cortex coagulative necrosis. High dose steroids and sirolimus were given with no response and required initiation of hemodialysis. In the following weeks, presented to the ED complaining of gross hematuria and clots. Cystoscopy with bladder biopsy was performed and showed no bladder origin and normal mucosa. The hematuria was found to be secondary to kidney graft rejection and he was started on high dose of steroids with mild improvement. Nephrectomy was not an option due to poor nutritional status and overall health condition. Palliative radiation therapy to the kidney was the only option for immunosuppression. He received local graft irradiation of 7.5 Gy in 5 fractions with resolution of hematuria.

Discussion: The case illustrates first, that the use of checkpoint inhibitors in patients with kidney transplant conveys a high risk of severe irreversible allograft rejection and can occur after only one dose. Second, the viability of palliative radiation as a non-surgical option for acute kidney graft rejection causing symptomatic hematuria resistant to conventional immunosuppressant therapy.

PO2476

A Rare Presentation of Disseminated Nocardia in a Kidney Transplant Recipient

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Introduction: Nocardiosis is a very rare infection caused by the *Nocardia asteroids* bacterium. It most commonly involves the lungs but can spread to other areas of the body and is more likely to infect immunosuppressed patients. We report a case of a kidney transplant patient who presented with a tender lump of his right shoulder.

Case Description: Patient is a 58 year s old African American male with a history ESRD secondary to hypertension and reduced kidney mass status post right radical nephrectomy for renal cell carcinoma in 2001. He underwent deceased donor kidney transplant in May 2017 after being on dialysis for 13 years. He received alemtuzumab and methylprednisolone prednisone for induction followed by maintenance immunosuppression with Tacrolimus, mycophenolate mofetil and prednisone. In January 2020, he presented to the orthopedic clinic with a 10-day history of pain and a soft tissue mass of the right scapula and was diagnosed with a parascapular muscle tear. One week later he presented to an outside hospital with fevers and CT of chest showing pulmonary nodule with satellite lesions in the RUL concerning for malignancy. He was transferred to our hospital where PET CT scan showed multiple intensely FDG avid masses in the lungs, brain, cecum and soft tissue inferior to the right scapula concerning for malignancy. Core tissue biopsy from the right scapular region was negative for bacterial or acid-fast bacilli stain but showed gram positive beaded rods identified as Nocardia. He was initially treated with intravenous sulfamethoxazole/trimethoprim and intravenous meropenem and then based on susceptibility transitioned to intravenous ceftriaxone and oral sulfamethoxazole/trimethoprim. A follow-up MRI two months from diagnosis showed marked improvement in all lesions and he was transitioned to oral doxycycline to complete at least 12 months of therapy.

Discussion: Nocardiosis can present in unusual fashion in transplant recipients and one should have a high suspicion in patients who present with fever and disseminated lesions on imaging with plan for biopsy and culture of tissue early. In most cases, Nocardia can be treated successfully with appropriate antibiotics.

PO2477

Hypercalcemia Associated with *Pneumocystis jirovecii* Pneumonia in Renal Transplant Patients

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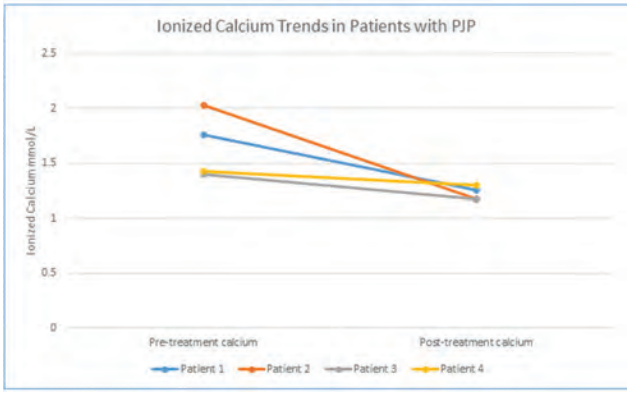
Introduction: *Pneumocystis jirovecii* pneumonia (PJP) is a common complication following solid organ transplantation with an estimated incidence of 5-15%. Although previously reported, hypercalcemia is not classically a sign of PJP. In the past 6 months at our institution, there have been six cases of PJP presenting with varying degrees of hypercalcemia.

Case Description: All patients in the table below presented with signs and symptoms concerning for pneumonia and were diagnosed with PJP by DFA and/or PCR from induced sputum or bronchoscopy. Patient demographics, labs, and calcium trends are outlined in the table. All patients were treated with Bactrim and prednisone for PJP (some later converted to alternative therapy); patients 1 and 2 were also given intravenous fluids and calcitonin specifically for treatment of their hypercalcemia. Patient 6 was initially thought to have aspiration pneumonia but was hypercalcemic on presentation. Because of our experience with the previous patients, when we noted elevated 1,25 vitamin D this prompted testing for PJP, which returned positive.

Discussion: PJP is a common infection following renal transplant and carries significant risk of morbidity and mortality, reported at 13-38%. The diagnosis of PJP can be challenging and confirmatory testing from induced sputum or bronchoscopy may take several days to result. Hypercalcemia has been reported in patients with PJP and is associated with elevated 1,25 OH vitamin levels, likely due to increased activity of 1-alpha hydroxylase in alveolar macrophages. Recognition of hypercalcemia in patients presenting with clinical features concerning for PJP can aid in early diagnosis and treatment.

Patient #	Age(yrs)/ Sex	Time from Transplant (yrs/mo)	Peak Ionized Calcium (ref. range 1.13 - 1.30 mmol/L)	1,25 Vitamin D (ref. range 19.9-79.3 pg/ml)	25 Vitamin D (ref. range 30-80 ng/ml)	PTH (ref. range 15-65 pg/ml)	PTHrP (ref. range 0-2.1 pmol/L)	Post-recovery Ionized Calcium
1	84/M	7/11	1.76	199	54	9	<2	1.25
2	47/M	18/11	2.03	240	34	4	2.9	1.17
3	57/F	0/4	1.40	—	—	—	—	1.17
4	62/F	18/10	1.36	--	--	--	--	--
5	71/M	12/0	1.42	45	23	22	3.6	1.30
6	72/M	0/8	1.49	85	27	4	<2	—



PO2478

Hypercalcemia: A Prodromal Feature of *Pneumocystis jirovecii* Pneumonia in Kidney Transplant Recipients

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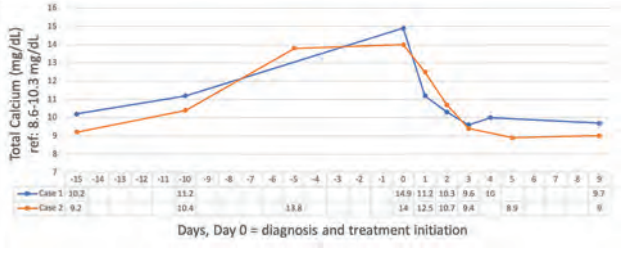
Introduction: Hypercalcemia in transplant recipients (KTRs) is frequently caused by persisting hyperparathyroidism. However, hypercalcemia can also be a prodromal feature of serious underlying infections and malignancy. We present 2 cases of parathyroid hormone (PTH) independent hypercalcemia that preceded Pneumocystis jirovecii pneumonia (PJP) diagnosis.

Case Description: Case1. A 21y.o. male with end-stage kidney disease (ESKD) from FSGS presented with 3 weeks of dyspnea and cough 8 months after transplant (Tx). Chest x-ray (CXR) showed interstitial opacities. Lab revealed acute kidney injury and severe hypercalcemia (Table 1). He was treated with IV fluid and calcitonin, and hypercalcemia improved (Figure 1). Workup showed significant elevation in 1,25 dihydroxyvitamin D (1,25(OH)2 VitD)and low PTH level, and his sputum was positive for PJP by DNA PCR. **Case2.** A 26-y.o. male with ESKD from nephronophthisis presented with 2 weeks of cough and dyspnea 10 yrs after Tx. He had severe hypercalcemia, and CXR showed nodular interstitial opacities. He was diagnosed with PJP by sputum DNA PCR. His hypercalcemia workup also revealed elevated 1,25(OH)2 VitD and low PTH.

Discussion: PJP occurs in 5–15% of KTRs without prophylaxis with significant morbidity and mortality. A timely diagnosis is challenging given its indolent presentation. Since hypercalcemia can occur in 20-30% of cases during early stages of PJP from increased production of 1,25(OH)2 VitD via 1-α-hydroxylase from alveolar macrophages, its presence should alert clinicians of its diagnosis. In 2019, 2 out of 5 PJP cases at our center had hypercalcemia at least 2 weeks prior to PJP diagnosis with high 1,25(OH)2 VitD and low PTH. In both cases, hypercalcemia resolved after treatment of PJP. These 2 cases illustrate hypercalcmia could be a prodromal feature in PJP. Early recognition with appropriate treatment would significantly reduce its morbidity and mortality.

Clinical characteristics

Case	Total Calcium (ref: 8.6-10.3 mg/dL)	Ionized calcium (ref: 1.12-1.30 mmol/L)	PTH (ref: 10-65 pg/mL)	1,25(OH)2 VitD (ref: 18-78 pg/mL)	Treatment
1	14.9	2.02	23	129	IV fluid, calcitonin, TMP-SMX
2	14	2.36	<6	141	IV fluid, calcitonin, pamidronate, clindmycin, primaquine



Calcium trend

PO2479

Effect of UNOS Kidney Allocation System on Transplantation Rates for Veterans Waitlisted at Veterans Affairs Transplant Centers

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Background: Impact of new Kidney Allocation System (KAS) on kidney transplantation (KT) rates for Veterans waitlisted at Veterans Affairs Transplant Centers (VATC) is unknown. This study compares effect of KAS on waitlisted patients at VATC and non-VATC.

Methods: UNOS data on adult patients waitlisted for KT during January 2009 to December 2016 were obtained. Logistic regression was used to assess association between center type (VATC vs. Non-VATC), time period (pre-KAS 2009-2014 vs. post-KAS 2015-2016) and outcomes (receiving KT or death on waitlist) within 2 years of waitlisting. Odds ratio (OR) was calculated adjusting for demographic factors, comorbidities, calculated Panel Reactive Antibodies (cPRA) and Estimated Post-Transplant Survival (EPTS) score.

Results: During study period, a total of 263,410 patients were listed at non-VATC (75% pre-KAS; 25% post-KAS) and 3,150 at VATC (68% pre-KAS; 32% post-KAS). VATC patients were significantly older (58.3 vs.51.7 years), diabetics (55.4% vs. 42.5%), had lower cPRA, higher EPTS (53 vs.39%) and longer duration of dialysis (762 vs. 727 days). Within 2 years of waitlisting, Veterans listed at VATC did not benefit from the new KAS like patients in non-VATC centers. Overall, independent of the era, Veterans tend to be transplanted lesser in this early waitlisting period. But death on waitlist was 29% lower in VATC patients. (Results are shown in the table).

Conclusions: Benefit of new KAS did not extend to Veterans listed at VATC who are older, less immunogenic and have higher EPTS score. Early benefit of KAS seen in non-VATCs could be due to "bolus effect" from transplantation of younger, highly sensitized patients. However, risk of death is significantly lower in VATC waitlisted patients.

Outcomes of patients within 2 years of waitlisting for kidney transplantation

	Kidney transplant rate (OR, 95% CI)	Death on waitlist (OR, 95% CI)
Post-KAS vs Pre-KAS (Non-VATC)	1.30 (1.27, 1.33)*	
Post-KAS vs Pre KAS (VATC)	0.94 (0.76, 1.14)	
VATC vs Non-VATC (Pre-KAS)	0.70 (0.63, 0.79)*	
VATC vs Non-VATC (Post-KAS)	0.49 (0.41, 0.58)*	
Post-KAS vs. Pre-KAS (Overall)		0.78 (0.75, 0.82)*
VATC vs. Non-VATC (Overall)		0.71 (0.60, 0.84)*

*p<0.01

PO2480

Lend Me Your Ear: An Unusual Presentation of a Transplant Complication

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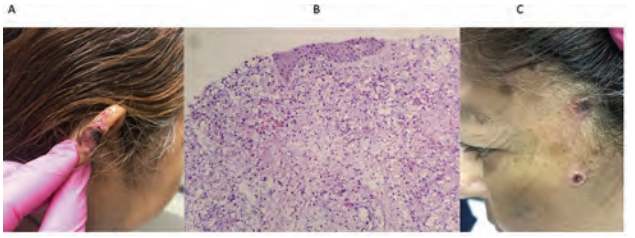
Introduction: Infections are a major complication in solid organ transplant (SOT) patients due to need for life-long immunosuppression. Incidence of fungal infections following solid organ transplant ranges from 5-20%. Cryptococcosis is an invasive fungal infection that can cause several types of infections including meningitis, pulmonary, cutaneous, and disseminated disease.

Case Description: A 66 yo F with past medical history of ESRD s/p deceased donor kidney transplant 15 months ago, DM, HTN presented to renal transplant clinic with right ear pain for the past 4 weeks after being evaluated in the emergency room. Her exam was notable for painful ear and cheek lesions (**Figures A and C**). Fungal serologies were obtained and patient was sent to dermatology clinic for evaluation. Punch biopsies were taken from several lesions and cultures obtained. Serum cryptococcal antigen was positive with titer of 1:4096, fungal culture from lesion grew *Cryptococcus neoformans*. Skin biopsy showed cyryptococcus (**Figure B**). Patient was admitted to the hospital and further testing revealed positive CSF cryptococcal antigen, CT chest with nodular opacities, leading to a diagnosis of disseminated cryptococcus. She was treated with amphotericin B and flucytosine and eventually transitioned to oral fluconazole.

Discussion: Cryptococcal infection is the third most common invasive fungal infection in SOT patients and typically presents later in kidney transplant patients, 16-21 months, compared to other transplanted organs. Risk factors include type of immunosuppressive agent and comorbid conditions such as diabetes. The majority of transplant patients with cryptococcus present with CNS manifestations or disseminated disease, cutaneous involvement is less common. Our patient had risk factors including diabetes, older age, and use of induction immunosuppression. Initial presentation with skin lesions is atypical for cryptococcal infection. It is important to have a high suspicion for fungal infections in immunosuppressed patients even those with atypical presentations.



PO2481

Pegloticase for Uncontrolled Gout in Kidney Transplant Recipients: Early Data Report of a Multicenter, Open-Label Efficacy and Safety Study

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Background: Gout is common and more severe in US kidney transplant (KT) recipients, with prevalence >10x higher than in non-transplant patients. The management of gout can be challenging in KT patients due to decreased urate lowering therapy (ULT) clearance and drug-drug interactions. Recent reports suggest that pegloticase, a pegylated uricase approved for treating uncontrolled gout, has improved efficacy and safety when co-administered with immunosuppressive medications (IMM). We conducted the PROTECT trial (NCT04087720) to examine pegloticase use in KT recipients.

Methods: Patients with uncontrolled gout (sUA ≥7 mg/dL, intolerance of or contraindication to ULT, and ≥1 of the following: tophi, chronic gouty arthritis, ≥2 flares in past yr) and functioning KT graft (eGFR ≥15 mL/min/1.73m^2) are included (KT>1 yr earlier). Pegloticase (8 mg q2w for 24 wks) safety and efficacy are examined. Primary endpoint is % pegloticase responders during Month 6 (sUA <6 mg/dL for ≥80% of time).

Results: 7 patients were enrolled by Apr 30, 2020 (age: 52.0±11.2 yrs, KT 15.3±5.0 yrs ago, sUA: 10.0±1.4 mg/dL, gout duration: 5.9±4.3 yrs; all on stable doses of ≥2 IMM) and received 2-12 infusions. 1 patient discontinued. In the 1 completed and 5 ongoing patients, all central lab sUA levels were <1 mg/dL, indicating treatment response; no infusion reactions occurred. No notable eGFR changes were observed; 2 patients with baseline albuminuria of >300 mg/g showed >35% reduction in UACR by wk 14. 2 SAEs (stomach ulcer, cellulitis) unrelated to pegloticase were reported.

Conclusions: Early data of this ongoing clinical trial are promising and suggest pegloticase is safe and effective for treating uncontrolled gout in KT recipients. Additional efficacy and safety data are planned.

Funding: Commercial Support - Horizon Therapeutics

Serum uric acid (sUA) and kidney function parameters

Patient	sUA (mg/dL)			eGFR (mL/min/1.73m^2)			UACR	
	Last Visit Prior to Data Cut (week)	Baseline	Last Value	Last Visit with eGFR and UACR values (week)	Baseline	Last Value	Baseline	Last Value
1	24	9.1	<1	24	61.2	51.0	376	56
2†*	20	7.9	<1	14	41.6	45.5	56	40
3*	23	9.3	<1	14	41.8	49.7	2196	1406
4*	2	10.9	<1	2	41.1	34.9	305	572
5*	6	9.7	<1	6	40.1	40.1	22	20
6*	6	10.9	<1	6	40.8	32.7	317	407
7*	4	12.2	<1	2	20.4	23.2	407	342

*ongoing, †experienced an SAE

PO2482

Minoxidil-Induced Chylous Ascites in a Renal Transplant Recipient

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Introduction: Chylous ascites is generally associated with malignancies and surgical trauma and rarely secondary to administration of drugs(Tsai et al J.Clin.Med.2019,8,466). Calcium channel blockers related chylous ascites is more common is Asian ethnicity we could not find any published report of minoxidil causing chylous ascites.

Case Description: This patient is a 64 years old diabetic and hypertensive male who underwent kidney transplantation on 09.06.2009. He was HBsAg positive for last 9 years. He was taking multiple medications namely carvedilol, amplodipine, lasix minoxidil, prednisolone, MMF, Tacrolimus, insulin, metformin and linagliptin and Entecavir. He came in May 2019 with ascites. Investigation revealed normal kidney function and ultrasound guided ascitic fluid tapping was done and it was found to be chylous. He underwent abdominal paracentesis and about 12 lt of ascitic fluid was drained but he came back within 10 days with ascites again. Portal hypertension was ruled out by transjugular hepatic venous pressure gradient measurement and liver biopsy did not show any evidence of chronic liver disease. An upper GI endoscopy and duodenoscopy including duodenal biopsy were normal. Whole body PET scan did not show any active infection or disease. Meanwhile literature review suggested association of amplodipine with chylous ascites and it was stopped but he continued to develop recurrent ascites. An abdominal CT lymphangiogram was done which did not show any lymphatic leak.

He also underwent diagnostic laparoscopy which also ruled out TB or any malignancy. This recurrent chylous ascitic fluid drainage continued for 6 months then we decided to discontinue minoxidil as it is known to cause fluid accumulation including pleural and percardial. He showed immediate improvement after stopping minoxidil and never developed ascites again. He was fine even 6 months later on follow up.

Discussion: Minoxidil causes vasodilatation like calcium channel blockers though by a different mechanism so the mechanisim of chylous ascites formation could be the same that it is also a lipophilic drug allowing it to pass rapidly into the lymphatic system and causes relaxation of smooth muscles of lymphatic vessels, interferes with lymphatic drainage, increases the hydrostatic pressure in lymph vessels and causing it to leak in the peritoneum. Minoxidil must be considered as a probable cause of atraumatic drug induced chylous ascites.

PO2483

COVID-19 in Kidney Transplant Recipients: Experience from a Large Health System in Louisiana

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Background: Infections are an important cause of morbidity and mortality among kidney transplant recipients. The novel Coronavirus Disease 2019 (COVID-19) has affected all kinds of populations world-wide. However, the role of immunosuppression in the outcomes of these patients is not well understood.

Methods: We conducted a retrospective study in kidney transplant recipients from a single health system that were diagnosed with COVID-19 based on a positive real-time reverse transcription polymerase chain reaction test for SARS-CoV-2 RNA between 03/01/2020 and 04/30/2020. We compared them with affected patients without a kidney transplant and without any kind of immunosuppressive medication (control). We examined the rates of hospitalization, intensive-care unit (ICU) admission, acute kidney injury (AKI) and mortality as outcome measures.

Results: A total of 8473 patients were diagnosed with COVID-19 within our Health System within the study period. Thirty-three (0.4%) were kidney transplant recipients. Sixteen of the 33 (48%) were admitted to the hospital (median age of 56, 68% males, 93% African American) vs 2201 admissions (25%) for the control group (median age 66, 48% males, 65% African-American), i.e., a significantly greater risk for hospitalization for transplant recipients ($p = 0.002$). Percentage of patients with hypertension in the transplant group was numerically higher (93% vs 80%, $p = 0.06$), as well as the number of ICU admissions (43% vs 28%, $p = 0.055$). AKI was more common in transplant patients (81% vs 33.8% $p<0.0001$). No difference in mortality was observed (31 vs 24%, $p = 0.34$). Among transplant patients, those hospitalized were more likely to be on prednisone (75% vs 35%, $p = 0.025$) and had a post-transplant graft life of 7.9 years compared to 5.5 years for those not hospitalized, p 0.08).

Conclusions: Kidney transplant recipients affected with COVID-19 exhibited a greater incidence of hospitalization, AKI and a trend for more ICU admissions. Use of immunosuppression with prednisone was associated with greater risk for hospitalization

PO2484

Recurrent Anemia due to Chronic Parvovirus B19 Infection in a Kidney Transplant Recipient: Can Everolimus Make a Difference?

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Introduction: Parvovirus B19 (PB19) is a common infection among transplant recipients. Usually, it is asymptomatic, but some patients may suffer severe infections, often presenting with recurrent flares despite standard treatment. Relapses are usually managed by reducing immunosuppressive treatment (IST), potentially increasing graft rejection risk.

Case Description: 45-year-old woman with ESKD due to ADPKD, received a living-donor kidney transplant on May 2013. Maintenance IST consisted of mycophenolate mofetil (MMF), prednisone and tacrolimus. A month after transplantation, she presented with fever and anemia. A bone marrow aspirate revealed pure red blood cell aplasia (PRCA) which was attributed to PB19 after positive serum qualitative PCR. She was treated intravenous immunoglobulin (IVIG) at 2g/kg and MMF was stopped with good response. However 3 new relapses occurred (anemia and malaise with viral loads for PB19 over a million copies). A monthly prophylactic dose of IVIG was initiated to control the infection. In spite of this, episodes of anemia and a high PB19 viral load (over half a million copies) continued to happen at least 3 times per year. Finally, given the potential antiviral properties of mTOR inhibitors (mTORi), conversion from tacrolimus to everolimus was decided, Since November 2017 her maintenance IST consists of everolimus and prednisone alone, her last prophylactic IVIG was on December 2017, and since then she has been non-anemic with serum viral loads below 1000 copies, and without IVIG treatment.

Discussion: Incidence of symptomatic PB19 infection is highest during the 1st year after transplantation, like in the case presented. Standard therapy consists of IVIG. However, early KTR, often relapse after the IVIG effect wears off. In such cases, reduction of IST is needed to control the infection and avoid recurrences. There are multiple studies indicating that mTORi have antiviral properites although their effect on PB19 has not been specifically studied. In conclusion, conversion from tacrolimus to an mTORi, could be an interesting approach in difficult-to-manage cases similar to ours, moderating the reduction of IST and minimizing the risk of rejection. Further studies are needed to establish this approach as "treatment of choice" in relapsing PB19 infection.

PO2485

Adjusted Donor Age Score: Validity and Influence on Deceased Donor Offer Decisions

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Background: Although a number of donor factors are known to affect outcome following deceased donor kidney transplantation, many units have no clear criteria for acceptance. Existing donor scoring systems, such as KDRI, perform poorly in the modern comorbid donor pool, and are difficult for patients to understand. Adjusted Donor Age (ADA) is a patient-friendly scoring system in which donor age is modified according to the presence or absence of a number of risk factors, and categorised by ADA decade (using cut-offs at 50, 60, 70 and 80 years) into quintiles (A – E) representing increasing donor risk (A – C favourable, D marginal, and E unfavourable).

Methods: All deceased-donor kidney offers at a single centre were analysed over a 3 month period (beginning after the September change in UK organ allocation) during which ADA was optionally available to clinicians at the time of considering the offer. The effect of ADA on acceptance decisions and outcome in those transplanted were analysed.

Results: Out of 230 offers median(IQR) ADA was 67(56–76). Kidneys were transplanted in 24%, declined due to concern over donor risk in 44%, with recipient and other factors responsible for non-transplantation in 32%. In those identified as favourable by ADA (quintiles A – C, without exclusion factors), organs were rejected due to donor risk in 28/104 offers (27%), compared to 50/186 (27%) in the 2018 cohort. In those identified as unfavourable by ADA (quintile E) organs were transplanted in 0/38 offers (0%), compared to 10/66 (15%) in the 2018 cohort. At 1 month post-transplantation (N=55, from quintiles A – D only, since no organs from quintile E were accepted) one recipient remained dialysis dependent (from quintile D). In those with functioning transplants (N=54) recipient GFR was strongly correlated with ADA ($R=0.52$, $p<0.001$) and was seen to reduce across quintiles A – D (74, 55, 43 and 38ml/min/1.72m^2).

Conclusions: ADA is a patient-friendly score, calculated from donor age but adjusted for 12 potential risk factors, which can be used to guide acceptance decisions. At this early stage of familiarity, clinicians appear to be more persuaded by an unfavourable ADA quintile, than a favourable one. In this validation cohort, ADA strongly predicts early post-transplant outcome.

PO2486

Kidney Offer Calculator: The Risk of Accepting an Offer vs. Waiting for a Better Offer

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Background: Currently, no tools exist to facilitate patients with decisions to accep or refuse an offer. Using the scientific registry of transplant recipients database, we formulated a risk calculator for allograft failure and patient mortality risk (if offer accepted) vs. mortality risk if the patient refused.

Methods: Using a multi-state model approach, we created multiple competing risk models for: 1) first kidney offer or dying on wait-list without any offer; 2) if offer is refused, the probability of a) receiving a transplant vs. b) death and 3) if an offer is accepted, the probability of a) allograft failure vs. b) death. All models were adjusted for candidate estimated post-transplant survival (EPTS) score while allograft failure and patient survival was adjusted for recipient EPTS, donor KDPI and cold ischemic time.

Results: Fig.1 shows our multi-state model for which the competing risk models were build. Table 1 depicts the hazard ratio for each stage described above and the kidney offer risk calculator created using the estimates generated from the models. We included a case scenario to demonstrate how the calculator works (Table 1).

Conclusions: In summary, creating a risk calculator is feasible. Next, we will refine our calculator to account for repeated offers and include other variables that may affect allograft offer and survival e.g. panel reactive antibody.

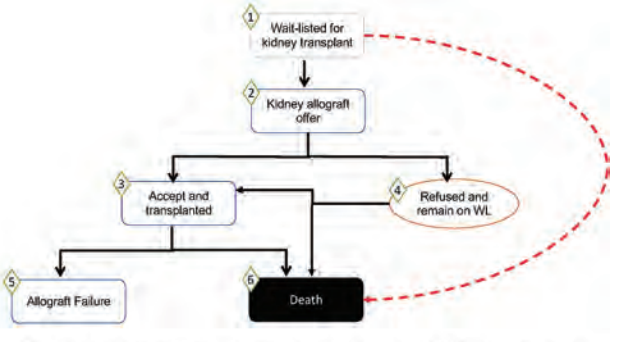


Figure 1. Kidney offer risk calculator multi-state model and associated hazard ratios [95% confidence intervals]

Table 1. Competing risk model summary for each stage of the multi-state model

Variables	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Table 1a. Competing risk model of 1st kidney offer						
		Offer			Death	
EPTS	1.037	1.036; 1.038	< 0.001	1.093	(1.087; 1.100)	< 0.001
Table 1b. Competing risk model if kidney offer is refused						
		Subsequent transplant			Death	
EPTS	0.927	0.926; 0.929	< 0.001	1.190	1.187; 1.193	< 0.001
Table 1c. Competing risk model if kidney offer is accepted						
		Allograft failure			Death	
EPTS	0.885	0.880; 0.889	< 0.001	1.269	1.263; 1.276	< 0.001
KDPI	1.107	1.102; 1.113	< 0.001	0.990	0.986; 0.994	< 0.001
CIT*	1.090	1.072; 1.109	< 0.001	1.055	1.038; 1.073	< 0.001

Data derived from SRTR candidate file from 1993-2017; transplant file from 2000-2017 and match-run file from 2000-2017
* at increments of 12 hours
Abbreviations:
CI= confidence interval; EPTS= estimated post-transplant survival; KDPI= kidney donor profile index; CIT= cold ischemic time
Table 1a: A total of 482,956 candidates were wait-listed, of which 396,280 received a kidney offer and 25,365 died
Table 1b: A total of 384,042 candidates refused their 1st kidney offer, of which 138,241 subsequently received a kidney transplant and 76,552 died
Table 1c: A total of 190,518 candidates received a transplant, of which 99,43,167 subsequently experienced allograft function failure and 47,417 died before allograft failure

Kidney risk offer calculator

Case scenario: 42 year old candidate with no diabetes or previous transplant, on dialysis for 3 years (EPTS 17%) receives a KDPI 78% kidney offer with cold ischemic time of 10 hours

Based on this scenario, the probability is shown below:

Probability of receiving a kidney offer vs. death while waiting

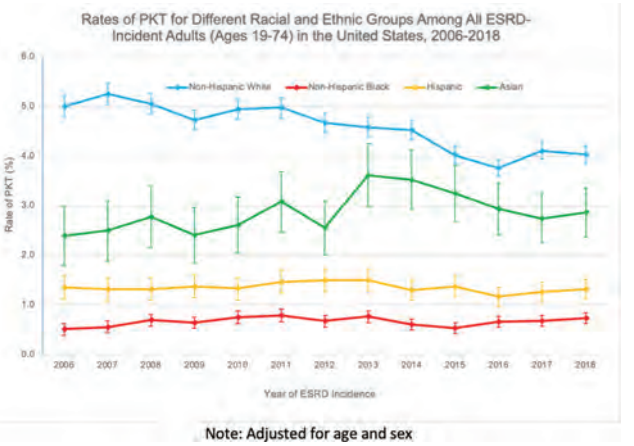
1st Kidney offer:	EPTS decile	Probability	Death:	EPTS decile	Probability
coef	0.0365		coef	0.0893	
value	2		value	2	
coef*value	0.073	0.518	coef*value	0.1786	0.545

If the offer is refused, the probability of subsequent transplant vs. death on dialysis

Transplant:	EPTS decile	Probability	Death:	EPTS decile	Probability
coef	-0.0756		coef	0.1739	
value	2		value	2	
coef*value	-0.1512	0.462	coef*value	0.3478	0.588

If the offer is accepted, the probability of allograft failure vs. death after transplant

Allograft Failure:	EPTS decile	KDPI decile	Cold Ischemic Time (12 hour increments)	Probability	Death:	EPTS decile	KDPI decile	Total Cold Ischemic Time	Probability
coef	-0.1225	0.1020	0.0862		coef	0.2384	-0.0101	0.0539	
value	2	8	1		value	2	8	1	
coef*value	-0.245	0.816	0.0862	0.659	coef*value	0.4768	-0.0808	0.0539	0.611



Note: Adjusted for age and sex

Rates and 95% CI of PKT (%) Among Different Racial and Ethnic Groups Derived from Multivariable Linear Regression Models, 2006-2018

	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian
Model 0	4.56% [4.50-4.61]	0.65% [0.61-0.68]	1.35% [1.30-1.41]	2.90% [2.75-3.06]
Model 1	4.08% [4.03-4.13]	1.27% [1.23-1.30]	1.66% [1.60-1.72]	2.57% [2.42-2.73]
Model 2	4.00% [3.95-4.06]	1.29% [1.25-1.33]	1.81% [1.74-1.88]	2.61% [2.45-2.78]
Model 3	3.84% [3.79-3.90]	1.55% [1.50-1.59]	2.43% [2.35-2.50]	2.43% [2.25-2.60]
Model 4	3.75% [3.70-3.80]	1.61% [1.57-1.66]	2.59% [2.51-2.67]	2.32% [2.14-2.49]

Note: Model 0 adjusts for age and sex. Model 1 adjusts for clinical factors: age, sex, BMI, primary ESKD cause, & comorbidities. Model 2 further adjusts geography: ESKD network & states. Model 3 further adjusts SES factors: employment status and insurance type. Model 4 further adjusts access to pre-ESKD nephrology care. All models adjust for ESKD incident year. All results are statistically significant ($p < 0.001$).

PO2487

Racial-Ethnic Disparities in Preemptive Kidney Transplantation Among Incident ESKD Adult Patients, 2006 to 2018

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Background: Preemptive kidney transplantation (PKT) is the preferred treatment for ESKD. Among kidney transplant recipients, black and Hispanics are less likely to receive PKT than whites, but less is known about disparities in PKT among the entire incident ESKD population. This is a critical gap in knowledge given the Advancing American Kidney Health goal of 80% of all new ESKD patients receiving transplant or home dialysis by 2025. This study assessed racial/ethnic disparities in initial treatment with PKT vs. dialysis among all incident kidney failure patients aged 19-74 from 2006 to 2018.

Methods: Treatment modality for incident ESKD patients was identified using the CMS Medical Evidence Report Form. Linear regression models estimated PKT rates for white, blacks, Hispanics and Asians, adjusting for clinical, geographic, socioeconomic, and access factors.

Results: Among 1,133,326 incident ESKD adult patients, the age/sex adjusted PKT rate declined from 3.0% in 2006 to 2.5% in 2018, with varied trends in each racial/ethnic group (white: 5.0% to 4.0%, black: 0.5% to 0.7%, Hispanic: 1.3% to 1.3%, and Asian: 2.4 to 2.9%) (Figure). In age-sex adjusted analyses, whites had 3.9, 3.2, and 1.7 percentage point higher rates of PKT compared to blacks, Hispanics, and Asians, respectively. These differences persisted after adjusting for clinical, geographic, SES, and pre-ESKD nephrology care (Table). Among patients aged 19-44, whites had 8.0, 6.3, and 3.3 higher rates of PKT, compared to blacks, Hispanics, and Asians.

Conclusions: Among incident ESKD adult patients, racial/ethnic disparities in receipt of PKT are substantial, persistent, and not explained by differences in observed clinical factors and socioeconomic status. Efforts to increase preemptive transplantation must address disparities in access to this preferred treatment for ESKD.

Funding: NIDDK Support

PO2488

Lower Prevalence of Kidney Transplant Waitlisting in Micropolitan Areas, Small Towns, and Rural Areas

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Background: The Percentage of Prevalent Patients Waitlisted (PPPW) measures the percentage of patients at a dialysis facility who were on the kidney or kidney-pancreas transplant waitlist. This measure joined the End Stage Renal Disease Quality Incentive Program in performance year 2020, with a weight of 4%. PPPW is adjusted for age, but not for other factors. Physical distance between residence and transplant center may influence PPPW. As an indirect test of this hypothesis, we assessed whether PPPW was associated with rural-urban commuting area (RUCA) levels.

Methods: We analyzed data in Dialysis Facility Compare (DFC), as of October 30, 2019. DFC included PPPW values that quantified waitlisting prevalence during 2018. According to ZIP code, we classified the location of each dialysis facility as metropolitan (RUCA values, 1-3), micropolitan (4-6), small town (7-9), or rural (10). We estimated weighted mean PPPW values in each location class, with the weight of each facility equal to the number of patients contributing to PPPW. We fit a linear regression model to test differences in PPPW values between the location classes.

Results: PPPW values were reported in 7086 (94%) of 7566 dialysis facilities, and RUCA values were identified in 6999 (99%) of 7086 facilities. The weighted mean PPPW value among all facilities was 17.5%. There were 5363 (77%) facilities in metropolitan areas, 954 (14%) in micropolitan areas, 550 (8%) in small towns, and 132 (2%) in rural areas. By location class, weighted mean PPPW values were 18.5% in metropolitan areas, 12.8% in micropolitan areas, 12.1% in small towns, and 10.8% in rural areas. Relative to the mean PPPW value in metropolitan areas, mean PPPW values were 5.8, 6.5, and 7.7 percentage points lower in micropolitan areas, small towns, and rural areas, respectively ($P < 0.01$ for each).

Conclusions: The PPPW measure takes significantly lower values in dialysis facilities located in micropolitan areas, small towns, and rural areas, relative to metropolitan areas. The physical distance between residence and transplant center may preclude many patients in non-metropolitan areas from completing the process of kidney transplant evaluation. New processes are needed to improve access to transplantation in outlying areas.

Funding: Commercial Support - Fresenius Medical Care

PO2489

Demonstrating Charitable Premium Assistance as a Mechanism for Overcoming the Cost Barrier to Transplant for Low-Income Patients in the United States

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Background: The optimal treatment for patients with end-stage renal disease (ESRD) is kidney transplantation. Adequate insurance coverage is one requirement for transplant eligibility. Many low-income ESRD patients cannot afford insurance coverage. Patients on dialysis are eligible for Medicare. Because Medicare covers only 80% of healthcare costs, most patients require supplemental insurance, often Medigap. Although Medigap

plans reduce out-of-pocket spending on healthcare services by almost 50%, spending on health insurance premiums more than doubles compared to Medicare premiums alone. For low-income patients who cannot afford such premiums, inadequate insurance coverage can become an insurmountable barrier to qualifying for a kidney transplant (KT). We evaluated a premium assistance program designed to help low-income ESRD patients maintain insurance coverage and the impact on KT access.

Methods: We performed a descriptive analysis of self-reported patient data collected from paper and digital applications submitted to American Kidney Fund's (AKF) Health Insurance Premium Program (HIPP) between November 15, 2018 and December 31, 2019.

Results: HIPP provided financial assistance grants to 1,357 (5.8% of all) kidney patients transplanted in the United States during the study period so they could maintain their health coverage in 2019. Of the 1,357 grants, 36% of grants issued helped patients pay Medigap premiums. Medigap recipients were more likely to be ≥ 65 (20% vs. 12%), more likely to be African American (38% vs. 34%), and had lower median income ($23,622 vs. $27,168 respectively) compared to the overall transplant population.

Conclusions: KT candidates face financial barriers to transplantation. Premium assistance significantly reduced the barrier to transplant among KT candidates who rely on Medigap by ensuring adequate coverage.

PO2490

"Some Person Behind a Desk Is Going to Be Looking at My File": Thematic Analysis of the Health Records of a National Sample of Patients with Advanced Kidney Disease Evaluated for Kidney Transplant

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Background: To be considered for kidney transplant, patients with advanced kidney disease must participate in a formal evaluation and selection process. Little is known about how this process unfolds in real-world clinical settings.

Methods: We conducted a thematic analysis of clinician documentation related to the kidney transplant evaluation in the VA-wide electronic medical records of patients who were referred to a transplant center among a random sample of 4,000 adults with advanced kidney disease between 2004 and 2014 who were followed through 2019.

Results: We identified 211 patients (5.2%) who were referred to a VA transplant center during follow-up. Four dominant themes emerged from qualitative analysis of clinician documentation in the electronic medical records of these patients: 1) far-reaching and inflexible medical evaluation: patients were expected to complete a demanding evaluation that could take a substantial physical and emotional toll on them and their family members, made little accommodation for their individual needs, and impacted many other aspects of their care; 2) psychosocial valuation: the psychosocial transplant assessment could be subjective and intrusive and placed substantial demands on patients' family members; 3) surveillance over compliance: clinicians monitored patients' adherence to a wide range of medical recommendations; 4) disempowerment and lack of transparency: patients had a strong desire to receive a transplant, but neither they nor their local clinicians had a clear understanding of what to expect from the evaluation process or the rationale for selection decisions, which left patients and their clinicians with little choice but to adhere to the transplant center's recommendations.

Conclusions: To be considered for kidney transplant, patients had little choice but to engage in a rigid, demanding, and opaque evaluation process over which neither they nor their local clinicians had much control. These findings call for a more evidence-based, transparent, and individualized approach to the kidney transplant evaluation process.

Funding: Veterans Affairs Support

PO2491

Implicit Bias in Recipient Selection

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Background: The decision to place or exclude a candidate from the waitlist is not exclusively based on medical criteria. Scant literature exists regarding the intergroup dynamics within selection committees that influence decision making. This study attempts to clarify how the composition of selection committee meetings may affect listing outcome of kidney transplant candidates.

Methods: We performed a single-center retrospective study of kidney transplant selection committee attendance sheets and minutes from January 2012 to December 2015. We sought to determine if candidates who were evaluated by the same providers in attendance at selection committee are more likely to be listed for kidney transplant.

Results: 3205 (48.4%) of 6630 donor and recipient candidates presented during 91 selection meetings from 2012 to 2015 were listed. 8 nephrologists, 9 surgeons and 3 social workers comprised the clinicians that both evaluated potential candidates and attended recipient selection meetings. Table 1 describes the frequency with which clinicians who were in attendance at selection meetings had previously evaluated the candidates being discussed. Using binary logistic regression, the presence of the nephrologist or the surgeon who had evaluated the patient was significantly associated with a greater likelihood of the candidate being listed (OR 4.443 and 3.952 respectively, p=0.000, see Table 2). White race was also associated with an increased propensity to list, OR 1.202, p =0.006. Interestingly, the presence of both the nephrologist and surgeon who evaluated the patient, or the presence of both physicians and the social worker, were associated with reduced likelihood of listing (OR 0.267 for both, p=0.000 ; OR 0.715, p=0.001 for all three, see Table 2).

Conclusions: The composition of attendees at recipient selection meetings may influence listing outcomes of potential kidney transplant candidates.

Table 1. Frequency the Clinician in Attendance at Selection had Evaluated the Patient

Nephrologist	3038 (45.8%)
Surgeon	2912 (43.9%)
Social Worker	2903 (43.8%)
Nephrologist and Surgeon	2520 (38.0%)
Social Worker, Nephrologist and Surgeon	2004 (30.2%)

Table 2. Likelihood of Candidate Being Listed, if the Clinician who Evaluated Patient Present

	OR	95% CI	p value
Age	0.993	0.989, 0.998	0.006
Male gender	1.123	0.981, 1.286	0.092
White race	1.202	1.055, 1.370	0.006
Nephrologist present	4.443	3.556, 5.551	0.000
Surgeon present	3.952	3.148, 4.963	0.000
Social worker present	1.186	1.007, 1.398	0.041
Both physicians present	0.267	0.186, 0.384	0.000
Both physicians and social worker present	0.715	0.584, 0.876	0.001

PO2492

Predictors of Kidney Transplant Evaluation Non-Attendance

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Background: We examined which medical and socio-cultural factors predict kidney transplant evaluation (KTE) non-attendance, because missing a KTE appointment precludes access to transplantation, and having empty clinic slots impacts access to care for others.

Methods: We collected patient characteristics in an interview prior to KTE, covering demographics (e.g., income, education), medical factors (e.g., on dialysis, co-morbidities), cultural factors (e.g., medical mistrust), psychosocial characteristics (e.g., social support, depression), and knowledge factors (e.g. knowledge about transplant). We used latent class analysis (LCA) to determine if we could identify meaningful classes (groups of patients with patterns across variables) that were associated with KTE non-attendance.

Results: Our sample (*N*=1119) was 37% female, 76% non-Hispanic White, median age 59.4 years (IQR= 49.2-67.5), 25% had income below federal poverty line, 47% were < high school graduate, 48% were married, 44% had public insurance only, and 142 (13%) did not attend KTE appointment. LCA analyses indicated that a two-class solution consisting of a (1) high burden and (2) low burden group was optimal. Relative to the low burden group, the high burden group was less likely to be married, more likely to be on dialysis, less likely to have potential living donor, had higher kidney disease burden, more experiences of healthcare discrimination, higher medical mistrust, less social support, more depression, less knowledge about transplant, and more worry about kidney transplant harm. Belonging to the high burden group was associated with approximately twice greater odds of KTE non-attendance (*OR*=1.92, *p*<0.001, 95% CI:1.57, 2.34).

Conclusions: Medical and socio-cultural factors predict KTE non-attendance. Transplant teams should consider targeting patients with characteristics indicating high burden for additional support (e.g., exploring motivation and barriers with patients, assisting with resources to attend appointment, and providing additional reminders or notifications). Given the association of clinic non-attendance with being on dialysis, a treatment with significant patient burden, future research should also focus on the benefits of referring patients for transplant evaluation prior to initiating dialysis.

Funding: NIDDK Support, Clinical Revenue Support

PO2493

Racial Disparities in Receipt of Medications for Secondary Prevention of Cardiovascular Disease in Kidney Transplant Recipients in the FAVORIT Trial

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Background: Cardiovascular disease (CVD) is the most common cause of death with a functioning graft in kidney transplant recipients. Black patients have been shown to have higher prevalence of cardiovascular (CV) risk factors and less intensive risk factor modification. We evaluated racial disparities in receipt of HMG-Co-A reductase inhibitors (statins) and aspirin for secondary prevention of CVD in kidney transplant patients in the Folic Acid for Vascular Outcome Reduction in Transplantation Trial (FAVORIT) trial.

Methods: FAVORIT was a multicenter international trial of vitamin therapy to lower homocysteine levels and improve CV outcomes in kidney transplant patients. We identified FAVORIT trial participants from US and Canada who had a self-reported

history of established CVD at baseline and/or developed a CVD event during the study. We used parametric interval-censored survival models to evaluate the effect of race on self-reported receipt of statins and aspirin for secondary CV prevention, adjusting for age, gender, ethnicity, and country of enrollment. In addition, we controlled for baseline cyclosporin use in the model assessing statin use and graft vintage in the model assessing aspirin use.

Results: Of the 4110 kidney transplant patients enrolled in FAVORIT, 978 met the inclusion criteria (78% White, 17% Black, 6% Other race). Mean age was 55.7±8.9 years, 70% were male, and mean graft vintage was 5.4±4.7 years. Black race was independently associated with lower hazard of receiving statin for secondary CVD prevention compared with White race (aHR=0.77, 95% CI: 0.60-0.97). There was no significant difference in aspirin use by Black race compared with White race (aHR=0.86, 95% CI: 0.67-1.09).

Conclusions: Findings from a large multicenter trial showed that Black race was associated with lower hazard of receiving statins for secondary CVD prevention. Underutilization of statins represents a potential target to improve CVD preventive care in Black kidney transplant recipients.

Funding: NIDDK Support

PO2494

Patient Barriers to Kidney Transplantation on the Mexican American Border

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Background: Hispanics are the largest minority group in the United states and are more likely to develop end-stage renal disease (ESRD) compared with non-Hispanic whites. However, Hispanics with ESRD are less likely to receive a deceased donor kidney transplant. We reviewed data from clinics on the Mexican American border to evaluate barriers to transplantation.

Methods: We gathered data from three dialysis clinics in Laredo, Texas, a city on the Mexican American border. It has a population of approximately 250,000 inhabitants of which 95.6% are Hispanic. The number of patients that were waitlisted or scheduled for living donor transplantation was evaluated. We also determined the number of patients that were referred but not listed and those that were not referred at all and investigated reasons for non-referral.

Results: A total of 285 patients were included in the analysis. 52 patients (18.2%) were waitlisted or scheduled for living donor transplantation. An additional 91 patients (31.9%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 140 (49.1%) were not referred. Of those not referred, the most common reasons included: advanced age (25%), weight (4.2%), malignancy (2.85%), cardiovascular (4.2%), peripheral vascular disease (3.57%), functional status (5.71%), noncompliance (5.71%), transportation (10.71%), and immigration status (7.14%).

Conclusions: Nearly half of ESRD patients were not referred for transplant evaluation and less than half of those referred were waitlisted or scheduled for living donor transplantation. This is lower than previous studies showing a greater percentage of referred patients as waitlisted (up to 66% in some studies). Major barriers to referral included age, immigration status, and transportation limitations. The latter two barriers are likely more of a factor in a Mexican American border town than in other areas of the United States. Identifying these barriers highlight areas for improvement in access to renal transplantation for Hispanics.

PO2495

The Strength of Weak Ties and Living Donor Offers: A Multi-Site Social Network Analysis of Hemodialysis Patients

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Background: Increasing the rate of living donor kidney transplantation is crucial. Little is known about hemodialysis patients' social networks and the members who offer to donate yet are never evaluated.

Methods: We administered a REDCap social network survey in an urban (Philadelphia) and suburban (North Brunswick) hemodialysis clinic. We asked participants to identify their social network members, who offered to donate, whose offers were accepted, and who got tested. We analyzed the associations between living donor offers and the size and strength of the connections in the networks. Strongly connected members are those connected to greater than 2/3 of the other network members.

Results: A total of 105 patients participated. Their mean age was 60 +/- 13 years. Half (54%) identified as male and 75% identified as black. Half were on the waiting list or undergoing testing (56%). The mean size of the networks was 5 members (SD2, range 1-10). Half (53%) of the participants received a living donor offer; 27% recieved one offer and 26% had 2 or more offers. Those with larger networks received more donation offers ($r = 0.39$; $p < 0.01$). Of the total 527 network members identified, 113 offered to donate, 43 of these offers were accepted with 12 being evaluated for donation. Most (83%) network members were strongly interconnected within the participants network, however, a greater of proportion of weakly interconnected network members offered a kidney donation compared to strongly connected members (31% v. 19%, $p = 0.02$). Participants accepted a greater proportion of offers from weakly connected members than strongly connected members (56% vs 33%, $p = 0.03$). Although a greater proportion of strongly connected members were evaluated compared to weaker connected members this was not significantly different (36% v. 17%, $p = 0.16$).

Conclusions: Weakly connected social network members tend to offer to be living kidney donors and a greater percentage of these offers are accepted. Unfortunately, most (89%) social network members who offer to donate never make it to the transplant center. Future interventions should focus on patients accepting living donor offers as well as identify methods to increase testing of interested donors especially those weakly connected in the network.

Funding: NIDDK Support

PO2496

Association of SNAP Benefit Use by Inner-City Kidney Transplant Recipients with Poorer Graft Function, Lower Fruit and Vegetable Intake, and Increased Psychosocial Stress

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Background: Longterm kidney graft survival may be affected by factors other than biologic, including social determinants of health such as food scarcity and psychosocial stress.

Methods: A face-to-face survey was conducted in a random convenience sample of 31 pts in transplant clinic. The Stress and Social Support survey and the Perceived Stress Scale were used. Dietary intake was assessed using 24-hr recall and analyzed with ASA-24 software. All comparisons are by Chi square or t-test.

Results: There were 11 women(36%), 20 men(65%), 22 Black(71%). Mean age was 55.2±1.9 yrs, time since transplant 63.9±14.1 mos. 24 (77%) reported income <$40K, with 12 (39%)<$20K.12 (39%) recieved SNAP benefits (SNAP+). Income or employment rate did not differ for SNAP+ vs SNAP-. SNAP+ had significantly worse kidney function(creatinine 2.17±0.24 vs 1.44±0.11 mg/dl,p=0.014) and eGFR(37.9±3.8 vs 53.7±2.5 ml/min,p=0.003), but did not differ for time since transplant, gender, race, BP, BMI, tacrolimus level or age. SNAP+ also were more likely to disagree with the statement "I feel I am in control of my health and it doesn't control me" (33% vs 0%, p=0.017), to report never or almost never feeling confident about handling personal problems(50% vs 16%, p=0.018), and to be unable to control irritations in their lives(67% vs 16%,p=0.043,p=0.043). No difference in caloric or macronutrient intake existed, but SNAP+ ate less fiber(11.1±1.3 vs 16.7±1.8 gm,p=0.023)and fewer servings of fruits/vegetables(1.5±0.28 vs 3.75±0.85, p=0.021). When asked about missed medication they did not report more missed doses.

Conclusions: In our patient population: 1. Pts receiving SNAP had worse kidney function than those who did not despite similar time since transplant, tacrolimus level, income, and employment status. 2. They ate less fiber and fewer servings of fruits/vegetables despite similar caloric intake, which should be investigated further as higher intake of fruit/vegetables is associated with delayed progression of kidney disease in non-transplant pts. 4..They also reported feeling less control over their health and less ability to handle daily stress. 4. These finding suggests that special attention should be paid to this population who have issues with social determinants that may affect kidney function.

PO2497

Impact of Ethnicity Matching on Kidney Transplant Outcomes Among African Americans: A Mate Kidney Analysis

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Background: Transplantation of kidneys from African American (AA) donors is associated with poorer outcomes compared to transplants from white Americans. Unmeasured variables such as APOL1 renal risk variants and sickle cell trait could contribute to the heightened risk. We used a mate kidney model to test the hypothesis that enhanced genetic risks associated with AA donor kidneys could be counterbalanced by favorable immunologic matching when AA donor kidneys are transplanted into AA recipients.

Methods: We identified AA deceased donors in OPTN/UNOS database from 2000 to September 2019 in which both kidneys were transplanted into first-time kidney-only recipients, and both recipients received induction therapy followed by tacrolimus/mycophenolic acid maintenance. Marginal models for hazards of graft failure, death censored graft failure (DCGF) and death were constructed, with adjustments for recipient and transplant variables. Outcomes of AA, Hispanic, and Asian recipients were compared, using white American recipients as reference. Results were compared to a parallel analysis of 41,886 recipients of white American donor kidneys.

Results: Median follow up of the study was 3.3 (IQR 1.1-6.5) years among 8194 paired recipients of AA donor kidneys. Despite donor ethnicity matching, DCGF was higher but mortality lower among AA recipients. Graft failure did not differ. Hispanic and Asian recipients had lower hazards of most unfavorable outcomes (table 1). In the parallel analysis, DCGF was again inferior for AA recipient of white American donor kidney (HR 1.37, 95% CI 1.28-1.47, $p<0.001$).

Conclusions: Our data indicate an increased risk of DCGF in AA recipients of AA donor kidneys, despite the potential benefits of favorable immunologic matching and does not support an ethnicity-matching strategy to improve outcomes and reduce disparities. Our observations suggest that other recipient factors predominantly influence graft outcomes. Improved outcomes in Hispanic and Asian patients merit further study.

Funding: Private Foundation Support

Table 1. Adjusted outcomes for paired recipients of AA donor kidneys with white American recipients as reference

Recipient ethnicity	African American		Hispanic		Asian	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Graft failure	1.07 (0.97-1.19)	0.2	0.72 (0.61-0.84)	<0.001	0.75 (0.59-0.95)	0.02
Death-censored graft failure	1.31 (1.14-1.50)	<0.001	0.80 (0.65-0.99)	0.04	0.79 (0.57-1.10)	0.2
Death	0.87 (0.77-0.98)	0.02	0.57 (0.47-0.69)	<0.001	0.68 (0.52-0.90)	0.006

PO2498

Cardio-Metabolic Risk Factors in Kidney Donors at a Third-Level Hospital of Care in Mexico

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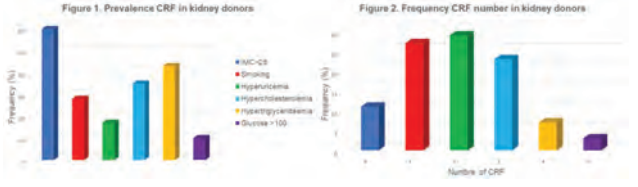
Background: Living donor kidney transplantation is the treatment of choice for chronic terminal kidney disease. A high prevalence of cardio-metabolic risk factors (CRFs) in the general population implies challenges when choosing the best candidate for kidney donation. Knowing the frequency of CRFs will allow us to make timely interventions in order to reduce cardiovascular complications after donation.

Methods: Cross-sectional, descriptive study, which included kidney donors who were admitted to the National Medical Center "Dr. Antonio Fraga Mouret" during the period from 2015 to 2019. Descriptive statistics were made, with a 95% IC. CRFs were included; systolic hypertension (SBP) higher than 120mmhg, diastolic hypertension (DBP) higher than 80mmhg, anemia hemoglobin less than 13 g/dl in men and less than 12 g/dl in women; impaired fasting glucose> 110 mg / dl, body mass index (BMI)> 25.

Results: 153 donors were included, 59% were women, 33% were siblings and 31% were the patient's mother; 34% had no social security. The mean age was 42.7 ± 10.7 years; the mean BMI 26.3 ± 5.4, with a mean GFR 101.9 ± 13.4 (61.6 -133) ml / min. 28% of donors smoked, 7% had SBP risk and 27% DBP risk, 60% had BMI> 25, 4% had anemia and 13% hypoalbuminemia; 10% with impaired fasting glucose. Figure 1 shows the prevalence of CRF. More than 25% of kidney donors had 2, 3 and 4 CRFs on admission to hospital for donation. 72% presented acute kidney injury (AKI) after surgery, none required renal replacement therapy. The highest AKI frequency was observed in subjects who had from 1 to 3 CRFs with frequencies of 26-34%.

Conclusions: A BMI higher than 25 was the most prevalent CRFs; associated with AKI when more than 1 CRF was observed. Timely detection of CRFs will allow for timely interventions that will reduce post-donation cardiovascular risk and decrease the risk of AKI.



PO2499

The Effect of Anemia Correction with ESA and Cholecalciferol Supplementation on Post-Transplant Malignancy Among Kidney Transplant Recipients: A Prespecified Analysis of a Randomized Clinical Trial

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Background: Kidney transplant recipients (KTRs) are at increased risk of cancer, and post-transplant malignancy (PTM) is among the leading causes of death with functioning allograft. Aggressive anemia correction with ESA slows the rate of decline in kidney allograft function but may increase the incidence of PTM. Vitamin D is proposed to exert pleiotropic effects including anti-cancer properties and may prevent the development of PTM.

Methods: We enrolled 153 KTRs with anemia and >1-year history of transplantation across 23 facilities in Japan and conducted a multicenter, two-by-two factorial, open-label, randomized clinical trial. Patients were randomly assigned to either a high or low hemoglobin (Hb) target (>12.5 vs <10.5 g/dL) and to either cholecalciferol 1000 IU/day or control. PTM was a prespecified secondary outcome.

Results: Patients were 51±12 years-old, among whom 54% were male. The median (IQR) of transplant vintage was 8 (5, 12) years. Their baseline eGFR, Hb, and serum 25(OH)D levels were 30.6±11.0 mL/min per 1.73 m^2, 10.7±1.2 g/dL, and 14.5±5.2 ng/mL, respectively. There was no between-group difference in the prevalence of prior malignancy in either arm. The mean Hb level was 11.4 g/dL and 10.6 g/dL in the high and low Hb target groups, respectively. The mean serum 25(OH)D level exceeded 30 ng/mL in the cholecalciferol group after Month 6 whereas it did not change in the control group throughout the study period. A total of 7 PTMs developed during 2 years of the follow up; 2 lung cancers, 1 breast cancer, 1 gastric cancer, 1 testicular cancer, 1 renal cell carcinoma, and 1 myelodysplastic syndrome. There was no between-group difference in the incidence of PTM in the hemoglobin target arm (i.e., n=3 [4.1%] vs. 4 [5.1%] in the high vs. low Hb target group, respectively; *P*=0.77). In the cholecalciferol arm, all 7 PTMs developed in the control group while none was observed in the cholecalciferol group (i.e., 9.1% vs. 0%, respectively; *P*=0.007).

Conclusions: The incidence of PTM was not increased by aggressive anemia correction with ESA and was reduced by cholecalciferol supplementation among KTRs. Large clinical trials with a long-follow up period are needed to validate these findings. Registered at ClinicalTrials.gov (NCT01817699).

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PO2500

Association Between Elevated Ferritin and Graft Survival During the First Year After Kidney Transplant

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Background: Both iron deficiency and iron overload are associated with adverse outcomes in patients with end stage kidney disease on chronic hemodialysis. In contrast, the effect of iron metabolism markers post kidney transplantation have not been thouroughly evaluated. In this study we aimed to evaluate the association between serum ferritin and transferrin saturation during the first year post transplantation on patients and graft survival.

Methods: Retrospective cohort study, using the Rabin Medical Center (RMC) kidney transplant registry. We included adults (>18 years) patients transplanted between 1/1/2006 and 31/12/2017 that had at least one available iron, transferrin and ferritin value during the first year post transplantation. Serum ferritin and transferrin saturation were log transformed and serum ferritin was also analyzed as a dichotomous variable with 500 ng/ml as a cutoff value. Primary outcome was the composite of graft and patients' survival. Secondary outcomes included death censored graft loss. Univariate and multivariate Cox models were used for the primary composite outcome of patients' and graft survival.

Results: Seven hundred and twenty-six patients were included in the study, of whom 219 (30.2%) had serum ferritin above 500 mg/dl. Patients with high serum ferritin were older with more diabetes mellitus (DM) and heart disease and tended to have deceased donor transplantation and delayed graft function. By univariate Cox analysis, ferritin level above 500 ng/ml was associated with increased risk of death and graft loss (Hazard Ratio (HR) 2.38, 95% Confidence Interval (CI) 1,69-3.35, p<0.001). By extensive multivariate model ferritin was still highly associated with increased rate of graft loss (HR 1.87, 95% CI 1,29-2.72, p=0.001). High ferritin was also associated with increased risk of the secondary outcome of death censored graft loss (HR 2.09, 95% CI 1,26-3.48, p=0.005). The results were similar when ferritin was evaluated as continuous variable. In contrast, transferrin saturation was not associated with overall and death censored graft survival.

Conclusions: High ferritin during the first year post transplantation was associated with reduced graft survival. Further research is needed to evaluate whether this association is due to inflammation, iron overload or combination of the two.

PO2501

Iron Deficiency in Kidney Transplant Recipients: Impact on Cognitive Functioning

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Background: Cognitive function impairment is common in kidney transplant recipients (KTRs). Brain functioning requires energy, for which iron is essential at the level of oxygen delivery and mitochondrial function. Iron deficiency (ID) has been linked to compromised cognitive functioning in premenopausal women. We aimed to investigate whether ID could be a potentially modifiable risk factor for cognitive function impairment in KTRs.

Methods: In a prospective study among KTRs participating in the TransplantLines Biobank and Cohort study, we analyzed KTRs >1 yr post-transplant with data on iron status. All participants underwent neurocognitive testing to measure memory (Digit Span Forward, Immediate and Delayed Recall of the 15 Word Test), attention and mental speed (Symbol Digit Modalities Test, Trail Making Test-A) and executive functioning (Trail Making Test-B, Digit Span Backward). ID was defined as ferritin <100 µg/mL or 100-299 µg/mL with transferrin saturation (TSAT) ≤20%. We used multivariable linear regression analyses to assess associations between ID and neurocognitive outcomes. Analyses were adjusted for hemoglobin, CRP, age, sex, eGFR, BMI, smoking, alcohol intake, time since transplantation, dialysis duration, donor type, educational level and immunosuppressives.

Results: We included 398 KTRs (age 56±14 yrs, 62% male, eGFR 52±14 mL/min/1.73 m^2). ID was present in 289 KTRs (73%). Associations of plasma ferritin, TSAT and ID with neurocognitive scores are presented in the table.

Conclusions: ID, low ferritin and low TSAT are consistently associated with poor performance on neurocognitive tasks measuring verbal memory, executive functioning,

mental speed and attention in KTRs, independent of hemoglobin and other potential confounders. Future studies should address whether ID correction restores cognitive function.

N=398	Ferritin	TSAT	Iron Deficiency
Memory			
¤Digit Span Forward	st.β=0.12, P=0.022	st.β=0.05, P=0.358	st.β=-0.09, P=0.074
¤15 Word Test, immediate recall	st.β=0.18, P<0.001	st.β=0.08, P=0.09	st.β=-0.08, P=0.089
¤15 Word Test, delayed recall	st.β=0.31, P<0.001	st.β=0.17, P=0.001	st.β=-0.22, P<0.001
Attention & Mental Speed			
¤Symbol Digit Modalities Test	st.β=0.16, P=0.001	st.β=0.17, P<0.001	st.β=-0.14, P=0.002
¤Trail Making Test-A	st.β=-0.20, P<0.001	st.β=-0.08, P=0.115	st.β=0.15, P=0.001
Executive Functioning			
¤Trail Making Test-B	st.β=-0.04, P=0.47	st.β=0.08, P=0.118	st.β=0.002, P=0.961
¤Trail Making Test- B/A ratio	st.β=0.14, P=0.009	st.β=0.18, P=0.001	st.β=-0.15, P=0.004
¤Digit Span Backward	st.β=0.18, P<0.001	st.β=-0.03, P=0.515	st.β=-0.14, P=0.006

PO2502

Anemia and Decreased Muscle Mass and Muscle Strength in Kidney Transplant Recipients

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Background: Anemia is highly prevalent in kidney transplant recipients (KTRs). It is known that anemia impairs quality of life, especially physical functioning. Although surmised, data about the latter in KTRs specifically are scarce. Hence, we aimed to investigate the association between anemia and muscle mass and muscle strength in KTRs.

Methods: In a prospective study among KTRs participating in the TransplantLines Biobank and Cohort study, we used KTRs >1 yr post-transplant with data on hemoglobin (Hb) levels and muscle mass. Muscle mass was assessed in two ways: by using 24-hour urinary creatinine excretion and with bioelectrical impedance analysis (BIA). Muscle strength was determined by means of hand grip strength using a dynamometer. The mean overall hand grip strength was calculated out of three attempts of both hands with 30 seconds recovery time in between. Anemia was defined as Hb <12 g/dL for women and <13 g/dL for men, according to WHO definitions. We used multivariable linear regression analyses to assess associations between anemia and muscle mass and strength.

Results: We included 824 KTRs (age 56±13 years, 60% males, eGFR 52±18 mL/min/1.73 m^2, serum Hb 13.5±1.8 g/dL). Anemia was present in 30% of KTRs. Hb levels were associated with creatinine excretion, independent of age, sex, eGFR, BMI, hs-CRP, smoking status, alcohol use and the use of RAAS-inhibitors, statins, calcineurin inhibitors, proliferation inhibitors or prednisolone (st.β=0.14, *P*=0.001). Similarly, the presence of anemia was independently associated with a lower creatinine excretion (st. β=-0.09, *P*=0.021). Hb levels (st.β=0.20, *P*<0.001) were also independently associated with muscle mass, estimated using BIA resistance measurements. In line with muscle mass parameters, Hb (st.β=0.18, *P*<0.001) and anemia (st.β=-0.11, *P*=0.005) were associated with handgrip strength independent of potential confounders as well.

Conclusions: Low hemoglobin levels and anemia are both strongly associated with lower muscle mass and muscle strength in KTRs, likely impairing physical functioning. Future research is needed to address whether correction of anemia improves physical performance in KTRs.

PO2503

Sevelamer-Associated Gastrointestinal Complications in Kidney Transplant Recipients

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Introduction: Sevelamer (SV) is a resin based oral phosphate binder used commonly in chronic kidney disease (CKD) patients. Clinical trials performed for approval for clinical use showed mild to moderate gastrointestinal (GI) intolerance in a minority of patients. In general clinical use of SV in CKD patients, there have been case reports of more serious GI problems than were reported in original trials, including GI bleeding and colonic complications including colitis and perforation. The majority of patients receiving kidney transplants have required long term oral phosphate binders at the time they are transplanted, often using SV. Delayed graft function (DGF) early post transplant may require ongoing use of oral phosphate binders to control hyperphosphatemia

Case Description: We report 3 cases of significant GI morbidity in association with SV occurring in transplant recipients within the first 2 weeks after kidney transplantation. In one patient, the post transplant course was complicated by sepsis due to perforated colonic diverticulum in the context of preexisting diverticular disease; surgical specimen showed SV crystals associated within the area of bowel perforation. Two patients had severe upper GI symptoms and abnormal findings on upper endoscopy, including severe esophagitis and esophageal ulceration. SV crystals were found in the biopsies of abnormal areas. Two patients had long-term use of SV prior to transplantation, whereas one patient was treated with SV for a short time only after transplantation. All had required more than one phosphate binder for long-term control of hyperphosphatemia; two required cinacalcet for management of secondary hyperparathyroidism.

Discussion: SV use may have more serious GI adverse effects in CKD patients than noted in the original clinical trials. Preexisting GI disease and/or abnormalities may increase the risk of adverse GI effects related to SV. Recent use of SV prior to kidney transplantation or use of SV for control of hyperphosphatemia in the context of DGF can be associated with GI morbidity in the early post transplant setting. Need for higher doses of phosphate binders and severity of hyperparathyroidism may be contributing factors to this risk.

PO2504

C-Terminal and Intact FGF-23 in Kidney Transplant Recipients and Their Associations with Kidney Transplant Loss and Mortality

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Background: Increased fibroblast growth factor 23 (FGF23) is a risk factor for mortality, cardiovascular disease, and progression of chronic kidney disease. Limited data exist comparing the association of either c-terminal FGF23 (cFGF23) or intact FGF23 (iFGF23) in kidney transplant at recipients (KTPs) with graft loss and all-cause mortality.

Methods: We conducted a prospective observational cohort study in 562 stable kidney transplant recipients. Patients were followed for graft loss and all-cause mortality for a follow-up of 48 months.

Results: During a median follow-up of 48 months, 94 patients had adverse outcome (graft loss or died). Both cFGF23 and iFGF23 concentrations were significantly higher in patients who had adverse outcome than those without adverse outcome (24.59 [11.43-87.82] versus 10.67 [5.99-22.73] pg/ml; p<0.0001 and 45.24 [18.63-159.0] versus 29.04 [15.23-60.65] pg/ml; p=0.002 for cFGF23 and iFGF23, respectively). cFGF23 and iFGF23 measurements correlated well (rho=0.54, p <0.0001). ROC analysis of cFGF23 and iFGF23 yielded AUC of 0.69 (p <0.0001) and 0.61 (p =0.002) for prediction of the composite endpoint, respectively. Cox regression analyses adjusted for confounding factors, showed that cFGF23 (HR for one unit increase of log transformed cFGF23: 1.35; 95% CI, 1.03-1.77; p=0.028) but not iFGF23 (HR for one unit increase of log transformed iFGF23: 1.03; 95% CI, 0.81-1.31; p=0.827) was associated with the composite endpoint (Figure 1).

Conclusions: Elevated cFGF23 levels at baseline are independently associated with an increased risk all-cause mortality or graft loss. iFGF23 measurements were not independently associated with the study endpoint. The cFGF23 ELISA might detect bioactive FGF23 fragments that are not detected by the iFGF23 ELISA.

Variable	Composite outcome	
	HR (95% CI)	P
Log cFGF23		
Univariate analysis	1.46 (1.31-1.63)	<0.001
Model 1	1.23 (1.07-1.42)	0.005
Model 2	1.28 (1.09-1.50)	0.003
Model 3	1.35 (1.03-1.77)	0.028
Log iFGF23		
Univariate analysis	1.28 (1.14-1.44)	<0.001
Model 1	1.05 (0.92-1.21)	0.473
Model 2	1.06 (0.92-1.23)	0.417
Model 3	1.03 (0.81-1.31)	0.827

Figure 1. Multivariable-adjusted Cox regression analyses of composite endpoint graft loss or all-cause mortality. Model 1 adjusted for eGFR; Model 2 adjusted for eGFR, gender, age; Model 3 adjusted for eGFR, gender, age, time post-transplantation, hemoglobin, albumin, donor's age, cold ischemia time, log serum calcium, log serum phosphorus, log parathyroid hormone, urinary protein excretion.

PO2505

The Time Is Now: Reducing Waiting Times in Minority Populations

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Background: A significant limiting factor to transplantation resides on waiting time based on blood type. Historically candidates in blood groups B and O experience higher waiting times for kidney transplantation. Our center has worked to increase the rate of acceptance in kidneys that would have previously been discarded to try to maximize the donor pool for these blood groups.

Methods: We retrospectively analyzed 1287 consecutive deceased donor kidney transplants from 2015 to 2019. This cohort was chosen to ensure baseline was after allocation system changes, so the change is a result of change in practice at our center. Average waiting time to transplantation and renal transplantation rates were analyzed based on ABO stratification as well as ethnicity to compare longitudinal disparities.

Results: We observed a decrease in waiting time across all blood types (Figure 1) over the 5 year period of this study. There was a substantial benefit in blood type B recipients with a 6.4 year decrease in average waiting time from 2015 to 2019. Waiting time in

blood type O recipients decreased by 3.4 years from 2015-2019 (Figure 1). We observed a decrease in disparity between African Americans and Hispanics versus Caucasians, with average waiting times decreasing from 2.5 years to 1.2 years and 1.6 years to 0.5 years, respectively. There were no type B recipients who received A2 donors in this cohort.

Conclusions: Waiting time at our center decreased significantly across all blood types with a disproportional benefit in blood group B recipients despite not utilizing the benefit of A2 donors transplanted into B. Thus, this reflects our increase in volumes by utilizing extended criteria donors such as acute kidney injury and high kidney profile index donors (KDPI). These efforts have reduced the disparities in waiting time particularly in African-American and Hispanic populations.

Funding: Clinical Revenue Support

Blood Type		2015	2016	2017	2018	2019	Total
A	N	75	54	75	103	107	414
	Avg. Wait Time (yrs)	5.9	5.3	4.4	4.1	3.3	4.4
	Avg. KDPI	48.5%	44.8%	52.9%	55.6%	55.1%	52.3%
AB	N	17	9	12	17	24	79
	Avg. Wait Time (yrs)	4.4	5.5	2.8	3.1	3.4	3.7
	Avg. KDPI	39.9%	41.4%	45.5%	46.8%	48.6%	45.0%
B	N	21	25	31	45	46	168
	Avg. Wait Time (yrs)	10.7	7.3	6.4	4.7	4.3	6
	Avg. KDPI	56.0%	54.4%	55.4%	65.2%	61.3%	59.6%
O	N	97	103	111	148	167	626
	Avg. Wait Time (yrs)	8.1	6.9	5.9	5.1	4.3	5.8
	Avg. KDPI	50.9%	55.0%	54.8%	63.8%	63.8%	58.7%
Total	N	210	191	229	313	344	1287
	Avg. Wait Time (yrs)	7.3	6.4	5.3	4.6	3.9	5.3
	Avg. KDPI	49.6%	51.4%	53.7%	60.4%	59.7%	55.9%

PO2506

Ethnic Disparities in Hospitalization After Deceased Donor Kidney Transplantation

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Background: African American (AA) recipients of deceased-donor (DD) kidney transplants have shorter allograft survival than recipients of other racial/ethnic groups. However, it remains unclear whether similar patterns are observed for healthcare utilization. Hospitalization rates (HR) for recipients of kidneys from 2,639 AA and 12,043 European American (EA) DDs who had one kidney transplanted into an AA and one into an EA recipient were analyzed. Four donor/recipient pairs (DRP) were studied: AA/AA, AA/EA, EA/AA and EA/EA using data from the Scientific Registry of Transplant Recipients for transplantations performed between January 1, 2001 and June 30, 2016.

Methods: All reported hospitalizations for the duration of the kidney allograft were counted. Negative binomial models were fitted to compare post-transplant HRs with adjustment for transplant era (2001-2005, 2005-2010 and post 2010), the kidney donor risk index (KDRI), estimated post-transplant survival (EPTS), donor- and recipient age and sex, recipient insurance, prior employment status, delayed graft function (DGF) and cold ischemia time.

Results: HRs were higher among recipients of kidneys from AA DDs 419.0 (390.4, 449.7) for AA/AA and 412.7 (379.8, 448.5) for AA/EA, compared to 362.8 (350.1, 375.9) for EA/AA and 331.9 (319.9, 344.3) per 1000 person-years for EA/EA DRPs. The adjusted HR was 67.9% (56.7%, 79.9%) higher for transplantations performed after 2005, compared to those performed during 2001-2005. HRs were also higher for recipients with Medicaid insurance 62.0% (16.4%, 125.5%), or DGF 25.9% (18.7%, 33.5%), but lower for employed recipients, -18.9% (-23.5%, -14.0%). These rates increased by 40.6% (28.4%, 53.8%) for a unit increase in the EPTS and by 24.6% (10.9%, 39.9%) for a unit increase in KDRI. Higher rates were observed among recipients of AA DD kidneys, independently of recipient race/ethnicity 19.2% (11.2%, 27.9%).

Conclusions: HRs among the DRPs have increased over time with higher rates among recipients of AA DD kidneys. Additional donor-level factors may contribute to the hospitalization rate after DD kidney transplantation.

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PO2507

A Randomized Trial of Vitamin D Supplementation on Skeletal Muscle in Patients Early Post Kidney Transplantation

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Background: Developing strategies for managing skeletal muscle weakness and loss in kidney transplant recipients (KTRs) is an important clinical challenge. Little is known about the effect of native vitamin D (VitD) supplementation on skeletal muscle in KTRs.

Methods: We conducted a 11-month, double-blind, randomized, controlled trial to assess the efficacy of VitD for improving skeletal muscle weakness and loss in KTRs receiving kidney transplantation within one month. Eligible patients were randomly assigned to a Vitamin D (cholecalciferol, 4000 IU / day) group or a placebo group in a 1:1 ratio. A prespecified secondary endpoints in this study included a percent (%) change in handgrip strength (HGS), and leg strength (LS) for skeletal muscle strength, and skeletal muscle index (SMI) for skeletal muscle mass.

Results: A total of 193 KTRs were randomized, but 6 KTRs were lost before taking the medication. We analyzed 92 KTRs in Vitamin D group and 95 in Placebo group. Dropouts during this study were 3 KTRs in Vitamin D group and 2 in Placebo group. In Vitamin D group, at baseline the mean age was 52.3 ± 12.5 years old and the number of males was 28 (30.4%), and in Placebo group, 51.7 ± 11.4 years old and 30 (31.5%), respectively. The mean changes in serum 25 hydroxyvitamin D levels from baseline to the end of this study were 11.2 ± 4.1 to 39.8 ± 13.0 ng/mL in Vitamin D group ($p < 0.001$)and 11.2 ± 4.1 to 14.5 ± 5.0 ng/mL in Placebo group ($p < 0.001$). In this study, there were no difference in % changes in HGS, LS, or SMI between those groups, respectively.

Conclusions: VitD supplementation alone appears not to be effective in improving skeletal muscle weakness and loss among KTRs early post-transplantation. Larger-scale trials are warranted to confirm these findings.

PO2508

Effects of Arteriovenous Fistulas on Outcomes of Kidney Transplant Recipients

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Background: Arteriovenous fistulas (AVFs) may exacerbate cardiovascular events (CVE) after kidney transplantation (KTx). We aimed to investigate the long-term effects of AVFs on KTx outcomes.

Methods: Prevalent 168 recipients were categorized at median 2yr. after KTx: recipients with functioning AVF (fAVF) (n=73), recipients with non-functioning AVF (nfAVF) (n=62) and recipients without AVFs (noAVF) (n=33) on pre-KTx peritoneal dialysis or underwent preemptive KTx. Baseline characteristics, echo findings and endothelial function were compared. During a median 11yr. follow-up after enrollment, CVE were defined as acute coronary syndromes or cerebrovascular accidents; additional outcomes included eGFRs at baseline and end of follow up, graft failure and death.

Results: Demographic, clinical, laboratory and echo characteristics and endothelial function at enrollment were not significantly different across all groups (Table 1). During follow up, CVE occurred in 9 (12.3%), 5 (8%), and 4 (12.1%) patients in fAVF, nfAVF and noAVF groups, respectively (p=0.70). Groups were comparable regarding graft and patient survival rates (p=0.13 and p=0.87, respectively). During follow-up, functioning AVFs thrombosed in 5 (7%) and were surgically closed in 20 (27%) patients in fAVF group. CVE rate was similar in patients with thrombosed (20%), closed (5%) and still functioning (15%) AVFs (p=0.47). Patient and graft survival rates were significantly lower in recipients with still functioning fAVFs (77% and 73%, respectively) compared to fAVF patients with thrombosed (100% and 100%, respectively) and closed (100% and 95%, respectively) AVFs (p=0.05 and 0.03, respectively).

Conclusions: Long-term CVE rate is similar in KTx recipients with and without patent AVFs. In a subgroup of KTx recipients with functioning AVFs, closure and thrombosis of AVFs may be associated with higher rates of patient and graft survival.

Table 1. Baseline demographic, clinical, laboratory and echocardiographic features of the study patients at enrollment

	fAVF (n=73)	nfAVF (n=62)	noAVF (n=33)	P value
Age (years)	38 ± 12	39 ± 10	37 ± 12	0.34
Gender (male/female)	46/27	34/28	23/10	0.84
BMI (kg/m^2)	24.2 ± 4.3	24.9 ± 5.1	24.8 ± 3.7	0.26
Current smoker (n, %)	6 (8.2%)	3 (4.8%)	-	0.21
Time on dialysis (months)	39 ± 36	43 ± 39	23 ± 20	0.08
SBP (mmHg)	125 ± 18	124 ± 18	126 ± 19	0.95
DBP (mmHg)	78 ± 11	79 ± 12	79 ± 9	0.61
Donor type (living/deceased)	55/18	41/21	29/4	0.07
Laboratory data				
Creatinine (mg/dL)	1.4 ± 0.4	1.5 ± 0.6	1.3 ± 0.4	0.24
eGFR (mL/min/1.73 m^2)	65 ± 21	62 ± 24	72 ± 22	0.15
Calcium (mg/dL)	9.74± 0.7	9.2 ± 0.6	9.2 ± 0.4	0.08
Phosphorus (mg/dL)	3.2 ± 1.1	3.4 ± 0.7	3.3 ± 0.6	0.53
Uric acid (mg/dL)	5.6 ± 1.4	6.0 ± 1.5	5.6 ± 1.2	0.22
Albumin (g/dL)	4.4 ± 0.4	4.2 ± 0.5	4.5 ± 0.2	0.001
Total cholesterol (mg/dL)	192 ± 47	190 ± 43	181 ± 32	0.48
HDL-cholesterol (mg/dL)	54 ± 23	48 ± 21	54 ± 13	0.27
LDL-cholesterol (mg/dL)	108 ± 36	113 ± 34	104 ± 31	0.49
Triglyceride (mg/dL)	171 ± 88	170 ± 84	134 ± 62	0.10
PTH (pg/mL)	99 ± 44	125 ± 84	95 ± 55	0.18
Hemoglobin (g/dL)	13 ± 1.6	12 ± 1.8	13 ± 1.7	0.09
hs-CRP (mg/L)	3.37 ± 4.82	3.48 ± 7.15	7.42 ±11.7	0.14
NT-proBNP (pg/mL) (median, IQR)	122 (61-253)	157 (111-339)	91 (45-202)	0.039
TSH	1.96 ± 1.17	1.85 ± 1.36	1.57 ± 0.82	0.51
Echocardiographic Parameters				
Septal Wall thickness (mm)	11.8 ± 2.5	11.5 ± 2.3	11.4 ± 2.5	0.85
LVMI (g/m^2)	134 ± 37	124 ± 40	122 ± 43	0.41
EF (%)	62 ± 5	63 ± 6	64 ± 7	0.47
PAP (mmHg)	26 ± 9	25 ± 7	26 ± 6	0.83
Diastolic dysfunction (%)	26.8%	29.6%	14.8%	0.34
Endothelial function				
Flow Mediated Dilation (%)	8.4 ± 6.8	11.8 ± 6.3	8.5 ± 6.6	0.32

Abbreviations: AVF, arteriovenous fistula; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; fAVF, functioning AVF; hs-CRP, high sensitive C-reactive protein; nfAVF, nonfunctioning AVF; noAVF, no history of AVF; NT-proBNP, N-terminal pro b-type natriuretic peptide; iPTH, intact parathyroid hormone; SBP, systolic blood pressure; TSH, thyroid stimulating hormone; LVMI, left ventricular mass index; EF, ejection fraction; PAP, pulmonary arterial pressure

PO2509

Recurrent Cardiovascular Events After Kidney Transplant Are Associated with Increased Risk for Graft Failure and Mortality

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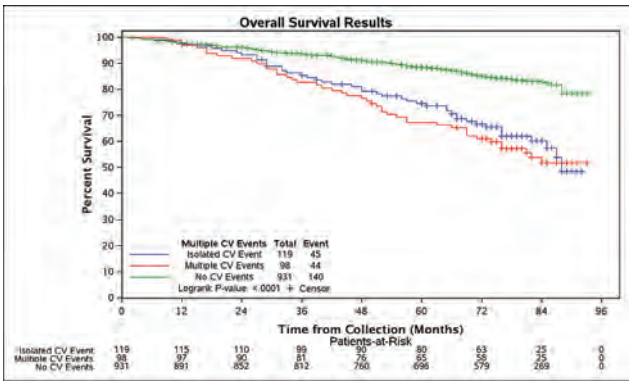
Background: Cardiovascular (CV) disease is prevalent after kidney transplant (KTx). The objective of this study was to describe patients with recurrent CV events in association with allograft function and mortality.

Methods: 1148 consecutive adults that received a KTx between 2011-2013 at a single center were evaluated. CV events were defined as: cardiac: myocardial infarction, heart failure, cardiac arrest requiring resuscitation, and vascular, any stroke, or peripheral vascular disease requiring intervention. Recurrent events were defined as more than one event (either cardiac or vascular).

Results: Mean age was 56.0years (SD14.2), 500(44%) were female, 403(35%) had diabetes, 1083(94%) had hypertension, 127(11%) had prior history of CV events, 602(53%) required dialysis, and 867(76%) received living donor KTx. After a median follow-up of 74 months there were 229(20%) deaths and 217(19%) CV events, of which 92(42%) were cardiac, 86(40%) were vascular, 39(18%) had both. 119 patients had an isolated CV event and 98 had recurrent CV events (median 3 (range 2,4)). Multivariate analysis revealed the following independent significant predictors of CV events: older age, prior history of CV event, diabetes, hypoalbuminemia and measured GFR. Compared to recipients with no CV events and those with an isolated event, recipients with recurrent CV events had increased: mortality (15% vs 38% vs 45%,p<0.0001) and graft failure (14% vs 26% vs 40%,p<0.0001). Hazard ratio for mortality associated with isolated CV events was 2.66 (1.90-3.73) compared to a HR 3.06 (2.18-4.29) for recurrent CV events, p<0.0001.[Figure 1]. Predictors of multiple CV events included measured GFR and increased c-reactive protein; on multivariate analysis only measured GFR was predictive.

Conclusions: Prevalence of recurrent CV events after KTx was 8.5%. Patients with recurrent CV events are at increased risk for mortality and graft failure. Decreased graft function was the primary predictor of recurrent CV events.



PO2510

Mitral Regurgitation and Aortic Stenosis After Kidney Transplantation

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Background: Valvular heart disease (VHD) is highly prevalent in patients with end stage kidney disease and has been associated with poor outcomes. The 5-year mortality rate among patients with at least mild aortic stenosis (AS) or mitral regurgitation (MR) is more than 50% greater than in persons without kidney disease (Samad et al, JAHA 2017). Current knowledge of VHD in patients after kidney transplantation (KT) is scarce.

Methods: This is an ongoing single center retrospective study. In our center, all KT recipients have echocardiograms within one year prior to KT. We included KT recipients at our institution between Jan 2016 and Dec 2016 who had underlying MR and/or AS of any severity. Participants had to have an echocardiogram (Echo) around one year post KT. Our primary objective was to compare the severity of MR and AS at one year post KT to the baseline severity. The secondary objective was to describe changes in left ventricle hypertrophy (LVH).

Results: Two hundred subjects were initially screened. The number of patients who met our inclusion criteria was 22 (Table 1). Mild MR was present in 10 recipients pre KT. MR improved in 4, remained stable in 4, and worsened in 2 out of these 10 recipients at one year post KT. Moderate MR was present in 7 recipients pre KT and all 7 had improvement in severity of MR at one year post KT. Two and three recipients had mild AS and moderate AS respectively pre KT and all of them were observed to have worsening of aortic valve area (AVA) at one year post KT (mean AVA 1.96 versus 1.15 cm2, p 0.07). Nine out of the total 22 recipients included had mild LVH pre KT and all the 9 continued to have mild LVH post KT.

Conclusions: Our study showed that most KT recipients with pre-existing MR had improvement in the severity of MR at one year post KT. However, recipients with AS prior to KT were observed to have worsening in severity of AS at one year post KT. Larger studies are needed to confirm these findings and identify factors that influence progression.

Table 1. Clinical Characteristics

Mean age (yr)	(64)
Gender	Male (14) Female (8)
Race	Non white (9) White (13)
Cause of CKD	Diabetes (4) Hypertension (5) Liver disease (3) FSGS (2) Other (8)
Source of organ	Diseased (17) Living (5)
Delayed graft function	Yes (17) No (5)
Dialysis modality	HD (18) PD (4)

PO2511

A Retrospective Analysis of Post-Transplant Erythrocytosis: The Experience of a Tertiary Kidney Transplant Unit

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Background: Post-transplant erythrocytosis (PTE) defined as persistently raised haemoglobin and haematocrit levels for over 6 months following kidney transplantation reportedly occurs in up to 20% of transplants and can influence physical and mental wellbeing. Reported complications include stroke, hypertension, NODAT and chronic fatigue. Our aim was to investigate the prevalence and potential risk factors of PTE in patients transplanted in our unit between 2013 and 2018.

Methods: We conducted a retrospective study of patients receiving a Kidney or Kidney-pancreas Transplant between 2013 and 2018 and followed up in our local clinic. We collected information on donor and recipient demographics, original kidney

disease, transplant type, CMV transmission, HLA mismatch and Immune-suppression. Independent t-tests were used to analyse age, haemoglobin, haematocrit and ischaemic time. Odds ratios were used for ethnicity, transplant type, index disease and pre-transplant mode of renal replacement therapy (RRT).

Results: Of 568 transplant patients, 46(8%) fulfilled the criteria for PTE given sustained haematocrit >0.5 with a haemoglobin of approximately 161g/L (std. 9.9). We found the risk of PTE was significantly higher in men compared to women (OR 5.375 CI 2.24-12.9 p<0.05) and in DCD SPK transplants compared to other types (OR 5.57, p<0.05). The average age of donors to patients developing PTE was 6.5 years younger than the non-PTE group, p=0.008. IgA nephropathy appeared to convey a higher risk of developing PTE (OR 2.296 p=0.04), as did pre-transplant haemodialysis (OR 3.48 CI 1.34-9.02 p= 0.01). Recipient age, CMV transmission, HLA mismatch, ischaemic times, immune-suppression and prior transplants did not convey significant risk for PTE. Increased incidence of PTE in SPK transplant patients has been previously described. To the best of our knowledge, this is the first study highlighting a potential relationship between PTE and IgA nephropathy, but should be interpreted with caution as a larger study is needed for confirmation.

Conclusions: Although PTE is relatively common after kidney transplant, an understanding of its pathophysiology, epidemiology and prediction remains poor. Our study demonstrates a statistically significant increased risk of developing PTE among men, persons with IgA nephropathy and DCD SPK recipients, particularly from young donors.

PO2512

Utility of the 6-Minute Walk Test in Coronary Artery Disease Screening Before Kidney Transplant

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Background: Coronary artery disease (CAD) screening is a cornerstone of kidney transplant (KTx) evaluation, but existing approaches result in excess testing and low intervention rate. We hypothesize that aerobic performance, based on a simple office test (the 6-minute walk test, 6MWT), may help risk stratify KTx candidates.

Methods: We performed 6MWT in waitlisted patients who were nearing KTx. Results were used for frailty counselling and not for cardiac evaluation. CAD screening was done according to our center protocol: invasive angiogram for patients with long-standing diabetes mellitus (DM) and non-invasive testing for other patients with risk factors and at the evaluating transplant nephrologist's discretion. We used subdistribution Cox regression and time-dependent receiver operator curve to evaluate time to CAD event (revascularization, myocardial infarction, waitlist removal for CAD, or cardiac death), treating waitlist removal for non-CAD and non-cardiac death as competing events.

Results: Of the 360 patients, 200 and 161 patients had 6MWT results <400 meters and >=400 meters (~4 metabolic equivalents), respectively. Patients with lower 6MWT results were older (59±10 vs 50±12 years) and more likely to be female (54% vs 34%), have DM (61% vs 33%) or known atherosclerotic disease (44% vs 22%), and have had prior cardiac evaluation (72% vs 61%). They were also more likely to exhibit cardiac symptom during 6MWT (36% vs 6%) and more likely to be censored due to waitlist removal for non-CAD reasons (follow-up 391±337 vs 541±277 days). 6MWT was not associated with CAD event (subdistribution hazard ratio 1.00 [0.90-1.10], 1-year area under the curve [AUC] 0.54). 196 patients had invasive (52%) or non-invasive (48%) CAD testing within 6 months of 6MWT: 6MWT did not predict the CAD test result (odds ratio 0.96 [0.81-1.14], AUC 0.54). Of the 94 patients who had concurrent non-invasive CAD testing, the 1-year AUC of 6MWT, symptom (at rest or during 6MWT), AST guidelines, or non-invasive testing for CAD event were 0.64, 0.52, 0.46 and 0.66 respectively.

Conclusions: The 6MWT did not perform better in risk stratification for CAD events compared to a symptom- or risk factor-based approach.

Funding: Private Foundation Support

PO2513

Abstract Withdrawn

PO2514

Median Waiting Time of Kidney Transplant Candidates with Initial Estimated Post Transplant Survival Score >90% According to Organ Procurement Organization Waiting Time

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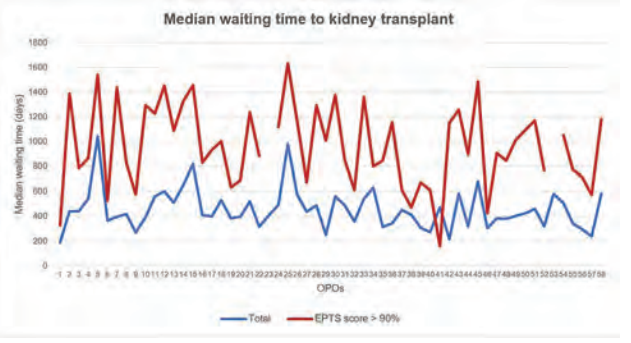
Background: The kidney allocation system (KAS) and the Estimated Post Transplant Survival (EPTS) score were introduced in the United States in December 2014. The transplant rate among very high EPTS candidates (>90%) may be impacted by lack of KAS priority, geographic factors based on the location of the listed Organ Procurement Organization (OPO), and/or differences in waitlist mortality/delisting. Here we study the impact of new KAS among the candidates with EPTS>90%.

Methods: The Organ Procurement Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data of newly listed first time transplant candidates from 2015-2018 were included. Individuals listed for multiple organs, at multiple centers, and age < 18 years were excluded. The outcomes included median waiting time to transplant, transplant rate, death rate and delisting rate among candidates with EPTS>90% compared to those with EPTS≤90%. Median waiting time was calculated by Kaplan-Meier model with censoring for still waiting candidates.

Results: A total of 114,870 candidates were included. Candidates with EPTS>90% (9.74%) had a lower rate of overall transplant compared with EPTS≤90% (30.3% vs. 45.9%, p<0.001), higher rate of deceased donor transplant (87.2% vs. 60.9%, p<0.001), lower rate of living donor transplant (12.8% vs. 39.1%, p<0.001), higher death rate (8.8% vs. 5.73%, p<0.001) and higher delisting rate (22.9% vs. 13.3%, p<0.001). Overall median waiting time to transplant was 444 days (range 188-1,042 days among OPOs) compared to 1,025 days (range 160-1,633 days among OPOs) in those with EPTS>90% (p<0.001).

Conclusions: Candidates with EPTS>90% had a longer median waiting time compared to total waitlisted in all but one OPO. Median waiting times were heavily influenced by the lower overall rate of kidney transplantation and living donor transplantation in this group.



PO2515

A Devastating Complication of Encapsulating Peritoneal Sclerosis (EPS) In Two Renal Transplant Recipients

Benjamin Lawson, Zar Chan, Lilly M. Barba. Renal Transplant Program *Los Angeles County Harbor-UCLA Medical Center, Torrance, CA.*

Introduction: EPS is a rare complication of peritoneal dialysis (PD) which carries great morbidity and mortality. The risk of EPS may be higher in PD patients who undergo renal transplantation as compared to PD patients who do not received a transplant. Pre-transplant EPS, progressive peritoneal remodeling, cessation of PD and use of calcineurin inhibitors are potential etiologies. We present two unique cases of post-transplant EPS requiring surgical intervention with devastating outcomes.

Case Description: Case #1 A 47-year-old female with end stage renal disease due to congenital kidney disease on PD for 8 years transitioned to hemodialysis due to peritonitis, underwent a deceased donor kidney transplant (DDRT) presented 4 weeks post operatively with nausea, vomiting, and abdominal pain. Imaging showed dilated loops of small bowel concerning for partial small bowel obstruction treated non-operatively with bowel rest. One month later she presented with similar symptoms and small bowel obstruction. Due to failure to improve, she was taken to surgery and was found to have a frozen abdomen with dense adhesions. Lysis of adhesions was complicated by enterotomies and small bowel resection. Multiple enterocutaneous fistulas prohibited wound closure. She is being evaluated for a small bowel transplant and remains on parenteral nutritional support. Case #2 A 39-year-old African female with history of ESRD secondary to Lupus on PD for 11 years received a DDRT. Eighteen months post-transplant, she presented with nausea, vomiting and abdominal pain. Imaging showed a small bowel obstruction treated non-operatively with bowel rest. Three weeks later she required emergent surgery for an acute abdomen undergoing lysis of adhesions, bowel resection and end ileostomy. She required parental nutrition for five months.

Discussion: We report two cases of EPS after DDRT who required surgical intervention with devastating outcomes. Fluid and nutritional support have complicated management and affected quality of life. Given the multifactorial etiologies and potential devastating outcomes of EPS, the pre-transplant evaluation should include a detailed assessment. Furthermore, long term PD patients and those with a history peritonitis should be monitored closely post-transplant.

PO2516

When a Peritoneal Dialysis Catheter Should Be Removed Post-Kidney Transplantation?

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Background: Approximately 15% of patients on the kidney transplant (KT) waiting list in the US receive peritoneal dialysis (PD), a growing home dialysis therapy for end stage renal disease (ESRD) patients. European guidelines recommend keeping the peritoneal dialysis catheter (PDC) in-situ during KT, due to the potential risk for delayed graft function (DGF). With this approach, a 10% risk for post-transplant PDC exit-site infections has been reported. In the US guidelines for l PDC removal timing are lacking, and determine by transplant center and operating surgeon's preferences.

Methods: We retrospectively reviewed the electronic medical records of all patients transplanted between 4/2017-7/2019 at our kidney transplant center. We studied basic donor and recipient characteristics, presence of DGF (defined as dialysis in the first week following KT), time interval between KT and PDC removal, and wound related complications.

Results: Of 259 patients received a KT during the study period, 28 were on PD prior to KT. Of those 10patients underwent a living donor transplant, 16had a deceased donor, and 2underwent a simultaneous kidney-pancreas transplant. Sixteen were female, 9were non-Hispanic blacks, and 4were aged >65 years. Three received induction with basiliximab (per center's protocol for recipients aged ≥70 years) and the rest received antithymocyte globulin. PDC was removed at time of KT in 17 patients while in the other 11 recipients PDC was removed 22 days (median) post transplantation. For patients developed DGF, with modality switched to hemodialysis. Three of these had their PDC removed at the time of KT. The 4th patient with DGF who had his PD catheter left in place, received hemodialysis due to hemodynamic instability. Readmission rates (excluding planned hospitalization for PDC removal) and wound infections were similar between Those who had their PDC removed at surgery, and those who did not.

Conclusions: Kidney transplant centers that do not routinely use PD for DGF should remove the PDC at time of kidney transplant to reduce costs and prevent patient and healthcare provider burden of additional surgery. As the prevalence of PD and KT is expected to grow in the near future with the new kidney health initiatives, kidney transplant centers should consider a protocol for optimal care for PDC removal.

PO2517

Could Targeting Dry Weight on Hemodialysis Patients Before Kidney Transplantation Leave Them Too Dry?

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Background: Delayed graft function (DGF) after kidney transplantation is associated with inferior kidney and patient outcomes. Studies suggest that avoidance of hypovolemia peri-kidney transplantation is associated with a reduced risk of DGF. Hemodialysis (HD) patients that have HD prior to transplant targeting their usual dry weight may be volume contracted pre-transplant and at increased risk for DGF. By definition the dry weight is the state of near maximal volume contraction for most HD patients. The objective of this study is to examine the proportion of HD patients who have a pre-transplant post-HD weight at or below their usual dry weight.

Methods: This is a retrospective study of sequential kidney transplants in HD patients at our center from Jan 2015 to Dec 2019. The primary outcome was the proportion of patients who had an HD session before transplantation that resulted in a post-HD weight equal to or less than their prevalent set target dry weight. Data was extracted from the electronic medical record and chart review. Recipients on home therapies and pre-emptive transplants were excluded.

Results: Of 68 kidney transplants done in the study period, 40 were in-center HD patients with available HD data. They were mean age 54.8±14.5 years, 12 (30%) female, and majority were Caucasian. Twenty-five (62.5%) patients had a pre-transplant post-HD weight equal to or less than their prevalent set target dry weight (mean - 0.26±0.25 kg). The other 15 (37.5%) patients achieved post-HD weights higher than their usual targets (+0.72±0.41 Kg).

Conclusions: The results of this study suggest that a high proportion of HD patients are at below dry weight after their dialysis and may be hypovolemic before kidney transplantation. This may represent at potentially avoidable increased risk for DGF. Further studies are planned to examine possible associations of achieved post-HD weight prior to transplant with perioperative central venous pressure, IV fluid administration, and graft function. There may be strategies to optimize volume status pre-transplantation to mitigate this risk of DGF including targeting a higher weight on HD or administration of IV fluid to raise weight above the prevalent set target dry weight before transplantation when feasible.

PO2518

Trends in Time to Graft Loss by Dialysis Exposure

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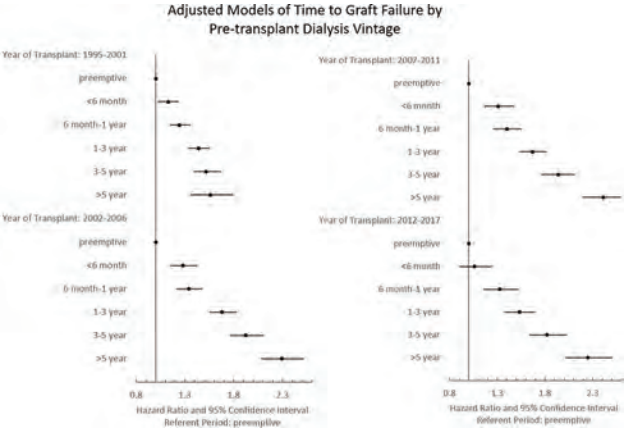
Background: Preemptive transplantation is believed superior to transplantation after dialysis initiation, and transplantation after shorter dialysis exposure is better than with longer exposure. Considering recent registry reports of improved survival on dialysis, we examined temporal trends of graft loss by time on dialysis prior to kidney transplantation.

Methods: Using the US Renal Data System, we identified adults who underwent first kidney transplant between January 1, 1995 and July 31, 2017. We excluded recipients of simultaneous multiorgan transplants. We used an adjusted Cox model to examine the association between dialysis exposure prior to transplantation (categorized as preemptive, <6 months, 6 months-1 year, 1-3 years, 3-5 years, and >5 years) and graft failure within 3 years of transplant. Our model was adjusted for donor and recipient demographic factors, donor type, cause of ESKD, BMI, panel reactive antibodies, diabetes status, and cardiovascular disease status. We organized patients into the following transplant era groupings: 1995-2001, 2002-2006, 2007-2011, and 2012-2017.

Results: A total of 277,158 transplant recipients were studied and 38,364 had graft loss within 3 years. In each era, the hazard ratio for graft loss was lower for preemptive transplant recipients (referent group) compared to all other dialysis exposures except for the group that received less than 6 months of dialysis in the 2012-2017 era (HR 1.06 (95% CI 0.91-1.24)). Those exposed to more than 5 years of dialysis exposure had the highest risk for graft loss within 3 years in all eras, with over 2 times the hazard compared to the referent group in the most recent eras (figure).

Conclusions: Although preemptive transplantation offers the best graft survival across the study period, those transplanted within 6 months of dialysis initiation had similar 3-year graft survival to those transplanted preemptively in the most recent era. The negative association between the longest duration of pre-transplant dialysis and post-transplant survival persists.

Funding: NIDDK Support



PO2519

Does the Timing of Dialysis Initiation Affect Peak Calculated Panel Reactive Antibody in Waitlisted Kidney Transplant Candidates?

Adam Price, Mohamed A. Mohamed Ahmed, Zemin Su, Maria Aurora C. Posadas, Karim M. Soliman, Vinaya Rao, Michael Casey. *Medical University of South Carolina, Charleston, SC.*

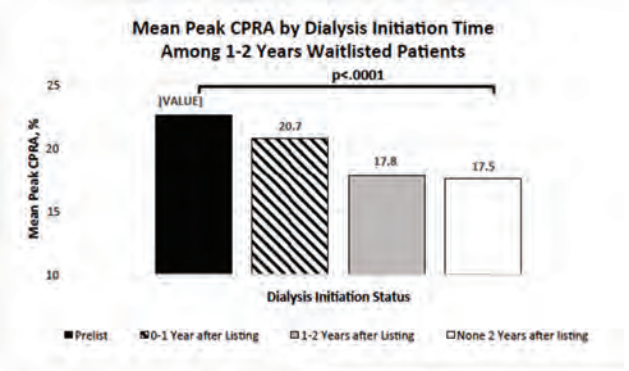
Background: Higher calculated panel reactive antibody (cPRA) restricts access to kidney transplantation, but it's unclear how the timing of dialysis initiation after listing might affect cPRA. We hypothesized that patients with earlier dialysis initiation would have higher cPRA scores.

Methods: This was a retrospective SRTR database study of adults listed for a solitary kidney transplant from 10/1/09 to 11/30/18. Waitlisted patients were stratified by dialysis initiation: prelist, 0-1 year after listing, 1-2 years after listing, or no dialysis within 2 years after listing. The outcomes studied were mean peak CPRA at 0-1 year and 0-2 years after listing. One-way ANOVA was used for statistical analysis.

Results: A total of 173,964 patients were identified who were waitlisted for 1-2 years. With later dialysis initiation, there was a stepwise decline in mean peak CPRA between those who initiated dialysis prelist, 0-1 year after listing, and 1-2 years after listing (Figure 1). There was no difference in mean peak CPRA between the dialysis initiation groups "1-2 years after listing" and "no dialysis 2 years after listing." A similar stepwise decline in mean peak CPRA was seen with patients who were waitlisted for 0-1 year (Table 1).

Conclusions: Our data suggest that waitlisted patients with earlier dialysis initiation may be at risk for developing higher cPRA scores. If verified with further studies, then this may be an incentive for early predialysis referrals for transplant evaluation.

Funding: Commercial Support - Dialysis Clinic Inc.



Graph 1: Mean Peak cPRA by Dialysis Initiation Time Among 1-2 Years Waitlisted Patients

Population	Dialysis Initiation Status	N (%)	Peak CPRA Mean ± SD	p-value
0-1 Year on Waitlist	Prelist	171,335 (65.2%)	19.3 ± 33.4	<.0001
	0-1 year post listing	11,980 (4.6%)	16.5 ± 30.4	
	None	79,424 (30.2%)	14.0 ± 28.0	
1-2 Years on Waitlist	Prelist	116,402 (66.9%)	22.5 ± 35.2	<.0001
	0-1 year post listing	10,693 (6.1%)	20.7 ± 33.5	
	1-2 years post listing	4,038 (2.3%)	17.8 ± 30.7	
	None	42,831 (24.6%)	17.5 ±30.7	

Tabel 1: Mean Peak cPRA Data

PO2520

Variations in Practice Patterns in Eligibility Assessments Across Kidney Transplant Programs in the United States

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Background: Kidney transplant programs are known to vary in terms of their practice patterns given lack of consensus surrounding many aspects of pre-transplant workup. The differences in national practice patterns related to transplant eligibility assessments have not been well described in the contemporary era.

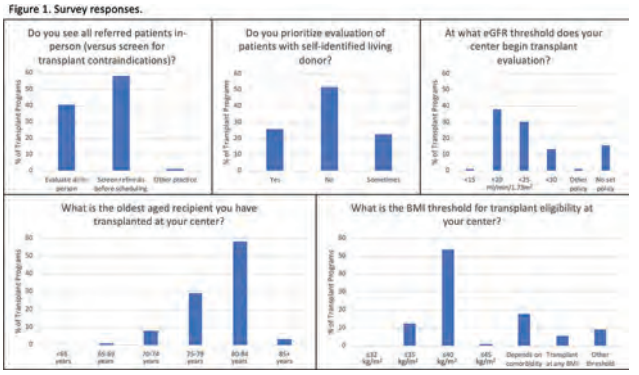
Methods: We conducted a survey of kidney transplant programs in the US to assess current practice patterns as it relates to criteria for prioritizing transplant referrals, candidate evaluation, and determination of eligibility for kidney transplantation. We distributed our survey to 171 adult kidney transplant programs in the US.

Results: 89 (52%) of programs invited to participate in the survey completed it, 45% of which were completed by the Medical Director, 48% by a Transplant Nephrologist, and 7% by other providers. The majority of programs (58%) screened referrals for contraindications to transplantation before scheduling an in-person evaluation (Figure 1). 52% of programs did not prioritize the evaluation of patients with a self-identified living donor candidate when scheduling patients referred for eligibility assessments (Figure 1). Centers differed in the kidney function threshold at which transplant evaluation was begun, and age and body mass index limits for transplantation also varied considerably (Figure 1).

Conclusions: There is wide variation across transplant programs in the assessment of eligibility for kidney transplantation. Further studies are needed to understand how these variations may be associated with access to transplantation and post-transplantation outcomes.

Funding: NIDDK Support

Figure 1. Survey responses.



PO2521

Post-Transplant Diabetes Mellitus in a Single Pediatric Kidney Transplant Center: Risk Factors, Outcomes, and Characterization of Clinical Course

Anjali Khanna,[1] Jee-Young N. Ham,[3,2] Margret Kamel,[3] Kathryn M. Ngo,[1] Amanda S. Thomas,[3] Rochelle Liverman,[2] Rouba Garro.[3,2] *[1]Emory University School of Public Health, Atlanta, GA; [2]Children's Healthcare of Atlanta Egleston Hospital, Atlanta, GA; [3]Emory University School of Medicine, Atlanta, GA.*

Background: The prevalence and outcomes of post-transplant diabetes mellitus (PTDM) in pediatric kidney transplant (KT) recipients vary among studies due to the lack of a consistent definition. Risk factors for and pathogenesis of pediatric PTDM are incompletely understood.

Methods: PTDM prevalence, risk factors and disease course was evaluated at a high volume, tertiary care pediatric hospital. We performed a retrospective review of pediatric KT recipients between 2006-2016 to evaluate PTDM prevalence. PTDM was defined as persistent hyperglycemia with serum glucose ≥200 mg/dl, HbA1C ≥6.5%, *and* requiring antihyperglycemic treatment for ≥ 30 days. Full data were available on all patients transplanted between 2010-2016 and were used to compare demographic and clinical characteristics between PTDM (n=9) and non-PTDM patients (n=173) using Chi-square and Wilcoxon rank sum tests.

Results: Between 2006-2016, 312 patients received KT. Five patients with pre-existing DM were excluded. Fifteen developed PTDM with a prevalence estimate of 4.89 % (95% CI: 3% - 8%) and median time from transplant to DM was 17.6 months (25^{th}-75^{th}: 3 – 83). The majority of PTDM patients had a family history of DM in 1st degree relatives (81%) and were maintained on tacrolimus at diagnosis (67%). PTDM diagnosis and insulin initiation occurred in the context of active rejection episode in only two patients. Despite a more stringent definition of PTDM, insulin therapy was discontinued in 3/15 (20%) patients who continued to be normoglycemic. Comparing patients with and without PTDM during the period 2010-2016 revealed that PTDM patients had higher BMI-Z scores at transplant (p=0.053) and higher average blood glucose during the first week post KT (p=0.095), with no difference in age, gender, race, donor status, or dialysis modality.

Conclusions: A more consistent definition of PTDM and larger studies are warranted to better understand the prevalence, risk factors, and pathogenesis of hyperglycemia and PTDM in children. Detailed patient-level data can provide nuance that may be missed with larger registry studies.

Funding: Private Foundation Support

PO2522

Diabetic Nephropathy: Is It All About Hyperglycemia?

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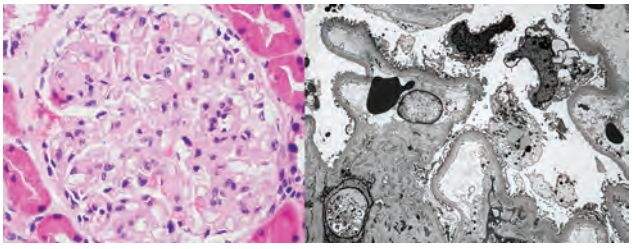
Introduction: Diabetic nephropathy (DN) is the most common cause of end stage renal disease (ESRD). Hyperglyemia has been suggested to be necessary for the development and maintenance of DN. Simultaneous pancreas and kidney transplantation (SPK) has revolutionized the treatment of type 1 diabetic patients with end-stage renal disease (ESRD), and prevention of recurrent DN is one of the main proposed benefits. We present a case of recurrence of DN after SPK despite normal endocrine pancreas allograft function

Case Description: A 47-year-old man with past medical history of ESRD due to diabetes type I who underwent a SPK transplant from a deceased donor in December 2003. His nadir serum Creatinine was 1.5 mg/dl and baseline urine protein creatinine ratio (UPC) is 110-250 mg/g. Maintenance immunosuppression consisted of tacrolimus, mycophenolate, and prednisone. His home medications also included benazepril for hypertension. Sixteen years after transplant, he was noted to have increase in UPC to 2100 mg/g and serum Creatinine to 1.9 mg/dL. Trough tacrolimus levels in the preceding 6 months ranged between 4.8 and 10.9 ng/mL. Donor specific antibodies were negative. He underwent renal allograft biopsy which showed early nodular mesangial matrix expansion and thickened glomerular basement membranes on electron microscopy

consistent with diabetic nephropathy (Figure 1), early chronic transplant glomerulopathy, and severe arteriolar hyalinosis. Additional laboratory findings showed serum lipase 34 (Normal 7-60 U/L), amylase 103 (Normal 21-101 U/L), fasting glucose 79 (Normal 65-99 mg/dL), hemoglobin A1c 5.3, and C peptide was 2.03 (Normal 0.80 - 3.85 ng/mL). Despite increasing Benazepril dose to 40 mg daily, UPC and Cr continued to increase but stabilized in a range of 3800-4500 mg/g and 2.5 mg/dL respectively.

Discussion: Our case suggests that development of DN can be linked to mechanisms independent of hyperglycemia and the usual metabolic disturbances seen in patients with diabetes. A comprehensive restudying of the pathophysiology of DN could further enhance our existing knowledge of the factors implicated in DN, and possibly our ability to develop a more targeted therapy.



PO2523

Use of Weight-Altering Diabetes Medications to Address Obesity as a Barrier to Kidney Transplant Evaluation in Patients with Type 2 Diabetes and Stage 4-5 CKD or ESKD

Kiran Chintam, Prince Mohan, Jamie A. Green, Alex R. Chang. *Geisinger Health, Danville, PA.*

Background: Many patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) are ineligible for kidney transplant due to high body mass index (BMI). Some medication classes are associated with weight loss (glucagon-like peptide-1 receptor agonists [GLP1-RAs]), neutral-weight (dipeptidyl peptidase-4 inhibitors [DPP4i]), or weight gain (sulfonylureas and insulin).

Methods: We examined the relationship between BMI and use of weight-altering diabetes medications in patients with type 2 diabetes mellitus and stage 4-5 CKD or dialysis-dependent ESKD at Geisinger (1/18-3/20). In addition, we examined whether access to kidney transplant evaluation varied by BMI in patients on dialysis.

Results: Out of 4200 patients with T2DM and stage 4-5 CKD or ESKD, 30% had BMI≥35kg/m^2 and 15% had BMI≥40 kg/m^2. Overall, use of T2DM medications with favorable weight effects was low, similar to use of sulfonylureas **(Table)**. Patients with severe obesity had higher GLP1-RA use (BMI ≥ 35 vs. <35 kg/m^2: 11%, 5%), higher insulin use (69%, 53%), and lower DPP4i use (9%, 13%). Similar findings were noted in the subset of patients on dialysis: GLP1-RAs (BMI ≥ 35 vs. <35 kg/m^2: 6% vs. 2%), DPP4is (3% vs. 6%), sulfonylureas (5% vs. 8%), insulin (77%, 74%). In unadjusted analyses, transplant clinic attendance was highest in ESKD patients with BMI 30-34.9 kg/m^2 (23%), followed by BMI 35-39.9 (17%), BMI 25-29.9 (15%), BMI 18.5-24.9 (13%), BMI ≥40 (7%), and BMI < 18.5 (5%).

Conclusions: The vast majority of patients with T2DM and advanced CKD are taking obesogenic rather than weight loss-promoting diabetes medications. Those with BMI ≥40 kg/m^2 were 3.6x less likely to have been evaluated in transplant clinic than those with class I obesity (BMI 30-34.9 kg/m^2). Consideration of the differential impact of certain diabetes medication classes on weight may help improve access to kidney transplantation and long-term outcomes.

Funding: NIDDK Support

Table. Diabetes Medications Use by BMI

	BMI 35+ (n=1103)	BMI <35 (n=3097)	Overall (n=4200)
Weight gain-associated meds			
Insulin	758 (68.7%)	1650 (53.3%)	2,408 (57.3%)
Sulfonylurea	152 (13.8%)	476 (15.4%)	628 (15%)
Meglitinides	28 (2.5%)	101 (3.3%)	129 (3.1%)
Thiazolidinediones	17 (1.5%)	46 (1.5%)	63 (1.5%)
Weight-neutral meds			
DPP4 inhibitor	95 (8.6%)	387 (12.5%)	482 (11.5%)
Alpha-glucosidase inhibitor	0	8 (0.3%)	8 (0.2%)
Weight loss-associated meds			
GLP1-4A inhibitor	119 (10.8%)	142 (4.6%)	261 (6.2%)
Biguanides	85 (7.7%)	203 (6.6%)	288 (6.9%)
SGLT inhibitor	4 (0.4%)	15 (0.5%)	19 (0.5%)

PO2524

Efficacy and Safety of SGLT-2 Inhibitors for Treatment of Diabetes Mellitus Among Kidney Transplant Patients: A Systematic Review and Meta-Analysis

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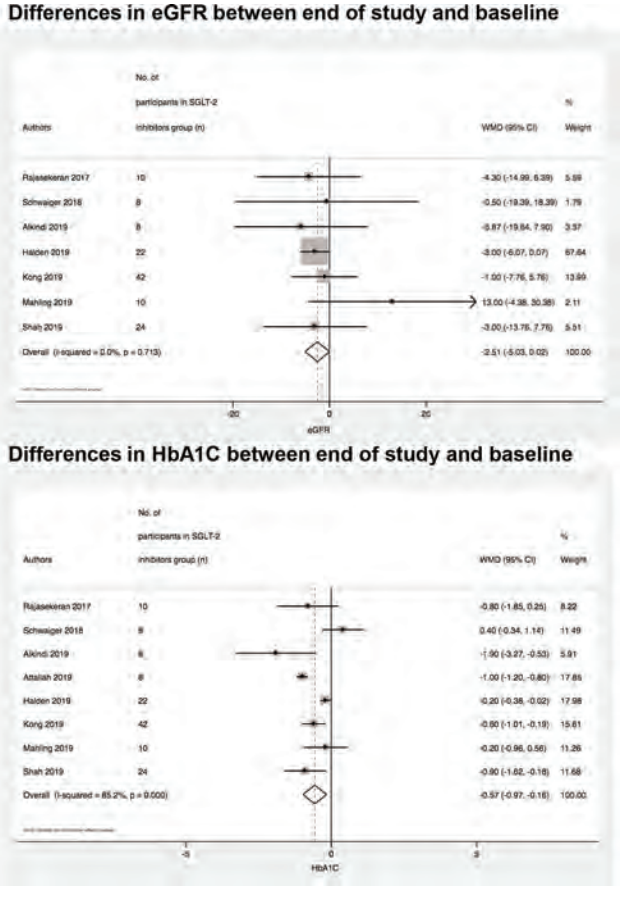
Background: The objective of this systematic review was to evaluate the efficacy and safety profiles of sodium glucose co-transporter 2 (SGLT-2) inhibitors for treatment of diabetes mellitus (DM) among kidney transplant (KT) recipients.

Methods: We conducted electronic searches in Medline, Embase, Scopus, and Cochrane databases from inception through April 2020 to identify studies that investigated efficacy and safety of SGLT-2 inhibitors in KT patients with DM. Study results were pooled and analyzed utilizing random-effects model.

Results: Eight studies with 132 patients [baseline estimated glomerular filtration rate (eGFR) of 64.5±19.9 mL/min/1.73m^2] treated with SGLT-2 inhibitors were included in our meta-analysis. SGLT-2 inhibitors demonstrated a significantly lower HbA1C (WMD = -0.56% [95%CI: -0.97, -0.16]; p=0.007) and body weight (WMD = -2.16 kg [95%CI: -3.08, -1.24]; p<0.001) at end of study compared to baseline level. There were no significant changes in eGFR, serum creatinine, urine protein creatinine ratio, and blood pressure. By subgroup analysis, empagliflozin demonstrated a significant reduction in BMI and body weight. Canagliflozin revealed a significant decrease in HbA1C and systolic blood pressure. In terms of safety profiles, 14 patients had urinary tract infection. Only 1 had genital mycosis, 1 had acute kidney injury, and 1 had cellulitis. There were no reported cases of euglycemic ketoacidosis or acute rejection during the treatment.

Conclusions: Among KT recipients with excellent kidney function, SGLT-2 inhibitors for treatment of DM are effective in lowering HbA1C, reducing body weight, and preserving kidney function without reporting of serious adverse events, including euglycemic ketoacidosis and acute rejection.



PO2525

Health System Encounters in Kidney Transplant Recipients Converted from Immediate-Release Tacrolimus Capsules to Extended-Release Tacrolimus Tablets

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Background: Kidney transplant recipients (KTRs) converted from immediate-release tacrolimus capsules (IR-TAC) to extended-release tacrolimus tablets (ER-TAC) may benefit from reduced dosing frequency and improved bioavailability. However, few studies have characterized health system encounters in these KTRs. Study aims were to (1) determine if conversion to ER-TAC decreased number of dose changes, TAC troughs, and transplant clinic visits and (2) characterize number of dose changes and days to achieve two consecutive therapeutic troughs (5-12 ug/L) under ER-TAC.

Methods: Retrospective review of KTRs at our center transplanted between 2/2010-3/2019, on IR-TAC for ≥90 days, and converted to ER-TAC for ≥90 days. Random-coefficient Poisson regression was used to compare number of dose changes, troughs, and clinic visits during the 90-day periods pre- and post-conversion.

Results: 64 KTRs met inclusion criteria. Mean (SD) age was 52.8 (13.7) years. 38 (59%) were male, 28 (44%) were Black, and 8 (13%) were in an ER-TAC financial assistance program. Median (IQR) time since transplant was 533 (211-1,483) days. KTRs were converted for tremor, 26 (41%); non-adherence, 12 (19%); high IR-TAC dose, 2 (3%); sub-therapeutic troughs, 2 (3%); and other/unknown, 22 (34%). The incidence rate of dose changes but not troughs or clinic visits decreased significantly post-conversion (Table). For the 24 (38%) KTRs with two consecutive therapeutic troughs within 90 days, median (IQR) number of dose changes was 2 (0-1) and days to achieve two consecutive therapeutic troughs was 33.5 (23.5-63).

Conclusions: The incidence rate of dose changes decreased significantly under ER-TAC, but most KTRs did not achieve two consecutive therapeutic troughs within 90 days of conversion. Closer follow up may be beneficial for these KTRs. Future research should determine if reasons for conversion resolved with ER-TAC.

	IR-TAC (90 days)		ER-TAC (90 days)				
	Median no.	IQR	Median no.	IQR	Adjusted IRR*	95% CI	P-value
Dose changes	1	1-1	0.5	0-2	0.59	0.40-0.89	0.011
TAC troughs	2.5	1-7	4	2-6	1.07	0.86-1.33	0.551
Transplant clinic visits	1	0-2	1	0-2	0.76	0.55-1.06	0.104

* Adjusted for age, sex, race, financial assistance, conversion reason, time since transplant, and achievement of two consecutive therapeutic troughs

PO2526

Looking Beyond the Allograft Survival: Long-Term, Five-Year Renal Outcomes in Lung Transplant Recipients

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Background: With the increase in incidence and overall survival of lung transplant recipients, the risk for chronic sequelae in terms of CKD is on the rise. However, the data on the long-term effect on kidneys in this population is scarce. Our study is the first to assess the five-year renal outcomes in Lung transplant recipients.

Methods: We did a retrospective chart review of 171 adults with lung transplants performed between 1st January 2014 - 1st January 2019 and meeting inclusion/exclusion criteria. Primary outcomes were - the prevalence of CKD/ESRD (requiring RRT), risk of development of CKD in patients with AKI during index hospitalization, and all causes mortality in recipients with CKD when compared to the non-CKD group. Secondary outcomes were calculation of the frequency of utilization of modalities for CKD (urinalysis, renal USG, biopsy, nephrology consults).

Results: 86% of patients were white, with a median age of 61 years, median BMI 27.3 kg/m^2, and 60% were males. Hypertension was present in 55% of recipients at baseline. COPD and IPF were the commonest etiology for lung failure, and 66% received a double lung transplant. Baseline median creatinine and egfr were 0.8mg/dL, and 54mL/min/1.73 m2 respectively. 6% (n=171), 60% (n=161), 67% (n=153), 79% (n=47), and 86% (n=7) had CKD at baseline, 3, 6, 12, 36, 60 months, respectively. Eight percent received dialysis during the index hospitalization. The odds ratio of development of CKD in patients with an AKI episode during index hospitalization versus no AKI was 6.22 (2.87 to 13.06, $p < 0.0001$). Whereas, the odds ratio of all causes mortality in patients with CKD when compared to non-CKD was 3.36 (1.44 to 8.64, p-value 0.005). Hematuria and proteinuria were measured infrequently. Renal biopsy done in 1.1% with renal USG abnormal in 22%, normal in 21 % and never performed in 57%. Sixteen percent of recipients were on dialysis, 3% received a renal transplant, and 27% of mortality noted over a five-year follow up period.

Conclusions: There is a high prevalence of CKD in lung transplant recipients, and increased in the patients who had an AKI during index hospitalization. With increased lung transplant nowadays, early involvement of nephrologists is prudent to prevent and manage CKD effectively in the future. Large prospective trials to delineate the problem is warranted.

PO2527

Incidence, Risk Factors, and Outcomes of Post-Transplant Erythrocytosis After Kidney Transplantation

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Background: Post-transplant erythrocytosis(PTE) is a common condition after kidney transplantation. PTE is known to increase the risk of stroke, pulmonary embolism, and deep vein thrombosis, commonly called vascular thromboembolism(VTE). In the current era of immunosuppressive medication and management, the incidence, risk factors, and outcomes of PTE among kidney transplant recipients(KTR) is unknown.

Methods: This was a retrospective study among all adult KTRs transplanted at our university hospital between 01/2001 and 12/2016. All recipients in the PTE group had at least 2 consecutive Hct levels of >51 within the first 2 years of transplant. Controls were selected in a ratio of 5:1 using event density sampling. Patient survival, graft survival, and VTE incidence were outcomes of interest.

Results: Of 4317 kidney transplants during the study period, 214(5%) had PTE and were compared with 1035 controls. While comparing baseline characteristics between PTE and control, KTRs in the PTE group were more likely to be younger, male, have lower BMI, higher prevalence of diabetes as the cause of ESRD and receive a non-preemptive transplant. Similarly, looking at donor characteristics, the PTE group was likely to receive the kidney from a younger donor and have lower KDPI. The median interval from transplant to the diagnosis of PTE was 9.9 months (IQR 5.89). 13 (6.1%) in the PTE group and 71(6.9%) in control had VTE events. In the multivariable analysis, patients with older age (HR: 0.98, 95% CI 0.97-0.99, p=0.005) and higher BMI (HR: 0.97, 95% CI 0.93-0.99, p=0.05) were less likely to develop PTE, while non-preemptive transplant (HR: 3.95, 95% CI 1.74-8.99, p=0.001) was significantly associated with increased risk of PTE. After adjustment for the multiple confounding factors, PTE was not associated with patient mortality (HR: 1.0, 95% CI 0.70-1.43, p=0.99), graft failure (HR: 1.13, 95% CI 0.69-1.83, p=0.61) or VTE (HR: 1.07, 95% CI 0.59-1.96, p=0.81). In a subgroup analysis among PTE with Hct >55 (n=39) compared with controls, similar findings were observed.

Conclusions: In this era, the prevalence of PTE is lower at 5% compared to around 15% in various previous studies. Similarly, there were no detrimental effects of PTE on patient survival, graft survival, or the risk of VTE in the current era.

PO2528

Post-Transplant Outcomes Among Kidney Transplant Recipients with Intentional and Unintentional Weight Loss

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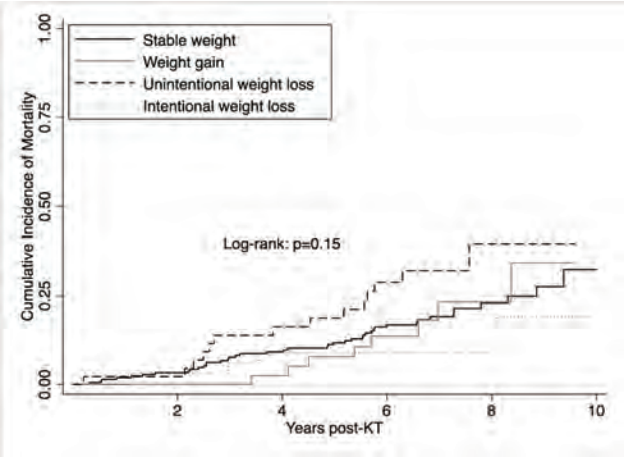
Background: Research has shown that kidney transplant (KT) recipients who lose weight before KT are at increased risk for post-KT weight gain, all-cause graft loss (ACGL), and mortality. No studies have examined whether these associations differ between KT recipients with intentional and unintentional weight loss.

Methods: Among 366 KT recipients from a prospective cohort study of frailty and KT, we used adjusted mixed effects models to estimate differences in post-KT BMI trajectories, ACGL, and mortality by 1-year pre-KT weight change, defined as stable weight, intentional weight loss, unintentional weight loss, and weight gain.

Results: Mean age was 53 years, 39% were black, and 39% were female. The majority (64%) had stable pre-KT weight, 12% had weight gain, 14% had unintentional weight loss, and 10% had intentional weight loss. By 3 years post-KT, BMI increased by 0.05 kg/m^2 (95% CI 0.02, 0.08 kg/m^2) among those with stable pre-KT weight; the increase was similar among those with pre-KT weight gain and intentional weight loss. Those with pre-KT unintentional weight loss had larger increases in post-KT BMI than those with stable weight (BMI change difference +0.15 kg/m^2 [0.04, 0.25 kg/m^2], p=0.01). Unadjusted cumulative incidence of mortality was similar across weight change categories (Figure). Adjusted for age, sex, race, BMI, and donor type, only unintentional weight loss was associated with higher mortality (aHR 2.31 [1.24,4.31], p=0.008) and ACGL (aHR 2.02 [1.24,3.31], p=0.005) relative to stable weight.

Conclusions: In this study, pre-KT unintentional weight loss was associated with higher post-KT BMI increases, ACGL and mortality than pre-KT intentional weight loss, stable weight, and weight gain. These results suggest that unintentional weight loss should be identified and addressed in KT candidates, independent of BMI.

Funding: NIDDK Support



Cumulative Incidence of Mortality among Kidney Transplant Recipients by Pre-Transplant Weight Change

PO2529

Obesity and Poorer Renal Allograft Function: Analysis of Longitudinal Data

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Background: Obesity is associated with worsened allograft function, but its effect on allograft function after established baseline allograft function at a 12-week post kidney transplant (KT) is unclear.

Methods: All 105 KT recipients were divided into obese (BMI ≥30 kg/m^2) and non-obese groups. Longitudinal data were analyzed by linear mixed model to examine association between obesity and eGFR during the 1st year post-KT.

Results: Mean age was 54±11 years and 64 patients (61%) was female. Seventy-one patients (68%) were obese. Generalized estimating equation revealed that eGFR increased 0.16 ml/min/1.73 m^2 (β±SE 0.16±0.04; 95%CI 0.09 to 0.23) for every 1 week after KT. Excluding eGFR at 4-week post-KT when baseline allograft function is generally not established, mean eGFR at 12-week post-KT was the lowest and assigned as the baseline allograft function. Given unequal spreading of time when eGFR were measured, a 1-year follow-up was categorized into every 4 and 12 weeks if eGFR were measured before and after a 12-week post-KT, respectively. Spline interaction term was created at the 12-week post-KT as well as categorized time-spline interaction term. By using a linear mixed model and after adjusted for age, gender, type of KT (deceased vs living donor KT), obesity category and its interaction team with categorized time and spline interaction term, obese group had a higher rate of eGFR decline of 2.9 ml/min/1.73 m^2 every 4 weeks prior to 12-week post-KT, and the rate declined to 1.1 ml/min/1.73 m^2 every 12 weeks after 12-week post-KT. At the 12-week post when baseline eGFR was established, eGFR were 74.1±30.5 and 78.0±30.5 ml/min/1.73 m^2 for obese and non-obese groups, respectively (random intercept); whereas, rate of increase in eGFR of those corresponding groups were 69.3±0.2 and 70.3±0.2 ml/min/1.73 m^2 every 12 weeks (random slope).

Conclusions: Although population-based estimated eGFR was significantly increased overtime, obese KT recipients had lower baseline eGFR at the 12-week post-KT and slower rate of increased eGFR than those of non-obese group when individual baseline eGFR at the 12-week post-KT and rate of eGFR change were taken into the consideration. Pre-KT obesity remains one of the associated factors of poor allograft outcomes, which may be mitigated by pre-KT weight loss.

PO2530

A Call to Action: Finding the Right Kidney for All Potential Recipients

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Background: The burden of dialysis among ESRD patients is a huge driver of morbidity, mortality, and cost. Thousands of deceased-donor (DD) kidneys that almost certainly have better outcomes than dialysis are discarded each year. Our center sought to find and transplant kidneys that would reduce waiting time for our patients while preserving post-transplant outcomes consistent with nationally expected results.

Methods: We reviewed 1119 consecutive DDKT recipients transplanted between 1/1/2016 and 12/31/2019 at our center. Endpoints were eGFR by MDRD death-censored graft survival using Kaplan-Meier survival estimation and the Cox Proportional Hazards Model. We reviewed on additional year (2015) for waiting time impact.

Results: DD KT volumes doubled from 2016 to 2019 (191 vs. 384). Growth was attributable to increased acceptance of hard-to-place imported kidneys, including kidneys with AKI (413% increase) and KDPI > 85 (296% increase). In 2016, 46.6% of DD kidneys were imported from outside our DSA and by 2019, 77.3% were imported. Overall one-year patient survival was 96.6% (CI: 95.4-97.6%) and death-censored one-year graft survival was 95.8% (CI: 94.4%-97.6%). Recipients with any stage of AKI saw no additional risk vs. donors without AKI (HR 0.94, p=0.854) while death-censored graft survival at one year was 91.9% for recipients of kidneys with KDPI >85% vs 96.7% with KDPI ≤85%, representing significant additional risk (HR: 1.91; p=0.017). This significantly decreased waiting time at transplant across all blood types (6.4 years in 2015 to 3.9 years in 2019). This benefit was even greater for blood group B (10.7 to 4.3), and significantly reduced the disparity in accrued waiting times for African-American and Hispanic populations. Kidney function was good at 1 year in all groups among those surviving with followup. Mean eGFR by MDRD formula was 60.0 (SD 23.2) in recipients with non-AKI donors and 61.9 (SD 26.1) in recipients with AKI donors (p=0.4384). Mean eGFR 49.0 in the KDPI > 85% group vs 62.3 in the <= 85% KDPI group (p<0.0001).

Conclusions: Transplant centers can answer the growing demands of patients enduring dialysis to better utilize kidneys that have previously been discarded. Our center has demonstrated that it is possible to reduce waiting time, and maintain outcomes using kidneys previously discarded.

Funding: Clinical Revenue Support

PO2531

Impact of High Body Mass Index on the Allograft Outcomes in Kidney Transplant Recipients with Presensitization to Human Leukocyte Antigen

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Background: The aim of this study was to investigate whether high body mass index (BMI) and pre-sensitization to human leukocyte antigen (HLA) in kidney transplant recipients (KTR) had a synergistic impact on the allograft outcomes.

Methods: From January 2010 to December 2018, 1,290 KTs were performed in Seoul St Mary's Hospital. Of these, 682 cases of ABO compatible KT were enrolled. They were divided into 4 groups (low BMI-non-sensitized, high BMI-non-sensitized, low BMI sensitized, high BMI-sensitized) according to the median BMI value (22.7 kg/m^2) and HLA pre-sensitization status (HLA-DSA MFI >3,000). Short-term and long-term allograft outcomes were compared between the groups.

Results: The rate of late antibody mediated rejection tended to be the highest in the high BMI-sensitized group, and the decline in allograft function in the high BMI-sensitized group was higher than in the other 3 groups. Death-censored graft loss (DCGL) rates and the hazard ratio (HR) for DCGL were the highest in the high BMI-sensitized group (4/21 (19.0%), HR 4.648, P = 0.022) and a significant interaction was detected between high BMI and HLA pre-sensitization status (P value for interaction = 0.008).

Conclusions: Our results suggest that pre-sensitization to HLA and high BMI in KTRs might have a synergistic adverse impact on the allograft outcomes.

Funding: Government Support - Non-U.S.

Table 1. Hazard ratios of death-censored graft loss according to BMI and presensitization status

	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	P-value for interaction
Low BMI-non sensitized	Reference		Reference		0.008
High BMI-non sensitized	1.661 (0.849-3.247)	0.138	1.495 (0.735-3.041)	0.267	
Low BMI-sensitized	2.650 (0.872-8.057)	0.086	3.377 (1.082-10.538)	0.036	
High BMI-sensitized	5.656 (1.859-17.211)	0.002	4.648 (1.251-17.276)	0.022	

Multivariate regression model was adjusted with parameters showing significant difference among the 4 groups according to BMI and pre-sensitization status. Parameters were as follows: Age, Sex, DM, HTN, Fasting glucose, Triglyceride, HDL-cholesterol, Hemoglobin A1c, ESRD causes, Dialysis modality, and Prior KT history.

PO2532

Association Between Post-Transplant Visit-to-Visit Pulse Pressure Variability and Late Transplant Systolic Blood Pressure in Non-Elderly Kidney Transplant Recipients

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Background: Visit-to-visit blood pressure variability is associated with vascular stiffness and cardiovascular outcomes, particularly in elderly. Association between visit-to-visit pulse pressure variability (VVPPV), which takes SBP and DBP into account, and late post-kidney transplant (KT) blood pressure (BP) in different age groups is unknown.

Methods: VVPPV was examined by average successive variability ASV), which is the average absolute difference between successive BP measured at 4, 12, and 24 weeks post-KT. Since the slope of the linear plot between VVPPV and SBP at 48 week post-KT abruptly changed when VVPPV was 15 mmHg, VVPPV was then categorized into <15 and ≥15 mmHg (Figure1A). Association between the categorized VVPPV and systolic and diastolic hypertension (SHTN, DHTN) at 48 weeks defined by SBP and DBP ≥130 and ≥80 mmHg, respectively was examined by multiple logistic regression and stratified into age <60 and ≥60 years old.

Results: Of all 105 KT recipients from a single KT center, mean age±SD was 54±12 years and 64 patients (61%) was female. Mean VVPPV was 13±9 (range 2 to 50). Mean post-KT SBP and DBP at 48 weeks post-KT were 133±16 and 77±11 mmHg, respectively. In the whole study population adjusted by gender, donor type (deceased vs. living), and types of induction immunosuppressive medications, patients with VVPPV ≥15 mmHg had 3.36 times higher risk of developing SHTN (OR 3.36, P 0.02, 95%CI 1.17, 9.65). However, after additional adjustment by age and interaction term between age and ASV, the association was persist only in patients whose age <60 years old ($OR_{<60\text{-}y/o}$ 3.80, p 0.04, 95%CI 1.04, 13.91 vs. $OR_{\geq 60\text{-}y/o}$ 2.18, p 0.40, 95%CI 0.36, 13.31)(Figure1B). There was no association between VVPPV and DHTN in the whole study and age-stratified populations.

Conclusions: Higher VVPPV is associated with late post-KT SHTN in younger age group (< 60 years old), but not in elderly. Further studies are required to elucidate the mechanism.

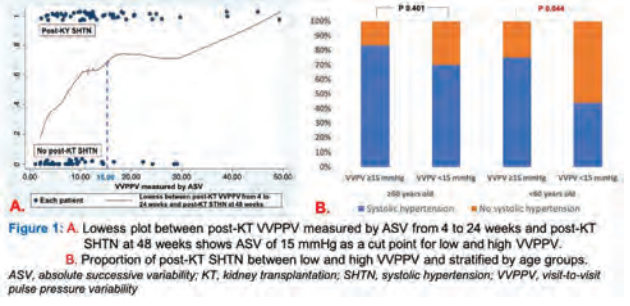

Figure 1: A. Lowess plot between post-KT VVPPV measured by ASV from 4 to 24 weeks and post-KT SHTN at 48 weeks shows ASV of 15 mmHg as a cut point for low and high VVPPV.
B. Proportion of post-KT SHTN between low and high VVPPV and stratified by age groups.
ASV, absolute successive variability; KT, kidney transplantation; SHTN, systolic hypertension; VVPPV, visit-to-visit pulse pressure variability

PO2533

Kidney Transplant Outcomes for Patients with Enteric Oxalosis

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Background: Patients with enteric disorders associated with hyperoxaluria and systemic oxalate burden (enteric oxalosis) are at increased risk for calcium oxalate deposition causing ESRD. The objective of this study is to evaluate kidney transplant (KTx) recipients with enteric oxalosis at our institution.

Methods: KTx recipients with suspected oxalosis due to any of the following: inflammatory bowel disease, bariatric surgery, or pancreatic insufficiency from 2015 to 2019 were included. At our institution, pre-KTx serum oxalate>30mcmol/L is the threshold for treatment.

Results: 31 patients were identified. Mean age was 58.5 years, 55% were female, 81% white, and 94% first KTx. Most common cause of ESRD was diabetes (45%), and 84% were on dialysis prior to KTx (median 30.5 months). The most common enteric cause was Roux-en-Y gastric bypass (RYGB, 77%) with surgery 11 years (median) prior to KTx. 39% had history of nephrolithiasis. Median peak serum oxalate (SOx) pre-KTx was 24mcmol/L. 87% received deceased donor KTx and 52% had delayed graft function (DGF). Post-KTx, 36% received calcium with meals for oxalate binding, and 39% had low oxalate diet education. 5 patients had pre-KTx SOx >30mcmol/L at the time of KTx, of whom 4 had DGF and required either longer dialysis (up to 5 hours long) or increased dialysis sessions (up to 6 per week) to reduce SOx levels post-KTx. The median duration of dialysis after KTx was 13.5days. After median follow up of 27months, mean (SD) estimated glomerular filtration rate (GFR) was 47.6 ±21.7mL/min/1.73m^2 and 68% of patients had GFR <60. One-year GFR was 48.4±21.4mL/min/1.73m^2 which is lower than expected 1-year GFR for our Transplant Center (mean GFR 58.9 ±20.6ml/min/1.73m^2). RYGB patients (n=24) had lower GFR vs patients with other EH causes (n=7) (1 year: 48.7±20.4 vs 56.7±4.9; last follow-up 47.3±21.1 vs 57.5±14.8 mL/min/1.73m^2). Only 2 patients had oxalate crystals on protocol allograft biopsy, both with RYGB, and one with DGF and died 22 months after KTx. GFR at 1 year was 34±2.83 ml/min/1.73m^2 for these 2 patients.

Conclusions: RYGB is the most common cause of enteric oxalosis in KTx recipients. DGF is common and graft outcomes are inferior compared to deceased donor KTx at our institution. The lower GFR in RYGB patients raise concern for enteric hyperoxaluria as an unrecognized risk for allograft dysfunction.

Funding: Commercial Support - ALLENA pharmaceutical

PO2534

Middle Cerebral Artery Hemodynamics Is Blunted in Kidney Transplant Recipients

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Background: Kidney transplant (KT) recipients have a higher risk of dementia and cerebrovascular events than the general population. Cerebrovascular hemodynamic response (CVR) to constant-load moderate-intensity exercise marks the ability of the brain to respond to increased oxygen requirements with exercise. Blunted CVR seen with vascular disease and aging can increase risk of dementia and stroke. We evaluated the middle cerebral artery blood velocity (MCAv) dynamic response in KT recipients and compared it to age matched non-CKD controls.

Methods: 35 KT recipients and 35 healthy controls completed a 90-second rest followed by a 6-minute moderate intensity exercise on a recumbent stepper at a prescribed step rate and workload. We used transcranial doppler (TCD) monitoring for MCAv while continuously monitoring heart rate and beat-to-beat mean blood pressure during rest and exercise. Baseline resting MCAv and steady state response during exercise was recorded. Outcome measures included resting MCAv and CVR (MCAv during steady state exercise – baseline MCAv) and workload needed to achieve target heart rate. Statistical analysis employed independent t-test.

Results: KT recipients were 52.4±1.7 years old, 74.3% male, 91.4% white, 22.9% with diabetes, and 91.4% with hypertension. Controls were 54.4±2.0 years old, 74.3% male, 80% white, without diabetes, and 14.3% with hypertension. Baseline MCAv was similar in the two groups, but the response during moderate intensity exercise differed; CVR for KT recipients was 8.12 ± 0.8 cm/s compared to 12.9 ± 1.4 cm/s for controls (p=0.003) and target workload for KT recipients was 84.1 ± 2.8 watts compared to 123.1 ± 5.3 for controls (p<0.001) (Table 1).

Conclusions: KT recipients have a blunted middle cerebral artery hemodynamic response to exercise compared to healthy controls. This may be due to vascular disease and can explain the higher white matter disease, dementia, and stroke in this population.

Funding: Other NIH Support - Grant K23-AG055666, Commercial Support - Veloxis and Novartis

Table 1. Middle cerebral artery kinetics parameters for rest and response to moderate intensity exercise in kidney transplant recipients and healthy controls.

	KT recipients (n = 35)	Controls (n = 35)	p value
Age	52.4 ± 1.7	54.4 ± 2.0	0.44
Male gender (%)	26 (74.3)	26 (74.3)	1.00
White race (%)	32 (91.4)	28 (80)	0.18
Target workload (Watts)	84.1 ± 2.8	123.1 ± 5.3	< 0.001
Baseline MCAv (cm/s)	51.9 ± 2.1	53.2 ± 1.5	0.62
CVR (cm/s)	8.12 ± 0.8	12.9 ± 1.4	0.003
Baseline MAP (mmHg)	102.1 ± 3.5	81.2 ± 2.4	< 0.001
Steady State MAP (mmHg)	126.1 ± 3.6	106.1 ± 3.3	< 0.001
Baseline HR (bpm)	74.4 ± 2.1	66.5 ± 1.7	0.005
Steady State HR (bpm)	106.3 ± 3.0	111.1 ± 2.0	0.19

Values are means ± SEM. MCAv, middle cerebral artery velocity; CVR, cerebrovascular hemodynamic response; MAP, mean arterial pressure; HR, heart rate.

PO2535

Longitudinal Physical Performance Following Kidney Transplant

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Background: Frailty and poor physical performance are strongly associated with poor outcomes in kidney transplantation (KTx). However, the effect of KTx on physical performance remains poorly understood.

Methods: We measured 6-minute walk test (6MWT, meters) and 1-minute sit-to-stand test (STS, number of repetitions from standing to sitting position) performances within 1 year prior to KTx. Physical performance indices were re-measured at 3 and 6-months, and 1-year post-KTx. Multivariable linear regression was used to assess which baseline characteristics were associated with 6MWT and STS. Trajectories of 6MWT and STS were assessed by baseline performance using a generalized estimating equation.

Results: Among 85 patients who performed baseline assessments, 39, 33 and 40 completed 3, 6, and 12-month evaluations, respectively. Average age was 53 and average dialysis vintage was 7 years. 49% had diabetes mellitus, 18% had coronary artery disease, 5% had cerebrovascular disease, and 10% had peripheral arterial disease (PAD). In the multivariate model, age, female sex, and the presence of PAD were associated with lower 6MWT, while age and female sex were associated with lower STS. Median 6MWT and STS were 419m and 20 repetitions, respectively. 6MWT decreased somewhat after transplant across timepoints, and the trajectory was not significantly modified by baseline 6MWT (Figure 1). In contrast, STS increased post-Tx (Figure 2), but more so in patients with higher baseline STS (*p=0.001*), an effect which persisted after multivariate adjustment for age, sex and PAD (*p=0.002*).

Conclusions: Walking ability did not improve appreciably after KTx. STS, a measure of lower body strength, improved progressively post-KTx, but was mostly observed in patients with higher baseline STS. Results must be interpreted with caution, since all patients, even those with lower physical performance, were selected to proceed with KTx.

Figure 1. 6MWT Post-Transplant

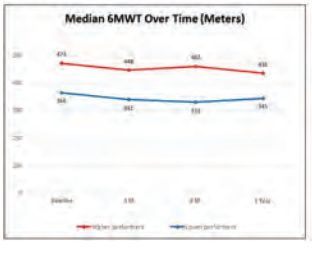
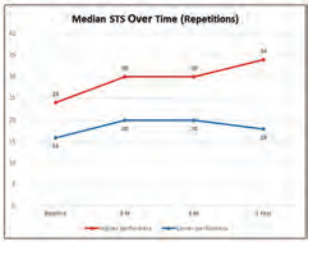


Figure 2. STS Post-Transplant



PO2536

Outcomes of Kidney Transplantation in Fabry Disease: A Meta-Analysis

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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder with progressive systemic deposition of globotriaosylceramide, leading to life-threatening cardiac, central nervous system, and kidney disease. Current therapies involve symptomatic medical management, enzyme replacement therapy (ERT), dialysis, kidney transplantation, and more recently gene therapy. The aim of this systematic review was to assess outcomes of kidney transplantation among patients with FD.

Methods: Comprehensive literature review was conducted utilizing MEDLINE, EMBASE and Cochrane Database, from inception through February 28, 2020 to identify studies that evaluate outcomes of kidney transplantation including patient and allograft survival among kidney transplant patients with FD. Effect estimates from each study were extracted and combined using the random-effects, generic inverse variance method of DerSimonian and Laird.

Results: Eleven studies including 424 kidney transplant recipients with FD were enrolled. The post-transplant median follow-up time ranged from 3 to 11.5 years. Overall, the pooled estimated rates of all-cause graft failure, graft failure before death, and allograft rejection were 32.5% (95%CI: 23.9%-42.5%), 14.5% (95%CI: 8.4%-23.7%), and 20.2% (95%CI: 15.4%-25.9%), respectively. A sensitivity analysis limited only to the recent studies (year 2001 or newer when ERT became available), the pooled estimated rates of all-cause graft failure, graft failure before death, and allograft rejection were 28.1% (95%CI: 20.5%-37.3%), 11.7% (95%CI: 8.4%-16.0%), and 20.2% (95%CI: 15.5%-26.0%), respectively. The pooled estimated rate of biopsy proven FD recurrence was 11.1% (95%CI: 3.6%-29.4%), respectively. There was no significant difference in the risk of all-cause graft failure (P = 0.10) nor mortality (0.48) among recipients with vs. without FD.

Conclusions: Despite possible FD recurrence after transplantation of 11.1%, allograft and patient survival are similar among kidney transplant recipients with vs. without FD.

PO2537

Urine Supersaturation in Patients with Kidney Transplant Nephrolithiasis

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Background: Urine supersaturation (SS) has not been reported for kidney transplant (KTx) recipients with de novo transplant-derived nephrolithiasis. The objective of this study is to evaluate supersaturation studies, treatment, and stone and allograft outcomes in KTx recipients with allograft nephrolithiasis.

Methods: Retrospective review from 2009-2019 of KTx recipients with nephrolithiasis at Mayo Clinic was completed. Stone event was defined as radiologic evidence.

Results: Fifty six transplant nephrolithiasis cases were identified. Mean transplant age was 56.5 (±12.1) years, 32 (57.1%) were male, 46 (82.1%) receiving first KTx, 41 (75.9%) required dialysis, and 17 (30.9%) had stone event prior to KTx. Twenty one (37.5%) had at least 2 stones in the allograft, median stone size was 6 mm, and most common location was the lower pole (n=20 [41.7%]). Median time from KTx to stone event was 1 year. Thirty four (60.7%) had a 24-hour SS study at a median of 2 years after KTx. Select results are shown in Table 1. Of the 34, 14 (41.2%) had a stone event prior to KTx, and 6 (19.4%) had a donor-derived stone. Thirty one (91.2%) had increased SS of calcium oxalate, 17 (50%) calcium phosphate, and 9 (26.5%) uric acid. Thirty two (94.1%) had urine citrate <450mg/24hrs. Management of the initial 56 included potassium citrate in 13 (23.2%), calcium citrate in 10 (17.8%), and dietician referral in 18 (32.1%). Forty five (80.4%) were seen by urology, 28 (50%) needed surgical management, and 14 (27.5%) passed the stone. At median follow-up of 4 years after KTx, 37 (66.1%) had persistent stone disease in the allograft, 3 (5.4%) had graft failure, and 2 (3.6%) had died.

Conclusions: This is the first study of urine SS in patients with transplant-derived nephrolithiasis. Profound hypocitraturia was the most prevalent risk, and increased supersaturation for calcium oxalate crystals predominated. Allograft stone clearance was rare, and many required surgical intervention.

Funding: Clinical Revenue Support

Table 1

Select 24-hr urine supersaturation parameters	Median (Range)
Volume (ml)	2174.5 (745, 3960)
Sodium (mmol)	125.5 (26.0, 400)
Calcium (mg)	103.5 (26.0, 592)
Magnesium (mg)	88.5 (22.0, 240)
Citrate (mg)	124.5 (20.0, 763)
Oxalate (mg)	34.35 (9.8, 136)
pH	5.9 (5.1, 7.7)

PO2538

Exposure to Tacrolimus Trough Levels Below 6 ng/mL During the First Year Is Associated with Inferior Kidney Graft Survival

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Background: Accumulating data indicates that sub-therapeutic levels of calcineurin inhibitors are associated with long-term graft loss. However, while tacrolimus (TAC) was shown to provide adequate immunosuppression with lower acute rejection rate, its optimal maintenance dose for long term graft survival is still unknown. The aim of our study was to determine the minimal TAC trough level, which is associated with improved kidney graft survival.

Methods: We conducted a retrospective cohort study based on the RMC registry. We defined five TAC trough level intervals: 3-4, 4-5, 5-6, 6-7, and 7-8ng/ml. We calculated the exposure time for each drug level interval during the first year following transplantation, defined as the cumulative number of days at each interval. This measure

was adjusted to the exposure time below a given interval-level, allowing us to define the threshold for optimal TAC trough level as the upper limit of the interval. We then determined the association between the adjusted exposure time at each TAC level-interval and our primary outcome, death-censored graft survival.

Results: We included 1417 patients with a median follow up of 5.3 years (IQR 2.9-8.5 years). TAC through level interval of 5-6ng/ml was the highest interval which demonstrated a statistically significant association between exposure time and increased risk of graft loss, even after adjustment to the exposure time below 5ng/ml (HR 1.58 per log days, p<0.001). These results remained consistent in an extensive multivariate analysis (HR 1.44, p<0.004) and were not significantly changed when we analyzed for death-included graft survival (HR 1.2, p<0.026) or the first three months and the subsequent nine months separately (HR 1.93, p<0.001, HR 1.56, p<0.001 respectively). Cumulative exposure time above 14 days to TAC trough level< 6ng/ml, was significantly associated with increased risk of graft loss in most studied subgroups including age, gender, low and high immunologic risk recipients, except for the subgroup of recipients with diabetes.

Conclusions: Prolonged exposure time to TAC trough level between 5-6ng/ml within the first-year post-transplant was independently associated with increased risk of long-term graft loss. These results imply that keeping TAC trough levels above 6ng/ml during the first year might improve kidney transplantation outcomes.

PO2539

High Intrapatient Variability of Tacrolimus in Pediatric and Adolescent Renal Transplant Recipients Is Associated with Worse Graft Outcomes

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Background: High intra-patient variability (IPV) in tacrolimus (TAC) levels has been associated with the development of *de novo* donor-specific antibodies. The degree of TAC IPV in relation to poor graft outcomes in pediatric kidney transplant patients is unknown.

Methods: Patients ages 0-25 years who were transplanted from 01/01/2010-01/01/2018 at a single center were considered for inclusion. Minimum required follow-up time was 12 months. Primary outcomes were formation of C1q+ *de novo* DSAs (*dn*DSAs) and graft loss. *dn*DSAs were identified by routine screening or at investigation of allograft dysfunction. TAC IPV was determined using the mean coefficient of variation (CV) over the immediate 6-month time period prior to each TAC level. All available TAC levels were included in the analysis. Mean CV was calculated using CV from 10 months post-transplant until end of follow-up. Patients were followed until 01/03/2019 or until graft loss. Analyses were performed using descriptive statistics and the Mann-Whitney U test.

Results: 225 pediatric kidney transplant patients met inclusion criteria. Median age was 12.5 years (range 15 mo.-21 yrs.). 46% were female, and 24% received a living donor transplant. 51 formed C1q+ *dn*DSA, and 174 did not. Among patients who formed C1q+ *dn*DSA, 13/51 (25.5%) lost their graft, compared to 2/174 (1.1%) in patients who did not form *dn*DSA by C1q. C1q+ *dn*DSA formers had higher mean CVs compared to patients who did not form *dn*DSA by C1q (median CV 33.9% vs 26.1%, p<0.0001), including when stratified by age subgroups of 0-12 years (p=0.0217) and 13-25 years (p=0.0001) [Figure 1]. Patients with graft loss had higher mean CVs compared to those who did not have graft loss (median CV 39.0% vs 25.8%, p=0.0006).

Conclusions: High tacrolimus IPV was associated with C1q+ *dn*DSA formation and graft loss. Tacrolimus IPV is a potential prognostic tool for optimizing transplantation outcomes.

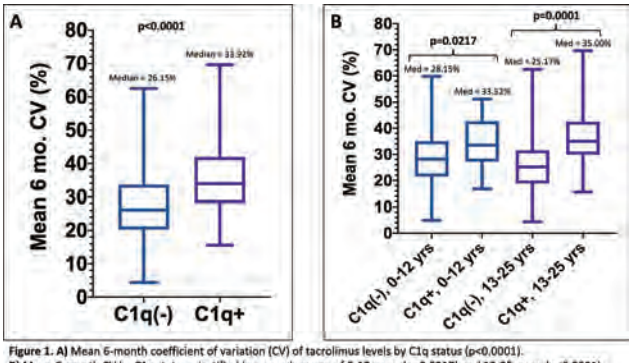

Figure 1. A) Mean 6-month coefficient of variation (CV) of tacrolimus levels by C1q status (p<0.0001).
B) Mean 6-month CV by C1q status, stratified by age subgroups of 0-12 years (p=0.0217) and 13-25 years (p=0.0001). Ages 0-12 yrs: n=117, C1q(-): n=95, C1q+: n=22. Ages 13-25 yrs: n=108, C1q(-): n=79, C1q+: n=29

PO2540

Impact of Renal Transplantation on Functional Status in Tacrolimus Era

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Background: Despite a large body of literature describing survival's outcome after renal transplantation, little is known about the progress of functional capacity post-transplant. Our aim is to assess the effect of renal transplantation and various factors on functional capacity.

Methods: From the United States Organ Procurement and Transplantation Network files, we identified a total of 19,704 renal transplant recipients (RTR) maintained on tacrolimus-based immunotherapy, who had Karnofsky Performance Status Scale (KPSS) defined functional capacity assessment at the time of transplant evaluation with five-years data follow up. Age, gender, ethnicity, functional status, diabetes, body mass index, cold ischemia time, number of previous transplants, panel reactive antibodies, donor type, donor age, HLA-mismatches, number of acute rejection episodes, induction therapies, maintenance immunotherapy on discharge were collected. According to KPSS, RTRs at time of transplant evaluation were divided into 3 groups (A: 13,701 RTRs with mild impairment: >80%, B: 5,557 RTRs with moderate impairment: 40-80%, C: 446 RTRs with severe impairment: <40%). The outcome measured was KPSS functional status five-years post-transplant. Multiple logistic regression analysis was used to assess factors affecting functional status post-transplant.

Results: In group A, 86.45% of patients showed improvement in functional capacity, 65.5% in group B, while 88.56% improved in group C (64.57% improved from severe to mild and 23.99% improved from severe to moderate functional capacity). Furthermore, multiple logistic regression analysis showed that steroid withdrawal protocol was associated with significant improvement in functional capacity (OR=1.28, 95% Confidence Interval (95% CI): 1.1 - 1.49; P=0.007), while dialysis duration before transplantation was associated with abnormal functional capacity post-transplant (OR=0.74, 95% CI: 0.61 - 0.89; P=0.003).

Conclusions: Renal transplantation is associated with substantial improvement in all stages of functional capacity in RTRs. Steroid withdrawal as well as the duration of dialysis are important novel determinant factors of functional capacity post-transplant and merit considerations during transplant selection and subsequent immunosuppressive therapeutic planning.

PO2541

Calcineurin Inhibitor-Based Immunosuppression Has Negligible Negative Effects on Pregnancy Outcomes After Renal Transplantation in the Netherlands

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Background: Pregnancy among renal transplant recipients (RTR) has increased over the past years, also in patients with compromised renal function and/or proteinuria. Immunosuppressive regimens may influence pregnancy outcomes and it is not yet clear whether replacing a calcineurin inhibitor (CNI) by a CNI-free (CNI-) regimen has a favourable effect.

Methods: We therefore retrospectively compared the effect of CNI-based (CNI+) and CNI- immunosuppression in the first trimester of pregnancy on maternal and fetal outcomes in Dutch pregnancies between 1986-2017 in RTR.

Results: We identified 129 CNI+ and 125 CNI- singleton pregnancies. Demographics did not differ except for higher BMI in CNI+ (median 25.3 vs 23.7 kg/m2, p=0.01), year of renal transplantation (2000 in CNI+ vs 1989 in CNI-, p<0.01), year of pregnancy (2006 in CNI+ vs 1998 in CNI-; p<0.01) and interval of transplantation to pregnancy (69 in CNI+ vs 104 months in CNI-; p<0.01). In the third trimester creatinine levels were significantly higher in CNI+ (127 vs 105 µmol/L in CNI-, P<0.01) but this difference had disappeared 6-18 months postpartum. The percentual change in creatinine from preconceptional to the third trimester level was slightly different (+3.1% in CNI+ vs 2.2% in CNI-, P=0.05). In both groups, a postpartum 11-12% creatinine increase from preconceptional level was observed (p=0.92). Regarding fetal outcomes, a trend in increased incidence of birthweight <2500 grams was seen in CNI+ (52% vs 40%, p=0.07) and in both groups there was a high rate of preterm delivery <37 weeks (49% vs 45% in CNI-; p=0.55).

Conclusions: Our data indicate that CNI do not negatively influence the course of renal function up to 18 months postpartum, but only lead to a more pronounced increase in serum creatinine levels towards the end of pregnancy. However, the substantial short term loss of renal function and the high rates of premature birth rate and low birthweight classify them as high-risk pregnancies that should be followed carefully in tertiairy obstetric/nephrologic care programs. Our data do not exclude possible long term negative effects of CNI on overall health, renal function or hypertension in the offspring of these women.

PO2542

The Natural History of Waitlist Candidates in the United States

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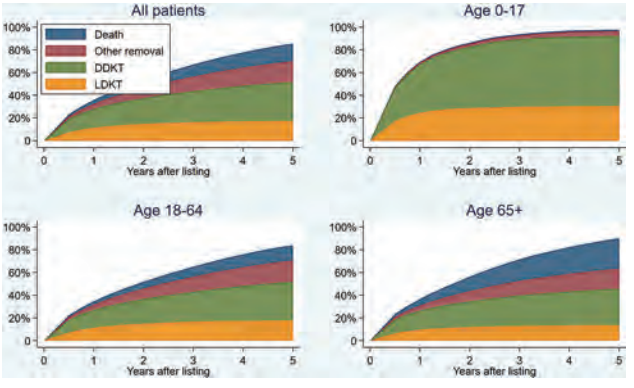
Background: Estimates of time to deceased-donor transplantation (DDKT) generally fail to take into account the competing risks of mortality. Understanding the natural history of KT registrants - their chance of DDKT/LDKT/death based on individual characteristics - can inform referrals for transplantation, counseling for transplant candidates, and allocation policy.

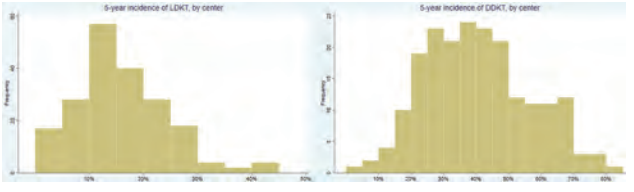
Methods: Using SRTR data on 186,174 waitlist registrants 12/2014-12/2019, we modeled time to DDKT, LDKT, or waitlist mortality in a competing-risks framework, overall and for clinically relevant subgroups of patients (based on candidate age, sex, race, ABO blood type, PRA). Competing-risks regression was used to model individual n-year chance of DDKT/LDKT/mortality based on candidate characteristics.

Results: Among all candidates, 5-year cumulative incidence of LDKT/DDKT/mortality/other removal was 17.3%/34.4%/15.7/18.1% respectively. 85% of LDKT recipients received LDKT within 2 years of listing. Pediatric registrants had substantially higher incidence of DDKT than waitlist mortality (61.7% vs 1.1%), but adults had higher combined of waitlist mortality/other removal DDKT, particularly patients above age 65 (44.4% vs 32.3%) (Figure). Center-level 5-year incidence of LDKT (DDKT) 1.3%-44.8% (4.4%-82.6%) (Figure 2).

Conclusions: Despite a focus in the transplant community on small differences in one-year posttransplant outcomes and a reluctance to transplant kidneys with slightly worse expected outcomes, most adult patients wait >5 years for a kidney, incurring substantial waitlist mortality risk. High incidence of waitlist mortality will only be remedied through aggressive efforts to increase the living and deceased donor organ pool.

Funding: NIDDK Support





PO2543

Unusual Cause of Calcium Oxalate Nephropathy in a Renal Allograft

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Introduction: Crystal nephropathy is a well-known cause of acute kidney injury that is often overlooked. We present a case of oxalate nephropathy in a renal allograft that led to a rare diagnosis.

Case Description: A 63-year-old female with a kidney transplant for end-stage kidney disease (ESKD) caused by acute interstitial nephritis (AIN) presented with acute kidney injury. Her creatinine on presentation was 2.2mg/ dL from her baseline of 1.0mg/dL and increased to around 3.0mg/dL despite hydration. It was decided that she would benefit from allograft biopsy. The biopsy was devoid of any rejection but did have many foci of calcium oxalate crystal deposition with tubular injury. She was planned for a 24-hour urine collection for stone evaluation that showed an elevated urine oxalate level, 140mg. She changed her diet and the 24-hour urine collection was repeated in 3 months with no change. With the continued elevation, genetic testing was sent for primary hyperoxaluria which revealed that she has homozygote mutation in the AGXT gene, confirming that she has type 1 primary hyperoxaluria. Reevaluation of her biopsy diagnosing AIN before transplant was found to have interstitial multinuclear infiltrate with some crystallization consistent with oxalate nephropathy. Her particular mutation responds well to pyridoxine (vitamin B6) so she was started on 600mg per day. Since treatment, her creatinine has stabilized at 3.0mg/dL. Her 24-hour urine evaluation has shown improvement in urine oxalate to 79mg, a 43.5% reduction.

Discussion: Primary hyperoxaluria type 1 (PH 1) is described by recurrence in a renal allograft in only 10% of cases. Delay in the diagnosis is common and results in a significant number of patients who have end-stage kidney disease (ESKD) at initial presentation. The rapidity of progression is determined by the residual enzyme activity and response to pyridoxine(vitamin B6). The definitive cure for PH 1 is liver transplantation that carries significant mortality risk. Medical management includes large fluid intake of greater than 3L/day to decrease tubular fluid oxalate concentration, potassium citrate-citric acid to increase the solubility of calcium oxalate and prevent precipitation, avoidance of oxalate in diet, and high dose pyridoxine to promote the conversion of glyoxylate to glycine rather than to oxalate. A trial of 5mg/kg of pyridoxine is suggested in all PH 1 patients to see how they respond.

PO2544

Secondary Oxalosis with Enteric Oxalate Nephropathy in a Transplant Recipient: Is Mycophenolate the Culprit?

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Introduction: Secondary oxalosis causing acute kidney injury has been widely reported in native kidneys but its occurrence in allograft kidneys is relatively uncommon. Intestinal malabsorption can be present in transplant recipients as a result of factors that differ from the general population such as immunosuppressive medications and some enteral infections. We present a case of enteric oxalate nephropathy as a result of mycophenolate toxicity.

Case Description: A 66-year-old male status post kidney transplant 3 years back for ESKD due to DM and HTN with a baseline creatinine of 1.5 mg/dL presented with a 2-month history of GI symptoms of vomiting, diarrhea and 22 lbs weight loss. He was on tacrolimus, mycophenolate and prednisone for immunosuppression. The patient denied any recent infection or antibiotic use, any medication change, supplements or OTC drug use. The vitals and the physical examination on admission were unremarkable. Lab findings showed Na 139, K 5.5, Cl 117, Bicarb 11, AG 22, Ca 9.6, BUN 71 and creatinine 3.5. Lactate and serum osmolar gap were normal. Lipase, amylase, Vit B1 and B6 were normal. UA showed trace ketones and blood with no protein or bacteria. Serology for CMV and BK virus was negative. Tacrolimus level was at goal. MPA level was noted to be elevated at 9.7 at an office visit 1 month prior to admission with no recent adjustment in dosing. Plasma oxalate was elevated at 3.9. The stools studies and GI panel were negative. CT scan showed a 3mm non-obstructing stone. The renal biopsy showed interstitial fibrosis, tubular atrophy and calcium oxalate deposits with birefringence within the tubules. MMF was discontinued. The patient was given iv fluids and citrate to alkalize the urine. At discharge, his Cr improved with resolution of symptoms.

Discussion: Medication-induced malabsorption should be considered among potential causes of secondary oxalosis. The MMF metabolites indirectly affect lymphocytes in the GI tract leading to mucosal damage with malabsorption and enteric oxalosis. The hyperoxalosis causes saturation of oxalate crystals creating an interstitial nephritis, macrophage recruitment and inflammation leading to tubular atrophy. The transplant recipients with chronic diarrhea and no infection should be suspected for MMF toxicity. The oxalate and MMF levels must be checked and MMF dose should be adjusted accordingly.

PO2545

Prophylactic Use of Eculizumab and Graft Loss in Kidney Transplant Recipients due to Hemolytic Uremic Syndrome in the United States

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Background: Among kidney transplant recipients (KTRs) with end-stage kidney disease (ESKD) due to hemolytic uremic syndrome (HUS), recurrence is associated with poor allograft outcomes. We examined the prophylactic use of eculizumab, a monoclonal antibody that binds complement protein C5, and graft loss among HUS KTRs.

Methods: We conducted a retrospective cohort study using the United States Renal Data System. Out of 123,624 ESKD patients transplanted between January 1, 2008 and June 1, 2016, we identified 348 (0.28%) patients who had HUS as the primary cause of ESKD. We then linked these HUS patients to datasets containing the Healthcare Common Procedure Coding System (HCPCS) code for eculizumab infusion. We calculated crude incidence rates of overall graft loss and death-censored graft loss and conducted exact logistic regression, adjusted for recipient age and sex. Patients who received eculizumab prior to or within 30 days of transplant represented the exposure group.

Results: Our final study cohort included 335 HUS KTRs (23 received eculizumab, 312 did not). There were no significant differences in baseline demographic and clinical characteristics between the eculizumab vs. non-eculizumab group. For those who received eculizumab, the median number of infusions per patient was 42 (IQR 16, 66). The median payment amount per patient was $706,518 (IQR 241,237, 1,306,453). Eculizumab was discontinued in 9 out of 23 patients (39%), after a median prophylactic duration of 329 days (IQR 127, 791). As shown in the Table, the eculizumab group had no graft loss vs. 20% in the non-eculizumab group, with an adjusted odds ratio of 0.13.

Conclusions: Prophylactic use of eculizumab in HUS KTRs was significantly associated with a lower risk of graft loss. Given the high cost of eculizumab, randomized controlled trials are much-needed to guide prophylactic strategies to prevent graft loss.

	Percentages		Crude incidence rates		Adjusted Odds Ratio	
	Overall graft Loss	Death-censored graft loss	Overall graft Loss (per 1000 patient-years)	Death-censored graft loss (per 1000 patient years)	Overall graft Loss (Eculizumab vs. No Eculizumab)	Death-censored graft loss (Eculizumab vs. No Eculizumab)
Eculizumab	0/23 (0%)	0/23 (0%)	0	0	0.13	0.18
No Eculizumab	64/312 (20.5%)	48/312 (15.4%)	35 (95% CI 27-45)	26 (95% CI 20-35)	(95% CI 0-0.74)	(95% CI 0-1.05)
P value	0.02	0.04	0.02	0.04	0.02	0.06

PO2546

Post-Kidney Transplant Serum Magnesium Exhibits a U-Shaped Association with Subsequent Mortality

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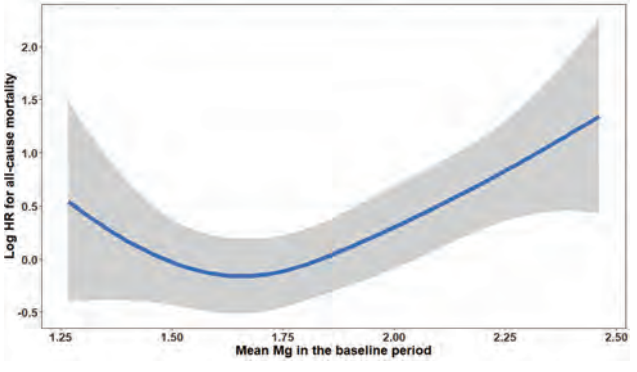
Background: Hypomagnesemia is common in kidney transplant recipients (KTR), likely due, at least in part, to renal magnesium (Mg) wasting related to calcineurin-inhibitor (CNI) use. The association of serum Mg levels and KTR outcomes may provide insight into the optimal serum Mg levels in this population.

Methods: KTRs between 01/2000 and 12/2016 at a large US transplant center who were alive with a functioning graft at 6 months post-transplant were included. Mean of the outpatient serum Mg in the baseline period, i.e. 6 to 18 months post-transplant, was used. Cox proportional-hazards regression was used to analyze the association between Mg and all-cause mortality, cause-specific mortality, and risk of new-onset cardiovascular events post-transplant.

Results: 2,131 KTRs met our inclusion criteria. Mean number of Mg measurements per patient in the baseline period was 2.76. A U-shaped association between the mean baseline Mg level and all-cause mortality was observed in both unadjusted analysis and after adjusting for baseline characteristics, including eGFR and CNI levels. A mean Mg of 1.5 - 1.8 mg/dL was associated with the lowest incidence of death (Figure). Compared with Mg of 1.5 - 1.8 mg/dL, Mg level ≤ 1.5 mg/dL was also associated with higher incidence of mortality due to infection and arrhythmia but not ischemic heart disease or heart failure.

Conclusions: The relationship between serum Mg levels and mortality in KTRs is U-shaped. Interestingly, the risk is lowest with Mg levels 1.5 - 1.8 mg/dL; which represents the lower end of normal (1.6 - 2.6 mg/dL). Mg supplements for levels ≤ 1.5 mg/dL may be beneficial, but may cause increased renal wasting and diarrhea. Further studies are needed to understand why Mg > 1.8 mg/dL but well within the normal range was associated with higher risk despite adjustment for eGFR.

Funding: Private Foundation Support



PO2547

A Case of Subretinal IgA Deposition in a Patient with IgA Nephropathy and Early Allograft Recurrence

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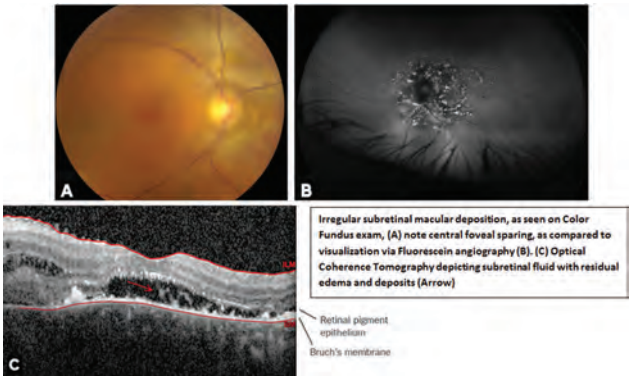
Introduction: IgA Nephropathy (IgAN) has variable clinical manifestations and a 30% recurrence, which is typically a late complication in renal transplant recipients. Ocular involvement in patients with IgAN is extremely rare. Thus, eye findings as a predictor of worse prognosis, including higher risk of recurrence, remains unexplored.

Case Description: A 66 year old Caucasian male with end-stage renal disease secondary to a 10 year history of IgAN complicated by retinal detachment and optic neuropathy with recent decline in visual acuity, underwent living related donor renal transplantation from his twin sister with Basiliximab induction. A month prior, Optical Coherence Tomography (OCT) had revealed bilateral macular edema and subretinal pigment deposits with central foveal sparing, consistent with IgA maculopathy. Post-operative course was uneventful with immediate allograft function and normalization of creatinine. 4 months later, repeat OCT showed improved retinopathy and ocular edema. However, renal function declined 2 months later, with persistently elevated Creatinine between 1.4-1.5 mg/dL. Allograft biopsy showed hypercellular endocapillary proliferation, glomerulitis and granular mesangial staining for IgA, IgM, Kappa and Lambda on Immunofluorescence, consistent with recurrent IgAN. Pulse-dose steroids were subsequently initiated.

Discussion: The pivotal role of the complement system has been implicated in IgA deposition between the retinal pigment epithelium (RPE) and Bruch's membrane, a complex exposed to circulating immune complexes similar to glomerular basement membrane. To our knowledge, this is the first reported case of IgA maculopathy involving subretinal deposition with recurrence of primary disease in the renal allograft within 1 year. Given the lack of non-invasive testing and dynamic clinical features encompassed by IgAN, the link between ocular pathology and patient-specific morbidity including recurrence, despite clinical improvement in initial eye disease, needs exploration.



PO2548

Virtual Reality, a New Vision Becoming Our New Actuality: A Retrospective Study Comparing Virtual Crossmatch vs. Physical Crossmatch at Tampa General Hospital

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Background: A crossmatch (XM) is required prior to kidney transplantation to ensure immunological compatibility between recipient and donor. This test is prone to false positive reactivity and can increase cold ischemic time (CIT) especially for organs procured outside the region of the transplanting hospital. Advances in HLA antibody testing and donor HLA antigen typing facilitate the use of a virtual XM (VXM) based on pre-transplant testing results to accurately predict a physical XM (PXM) result. Frequent antibody screening and an accurate history of sensitizing events further ensures that the VXM can predict immunological compatibility, even without retrospective PXM.

Methods: We compared the 6 mo. clinical outcomes of kidney recipients who proceeded to transplant with only a VXM (without retrospective PXM) to those receiving a PXM. 182 recipients with 6 mo. follow-up were reviewed for biopsy data, serum Cr and UPCR. Patients were grouped according to the transplant type (living donor (LD) vs. deceased donor (DD)) and XM type (PXM vs. VXM). LD recipients had a PXM (n=42). Patients with a VXM (n=76) were donor-specific antibody (DSA)-free and had a current tested sample within 30 days. DD recipients had PXM (n=64) due to the presence of DSA (current or historic) or the absence of a current tested sample within 30 days. All patients with PXM had an acceptable flow cytometric XM.

Results: Patients proceeding to transplant with a VXM tended to be less sensitized (32% with PRA >0%) compared to DD-PXM (66%) and LD-PXM (49%). For DD recipients, CIT was significantly reduced in patients receiving a VXM (727 vs 871 min; p=0.013). Within the first 6 mo. of follow-up, 67 for cause biopsies were performed. Rejection (T-cell or antibody mediated) was observed in 15 patients (7 DD-VXM, 6 DD-PXM and 3 LD-PXM). Interestingly, antibody mediated rejection was only observed in DD-PXM (n=3) or LD-PXM (n=1) groups.

Conclusions: In our cohort, kidney transplantation with an acceptable VXM was beneficial in reducing CIT and rejection was similar to DD recipients needing a PXM within the first 6 mo. post-transplant. Utilizing VXM helps facilitate kidney transplantation, permits entertaining offers from greater distances, and reduces laboratory burden with similar outcomes to when a PXM is performed.

PO2549

Reassessing Renal Transplantation in Light-Chain Deposition Disease

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Background: Light chain deposition disease (LCDD) is a systemic rare condition that usually leads to end stage renal disease. Treatment with a bortezomib-based regimen, followed by autologous stem cell transplantation (ASCT) has been increasingly used with improvements in the response rates and the renal graft outcomes in kidney transplant recipients.

Methods: Retrospective study of 6 patients diagnosed of LCDD with complete response but not renal response after hematologic treatment that underwent kidney transplant in our institution between 2010 and 2019.

Results: A total of 6 patients (5 women) were analyzed, with mean age at diagnosis of 47 years, mean eGFR of 18 mL/minute and mean proteinuria of 5.5 g. Deposit was kappa type except in 1 case (heavy and light lambda type chains). In all of them there was an absence of monoclonal component in blood and urine but positive immunofixation in 5 cases (2 only in urine). 3 started chronic hemodialysis during admission and the others at 3, 5 and 44 months after diagnosis. As hematological treatment, all received bortezomib followed by ASCT, being under complete hematological response at the time of kidney transplant, which was performed at 28 months on average from ASCT. Mean kappa/lambda ratio was 2.6. 3 patients received induction with thymoglobulin and 3 with basiliximab, followed by triple therapy with tacrolimus+prednisone+mTOR inhibitor (4 patients) or mycophenolate (2 patients). After 36 months of mean follow-up after kidney transplant, 3 patients have suffered an hematological relapse, one of them including kidney involvement with graft loss at 46 months post-transplant. The remaining 5 continue with a functional graft with a mean creatinine of 1.54 mg/dL.

Conclusions: When sustained complete hematologic response is achieved but renal impairment with dialysis requirement persists, patients could benefit from a kidney transplant with good results.

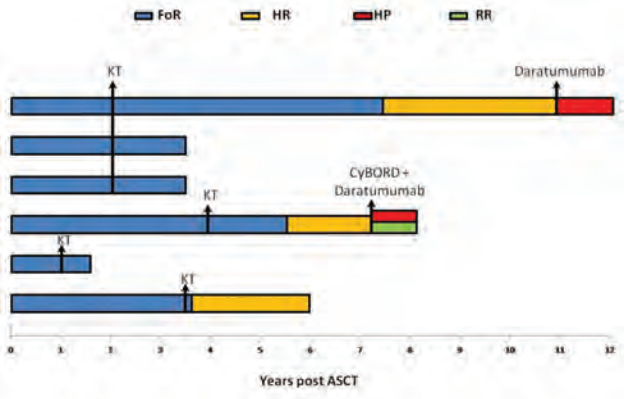

Figure 1. Patient outcomes. ASCT: autologous stem cell transplantation, FoR: free of relapse, HR: hematologic relapse, HP: hematologic progression, RR: renal relapse, KT: kidney transplant, CyBORD: Cyclophosphamide, bortezomib and dexamethasone

PO2550

Granulomatous Interstitial Nephritis and Allograft Failure Secondary to Adenovirus Reactivation

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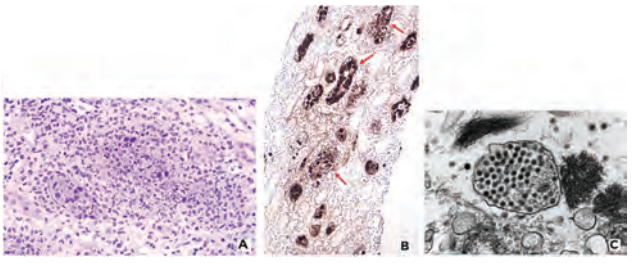
Introduction: With an incidence of about 4% in renal transplant recipients, the typically self-limited adenovirus renders an infrequent propensity to cause allograft failure and life-threatening opportunistic infection in severe cases.

Case Description: A 29 year old female with history of living donor kidney transplant due to Henoch Schonlein Purpura (HSP) Glomerulonephritis with subsequent allograft failure underwent deceased donor re-transplantation with Anti-Thymocyte globulin induction. Post-op course was uneventful. Creatinine was 0.8 mg/dL on 4 month follow up. 6 months post-transplant, patient developed gross hematuria with clots, fever and acute kidney injury with creatinine of 2.82 mg/dL. Biopsy revealed granulomatous tubulointerstitial nephritis, extensive intra-nuclear viral inclusions with positive adenovirus immunohistochemistry (IHC). Mycophenolate Mofetil was discontinued and creatinine improved to 1.1 mg/dL. 3 months later, she was admitted for renal failure with creatinine of 7.2 mg/dL. Adenovirus was detected in the serum and urine. Repeat biopsy revealed markedly reactive tubular epithelium, widespread viral inclusions with negative adenovirus IHC, consistent with adenovirus nephropathy. Following a decrease in immunosuppression with improvement in renal function, adenovirus viral load became undetectable in both plasma and urine. The use of Cidofovir was considered for treatment; however, given risk of nephrotoxicity, was ultimately deferred after response to conservative treatment.

Discussion: Recurrence of HSP was in the broad differential given the initial presentation. Given its rarity, a paucity of cases and epidemiologic literature exists in illustrating allograft failure due to adenovirus nephropathy. Further research is not only needed to expand awareness of its presenting features and characteristic biopsy findings, but also, to limit more familiar culprits in masquerading as the elusive adenovirus infection, particularly in light of indeterminate therapeutic modalities.



A. Granulomatous interstitial nephritis; H&EB. + Adenovirus Immunohistochemistry (Arrows)

C. Viral inclusions; EM

PO2551

Phospholipase A2 Receptor Antibody Level Directed Management of Membranous Glomerulopathy After Transplant

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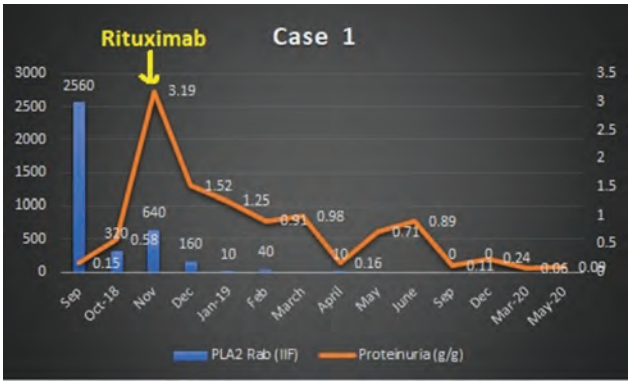
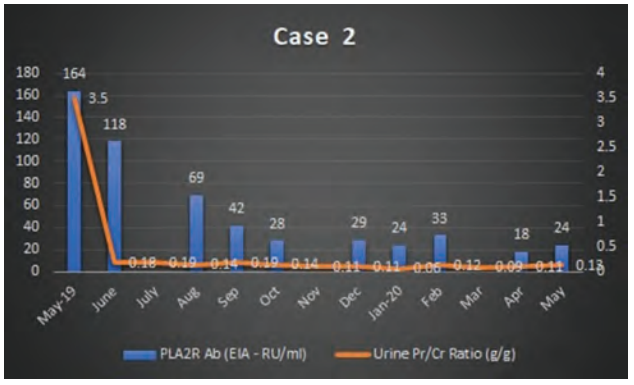
Introduction: MN can recur after transplantation. Patients with high PLA2R Ab are at higher risk. There is equipoise on how to manage these patients. We present two cases to highlight PLA2R Ab level directed approach to management.

Case Description: Case 1: 35 YO AA female with MN diagnosed in 2013. Failed cytotoxic therapy and started RRT. Received a DD kidney transplant in Sep 2018. Given Thymoglobulin, tacrolimus, mycophenolate and prednisone. Pretransplant PLA2R titer 1:2560 by IIF. Titer serially monitored. After an initial decline, titer increase with precipitation of proteinuria noted. Biopsy confirmed early recurrent MN. Treated with 2 doses of Rituximab. Subsequent titers dropped with complete remission. Case 2: 65 YO W male with biopsy demonstrated MN (2015), on RRT since 2017 underwent DD kidney transplant in May 2019. Given Thymoglobulin and maintained on tacrolimus, mycophenolate and prednisone. Pretransplant PLA2 R Ab level was 164 RU/ml by EIA with 3.5 g/g of protein. His PLA2R Ab levels dropped and proteinuria rapidly & durably resolved after transplant. One year out, his PLA2R Ab is at 24 RU/ml with 0.11 g/g protein in the urine and a creatinine of 1.2 mg/dl.

Discussion: High PLA2 R Ab at the time of transplant is a significant risk factor for recurrent MN. PLA2R Ab levels should be monitored to direct care: decreasing PLA2R Ab should be followed conservatively. If Ab levels increase or proteinuria develops, perform biopsy to confirm diagnosis and initiate therapy expeditiously. PLA2R Ab levels should be monitored post treatment to ensure resolution. This approach allows stratification and directed therapy of patients with MN undergoing transplantation and avoids over treatment.



Case 1



Case 2

PO2552

De Novo Membranous Nephropathy and Donor-Specific Alloantibodies: A Path to the Pathophysiology?

Megan A. Tierney, Pradeep Vaitla, Wisit Cheungpasitporn, Franco H. Cabeza Rivera. *University of Mississippi Medical Center, Jackson, MS.*

Introduction: While pathophysiology of post-transplant membranous nephropathy due to recurrence of primary disease is established, less is known about the development of primary de novo membranous nephropathy (dnMN). We report a case of dnMN associated with antibody-mediated rejection in a transplant recipient with end-stage kidney disease secondary to focal segmental glomerulosclerosis (FSGS).

Case Description: A 20-year-old African American female with FSGS status-post deceased donor kidney transplant eight years ago presented with acute lower extremity edema and acute kidney injury concerning for acute rejection. She has no history of prior rejection or medication non-adherence. Ultrasound showed mild hydronephrosis. Biopsy showed Banff Type IB acute-cell mediated rejection (t2, i2) and Stage 1 membranous glomerulopathy. Serum phospholipase A2 receptor (anti-PLA2R) antibodies were negative. Donor specific antibodies (DSA) testing revealed the presence of DQ5, DQ7, and DRB1*01:03. Diagnosis of coexistence of Banff Type IB acute-cell mediated rejection, positive de novo DSA, and dnMN was made. She was treated with five doses of antithymocyte globulin (1.5 mg/kg/dose) and plasma exchange (PLEX) followed by IV immune globulin (IVIg). Repeat DSA after fifth session of PLEX showed clearance of DRB*01:03 and reduced DQ antibody levels; after seventh session of PLEX, however, DQ antibodies had plateaued. Biopsy performed after PLEX and antithymocyte globulin showed chronic active T cell-mediated rejection Grade IB (ti3, t3, and I-IFTA2) and persistent Stage 1 membranous glomerulopathy; in the setting of persistent DQ antibodies, this suggested failure of transplanted organ within the next 6-12 months. The patient was prepared for this eventuality, received a final session of PLEX and IVIg and discharged in otherwise stable condition.

Discussion: Only one case of dnMN associated with HLA-DQ7 DSA has been previously reported (El Kossi Clin Transplant 2008). This case not only reports the unique occurrence of two glomerulonephropathies in one patient, but also provides support that post-transplant dnMN can be seen in the context of humoral alloreactivity, and DSA might play some roles for the pathogenesis in some patients with dnMN after kidney transplantation (Honda Clin Transplant 2011).

PO2553

Histological Predictors of Graft Failure in Kidney Transplant Recipients

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Background: We aimed to identify the predictors of allograft failure in a large cohort of kidney recipients who underwent clinically indicated graft biopsies. We aimed to explore the importance of interstitial inflammation in biopsies with interstitial fibrosis and tubular atrophy(IFTA).

Methods: We retrospectively evaluated 516 patients who underwent transplant biopsy between 1/2009 and 1/2018. Acute and chronic allograft injury scores of Banff classification were used. We sub grouped the patients with chronic allograft injury score (ci+ct+cv) ≥ 3 or< 3 and sub grouped per interstitial inflammation (i score=0 and > 0)and compared to biopsies with both ci+ct+cv=0 and i=0.

Results: Biopsies were done at a median 12.5 months after kidney transplantation. The histopathological diagnosis were as following: acute antibody-mediated rejection (AMR) (6%), acute T-cell mediated rejection (9.3%), chronic AMR (6.7%), transplant glomerulopathy without donor-specific antibody (DSA) (10.2%), recurrent/de novo glomerular disease (10.8%), BKV nephropathy (2.5%), and the rest 54.2% had other diagnosis (normal, acute tubular necrosis, or non-specific IFTA). During a median follow up of 59.3 months after kidney biopsy, 36 %recipients lost their graft. In univariate analysis, the following factors were significant for graft loss: Black race (p=0.005), previous rejection (p<0.0001), DSA at the time of biopsy (p=0.014), ci+ct+cv ≥ 3 (p=0.0485), ci+ct+cv ≥ 3 with interstitial inflammation > 0 (p<0.0001), microvascular inflammation (p=0.0052), C4d positivity (p=0.008), serum creatinine at time of the biopsy (p<0.0001), and spot urine protein/creatinine (<0.0001). In the multivariate analysis ci+ct+cv < 3 with i>0 has the highest hazard ratio followed by ci+ct+cv ≥ 3 with i>0, ci+ct+cv ≥ 3 with i=0, black race, creatinine, and proteinuria.

Conclusions: Interstitial inflammation is the best predictor for allograft loss after clinically indicated kidney biopsy regardless of the severity of chronic allograft injury score.

Risk Factor	HR	95% CI	P-value
ci+ct+cv < 3 with i>0	8.38	3.22 – 21.78	<0.0001
ci+ct+cv ≥ 3 with i>0	2.92	1.47-5.82	<0.0001
ci+ct+cv ≥ 3 with i=0	2.69	1.33-5.44	<0.0001
Black Race	2.04	1.43-2.89	<0.0001
Serum Creatinine	1.27	1.18-1.37	<0.0001
Spot urine protein/creatinine	1.11	1.06-1.17	<0.0001

PO2554

A Case of Antibody-Mediated Rejection (ABMR) After Withdrawal of Etanercept in a Renal Transplant Recipient

Iris Jill E. Uy, Mohammad Abuzeineh, Sami Alasfar, Fizza F. Naqvi, Brandon L. Trollinger. *Johns Hopkins Medicine, Baltimore, MD.*

Introduction: Etanercept is a tumor necrosis factor (TNF) receptor fusion protein that is used to manage several forms of inflammatory arthritis and psoriasis. Herein, we present a renal transplant recipient who was concomitantly treated with Etanercept for psoriasis and subsequently developed two episodes of ABMR after the drug's withdrawal

Case Description: A 41-year-old man with history of psoriasis and end stage renal disease due to hypertensive nephrosclerosis and interstitial nephritis who underwent living related kidney transplant from his brother in December 2008. He was being treated for psoriasis with Etanercept which was withdrawn in September 2012. Subsequently he had rising serum creatinine (Cr) from baseline of 1.3 to 1.6 mg/dL and developed de-novo donor specific antibodies (DSA) to DR11 and DQ7 with positive cytotoxicity crossmatch. Renal allograft biopsy showed evidence of Banff 2A acute cellular rejection, ABMR, chronic glomerulonephritis and interstitial nephritis. He was treated with high dose steroids, 10 sessions of plasmapheresis with intravenous immunoglobulin (IVIG), and Rituximab. His Cr improved to 1.2 mg/dL but DSA remained positive. Later on he was restarted on Etanercept which was withdrawn again in March 2019. Accordingly, in September 2019, he developed acute kidney injury with Cr up to 1.7 from baseline of 1.3-1.5 mg/dL associated with nephrotic range proteinuria. He had a rise in DSA to DQ7, and developed new DSA to A2 and B60 with positive cytotoxicity crossmatch. Donor derived cell free DNA was elevated at 4.4%. Allograft biopsy showed glomerulitis, peritubular capillaritis with positive c4d, consistent with ABMR. He was treated with high dose steroids, 5 sessions of plasmapheresis with IVIG and Rituximab. Repeat DSA showed reduction in A2, but no change in DQ7. His serum Cr improved but his proteinuria remained at nephrotic range

Discussion: Despite the use of Etanercept in the treatment of graft versus host disease among transplant recipients, it hasn't been studied as a potential immunosuppressive drug. In our patient, Etanercept seemed to provide anti-rejection effect as shown by two episodes of ABMR with de-novo DSA after the drug's withdrawal. Close monitoring of renal function and DSA may be warranted once Etanercept or other TNF inhibitors are withdrawn in transplant recipients

PO2556

Molecular Analysis of Renal Graft Biopsies: Comparing the Edmonton Molecular Microscope with the NanoString Human Organ Transplant Panel

Jessica Schmitz,[1] Helge Stark,[2,3] Stephan Bartels,[4] Danny Jonigk,[2,3] Philip F. Halloran,[5,6] Gunilla Einecke,[7] Jan H. Braesen.[1] *[1]Hannover Medical School, Medizinische Hochschule Hannover, Institute of Pathology, Nephropathology Unit, Hannover, Germany; [2]Hannover Medical School, Institute of Pathology, Hannover, Germany; [3]Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Hannover, Germany; [4]Hannover Medical School, Institute of Pathology, Molecular Pathology, Hannover, Germany; [5]University of Alberta, Edmonton, Edmonton, AB, Canada; [6]Alberta Transplant Applied Genomics Center, Edmonton, AB, Canada; [7]Hannover Medical School, Department of Nephrology and Hypertension, Hannover, Germany.*

Background: The renal transplant biopsy is the diagnostic gold standard and usually evaluated with the continuously expanded and updated Banff classification which is based on on descriptive, empirically-derived criteria and thus lacks precision. High-resolution determination of the graft inflammation by NanoString analysis, which was developed for formalin-fixed paraffin-embedded-derived (FFPE) RNA, should be a sufficient approach for objective molecular diagnosis of renal transplant biopsies and may improve our understanding of graft biology.

Methods: We used well-annotated surveillance and indication biopsies from 63 patients whose time-matched second biopsy core had been frozen and analyzed by microarray in the INTERCOM/INTERCOMEX study. After reevaluation according to recent Banff consensus, RNA isolation of the FFPE biopsy was performed and led to sufficient RNA yields in 53 samples which were further processed for NanoString analysis using the nCounter Human Organ Transplant Panel.

Results: Morphologically, of the 53 samples analyzed (samples from 2011/12 and 2015), twenty-five patients showed no signs of rejection, twelve had borderline rejection,

four showed cellular rejection, seven had humoral rejection, and five presented with combined rejection. Preliminary analysis of gene expression by T-distributed Stochastic Neighbor Embedding (t- SNE), Random Forest and Principal Component Analysis (PCA) showed clear differences between samples with rejection (humoral and cellular) and without rejection. Rejection samples revealed high expression of chemokine ligands compared to rejection-free tissues. A common pattern of samples without rejection and borderline rejection was observed. Our results displayed good correlation with the former molecular microarray-based diagnosis from the INTERCOM/INTERCOMEX study.

Conclusions: Molecular diagnostic approach using the NanoString platform may supplement morphological diagnosis of renal grafts especially in unclear cases and thus enhance precision diagnostics with small tissue requirement. Morphological and molecular evaluation in the same biopsy core from FFPE tissue enables direct histological-molecular correlation. Additionally, this technology also improves our understanding of pathophysiology in renal and other transplants.

PO2557

Donor Biopsy and Kidney Transplant Outcomes in Pediatric Recipients

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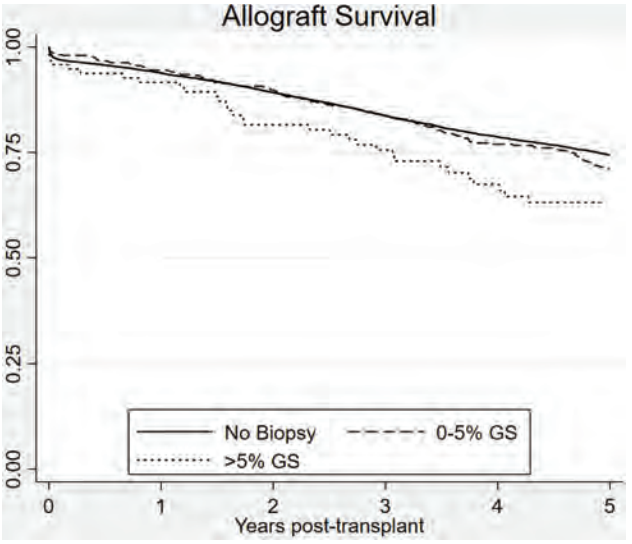
Background: Deceased Donor DD kidney biopsies are routinely used in the context of clinical concerns about donor quality in adult kidney transplants. We sought to examine the use of DD kidney biopsies in pediatric transplants. We aim to evaluate prognostic utility of glomerulosclerosis GS level in predicting graft outcomes.

Methods: Data was used from recipients who received kidney transplant between 1994 and 2018 documented in the Scientific Registry of Transplant Recipients database. Pediatric recipients were defined as recipients < 18 years who received DD kidney transplant excluding multi-organ transplants. The recepients were further stratified according to degree of donor kidney GS into 0-5% and > 5% categories. Demographic and outcome data were examined and graft survival was evaluated using STATA 16.

Results: 10,045 pediatric recipients received DDKT during this period. 644 had left and/or right DD kidney biopsies, 548 biopsies had 0-5% GS, 96 biopsies had > 5% GS. Biopsies were mostly performed on kidneys harvested from higher risk donors. There was a significant difference in the number of biopsies performed across regions (region 5 lowest at 2.6% and region 9 highest at 17.5%). There was no significant difference among share characteristics or transplant center volume. Allograft survival was significantly worse for donor kidneys with GS>5% compared to 0-5% group and no biopsy group. There was no significant difference in the incidence of DGF, acute rejection, or chronic rejection.

Conclusions: Although the biopsied kidneys are mostly from higher risk donors, the majority of biopsies have GS level 0-5%. At this level of GS there is no difference in allograft survival compared to DD kidneys without biopsies. Thus utilizing kidneys with GS 0-5% can expand the DD kidney pool and should be strongly considered for use in pediatric population.



Kaplan-Meier curve of 5-year allograft survival for pediatric kidney transplant patients by donor kidney glomerular sclerosis (GS)

PO2558

Predictors and Impact of Nephrocalcinosis in Renal Transplant Population: A Monocenter Retrospective Study

Jessie Beaulieu,[1] Léa Thérien,[1] Julie Riopel,[1] Eva Latulippe,[1] David Simonyan,[2] Isabelle Houde,[1] Mohsen Agharazii,[1] Fabrice Mac-Way.[1] *[1]CHU de Québec-Université Laval, CHU de Quebec-Universite Laval, Quebec, QC, Canada; [2]Centre de recherche du CHUQ, Quebec, QC, Canada.*

Background: Persistence of bone and mineral anomalies in post-transplant population has been suggested as contributing factors to nephrocalcinosis (NC) that could lead to graft dysfunction. However, adequate characterization of calcium deposits in biopsies from renal transplant patients are lacking. We thus aimed to determine: 1) the prevalence of NC in renal transplant patients, 2) the factors associated with NC and 3) the impact of NC on renal graft function.

Methods: This is a monocenter retrospective study using a protocolized renal biopsy from CHU de Québec, l'Hôtel-Dieu de Québec hospital from 2016-2018. All renal biopsies performed in 2016 at renal transplantation, at 6 and 24 months post-transplant were qualitatively and quantitatively analyzed for NC. Demographic, comorbidities and biochemistry parameters were collected from patients' records. Appropriate statistical analyses (Pearson's chi-squared, Wilcoxon-Mann-Whitney, Spearman's correlation and logistic regression) were performed to assess factors associated with NC and its impact on graft function.

Results: We included 53 patients (mean age of 52±13 years, 55% of men, 94% with hypertension, 23% with peripheral arterial disease and 19% with prior parathyroidectomy). Forty-nine patients (92%) were on chronic dialysis treatment before transplant for a mean duration of 34±29 months. The presence of NC was observed in 14% at baseline, 37% at 6 months and 50% at 24 months. The severity of NC as assessed by the number of calcified foci in the tubulointerstitial compartment also tended to increase over time. Analyses showed that the presence of NC at 6 months was associated with male sex, presence of NC at baseline and high PTH levels (> 600 ng/L) at the time of transplant. Presence of NC at 24 months was also associated with prior NC and male sex. Interestingly, the presence of NC at 6 months was associated with use of phosphate supplements immediately after engraftment and with active vitamin D treatment at 6 months. Finally, NC at 24 months was correlated with the level of graft function as expected.

Conclusions: This study reveals that uncontrolled mineral and bone metabolism parameters before renal transplant are associated with development of NC in the post-transplant period that may contribute to deterioration of renal graft function.

PO2559

Outcomes of Biopsy-Proven Acute Rejection (BPAR) in ABO-Incompatible Kidney Transplants (ABOi KTx) Compared with a Propensity-Matched Cohort of ABO-Compatible Transplant Recipients (ABOc KTx)

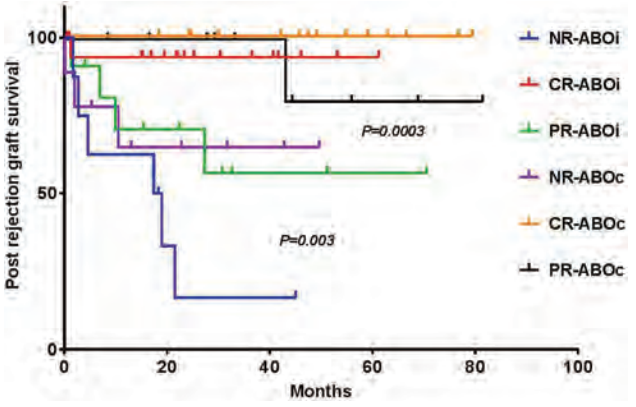
Sabarinath S, Amit Gupta, Manas R. Patel, Ravi S. Kushwaha, Narayan Prasad, Anupama Kaul, Dharmendra Bhadauria. *Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.*

Background: Although available outome data is equivocal for its non-inferiority compared to ABOc KTx, the data on graft survival after an BPAR episode are scarce in ABOi KTx.

Methods: Single centre, retrospective study, ESRD patients transplanted between 2014 and 2019 were included. Among 100 ABOi KTx, 37 had BPAR and were included. A matched cohort of 37 ABOc KTx with BPAR were identified as controls from 680 ABOc KTx by propensity score matching (nearest neighbour matching) using recipient age and sex, donor age and sex, donor GFR, HLA match and induction agent used as matching covariates. Rejection rates, BANFF score, response to antirejection treatment, overall graft survival, post rejection graft survival were compared between both the groups.

Results: The hazard ratio for BPAR was 1.4 in ABOi KTx, compared with ABOc KTx. Overall graft survival at 1, 3 and 5 years were 86%, 72% and 50% in ABOi KTx; 97%, 91% and 79% in ABOc KTx, respectively. The post BPAR graft survival at 1 and 3 years were 80% and 63% in ABOi KTx; 92% in both 1 and 3 years in ABOc KTx. ABMR was more common in early period in ABOi KTx and ACR was predominant in late period in both the groups. The response to anti-rejection therapy were similar between two groups, no response group (NR) in the ABOi KTx had the poorest graft outcome, complete response group (CR) in the ABOc KTx had the best graft survival. Between CR, PR (partial response) and NR groups, no histopathological parameters were found significant in ABOi KTx, whereas in ABOc KTx, TI scores were higher in PR compared to CR group.

Conclusions: The graft survival after an acute rejection depends upon response to antirejection therapy. After an episode of acute rejection, the overall post rejection graft survival was inferior in ABOi compared to ABOc KTx.



Graft survival after BPAR according to response

PO2560

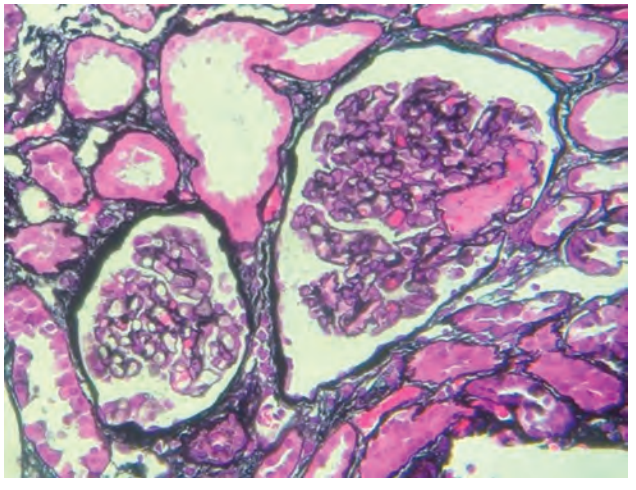
Antiphospholipid Antibody Syndrome Causing Thrombotic Microangiopathy in the Immediate Post-Transplant Patient: A Case Report

Anna R. Gaddy, Muhammad S. Yaqub. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Differential diagnosis of thrombotic microangiopathy on kidney biopsy specimen includes infection, hypertension, malignancy, or inherited complement disorders. In the the post-transplant period the differential also includes calcineurin inhibitor toxicity and rejection.

Case Description: A 29 year-old AA female with ESRD disease due to lupus nephritis and HTN. Her care was provided in another state until 2011- she had a stroke in the past which she reports was secondary to uncontrolled HTN. No h/o blood clot, never been pregnant. Native kidney biopsy in 2015 showed lupus: class V membranous GN, focal segmental and diffuse glomerular sclerosis with collapsing features, and focal acute thrombotic microangiopathy. In 2019, she underwent deceased donor kidney transplant. On post-op day 4, Sr Cr began to increase and biopsy demonstrated thrombotic microangiopathy. Chart review revealed increased aPTT prior to surgery. DsDNA was negative, Tacrolimus troughs were low, donor-specific antibodies were negative. She was treated empirically with high-dose steroids and plasma exchange. Workup revealed positive anti-cardiolipin IgG (46 GPL units/mL) and positive anti-beta-2 glycoprotein IgG (532 units/mL.). She recalled being on warfarin following her CVA in 2010, for embolic stroke. She received a dose of Rituximab, has been maintained on tacrolimus and mycophenolic acid along with warfarin for her antiphospholipid syndrome (APLs) and has normal graft function

Discussion: This case highlights the importance of a complete serological workup to rule out APLs in the pre-transplant patient, even in the presence of alternate explanatory diagnoses. Patients with APLs should be treated with lifelong anticoagulation to prevent further embolic complications, including loss of transplanted organs.



PO2561

Impact of Out-of-Hospital Organ Donor Cardiac Arrest and Cardiopulmonary Resuscitation on Donor Kidney Histology and Function

Sami M. Akram, Claudia G. Olano, Nehemias A. Guevara, Lilly M. Barba. Kidney Transplantation Group *Harbor-UCLA Medical Center Department of Internal Medicine, Torrance, CA.*

Background: The mortality rate of patients listed for kidney transplantation (KT) is 5 per 100-patient years. Due to an organ shortage crisis, expansion of KD pool (KDP) is critical (1). Kidney donors (KD) with out-of-hospital cardiac arrest (OHUS-CA) and cardiopulmonary resuscitation (CPR) have low acceptance rate due to presumed delayed graft function (DGF). Donor CA in controlled setting (in ICU) does not impact KF post engraftment (PE) (2) but impact of OHUS-CA is unknown. We propose that terminal serum creatinine (TSC) and Kidney histology (KH) immediatley prior to Kidney transplantation predict KF post KT. We did a nested cohort study to study the impact of OHUS-CA and CPR of KDs on KF and KH. .

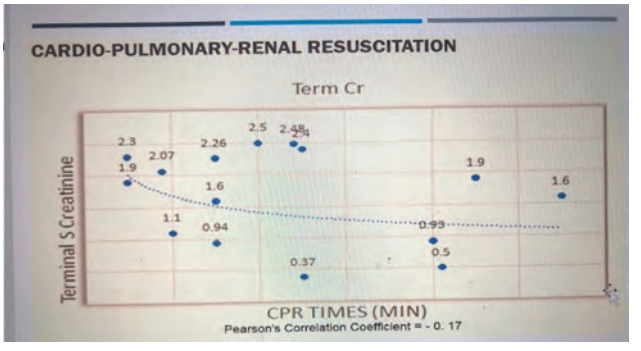
Methods: Our transplant program received thirty-five kidney organ donors offers with a procurement biopsy from UNOS during July to December 2019. Retrospectively we reviewed demographics, pre- hospitalization resuscitation information, hemodynamic data and KH. Four patients were excluded; two had missing data; one patient had ischemic infarct and one patient had kidney tumor. The study cohort (N=31) divided into CA-OHUS (N1 =16 and No Cardiac Arrest (No-CA, N2=15) groups. The change (delta) in serum creatinine (DSC) while under donor management (DM) compared in each group. Hypotension during donor management (H-DM) and acute tubular damage score (ATDS) from donor kidney biopsy compared within each group of the cohort.

Results: TSC and ATDS prior to KT were evaluated as surrogates for KF post engraftment and there was no difference between OHUS-CA and No-CA (standard) donors. Effect of ischemic preconditioning was noted in OHUS-CA group (Table). Longer the duration of CPR greater was the residual KF (Fig 1).

Conclusions: KF and KH in KD with OHUS-CA are similar to standard criteria donors hence should not be prejudiced. This will expand the KDP.

Results

Nested Cohort (N=31)	Delta SC (DSC)	H-DM (P val = 0.56)	ATDS (0 = none; 1=mild)
OHUS-CA (n1=16)	0.34 (SD 0.19), P val = 0.1	9/7	5/11
No-CA (n2=15)	0.72 (SD 0.27, P val = 0.02)	10/5	8/7



PO2562

Living Donor-Derived APOL1-Associated Collapsing FSGS in a Kidney Transplant Recipient

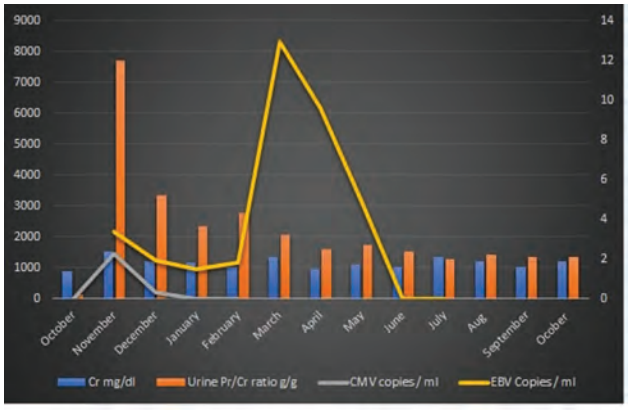
Irfan Agha,[1,2] Amna Ilahe,[1,3] Silvi Simon,[1,3] Rama Nadella,[1,2] Diana Mahbod,[1] Richard Dickerman.[3] *[1]Dallas Renal Group, Dallas, TX; [2]Medical City Dallas Hospital, Dallas, TX; [3]Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Homozygous high risk APOL-1 mutations in donors can drive disease in recipients. We present a living kidney recipient with de-novo collapsing FSGS. His donor was homozygous for high risk mutations.

Case Description: 47 YO AA male with CKD due to biopsy proven diabetic nephropathy s/p LUKT in May 2018. Got thymoglobulin (5 mg/kg) with tacrolimus, mycophenolate sodium and prednisone. High risk for CMV (D+ / R-). EBV IgG +. Donor was his 35 years old AA wife. We were not testing APOL-1 on AA donors at the time. At month 6: Cr 1.4 mg/dl, Ur Pr/Cr of 0.22 g/g. Valganciclovir stopped. Two weeks later, Ur Pr/Cr 2.92 g/g. CMV PCR + 276 copies / ml and EBV PCR + 492 copies / ml. PCR for Parvo Virus B-19 as well as DSA negative. Given steroids, plasmapheresis (X3) and IV ganciclovir. Biopsy C/W collapsing FSGS. IF negative, including CMV and C4d. Donor tested for and found to be homozygous for APOL1 G1 mutations confirming donor derived APOL -1 gene associated collapsing FSGS, presenting as an acute diffuse podocytopathy. Trends in his renal function, CMV, EBV and proteinuria are tabulated in Figure 1. Treated with RAAS blockade, antivirals & immunosuppression. He cleared his CMV Viremia promptly. However, EBV viremia worsened. Eventually, in May 2019, received Rituximab with resolution of EBV viremia. He is 18 months out from presentation. Cr is in the 2 mg/dl range with persistent proteinuria. The life of the allograft will be significantly curtailed. His donor is doing well with stable kidney function and no proteinuria.

Discussion: APOL-1 mutations place recipients of these kidneys at risk for adverse outcomes. Few instances of APOL-1 mutation driven kidney disease in recipients from

living donors are documented. This presentation supports the two-hit hypothesis - The high interferon state due to CMV and EBV viremia precipitated APOl-1 associated FSGS in this kidney with homozygous high risk mutations. APOL-1 screening in AA donors, especially young donors, should be considered for risk stratification and counseling.



Clinical Course

PO2563

Pediatric Donor Glomerulopathy in Pediatric En-Bloc Kidney Transplants

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Background: Use of pediatric en-bloc kidneys (EBK) have equivalent outcomes to standard deceased donor kidneys and has helped expand the pool of donor kidneys. The size mismatch related hyperfiltration injury in pediatric EBK and pediatric single kidney allografts is associated with pediatric donor glomerulopathy whose effect on allograft outcomes is not well documented.

Methods: We retrospectively reviewed for cause biopsies of pediatric EBK from 1/2015 to 1/2020. Our center performed 37 transplants using pediatric EBK. Recipient weight criteria was ≤ 75 kg to minimize donor-recipient size mismatch. One recipient died with a functioning graft at 4 months; one graft failed due to fungal infection of the vascular anastomosis requiring nephrectomy at 1 month.

Results: Fourteen biopsies were performed in 10 patients between 1 to 24 months after transplantation. Indications for biopsy were: graft dysfunction (10; 3 with proteinuria), proteinuria alone (2), BK viremia with proteinuria (1), and de novo donor specific antibody (DSA) (1). Biopsies from 5 EBK recipients demonstrated pediatric donor glomerulopathy represented by the presence of glomerular abnormalities including subepithelial multi-layering/remolding of the basement membrane, segmental glomerulosclerosis, mesangial hypercellularity, mesangial sclerosis, podocyte hypertrophy, and/or segmental mild podocyte foot processes effacement. Ten biopsies also showed thin basement membranes (BM) on EM consistent with the age of the donor kidney. Other diagnostic findings among the entire biopsy cohort were acute cellular rejection (ACR), antibody mediated rejection (AMR), or mixed ACR and AMR (5), acute tubular necrosis (ATN) (3), and pyelonephritis (1). Biopsies with pediatric donor glomerulopathy were performed early after transplantation and were associated with proteinuria. Semiquantitative proteinuria in the 5 recipients at the time of biopsy was 1-3+; 1.2-9.5 g/day in 4. Follow up 4-39 months post-transplant (mean 17 months) in patients with pediatric donor glomerulopathy showed serum creatinine 0.55-2.07 mg/dl (mean 1.1) and urine protein 0.4 to 1.2 g/day (mean 0.73).

Conclusions: Overall, pediatric donor glomerulopathy seen early post transplant period did not appear to negatively affect long-term graft function; this outcome may be related to growth of these kidneys occurring early post transplant.

PO2564

Pre-Transplant Genetic Testing of Living Related Donor in a Case of Atypical Hemolytic Uremic Syndrome

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Introduction: Atypical HUS (aHUS) is a rare thrombotic microangiopathy caused by dysregulation of the alternative complement pathway either through mutations in regulatory genes or autoantibodies directed against regulatory proteins. Here we report a case of genetic testing pre-transplant in a patient who developed aHUS with variants in the *CFH* and *PLG* genes and her living related donor.

Case Description: A 27-year-old female presented to the hospital with diarrhea, abdominal pain, AKI, and microangiopathic hemolytic anemia requiring dialysis. She was initiated on eculuzimab but progressed to ESRD. Renal biopsy showed TMA with focal crescents and severe interstitial fibrosis and tubular atrophy. Workup revealed aHUS with complement dysfunction—low C3 and C4, normal CD46 and Factors H, I, and B, and no autoantibodies to CFH. Genetic testing showed mutation on exon 9 (SCR7) of *CFH* that has been shown to cause aHUS as well as another variant on exon 7 of *PLG*, which is present in 0.3% of European Americans and may be pathogenic but is of uncertain significance for her. Ten months later, she was evaluated for living related renal transplant from her brother. Since she had a mutation known to cause aHUS, genetic testing was done for her brother as part of donor evaluation. He was found to have the same mutation in *CFH* but not *PLG*, despite being asymptomatic with no hemolytic anemia, normal kidney function. The transplant was cancelled because of increased risk of disease in the future in the brother. Genetic counselling was provided to brother about his possible risk of aHUS.

Discussion: Mutations in *CFH* are associated with aHUS; however, it is thought that a trigger—e.g. infection or additional acquired genetic variant leads to progression to aHUS in carriers of complement gene mutations. Genetic testing is recommended for patients with aHUS to determine cause and inform long-term treatment. This patient had a combination of a variant in the complement pathway gene *CFH* and coagulation pathway gene *PLG*, while her brother, a candidate for living related donor, had the same variant in *CFH*. We recommend genetic testing for a living related donor if any mutation is found in the index case to minimize posttransplant recurrence or precipitation of aHUS in the donor.

PO2565

Trouble Brui-ing: A Case of Doppler Discovery

Brandon M. Fairless,[1] Anil S. Paramesh,[2] Isa Ashoor.[1] *[1]Louisiana State University Health Sciences Center, New Orleans, LA; [2]Tulane University School of Medicine, New Orleans, LA.*

Introduction: This case highlights the clinical presentation and management of an uncommon kidney transplant biopsy complication.

Case Description: A 19 year old male with ESKD, now status-post second deceased donor kidney transplant, presented to clinic with hypertension. Post transplant course included 3 prior normal surveillance kidney transplant biopsies. Graft function was stable (creatinine 1 mg/dL), and tacrolimus trough level was therapeutic. His blood pressure was 130/85. Exam showed a palpable thrill with audible bruit over the graft site. Ultrasound showed a sonolucent lesion in the lower pole of the transplant kidney, which was not present on prior imaging. Doppler revealed turbulent flow concerning for an arteriovenous malformation (AVM). Renal angiography confirmed the diagnosis, and he underwent endovascular embolization with coiling **[Image]**. Graft function and blood pressure readings remain normal on most recent follow-up

Discussion: Kidney biopsy is commonly utilized for diagnosis and management of transplant complications. It is generally a safe procedure, with post-biopsy bleeding being the most common complication, often with no clinical significance. However, serious complications can occur, with AVM among them. Patients with kidney transplants have been noted to have a higher incidence of post-biopsy AVM. A portion of AVMs remain asymptomatic and self-resolve, while others manifest as hypertension, graft dysfunction, and hematuria. An ultrasound with Doppler is critical for the diagnosis. Endovascular embolization is an effective and minimally invasive management option for most patients.
Teaching Points -Ultrasound with Doppler assesses for the presence of AVM -Symptoms of post-biopsy AVM include hypertension, renal graft dysfunction, and gross hematuria -Transplant patients are at increased risk for post-biopsy AVM

Renal ultrasound with Doppler (left), renal angiography (middle), post-coiling (right)

PO2566

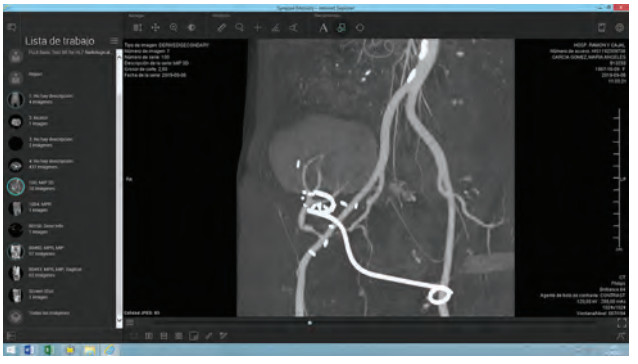
Renal Transplant Artery Stenosis and Kinking: An Unusual Association

Haridian Sosa Barrios,[1] Victor Burguera,[1] Ester Casillas,[1] Daniel E. Villa,[1] Sara Jimenez Alvaro,[1] Irene Martin Capon,[1] Milagros Fernandez-Lucas,[1,2] Maite Rivera.[1,2] *[1]Hospital Universitario Ramon y Cajal, Madrid, Spain; [2]Universidad de Alcala de Henares, Madrid, Spain.*

Introduction: Renal artery stenosis of the kidney graft associated with kinking is not a frequent finding. As a correctable cause of graft dysfunction it is important to diagnose it as soon as possible to avoid further graft damage.

Case Description: A 62 year-old woman with ESRD due to ADPKD had a deceased donor kidney transplant (KTx) in her right iliac fossa (1 vein/1 artery) anastomosed to external iliac vessels. Immunosuppression:basiliximab, tacrolimus, everolimus and steroids. Creatinine drop halted 2 weeks post-op. Blood pressure was normal, CMV load : undetectable. Tacrolimus level:7-9 ng/ml. A KTx US was done, showing high velocities within KTx renal artery close to the anastomosis, increasing near a kinking image adjacent to the hilum (image 1), not present on Doppler US 1 day post-op. A CT angiography confirmed renal artery stenosis at anastomosis level and kinking of the graft renal artery (image 2). Endovascular angioplasty of the stenotic area without stenting was performed, but unsuccessful. Open surgery vascular reconstruction was carried out a week after angioplasty: renal artery was shortened and reimplanted. Within a week, graft function improved and Doppler US was normal.

Discussion: Renal artery stenosis is a correctable cause of hypertension and graft dysfunction in KTx. Graft renal artery kinking is rare, even more in association with stenosis, worsening its prognosis as kinking renders angioplasty less effective. Complete Doppler US mapping of the graft's arteries is essential to make an early diagnosis and nephrologists could do this examination promptly.



PO2567

Proliferative Glomerulonephritis Monoclonal Immunoglobulin Deposits (PGNMID) in a Kidney Allograft Successfully Treated with Rituximab

Rasha Alawieh, Mohankumar Doraiswamy, Seth Scheetz, Anjali A. Satoskar, Todd E. Pesavento, Priyamvada Singh. *The Ohio State University, Columbus, OH.*

Introduction: PGNMID is a rare distinct form of glomerulonephritis (GN) characterized by glomerular monoclonal immunoglobulin deposits. There is no definite treatment for this condition. We present a case of PGNMID in a recurrent renal transplant patient who responded well to rituximab.

Case Description: A 43-year-old male with ESRD secondary to MPGN s/p 3rd renal transplant complicated with failure of previous transplants due to rejections (on cyclosporine and everolimus) presented with worsening pain at the graft site and AKI. Creatinine 5.6 mg/dL (baseline 2.5mg/dL), UPC 1.5 gm/dL, RBC, and RBC casts on microscopy. Detailed serological, immunological, and infectious workup was negative. Renal biopsy showed mesangial, subepithelial, and subendothelial proliferation with electron dense deposits of IgG1 and IgG3 with kappa predominance most consistent with PGNMID. Monoclonal workup was negative and bone marrow biopsy showed no clear evidence of hematologic malignancy. He received two doses of rituximab in addition to home immunosuppression. Renal function improved to baseline (creatinine 2.5, negative blood, UPC 0.5) and has been stable for past year.

Discussion: GN recurrence in kidney allografts is responsible for around 24% of kidney graft losses. Approximately 70% of PGNMID patients have no detectable monoclonal proteins in serum or urine. Multiple regimens have been used for the treatment of PGNMID after renal transplant, including RAAS blockers, steroids, rituximab, bortezomib and plasmapheresis. Few reported cases of PGNMID responded well to rituximab, and a large prospective multicenter controlled study is warranted to better understand this rare disease.

Fig. 1

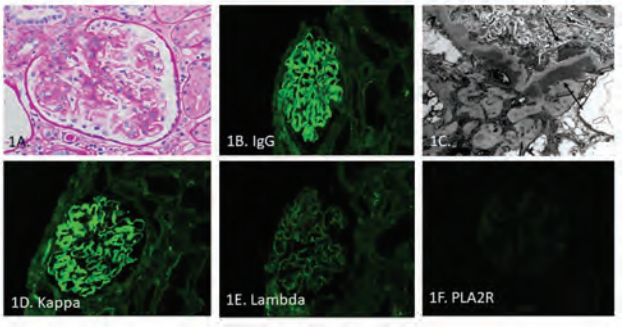
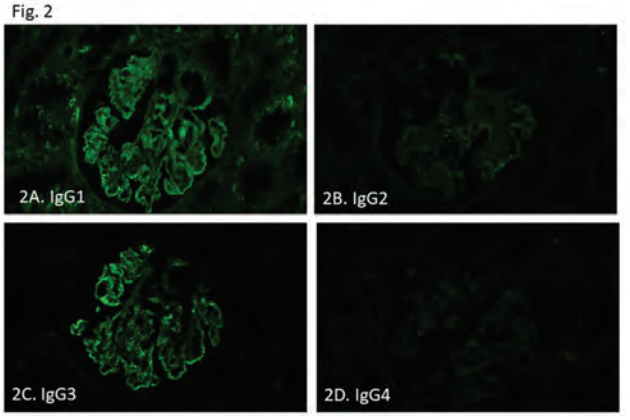


Fig. 2



PO2568

Rituximab or Plasmapheresis for Prevention of Focal Segmental Glomerulosclerosis Recurrence After Kidney Transplantation: A Meta-Analysis

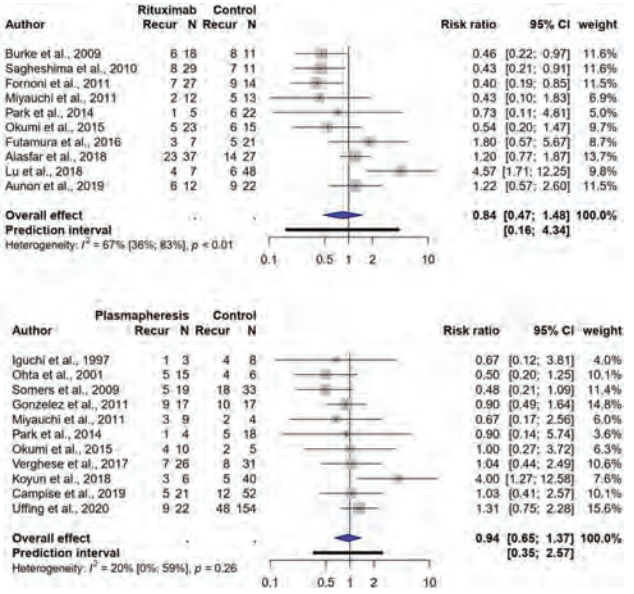
Boonphiphop Boonpheng,[1] Charat Thongprayoon,[2] Wisit Cheungpasitporn.[3] *[1]University of California Los Angeles, Los Angeles, CA; [2]Mayo Clinic Minnesota, Rochester, MN; [3]University of Mississippi Medical Center, Jackson, MS.*

Background: Focal segmental glomerulosclerosis (FSGS) can recur after kidney transplantation. Prevention of FSGS recurrence with rituximab and/or plasmapheresis has been evaluated in multiple small studies with conflicting results. We performed this meta-analysis to assess the post-transplant recurrence risk of FSGS with prophylactic rituximab and/or plasmapheresis in addition to standard immunosuppression.

Methods: A systematic review was conducted in MEDLINE, EMBASE, Cochrane databases from inception through April 2020 to identify studies that evaluated the risks of post-transplant FSGS after rituximab with or without plasmapheresis or plasmapheresis alone compared to controls. Effect estimates from the individual study were extracted and combined using random-effects model.

Results: 10 studies with a total of 381 FSGS patients undergoing kidney transplantation evaluated rituximab with or without rituximab and 11 studies with a total of 520 kidney transplant recipients with FSGS evaluated plasmapheresis alone. There was no significant difference in recurrence between the group that received rituximab with or without plasmapheresis and the standard treatment group, with a pooled risk ratio of 0.84 (95% CI, 0.47-1.48, I^2= 67%). Plasmapheresis alone was also not associated with any significant difference in FSGS recurrence compared to no plasmapheresis with a pooled risk ratio of 0.94 (95% CI, 0.65-1.37, I^2= 20%). Subgroup analysis in the pediatric or adult group did not yield significant recurrence risk difference.

Conclusions: Rituximab with or without plasmapheresis or plasmapheresis alone was not associated with lower risk of FSGS recurrence after kidney transplantation.



Forest plots(A) preventive rituximab on FSGS recurrence

(B) plasmapheresis on FSGS recurrence

PO2569

Case Study of Repository Corticotropin Injection (RCI) Prophylaxis for FSGS Recurrence in Kidney Transplant

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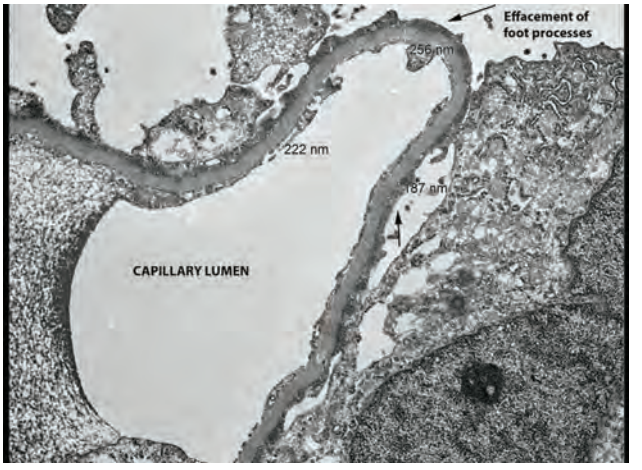
Introduction: Idiopathic FSGS recurs post-transplant in one third of cases and is associated with a five-fold higher risk of graft loss[1].

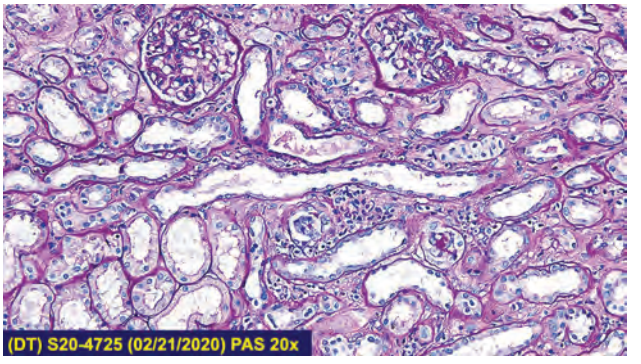
Case Description: In this single center pilot case study, 8 patients with biopsy-proven FSGS were treated with RCI prophylaxis 80 units subcutaneously twice a week for 6 months from day of kidney Tx, compared with a group of 6 patients who were treated with RCI later after the diagnosis of FSGS recurrence.

Discussion: All patients received rATG as induction and were on standard immunosuppression with FK, MMF, and prednisone. Patients in the control group were diagnosed with recurrent FSGS between 5-63 days post Tx. There where 3 patients in the study group that developed recurrent FSGS, 2 of them required plex. Patient 1 in the study group had DGF after a live donor kidney Tx from recurrent FSGS. Her protocol biopsy performed one year after transplant and still shows foot process effacement but no fibrosis or sclerosis in light microscopy. All but one patient in the control group have still functioning allografts. Conclusions: This is a small pilot study, but its findings suggest that use of RCI at time of kidney transplant surgery in patients with FSGS decreases the severity of the disease with less fibrosis in follow up biopsies despite the presence of foot process effacement. There may also be a decreased need for plex in the study group, however, further studies are needed to confirm this

	Sex (M=male, F=female)	Race (C=Caucasian, AA=African-American, H=Hispanic)	Average Proteinuria at 3 months Post Transplant (mg/mg)
Study Group (n=8)	3 F, 5 M	5 C, 1 AA, 2 H	0.925
Comparison Group (n=6)	6 M	3 C, 3 H	4.486



Patient 1 in study group, 1 week after live donor kidney transplant.



Patient 1 in study group, one year post transplant.

PO2570

Does Therapeutic Plasma Exchange Improve Kidney Function in Renal Transplant-Associated Thrombotic Microangiopathy?

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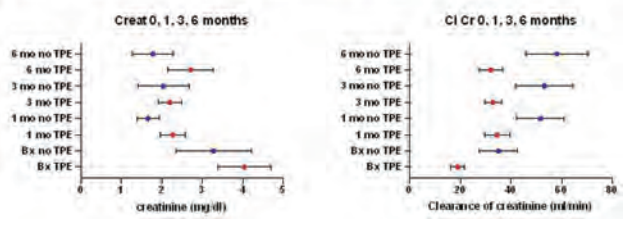
Background: Therapeutic plasma exchange (TPE) is performed in patients with renal transplant thrombotic microangiopathy (t-TMA) to improve the kidney function. The goal of our study is to evaluate the short-term efficacy of TPE in patients with renal t-TMA.

Methods: We retrospectively compared the outcome of TPE-treated vs. non-TPE-treated patients with biopsy-proven diagnosis of t-TMA. Histologic criteria for diagnosis of t-TMA included presence of thrombi in the artery/arteriole/glomeruli, mesangiolysis & double contours, and electron microscopic evidence endothelial cell injury including subendothelial rarefaction/ accumulation of fluffy material and mesangial interposition. Both groups received concomitantly other modalities of treatment. Creatinine and creatinine clearance levels were determined at the time of biopsy (T0) and after 1, 3 and 6-months (T1, T3, T6 respectively).

Results: In 13 TPE-treated and 9 non-TPE-treated patients, the mean creatinine levels at 6 months decreased 32.5% and 45% respectively over baseline, while the creatinine clearance increased by 68% and 65% respectively, although not statistically significant (p>0.05) Graph1.

Conclusions: No significant differences were noted in creatinine or creatinine clearance levels within and between either groups at any time point. Our study suggest that no significant benefit in renal function is associated with performing TPE in patients with renal t-TMA. Larger studies are needed to confirm our data.

Graph 1. Creatinine and Creatinine Clearance Levels (Mean±SEM).



PO2571

Patient and Graft Outcomes of Kidney Transplant Recipients with Anti-Human Neutrophil Antigen Antibodies

Christina Irene Mejia, Goni Katz-Greenberg, Beth W. Colombe, Pooja Singh, Anju Yadav. *Thomas Jefferson University, Philadelphia, PA.*

Background: Antibody mediated rejection (AMR) is a well-established cause of poor graft outcomes in kidney transplant recipients (KTR). While the most common targets are human leukocyte antigen (HLA) antibodies (abs), there are data implicating some non-HLA abs in the process of AMR. Human neutrophil antigens (HNA) are glycoproteins expressed on neutrophil surfaces. Anti-HNA abs have been associated with transfusion-related acute lung injury but their role in AMR in KTR is unclear. The aim of our study was to examine the outcomes of KTR with anti-HNA abs at our center.

Methods: We retrospectively reviewed the medical records of KTR with non-HLA abs between 1/2008-5/2020. Relevant clinical and graft outcome data were obtained. Descriptive statistics were expressed as absolute numbers (%) for categorical data and as medians with interquartile range (IQR) for skewed distribution.

Results: There were 6 KTR with non-HLA abs during the study period, all anti-HNA abs. Three patients (pts) were male (50%), 5 white (83%), and 4 had polycystic kidney disease (PCKD) as primary disease (66%). Median age at KT was 46 (29.75-57). Pts' characteristics, clinical course and outcomes are detailed in Table 1. Five pts developed biopsy-proven AMR at a median of 32 months (13.8-68.2) from KT. During follow-up (f/u), 3 pts had graft loss, 1 of which was re-transplanted while 2 are re-listed but dialysis-dependent. Mean creatinine of the 4 pts with working allografts is 1.21mg/dL(1.14-1.27) at median f/u of 68 months(52-105).

Conclusions: We observed varied clinical courses and graft outcomes in our pts, partly due to our small cohort. Although majority developed AMR, it was not necessarily associated to graft loss or shortened graft survival. Of note, PCKD was the primary kidney disease in the majority of pts, similarly observed in one other case series. More studies are needed to determine the specific significance of anti-HNA abs in KTR.

Table 1. Patient and donor characteristics and allograft outcomes.

Patient	Gender	Race	Age at transplant	Cause of kidney disease	Dialysis Modality	Transplant number	Donor type	Induction	Baseline Immunosuppression (IS)	Delayed Graft Function	Anti-HNA ab Genotype	HLA DSA (at time of biopsy)	Biopsy-proven AMR	Treatment	Graft loss	Current status
1	Male	White	20	IgA Nephropathy	Hemodialysis	1	Living unrelated	Anti-thymocyte globulin (ATG)	Tacrolimus, Mycophenolate	No	2a,3b,2a	Yes	Yes	Intravenous immunoglobulin (IVIG), Plasmapheresis, Rituximab	Yes	Re-transplant, Creatinine 4Cr 1.25 mg/dl
2	Female	White	35	Polycystic kidney disease	Hemodialysis	2	Donation after brain death	ATG	Tacrolimus, Mycophenolate, Prednisone	Unknown	2, 3a, 5b,5b	No	Yes	ATG, IVIG, Plasmapheresis, Rituximab	Yes	Dialysis dependent
3	Female	Non-hispanic black	45	Hypertension	Hemodialysis	4	Donation after brain death	ATG	Tacrolimus, Mycophenolate, Prednisone	Yes	1b, 2, 3c, 5b	No	Yes	None	No	Cr 1.17 mg/dl
4	Male	White	47	Polycystic kidney disease	Peritoneal dialysis	1	Living unrelated	ATG	Tacrolimus, Mycophenolate	No	2, 3b	No	Yes	Prednisone added to IS regimen	No	Cr 1.25 mg/dl
5	Male	White	33	Polycystic kidney disease	Preemptive	1	Living unrelated	ATG	Tacrolimus, Mycophenolate, Prednisone	No	2, 3b,5a (performed)	Yes	No	IVIG, Plasmapheresis (post-transplant)	No	Cr 1.20 mg/dl
6	Female	White	57	Polycystic kidney disease	Preemptive	1	Living related	Basiliximab	Tacrolimus, Mycophenolate, Prednisone	No	3a (performed)	No	Yes	ATG, IVIG, Plasmapheresis	Yes	Dialysis dependent

PO2572

Transplant Outcomes in Children with Lupus Nephritis

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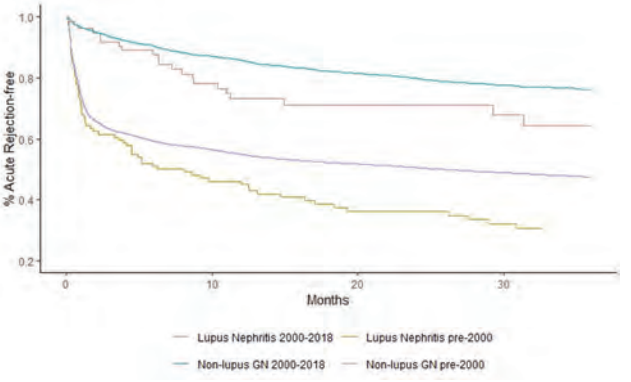
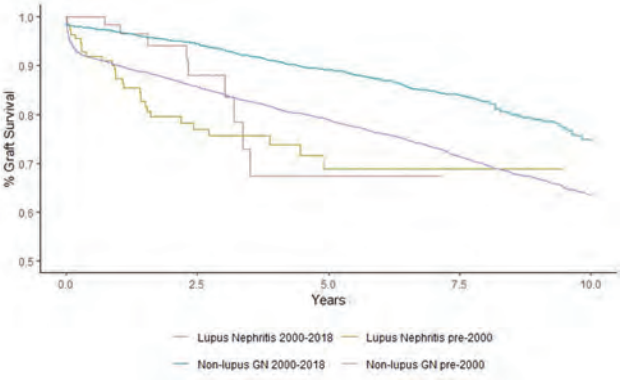
Background: Children receiving dialysis for end stage kidney disease secondary to lupus nephritis (LN) have decreased survival and a lower likelihood of kidney transplantation compared to children with non-lupus glomerular diseases (NLGN). Whereas a previous North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) analysis reported equivalent patient and graft survival for LN patients when compared to matched controls, a comparison of recent transplant outcomes in children with LN and NLGN has not been conducted.

Methods: Retrospective analysis of the NAPRTCS registry data of subjects <21 years old who received a kidney transplant between 1987–2018. Outcomes for LN patients (n=191) were compared to NLGN patients (n=8675) during pre & post 2000 eras. Statistical analyses included Kaplan-Meier curves and multivariable logistic and Cox regression models.

Results: After adjusting for race, LN patients were less likely ($p<0.001$) to receive a preemptive transplant (OR=0.12). There was also a trend for LN patients being less likely to receive a living donor (LD) transplant (OR=0.8). When comparing pre- and post-2000 eras, time to 1st rejection and graft survival improved for both LN and NLGN groups, although the graft survival benefit in LN group was not sustained after 3.5 years of follow-up. Time to 1st rejection and graft survival for LN patients remained inferior to NLGN group during both eras (Figure 1 & 2).

Conclusions: LN patients are less likely to receive a preemptive, and possibly a LD transplant. Overall, outcomes for both LN and NLGN transplant patients improved after 2000, but the outcomes of the LN group were inferior to those of the NLGN group during both time periods.





PO2573

Effect of Rituximab Dose on Induction Therapy in ABO-Incompatible Living Kidney Transplantation: A Network Meta-Analysis

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Background: Rituximab is an induction immunosuppressant essential for ABO-incompatible kidney transplantation, but studies on its dosing, which differs between countries and transplant centers, are lacking we retrospectively investigated this phenomenon

Methods: we retrospectively investigated this phenomenon by including five groups: ABO compatible; placebo; and rituximab 200 mg, 200–500 mg, and 500 mg. *Publications were retrieved using* CENTRAL, MEDLINE, EMBASE, and Science Citation Index Expanded databases from 1970 to February 2020 and analyzed. Reviews, observational studies, and clinical trials with unclearly defined outcomes or omitted graft failure as an outcome were excluded. We performed direct and indirect network meta-analyses using Bayesian models and ranked different rituximab doses using generation mixed treatment comparison. The GRADE of network meta-analysis approach specified four levels of certainty for a given result: high, moderate, low, and very low. The outcomes were patient survival, graft failure, and infections including bacterial and viral.

Results: Twenty-one trials with 4,256 subjects were analyzed for glomerular filtration rates, graft loss, antibody-mediated rejection, T-cell mediated rejection, fungal infection (*Candida*), and patient survival rates, which did not differ among four groups. However, incidence of sepsis and cytomegalovirus infection (0.728 and 0.855, 95% confidence interval: 0.572–0.926 and 0.724–0.921, respectively) were significantly lower in rituximab 200-mg group than in other groups.

Conclusions: In conclusion, in ABO-incompatible kidney transplantation, low-dose rituximab is more efficacious than higher doses and reduces serious infection risks. Future studies of large-scale, long-term data and further discussions on using lower rituximab doses are necessary.

PO2574

Delayed Diagnosis of Renal Allograft Uroenteric Fistula in a Pediatric Transplant Patient

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Introduction: The diagnosis of uroenteric fistulae can be challenging and is often delayed for several months after symptoms begin. Here, we describe a rare case of a pediatric patient post en bloc kidney transplant who developed a urinoma post biopsy with a ureteral fistula into the small bowel resulting in profound acidosis and deceptive watery diarrhea.

Case Description: The patient is an 8 year old girl with end stage kidney disease secondary to steroid resistant nephrotic syndrome and focal segmental glomerulosclerosis (FSGS). She underwent a right native nephrectomy and a deceased donor "en bloc" kidney transplant with two separate ureters. She had a renal allograft biopsy for suspected rejection. A few days after the biopsy, she began experiencing watery diarrhea and metabolic acidosis. A comprehensive screening for diarrhea produced inconclusive findings. She was maintained on parenteral nutrition with no oral intake to try to slow the diarrhea. However, the watery diarrhea increased while urine output decreased. Throughout this period, the patient maintained normal kidney function. The watery stool and bladder urine were analyzed for solutes, pH and creatinine. An MRI with contrast was performed which demonstrated fistulization of the distal transplanted ureters into the small bowel. She underwent corrective surgery which identified the fistulous tract which was resected and the ureters were re-implanted. The surgery went well without complications. The diarrhea resolved and she was discharged 2 weeks later with normal renal function.

Discussion: This is a perplexing case of the development of a uroenteric fistula in a pediatric transplant patient that went undiagnosed for almost 3 weeks due to the deceptive nature of the watery diarrhea which was actually urine. An important aspect of the uroenteric fistula is the severe acidosis that results when urine is diverted in to the intestinal tract. This occurs in some cases of bladder augmentations that use the intestine. Another important diagnostic tool is the solute excretion in the diarrhea. Despite the watery nature of the diarrhea, the stool was not hyperosmolar and did not contain reducing substances. This made osmotic diarrhea unlikely and a fistula more likely.

PO2575

Effect of Therapeutic Plasma Exchange on Glomerular Filtration Rate in Patients with Antibody-Mediated Rejection

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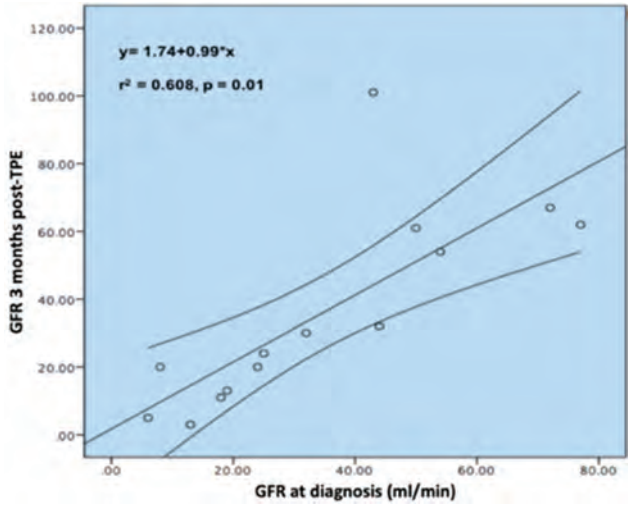
Background: AMR is the main risk factor for graft loss, especially after the first post-transplant year. Up to 80% of patients achieve response with immunosuppressive treatment and TPE, although the response is lower in patients with lateAMR. The objective was to determine the effect of TPEonGFR at 0,1, and 3 months postTPE.

Methods: Retrospective study that included patients with a renal transplant of the CMN"November 20"in MexicoCity, from 2016to2019, undergoing membrane TPEforAMR. Analysis was performed using student's t or MannWhitneyU, repeated measures analysis, and Spearman or Pearson test. Significant p was less than 0.05.

Results: 25 patients with AMR who received TPE were evaluated. Age:32±11.6 years, 72% from living donor, 52% received Basiliximab. 87% received tacrolimus. 80% of AMR were late. Prevalence of HLAclass II DSA(66%), specifically vs DQandDR (57.2% and 28.8%). There was a significant difference between preTPE GFR and at the end of treatment(p=0.015, r=0.53), and no significant differences between preTPE GFR, with 1or3 monthGFR(p=0.58; p=0.36). When evaluating IFTA or histological score(g+ptc), no difference was detected in the GFR at 1or3 months post-TPE. When comparing the effect of the AMR temporality on the GFR, difference was found at 1and3 months (p=0.022; p=0.01) postTPE, with lower recovery of GFR in patients with early AMR. There was a moderate correlation between GFR at the time of diagnosis of rejection and GFR at 3 months postTPE(r2=0.68,p=0.01), Fig. 1.

Conclusions: Significant difference was demonstrated between the preTPE GFR and immediate postTPE GFR. In our study patients with early AMR presented a poor response to treatment. The GFRupon admission correlated positively with theGFR detected at 3months post-TPE. This suggests a beneficial effect of TPE over GFRfall during the first 3months after diagnosis.



PO2576

Significant Variability in Results from Different Tacrolimus Assays Is a Potential Recipe for Toxicity and Kidney Allograft Rejection

Adnan A. Khan, Jennifer C. Smith. *University of California San Diego, La Jolla, CA.*

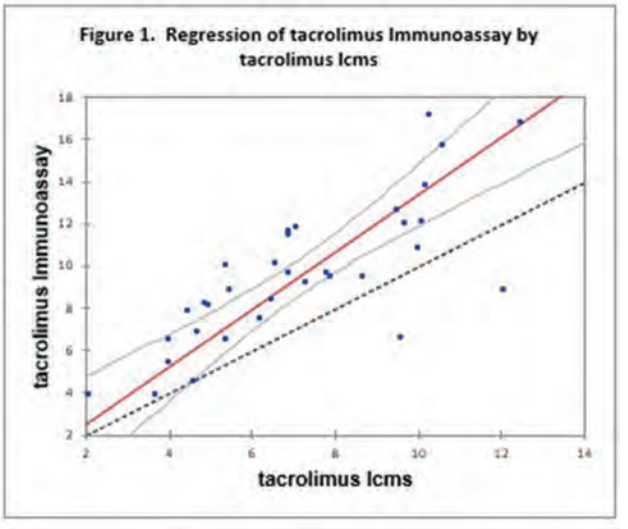
Background: Tacrolimus (tac) is an immunosuppressive medication used to prevent organ rejection and prolong graft survival after transplantation. It is the main pillar of any combination immunosuppression regimen. Due to its narrow therapeutic window; it requires timely administration, close monitoring with 12/24 hours trough levels and dose adjustments. Previously done studies have shown a discordance between different assays, with a positive bias for immunoassay (2.8 -9.2%) compared to LC/MS-MS assay; due to cross-reactivity with tac metabolites.

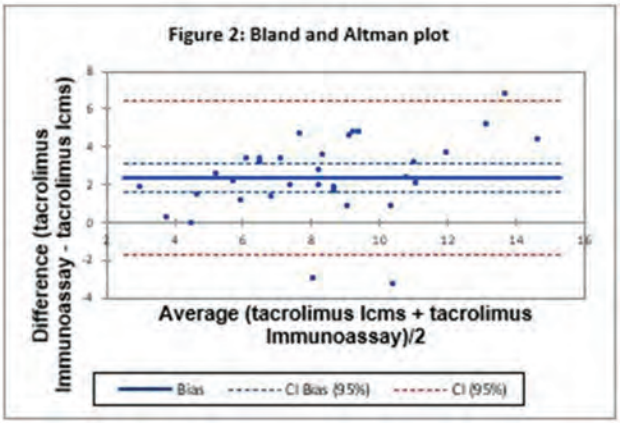
Methods: Results from 33 stable kidney transplant patients who had routine transplant labs drawn at Labcorp® were reviewed. Each of these patients had tac trough levels checked by both LC/MS-MS assay and QMS immunoassay(Thermo-Fischer). The comparison of two assays was done with Deming regression and a Bland-Altman analysis for bias done using XLSTAT®. Linear regression was done using SPSS v26.

Results: Deming regression analysis shows that there is a statistically significant difference between the two assays with *y=1.36x-0.26*. Bias(avg.) calculated by Bland-Altman plot was 2.35 ng/mL(Figure). Percentage difference in tacrolimus immunoassay and LC/MS-MS correlated with tacrolimus dose (p = 0.031).

Conclusions: A significant discordance of tac troughs (upto 85%) was found on our analysis; obtained by the two assays. This is clinically significant as tac has a narrow therapeutic window and adjustments of dose based on these assay results; can risk immunologic injury, DSA formation, rejection and nephrotoxicity at either ends of the spectrum. Standardization of assays in future, would be ideal. In the meantime, nephrologists should be adjusting trough goals based on the assay used, especially when different assays are in play.

Funding: Clinical Revenue Support





PO2577

Single-Dose Rituximab and Antithymocyte Globulin (ATG) in Hypersensitized Kidney Transplant Recipients

Aileen Wang, Uerica K. Wang, Megan L. Troxell, Stephan Busque, Colin R. Lenihan. *Stanford University School of Medicine, Stanford, CA.*

Background: Hypersensitized kidney transplant recipients (calculated panel reactive antibody (cPRA) ≥ 98%), may represent a population at high risk of posttransplant immunologic events. Their optimal induction regimen so far remain uncertain. The goal of this study was to compare 1-year outcomes of patients receiving rituximab and ATG as induction, the majority of whom were hypersensitized, with highly sensitized recipients (cPRA ≥ 80%) who received ATG alone.

Methods: All patients ≥ 18 years received a flow cross-match compatible kidney transplant between December 2014 and May 2020. We excluded patients who underwent pretransplant desensitization, simultaneous multi-organ transplantation, or received 0-HLA antigen mismatched organ. The exposure of interest was receipt of single dose rituximab (500mg) at induction. The 1-year outcomes were 1) patient and death censored graft survival, 2) glomerular filtration rate (GFR), 3) de novo DSA formation, 4) biopsy proven T-cell or antibody mediated rejection, 5) the composite of dnDSA and rejection, 6) BK viremia, and 7) CMV viremia.

Results: 70 patients received rituximab and ATG (Ritux) and 39 received ATG alone (Control). The Ritux group were (numerically) younger, more sensitized, received kidneys with a longer cold ischemia time, and lower kidney donor profile index. ATG doses were similar. The majority were deceased donor transplants. 1-year patient and death censored graft survival, mean GFR, incidences of BK viremia and CMV viremia were similar for Ritux and Control. 2 patients with primary graft non-function (1 in each group) and 1 patient with early posttransplant death (in Ritux) were excluded from the remaining outcome analyses (Table 1).

Conclusions: The addition of rituximab to ATG as induction for hypersensitized patients appear to be safe and is associated with excellent 1-year outcomes in patient and death cenosred graft survival. Rituximab at induction was associated with reduced incidence of dnDSA formation and/or rejection at 1-year post transplant. Our observations warrant further evaluatoin of anti-B cell therapy induction for hypersensitized kidney transplant recipients.

Table 1

1-Year Outcomes	Ritux (n=68)	Control (n=38)	P Value
Rejection	5 (7.0%)	6 (15.8%)	0.20
De Novo DSA	5 (7.3%)	7 (18.4%)	0.11
De Novo DSA and/or Rejection	9 (13.2%)	12 (31.6%)	0.04

PO2578

Risk Factors and Outcomes of Acute and Refractory Antibody-Mediated Rejection

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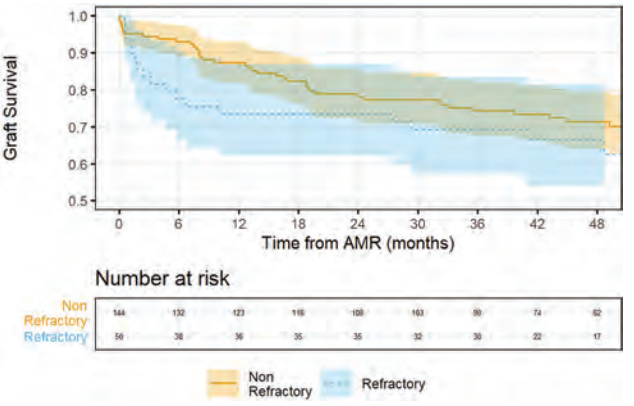
Background: Major gaps remain in our understanding of antibody-mediated rejection (AMR) after kidney transplantation. We examined incidence, risk factors, response to treatment, and effects on outcomes of locally-managed AMR at 7 transplant programs in the Long-Term Deterioration of Kidney Allograft Function (DeKAF) prospective study cohort.

Methods: Consecutive kidney or kidney-pancreas transplant recipients were enrolled in the DeKAF study from October 2005 through April 15, 2011. To determine the effect of AMR on death censored graft failure (DCGF), we performed Cox proportional hazards analyses including AMR as a time-dependent covariate.

Results: Among 3131 kidney and kidney-pancreas recipients, there were 194 with a first AMR episode during a mean 4.85±1.86 years of follow-up for the entire cohort. Mean time to first AMR was 0.97 ±1.17 years post-transplant. After adjusting for other risk factors, patients with AMR had 10 times the risk of DCGF compared to patients with no AMR (aHR 10.1, 95% CI 6.5-15.7). Among the 50 (25.8%) patients whose AMR was refractory to treatment, defined as 2nd AMR diagnosis within 100 days or no improvement in eGFR by 42 days, the HR for DCGF was 7.5 (2.2-25.6, P=0.0013) in the first 180 days post biopsy; 3.8 (1.4-9.8, P=0.007) in the 1st year post biopsy, and 1.6 (0.9-3.0, P=0.11) at any time during follow-up compared to patients whose AMR responded to treatment.

Conclusions: Patients with AMR had substantially greater risk of DCGF compared to patients without AMR. While patients with refractory AMR were more likely to lose their graft compared to non-refractory cases in the first year following the AMR diagnosis, the likelihood of graft survival after that year was the same regardless of response to treatment.

Funding: Commercial Support - CSL Behring



Time to death-censored graft failures among recipients with refractory antibody-mediated rejection (N=50) and non-refractory antibody-mediated rejection (N=144)

PO2579

Allograft Loss and Patient Death Among Kidney Transplant Recipients: Is Therapy Nonadherence the Underlying Perpetrator?

Kartik Kalra, Puneet Sood, Rajil B. Mehta, Chethan M. Puttarajappa, Christine Wu, Sundaram Hariharan, Nirav A. Shah. *University of Pittsburgh Medical Center, Pittsburgh, PA.*

Background: To ascertain causes of allograft dysfunction, loss and death in a cohort of kidney transplant patients

Methods: Retrospective cohort study, 943 patients with isolated Kidney transplants between years 2013-17 were analyzed for the following transplant outcomes: 1. Death-censored allograft loss 2. Graft dysfunction 3. Death.

Results: 80 of 943 (9%) patients died while 63 (7%) lost their graft and 38 (4%) suffered allograft dysfunction. **Death**- Death was attributed to a combination of infection (29%), Cardiovascular (CV) disease (29%) and malignancy (12%), a significant proportion of patients who died from either CV disease (43%), infection (26%) or malignancy (20%) had prior biopsy proven T-Cell Mediated Rejection (TCMR) in 1st post-transplant year. **Graft Loss**- In this cohort TCMR (39%) was the most widespread factor contributing to allograft loss. While Infection (17%) and surgical causes (14%) were the next common associations, donor related disease accounted for 2% of graft losses. **Graft Dysfunction**- TCMR (42%) was strongly associated with allograft dysfunction in our patient cohort. The other factors associated with Allograft Dysfunction included a). Infection (21%) b). Donor Related causes (11%) and c). Other Causes (15%). Surprisingly ABMR was only noted in 11% of patients with allograft decline. **Rejection and Non-Adherence**- As TCMR was a common contributing factor to all the three hard outcomes in our study cohort, we examined the factors associated with TCMR. 40% of patients with TCMR were found to be non-adherent (defined by > 3 consecutive sub- therapeutic CNI levels, clinic no shows and poor adherence to regular lab draws). Importantly, patients who were non adherent were significantly younger (mean age 38 y vs 55 y; p=0.0001) and a greater proportion of them were of African American (47% vs 22%;p=0.055) compared to those who were adherent to therapy.

Conclusions: While the causes of death, early allograft loss and dysfunction were diverse, TCMR was the most dominant contributor. Non-Adherence was strongly associated with TCMR and was more common in younger patients and those with African American ethnicity. Addressing non adherence in this cohort of patients early with novel interventions could be a key to optimizing patient outcomes in this high risk cohort.

PO2580

Identifying the Causes for Kidney Allograft Failure

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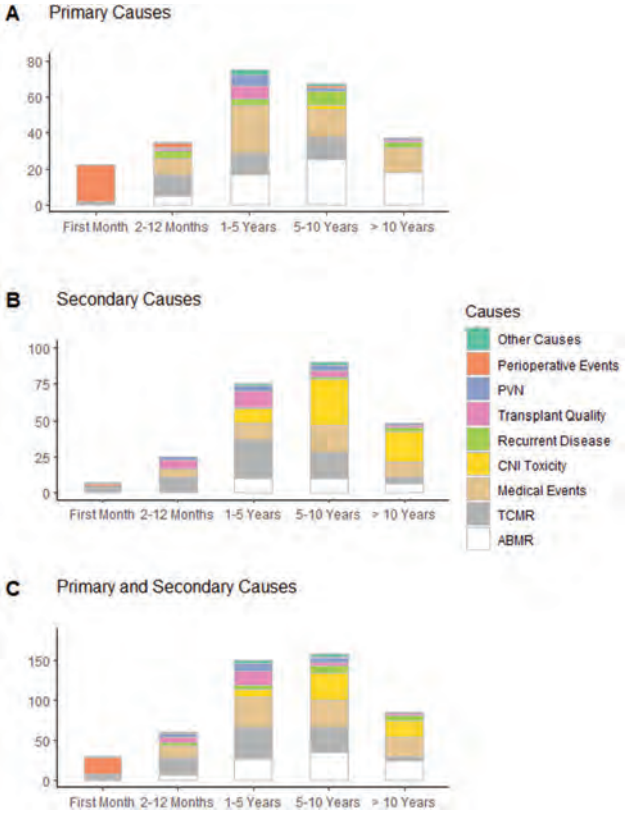
Background: Since it has been proposed that several causes (C) can contribute to graft loss (GL), we analyzed transplant (Tx) recipients in our center and attributed a C to each persistent decline in renal function, finally leading to GL.

Methods: We retrospectively analyzed 1477 Tx, transplanted between 1997 and 2017 in a single center, of which 303 progressed to GL. An adjudication committee consisting of 3 physicians evaluated biopsies, laboratory data and medical history. Nonreversible decreases in renal function were attributed to primary and secondary C.

Results: Overall graft survival for all patients is 93.7% for 1 year, 80% for 5 years and 60.6% for 10 years. The most frequent C leading to GL were intercurrent medical events in 36.3%, followed by T-cell mediated rejection (TCMR) in 34% and antibody-mediated rejection (ABMR) in 30.7% (table1). For primary C, ABMR (21.5%) was the leading C, followed by medical events (21.1%) and TCMR (12.9%). As expected, we observed an increasing relevance of ABMR in late GL (figure 1). Over 50% of GL had >1 C.

Conclusions: Analyzing GL, we observed that >50% were multifactorial. Our results show a significant role of TCMR in GL. Additionally, we were able to attribute medical events to GL in 36.3% of Tx and to highlight the role of ABMR in late GL.

Characteristics			Value
Donor			
Age (years, mean ± SD)			55.9 ± 15.9
Sex (% female)			50.2%
Donor type (% living donor)			20.8%
Recipient			
Age (years, mean ± SD)			49.9 ± 16.1
Sex (% female)			40.6%
First transplantation			238 (78.5%)
Adherence (% of non-adherent)			17.8%
DSA before transplant loss, n (%)			117 (38.6%)
Biopsy, n (%)			
< 1 year before transtplant loss			183 (60.4%)
< 2 years before transplant loss			212 (70.0%)
Available			282 (93.1%)
Transplant survival (years, mean ± SD)			5.6 ± 4.5
Number of causes per graft failure n (%)			
1			132 (43.6%)
2			123 (40.6%)
3			27 (8.9%)
4			5 (1.7%)
Unknown			16 (5.3%)
Causes for graft failure, n (% of graft failures)	Primary	Secondary	Total
TCMR	39 (12.9%)	64 (21.1%)	103 (34.0%)
ABMR	65 (21.5%)	28 (9.2%)	93 (30.7%)
Medical Event	64 (21.1%)	46 (15.2%)	110 (36.3%)
CI Toxicity	2 (0.7%)	62 (20.5%)	64 (21.1%)
PVN	10 (3.3%)	11 (3.6%)	21 (6.9%)
Perioperative Event	23 (7.6%)	1 (0.3%)	24 (7.9%)
Poor Transplant Quality	9 (3.0%)	23 (7.6%)	32 (10.6%)
Recurrent Disease	19 (6.3%)	6 (2.0%)	25 (8.3%)
Other Cause	5 (1.7%)	4 (1.3%)	9 (3.0%)
Total	236 (77.9%)	245	481



PO2581

Assessing Cumulative Immunosuppressive Drug Exposure: Metrics, Outcomes, and Implications for Kidney and Non-Kidney Transplant Patients

Cavizshajan Skanthan, Emily Nguyen, Lakindu Somaweera, Madhumitha Rabindranath, Olusegun Famure, Joseph Kim. *University Health Network, Toronto, ON, Canada*.

Background: Immunosuppressive drugs are used in the long-term management of post-transplant patients to prevent rejection of transplanted organs. Lacking a prior qualitative systematic review on this topic, we aimed to characterize the metrics used to measure cumulative immunosuppressant exposure and their associated outcomes in kidney and non-kidney transplant patients.

Methods: We conducted a literature search using search terms related to immunosuppressants and cumulative exposure in Ovid MEDLINE, Ovid EMBASE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews. No date restrictions were applied. An additional search was performed on Google Scholar and references of studies included in the primary search were screened. Studies were limited to the English language with adult human transplant patient populations. Study risk of bias was assessed using the Quality in Prognostic Studies Tool where each domain was rated as low, medium, or high risk of bias.

Results: A total of 29 articles were included in our qualitative synthesis. Kidney transplant populations account for 12 (41%) of the studies in our analyses. Fifteen of the articles (51%) calculated the total dose of immunosuppression over the treatment period while 9 (31%) used long term area-under-the-curve (LT-AUC) of trough level concentrations to quantify cumulative immunosuppression exposure. Nine articles found certain cumulative exposure metrics to be predictive of adverse outcomes such as decreased kidney function, cancer recurrence, and bone fractures. Furthermore, an adequate mycophenolic acid LT-AUC was associated with a decreased risk of allograft rejection, while cumulative corticosteroid exposure was not associated with allograft rejection.

Conclusions: This review analyzed a comprehensive set of articles and metrics that predict long-term outcomes of immunosuppressants in transplant patients. The wide variety of metrics studied highlight the lack of agreement on the best measures of drug exposure in transplant patients. Although certain metrics may demonstrate an association with outcomes, future studies should investigate the predictive power and validation of these metrics.

PO2582

Fludrocortisone Corrects Tacrolimus-Associated Hyperkalemia in Renal Transplant Patients

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Background: Hyperkalemic metabolic acidosis is commonly observed following kidney transplantation. This is often due to calcineurin inhibitors which are known to cause type 4 renal tubular acidosis either due to hyporeninemic hypoaldosteronism or due to direct effect on aldosterone responsive potassium secretion in the distal nephron.

Methods: We report 5 post-renal transplant patients (5 males) on tacrolimus with hyperkalemia treated with daily doses of either 50 mcg (n=3) or 100 mcg (n=2) of fludrocortisone. We retrospectively collected data at 3 time points before and after fludrocortisone on serum concentrations of sodium, potassium, bicarbonate, creatinine and tacrolimus as well as eGFR and blood pressure (BP). We recorded emergency admissions and length of stay (LoS) for treatment related to hyperkalemia. Data are presented as mean +/-SD and analysed with a paired students t-test.

Results: Pre and post-fludrocortisone serum concentrations for potassium was 6.3 ± 0.3 mmol/L and 5.1 ± 0.3 mmol/L (p=0.002); venous bicarbonate 18.4 ± 1.8 mmol/L and 20.4 ± 2.0 mmol/L (p=0.108); sodium 135 ± 1.6 mmol/L and 135 ± 2.2 mmol/L (p=0.875); creatinine 184 ± 12.2 mmol/L and 155 ± 10.6 mmol/L (p=0.058); eGFR 39 ± 3.4 ml/min and 47 ± 4.2 ml/min (p=0.035); blood tacrolimus levels 9.8 ± 2.1 ng/mL and 11.2 ± 1.0 ng/mL; BP was 133/69 ± 12/9 mmHg and 129/70 ± 8/6 mmHg before and after fludrocortisone respectively. We were able to either reduce or stop sodium bicarbonate after starting fludrocortisone due to increase in serum bicarbonate levels. Prior to fludrocortisone there were 6 episodes of serum potassium greater than 6.5 mEq/L, of which 3 patients required admission for hyperkalaemia management, with LoS 1-3 days. The majority occurred with tacrolimus levels in target range. Reduction in potassium levels to 'safe levels' were noted within 24-48 hours of starting fludrocortisone.

Conclusions: Treatment of hyperkalemic metabolic acidosis with fludrocortisone resulted in rapid normalization of serum potassium. There were no adverse effects on BP, serum sodium levels or clinical evidence of fluid retention. Instigation of fludrocortisone prevented emergency admissions for treatment of hyperkalemia and allowed the clinicians to run adequate tacrolimus levels. Fludrocortisone can be a cheap, safe and effective option for the treatment of hyperkalemia in renal transplant patients on tacrolimus.

PO2583

Changes in Serum Klotho in Kidney Transplant Recipients and Prognostic Marker for Allograft Function: A Systematic Review and Meta-Analysis

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Background: α-Klotho protein is a well-known anti-aging factor that regulates systemic phosphate metabolism. Mutation of klotho in mice can lead to phenotypes resembling human aging. Since klotho expression is highest in the kidney, patients with advanced chronic kidney disease have progressive decline in klotho levels. However, changes in serum klotho levels in kidney transplant (KTx) patients and its prognostic significance on allograft function remain unclear.

Methods: A literature search was conducted using MEDLINE, EMBASE and Cochrane Database from inception through October 2019 to identify studies evaluating 1) change in serum klotho levels after KTx, 2) klotho levels among KTx vs non-KTx patients, and 3) prognostic significance of klotho levels on allograft function after KTx. Study results were pooled and analyzed utilizing random-effects model.

Results: 10 cohort studies with a total of 431 KTx patients were identified. After KTx, there was significant increase in serum klotho levels (at 4 to 13 months post-KTx) with mean difference (MD) of 243.11 (3 studies; 95%CI 67.41 to 418.81). Although KTx patients had lower serum klotho level with MD of = -234.50 (5 studies; 95%CI -444.84 to -24.16) compared to healthy volunteers, a study demonstrated comparable klotho level between KTx patients and eGFR-matched controls. Two studies demonstrated high serum klotho levels in deceased donors as prognostic marker for good allograft function within 1 year after KTx ($p<0.05$).

Conclusions: There is a significant increase in serum klotho levels after KTx. There is potential role of klotho levels as prognostic marker for renal allograft function.

PO2584

Braving the Storm: Cytokine Release Syndrome with Rabbit Antithymocyte Globulin Therapy after Kidney Transplant

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Introduction: Cytokine release syndrome (CRS) is an acute systemic inflammatory syndrome associated with chimeric antigen receptor (CAR)-T cell therapy or therapeutic antibodies. CRS can present with a variety of symptoms ranging from mild flu to severe life-threatening manifestations of shock, vascular leakage, DIC and multi-organ failure. We present a case of a CRS following rATG induction.

Case Description: A 29-year-old female with a history of T1 DM s/p kidney/pancreas transplantation 12 years ago experienced the rejection of transplanted kidney 1 year back. Her home immunosuppression included Tacrolimus, MMF and Prednisone. She underwent a kidney retransplant from a living donor. The induction immunosuppression consisted of rabbit anti-thymocyte globulin (ATG), methylprednisolone and MMF. Two hours after the rATG infusion (1.5mg/kg) on day 1 of transplant; she developed breathing difficulty, temp of 102.7, RR of 23, HR of 160 and fall in BP to 108/55 mmHg. Lab work showed a drop of Hb from 11.4 to 9, platelets from 187 to 126 and WBC from 17 to 9.8. CXR was unremarkable. ECHO showed normal cardiac function. LE Doppler was negative for DVT. The patient was quickly diagnosed to have CRS and instead of giving fluids and causing pulmonary decompensation, she was given Solumedrol, Benadryl and Tylenol. rATG was discontinued. Cultures were obtained that resulted negative. She improved within a couple of hours with stabilization of vitals. We suspect that the CRS following ATG infusion caused the patient's acute decompensation, given the temporal relationship, rapid recovery following withdrawal and lack of proven infectious etiology. She was finally premedicated and given ATG at a slower rate over 12 hrs and tolerated it well.

Discussion: CRS is an inflammatory cascade that develops within minutes to hours after immunotherapy. The case emphasizes the successful rapid recognition and proper management of CRS in preventing the patient decompensation. The massive cytokine release triggers an inflammatory response leading to capillary leakage, severe hypotension and respiratory failure. The management differs from usual shock as the aggressive hydration leads to pulmonary edema and should be avoided. Steroids and pressors are the mainstay of therapy and should be administered early. The treatment is largely supportive with ventilation for respiratory failure and steroids for inflammation.

PO2585

Proton Pump Inhibitor Prevalence and Documented Indication in a Small Kidney Transplant Program

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Background: Proton pump inhibitors (PPIs) are commonly prescribed post kidney transplantation, and their use was prevalent in 44-48% of recipients. Prolonged exposure to PPIs could be associated with renal and non-renal adverse outcomes, including hypomagnesemia and hip fracture (OR: 1.39, 95% CI: 1.04-1.84). The objective of this report is to evaluate the prevalence and the documented indication of PPI use in our kidney transplant program, while exploring the potential PPI withdrawal and GERD recurrence in a future Quality Improvement (QI) project.

Methods: This is a retrospective study to assess the prevalence and the documented indications of PPI use among all of kidney transplant recipients in our program by March 31st, 2020. The primary variables were the prevalence of PPI use and the percentage of patients with documented indication of PPI use in our Health Information System (HIS).

Results: Out of 202 kidney transplant recipients, 113 (55.9%) patients were on PPIs (Mean age 58 years, Male 68 (60.2%), mean post-transplant longevity 106 months), compared with 12 (5.9%) patients on H2 blockers. Thirty three (29.2%) patients who used to be on H2 blockers were switched to PPI in late 2019 due to contaminated and backordered ranitidine resulting in an adjusted prevalence of PPI use of 39.5% (Figure 1). The indication of PPI use was documented in our HIS as gastro-esophageal reflux disease (GERD) in 53 (46.9%) patients, and as peptic ulcer disease (PUD) in 9 (8%) patients, while its indication was undocumented in 51 (45.1%) patients.

Conclusions: PPI use was prevalent among our kidney transplant recipients similar to other studies. Due to its association with multiple adverse outcomes, better documentation of its indication in the medical record is required. Consideration to withdraw PPI in our kidney transplant recipients and to reassess the risk of GERD recurrence will be assessed in a future QI project.

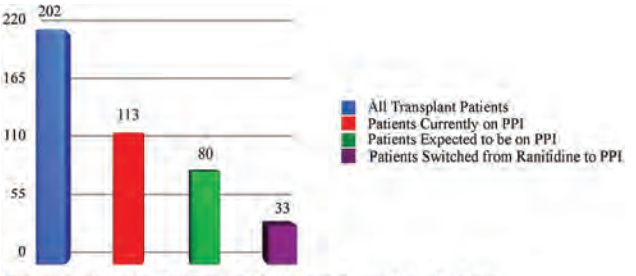

Figure 1: PPI Distribution In All Kidney Transplant Patients

PO2586

Unexpected Recurrence of Undiagnosed ANCA-Associated Vasculitis in a Kidney Transplant Recipient

Ruchi H. Naik, Heidi M. Schaefer, Saed Shawar. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: ANCA Associated Vasculitis (AAV) is one of the leading causes of End-stage Kidney disease (ESKD). The relapses of AAV after kidney transplant are relatively rare. As per the literature, the positive ANCA status in not a contraindication for transplant and patients usually get transplant once in clinical remission. Here, we are describing a unique case of ESKD due to renal limited AAV which was diagnosed retrospectively after the development of the recurrence two months post-transplant.

Case Description: A 69 years old Caucasian female with ESKD presumed due to hypertension received a deceased donor kidney transplant in Oct 2019 after being on dialysis for 4 years. She received alemtuzumab for induction followed by tacrolimus, mycophenolate mofetil, and prednisone for the maintenance immunosuppression. Her immediate post-transplant course was complicated by delayed graft function and her creatinine never went down below 2 mg/dl. Allograft biopsy was planned after 2 months due to persistent microscopic hematuria with progressive sub nephrotic range proteinuria. The immuno-histopathology and electron microscopy was suggestive of pauci-immune crescentic GN. Her serology workup was positive for ANA, ANCA with high titers of MPO. She lacked any other systemic involvement, and drugs induced ANCA was ruled out. She was treated with a pulse dose of methylprednisone and one dose of rituximab. Gradually her creatinine improved to 1.37 mg/dl with down trending MPO antibody titers within 4-6 weeks. The review of her chart retrospectively showed clinically asymptomatic ANCA positivity with high MPO titers 3.5 years back, suggestive of recurrence of AAV more than De novo AAV post-transplant.

Discussion: Physician should always be vigilant about the recurrence of the primary disease after transplant, especially when patients have undiagnosed primary kidney disease like AAV, where early diagnosis and treatment in the early stage of the disease is important to optimize results of renal transplantation. A randomized prospective study is needed to answer the question whether the ANCA positivity at the time of transplant adversely affect the outcomes.

PO2587

A Case of Porphyria Cutanea Tarda After Kidney Transplant

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Introduction: Porphyria cutanea tarda (PCT) is the most common subtype of porphyria and can be associated with kidney failure with reports of kidney transplantation curing the disease. We report the case of a patient who had previously undergone kidney transplantation and developed PCT after transplant.

Case Description: A 40-year-old man with end stage renal disease due to unknown chronic glomerulonephritis status post kidney transplant 4.5 years ago was admitted with non-healing blisters on both hands. Patient initially presented one month earlier with similar symptoms and was diagnosed with bullous impetigo due to methicillin resistance staphylococcus aureus. At that time, he was treated with vancomycin followed by trimethoprim-sulfamethoxazole (TMP-SMX) for a total of 14 days. He was also noted to have cytomegalovirus viremia which was treated with valganciclovir. Patient reported ongoing development of lesions despite antibiotic treatment and presented for follow-up where he was noted to have an acute kidney injury and hyperkalemia. At presentation his medications included mycophenolate sodium, tacrolimus, prednisone, triamcinolone cream and mupirocin ointment. There was no family history of skin disease and he did not drink alcohol. He underwent skin biopsy which was consistent with porphyria or pseudoporphyria. Urine and plasma porphyrins were checked showing elevated uroporphyrin and also elevate heptacarboxyl, hexacarboxyl and pentacarboxyl porphyrins with normal coproporphyrin I and III consistent with PCT. Additional workup was notable for a ferritin of 978 ng/mL, hepatitis A, B and C titers inconsistent with current or past infection and HFE gene testing showing the absence of mutations C282Y, H63D and S65C. Patient's kidney injury resolved with cessation of TMP-SMX and fluid resuscitation. Patient was treated with therapeutic phlebotomy and erythropoiesis stimulating agents along with counseling on sunscreen use and wearing sun protective clothing.

Discussion: PCT is the most common form of porphyria and is associated with hepatitis C, iron overload, estrogen administration and alcohol use. It has also been associated with hemodialysis often with resolution at the time of kidney transplantation. However, elevated iron stores are often present in kidney transplant patients and PCT can be misdiagnosed as bullous impetigo as it was in this case.

PO2588

Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplantation: A Single-Center Experience

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Background: Recurrent FSGS (r-FSGS) after Kidney Transplantation has a high risk of graft loss. However, the natural history, clinical predictors, and response to treatment remain unclear.

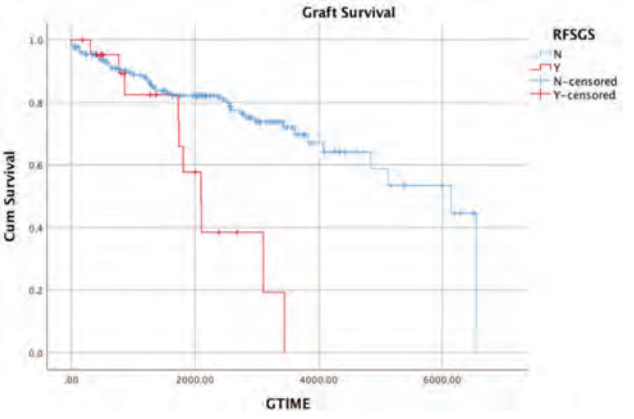
Methods: We retrospectively reviewed all transplant patients at our institition from 2000-2019 with a diagnosis of FSGS and identified and sub-analyzed all cases of recurrent FSGS cases (r-FSGS).

Results: Out of 198 transplants, there were 22 (11.1%) events of biopsy proven r-FSGS. Demographics of the rFSGS cases are described in the Table. 27% of cases had recurrence within 1 month of transplant. Treatments given for r-FSGS included ACE/ARB (100%), Therapeutic Plasma Exchange (40.9%), Rituximab (36.3%), conversion to Cyclosporin (36.3%) and Steroids (27.2%). 65% of cases had either a partial or complete remission. Mean proteinuria decreased and mean eGFR was improved at 1 year of recurrence ($p<0.05$). Over a median follow up period of 4.6 years, there was a 59% graft loss with no patient deaths. 31.8% of patients were re-transplanted after initial graft loss of which 42% had recurrence in their re-transplant. As compared to the cases without any recurrence, cases with rFSGS had a significantly lower long-term graft survival ($p=0.001$). Figure.

Conclusions: Recurrent FSGS continues to be a high risk for graft loss despite a multitude of therapies available.

Demographics & Outcomes of Recurrent FSGS Cases

Mean Age	49.7+/-13.9
Gender (M)	68.5%
Race (W)	68.5%
Living Donor	45%
Re-Transplants	31%
Pre-Emptive	22%
Median Duration to Recurrence	202 days
Mean Proteinuria at recurrence / at 1 yr post-recurrence	5.3±5.9 / 4.1±4.9 g/day
Mean eGFR at recurrence / at 1 yr post-recurrence	28.5±15.2 / 36.6±21.1 ml/min
Initial IS - ATG/MMF/Tac/Pred	72%/100%/100%/13.6%



PO2589

What Is the Safe Anti-A2 Titer for a Successful A2-Incompatible Kidney Transplantation?

Yorg Al Azzi, Pablo Loarte Campos, Gayatri D. Nair, Maria Ajaimy, Luz E. Liriano-Ward, Cindy T. Pynadath, Purna Bindu Nandigam, Enver Akalin. *Montefiore Medical Center, Bronx, NY.*

Background: The new kidney allocation system implemented in December 2014 allowed for use of A2/A2B donors to B recipients. However there is no mandate by UNOS regarding what anti-A2 titers are acceptable. We aimed to investigate the safety of kidney transplant in patients with anti-A2 titers equal or less than 1/16.

Methods: We performed 41 A2-incompatible kidney transplants at our institution if pre transplant anti-A2 titers are equal or less than 1/16. All patients received anti-thymocyte globulin induction. Patients with donor-specific-anti HLA-antibodies (DSA) received intravenous immunoglobulins 500 mg/kg for 3 doses.

Results: Of the 41 recipients, 85% were male, 48% African-American, with a median age of 53 (20-73) years. There were 38 deceased donor renal transplants and 3 living related. Median donor age was 42 (16-65) and median KDPI was 52 (2-86). Twenty-one patients had PRA 0% and 8 had pre transplant DSA. Pretransplant anti-A2 titers were 1/2 in 16, 1/4 in 9, 1/8 in 6, and 1/16 in 5 and too weak to titer in 5 recipients. During a median follow-up of 33 months (6-57) patient and graft survival were 100% and 90.2% respectively. Twelve patients underwent a clinically indicated kidney biopsy at a median 28 days post transplant (6-390). There was one case of acute T cell mediated rejection type IIA, and one chronic antibody-mediated rejection which was due to non-compliance leading to graft loss. Interestingly C4d positivity was seen in 9 biopsies, of which 8 did not have any findings of antibody mediated rejection and no microvascular inflammation. Median serum creatinine level at last follow up was 1.3 mg/dL (0.6-3.2) and only 3 patients had spot urine protein/creatinine more than 1 g/day.

Conclusions: A2-incompatible transplantation appears to be safe in patients with anti-A2 titers equal or less than 1/16 with or without DSAs and excellent short-term kidney allograft outcomes. C4d positivity is frequent in allograft biopsies without acute rejection suggesting accommodation to the allograft.

PO2590

Post-Transplant Outcomes for Highly Sensitized Kidney Transplant Recipients with Non-Highly Sensitized Recipients in the Era of the New Kidney Allocation System: A Single-Center Case-Control Comparison

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Background: The new UNOS kidney allocation system (KAS) of December 2014, gives substantial priority points to highly sensitized (HS) adult kidney transplant recipients (KTR) with cPRA of 99% or higher. There is a concern of worse post-transplant outcomes in HS KTR compared to non-HS KTR. When comparing pre-KAS to post KAS, similar 3-year patient and graft survival has been reported in HS KTR. The comparative outcomes of HS KTR to non-HS KTR in the post KAS era are unknown

Methods: We studied outcomes in HS adult kidney transplant recipients (KTR) and compared them to non-HS KTR in the post KAS era. We included all recipients of deceased donor kidney transplant at the University of Alabama at Birmingham, from December 2014 to March 2020. HS patients were defined as those with cPRA 99% or higher. The HS patients were matched 1:2 with non-HS patients on age, sex, and time of transplant. A Kaplan Meier analysis was performed for patient survival and the combined endpoint of graft and patient survival

Results: A total of 717 deceased donor kidney transplants were performed during the study period, of which 106 HS KTR were identified. The HS patients were more likely to be female (59.4% vs 34%, $p<0.001$), non-black (42.5% vs 30.9%, $p<0.022$) and were of similar mean age at transplant (49.9 vs 50.3 years, $p=0.46$) compared to non-HS patients. The HS-patients were then compared with 228 matched non-HS deceased donor controls.

The matched controls had a median cPRA of 0% (IQR 0-29.5%). There was no difference in death (p=0.17) or combined endpoint of death or graft survival (p=0.35) in the two groups (figure 1).

Conclusions: HS patients have similar mortality and graft survival as compared with non-HS controls. The results of our study support continuing to give HS patients priority in organ allocation

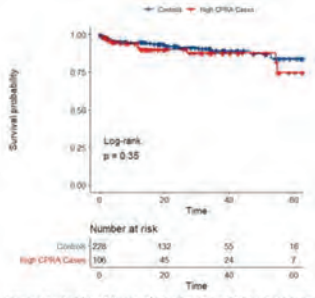

Figure 1. Kaplan-Meier plot comparing time to composite endpoint in highly sensitized patients and non-HS patients, using the log-rank test. Hatch marks represent censored cases in each group.

PO2591

Who Is at Risk for a Transplant Nephrectomy After Graft Loss?

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Background: Patients with failed kidney transplants who subsequently develop clinical symptoms such as fever, allograft pain and gross hematuria usually require a transplant nephrectomy to alleviate symptoms. Identifying patients at risk for a nephrectomy after graft loss may aid clinical decision-making and care at time of, and after graft loss.

Methods: We retrospectively reviewed all patients with death-censored graft loss (DCGL) from 1/2000 to 6/2018 at a single center. We collected baseline demographic and clinical characteristics at time of transplant, at time of, and after DCGL by manual chart abstraction. Data were analyzed using summary statistics. Predictors for nephrectomy were determined *a priori*. A Cox proportional hazards model was used to quantify the association of age, race, gender, body mass index (BMI) at time of graft loss, diabetes, acute rejection as cause of graft loss, and use of prednisone with the risk of nephrectomy.

Results: The study included 333 patients with DCGL of whom 75 (23%) underwent a transplant nephrectomy. Median (IQR) time from graft loss to nephrectomy was 135 (70, 267) days. Among 292 patients without missing data, baseline and transplant characteristics were as follows: age at transplantation 45 (36, 57), 59% male, 40% black, 20% diabetic, 53% with a deceased donor, 83% on calcineurin-based immunosuppression (CNI-IS), 71% on prednisone. Twenty four percent and 69% of patients lost their graft due to acute rejection and chronic allograft nephropathy, respectively. At the time of DCGL: BMI was 25.9 kg/m^2 (22.7, 31.4), SCr 7.5 mg/dl (5.6, 9.6), albumin 3.3 (3.0, 3.8), 86% on CNI-IS, 91% on prednisone. In the Cox model, black race was associated with more than twice greater risk of nephrectomy compared to non-blacks (HR 2.4, 95% CI 1.3-4.3, p=<0.01). Older age had a trend for decreased risk of nephrectomy (HR 0.98, 95% CI 0.95-1.0, p=0.06) but this did not reach statistical significance.

Conclusions: Transplant nephrectomies are common after graft loss and black race is associated with increased risk. Closer monitoring of these patients after graft loss may be warranted. Strategies and interventions to reduce the need for nephrectomy warrant further study.

PO2592

Contraceptive Use Among Women with Kidney Transplants in the United States

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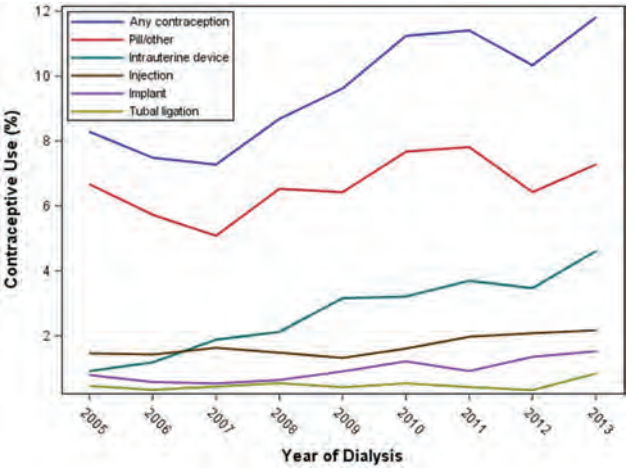
Background: Kidney transplant improves reproductive function in women with end-stage kidney disease (ESKD). Little is known about contraceptive use in women with history of kidney transplants.

Methods: Using the United States Renal Data System (2005-2014), we evaluated for each calendar year women with kidney transplantation who were aged 15-44 years with Medicare as the primary payer and linked data from the United Network for Organ Sharing, for up to three entire years after the date of transplantation. We determined rates of contraceptive use and used multivariable logistic regression to identify factors associated with contraceptive use.

Results: The study cohort included 13,150 women and represented 26,624 person-years (PY). The rate of contraceptive use in women with kidney transplant was 9.5% of person-years. Figure 1 shows the rates of types of contraceptive use from 2005-2013. Compared to women aged 15–24 years, contraceptive use was lower in women aged 30–34 years (OR, 0.67; CI, 0.58-0.78), 35-39 years (OR, 0.36; CI, 0.31-0.43), and 40-44 years (OR, 0.23; CI, 0.19-0.28). Compared to white women, contraceptive use was higher in black women (OR, 1.26; CI, 1.10-1.43) and Native American women (OR, 1.52; CI, 1.02-2.26). Women had lower rates of contraceptive use in the second-year post-transplant (OR, 0.87; CI 0.79-0.94) and third-year post-transplant (OR, 0.69; CI 0.62-0.76) than in the first-year post-transplant. Women with a history of diabetes had a lower likelihood of contraceptive use (OR, 0.80; CI, 0.65-0.99).

Conclusions: Among women with kidney transplants, contraceptive use remains low at 9.5%. Factors associated with a higher likelihood of contraceptive use include younger age and black and Native American race/ethnicity; second- and third-year post-transplant and history of diabetes are associated with a lower likelihood of contraceptive use. The study highlights the importance of counseling for contraceptive use in women with kidney transplants.

Funding: Private Foundation Support



PO2593

Evaluation of Reproductive Care Provided to Adolescent Patients in Pediatric Nephrology Clinics

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Background: An increasing number of adolescents are living with end-stage renal disease (ESRD) or chronic kidney disease (CKD) in the US. Therefore; it is important that nephrologists can manage reproductive and women's health issues in adolescents with CKD. In this study, we aimed to determine the confidence levels of nephrologists in the US in managing women's health issues in adolescent females with CKD.

Methods: Using Qualtrics Online Survey Platform, a survey was distributed by email to members of the Pediatric Nephrology Research Consortium. The survey contained 19 questions pertaining to provider demographics, training, current practice, frequency of documenting and/or discussing women's health issues, and level of confidence in managing women's health issues in adolescent female patients.

Results: Seventy-five nephrologists participated, with a majority practicing in academic centers (88%). For most providers, adolescents comprised 25-74% of all patients. Ninety-eight percent denied formal training in women's health or obstetric nephrology. History of pregnancy termination/loss, last menstrual period (LMP), contraceptive use, sexual activity, number of sexual partners, and history of sexually transmitted infections were infrequently documented. Most providers documented discussions about risks of teratogenicity with use of ACEi/ARBs or mycophenolate and risks of infertility and fertility-preserving options with use of cyclophosphamide. Most providers weren't comfortable managing pregnant adolescents and referred them to adult nephrologists. Most were uncomfortable discussing fetal risks with pregnancy in CKD. While most were confident discussing barrier methods, they were much less confident discussing oral contraceptives and long-acting reversible contraceptives (LARCs).

Conclusions: Sexual development and pregnancy appear not to be a focus of nephrologists caring for adolescent females with CKD. Providers also appeared to have a low level of confidence in discussing and managing fertility and pregnancy-related issues in adolescents. Nephrology training needs to incorporate focused women's health content to improve healthcare delivery to adolescent girls.

PO2594

Reproductive Health in Kidney Transplant Recipients

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Background: Women with advanced chronic kidney disease develop menstrual irregularities and infertility that can improve after kidney transplant. However, some women do not have menstrual cycles return after transplant and pregnancy rates are lower than in the general population, which could be due to a combination of biologic and social factors.

Methods: We sent a survey on reproductive health to all women aged 18 to 44 at the time of transplant at all 3 Mayo Clinic sites between 1996 and 2014. We sent a second survey to all non-respondents from the first mailing and then called all remaining women to ask for their participation. We included questions on menstrual cycles, pregnancy, and menopause. Parity at the time of transplant was determined by chart review.

Results: There were 816 unique women, aged 18 to 44 at the time of transplant, in the period from 1996 to 2014. After excluding women who had passed away (n=91), and those with no current address or living outside the US (n=10), there were 715 eligibile women and 190 responded (26.6% response rate). Respondents were more likely to be white and to have had a pregnancy post-transplant. Only 10% of women reported a pregnancy post-transplant, though 14.2% reported actively pursuing pregnancy at some point. Nearly half (42.1%) of women said they were advised not to get pregnant, most often by a nephrologist. There were 61 pregnancies post-transplant, of which 80.1% were planned pregnancies. The majority of pregnancies resulted in livebirths (57%), and miscarriage occurred in 39% of pregnancies. Amenorrhea occurred in 34.2% of women pre-transplant, and 23% of these women did not have cycles return after transplant. The median (interquartile range) age of menopause was 44.5 (36-49) years.

Conclusions: While only 14.2% of respondents reported actively pursuing pregnancy after transplant, nearly half said they were advised not to pursue pregnancy, often by their nephrologists, which could in part explain low pregnancy rates in the kidney transplant population. While amenorrhea prior to transplant occurred in the minority of women, 23% of these women did not have menstrual cycles return post-transplant. Furthermore, the median age of menopause was much earlier than the general population. These findings suggest that kidney disease and/or transplantation itself may impact long-term gonadal function, which should be a target of future study.

Funding: Clinical Revenue Support

PO2595

Menstrual Irregularities and Subfertility in Women with Glomerular Disease

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Background: Women with CKD are known to have high rates of irregular menses and subfertility (an extended period of unwanted non-conception). Those with glomerular disease may be at particularly high risk due to exposure to immunosuppression, such as cyclophosphamide, that may lower fertility.

Methods: A women's health survey was distributed to women ages 18-65 in the Glomerular Disease Collaborative Network, a longitudinal research registry in the southeastern United States. Descriptive statistics were employed to assess responses.

Results: The survery was completed by 192 women (response rate 16%) with median age 48 (34-57 interquartile range(IQR)) and BMI 28 (24-35 IQR). The most common diseases were IgA nephropathy/vasculitis (22%), Lupus nephritis (20%), ANCA vasculitis (18%) and FSGS (16%). At the time of the survey, 17% had a kidney transplant or required dialysis. Table 1 describes self-reported menstrual cycle length and permanent cessation of menses by age group. Of those over age 45, 41% reported permanent cessation of menses had occurred at ≤ 44 years old. Cyclophosphamide use was reported by 63 of 192 (33%), and their fertility preservation methods included leuprolide (6, 10%) and oocyte cryopreservation (1, < 2%). One in four women (50/192, 26%) reported a history of attempting to conceive for > 6 months without success. To aid conception, 26% (13/50) reported use of a medication (e.g. clomiphene) and 16% (8/50) underwent intrauterine insemination, in vitro fertilization, or received egg/sperm donation.

Conclusions: Women with glomerular disease and/or vasculitis had high rates of irregular menstruation and early menopause which may contribute to subfertility. Our data is limited as we do not know GFR, nor the timing or amount of cyclophosphamide prescribed. Response bias from women with a positive history may have also played a role. Future efforts should elucidate reproductive endocrinology utilization and success in this population.

Funding: NIDDK Support

Menstrual Cycle Length and Cessation Of Menses By Age Group

Age group	18-25	26-35	36-45	46-55	56-65
N	10	40	32	51	59
Menstrual cycle lasting 24-35 days (%)	30	68	69	26	0
Abnormal menstrual cycle (lasting < 24 days, > 35 days, or too irregular to say) (%)	70	28	19	12	2
Permanent cessation of menses (%)	0	5	13	61	98
Cessation of menses occuring ≤ 44 years old (% (*N respondents*))	N/A	N/A	N/A	61 (19/31)	30 (17/57)

N/A: not applicable

PO2596

Buffy Coat Methylation Is Representative of Methylation Patterns in White Blood Cell Types in Normal Pregnancy

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Background: Epigenetic changes through DNA methylation are increasingly identified in renal diseases and hypertensive disorders. Our previous studies identified an altered methylation pattern in preeclampsia compared to normotensive pergnancies. Epigenetic studies typically use buffy coat- a heterogenous cell population- that varies throughout pregnancy and could potentially interefere with DNA methylation results. The objective of the current study was to assess to what extent the buffy coat methylome is representative of the distinct cell types that it contains namely polymorphonuclear leukocytes(PMN) and lymphocytes(LYM) in normotensive pregnant women.

Methods: We performed a pairwise comparison of the differential methylation in the buffy coat, the polymorphonuclear fraction and the lymphocytic fraction drawn from the same individual in normotensive pregnant women (n=29) within the 24 hours prior to delivery. We analyzed 412481 cytosine-guanine (CpG) sites using an Illumina Human Methylation450 BeadChip.

Results: The three pairwise comparisons yielded a small number of probes that are differentially methylated. After multiple testing corrections, the smallest number of differentially methylated probes was found when comparing the buffy coat to the polymorphonuclear group (2.96%). Pathway analysis of the differentially methylated probes identified a matched process involved in leukocyte lineage. The differentially methylated CpG sites preferentially affected the open seas and shelf regions that have little effect on epigenetic regulation.

Conclusions: The buffy coat DNA methylation profile is representative of the PMN and LYM fractions on an Illumina Human Methylation450 BeadChip. The use of buffy coat is an acceptable approach for DNA sampling in DNA methylation studies and separation is only needed when studying lineage specific diseases.

Funding: Other NIH Support - NIH

		Original analysis			Without violating probe trios		
Comparison		BP	BL	PL	BP	BL	PL
	p < 0.05	12207	125962	143097	13926	124251	143048
DMP	p < 0.05 & Δβ > 0.1	2450	20271	26334	2963	20303	26495
	p < 0.05	596	5270	6086	627	5209	6120
DMR	p < 0.05 & Δβ > 0.1	0	164	25	0	157	24
	p < 0.05	15	0	0	14	0	0
GSEA - DMP	p < 0.05 & Δβ > 0.1	11	32	17	12	31	23
	p < 0.05	0	10	19	0	14	23
GSEA - DMR	p < 0.05 & Δβ > 0.1	0	1*	1*	0	0	0

PO2597

Pregnancy Outcomes in Women with AKI

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Background: Acute kidney injury (AKI) during pregnancy is a public health problem and is associated with maternal and fetal morbidity and mortality. Literature concerning pregnancy outcomes in women with AKI is scarce.

Methods: We evaluated a retrospective single-center cohort of all women who delivered infants between 2012-2019 at our center (N=21,038) to assess the AKI rate and whether the history of AKI during pregnancy was associated with adverse maternal and fetal outcomes. Using multivariate logistic regression models, we determined factors associated with AKI, and associations between AKI and pregnancy outcomes.

Results: Overall, 109 deliveries were identified with AKI during pregnancy. AKI rate was 0.5%. The mean age of women was 28 years, 55% were black, and 36% were white. 25% had a history of diabetes and 24% had a history of hypertension. With regards to maternal outcomes, 46% had preeclampsia, 27% had gestational diabetes, 40% had gestational hypertension, and 57% had cesarean section deliveries. Maternal mortality was 4%. With regards to fetal outcomes, among women with AKI during pregnancy, 19% had preterm deliveries, the live birth rate was 85%, the stillbirth rate was 5%, and neonatal mortality was 5%. Diabetes and hypertension were associated with a higher adjusted likelihood of AKI during pregnancy (OR, 4.59; 95% CI, 2.87-7.50 and OR, 5.97; 95% CI, 3.63-9.80 respectively). In the adjusted model, AKI during pregnancy was associated with a 5.6-fold higher likelihood of preeclampsia (OR, 5.57; 95% CI, 3.70-8.39), 2.2-fold higher likelihood of cesarean section (OR, 2.21; 95% CI, 1.50-3.27), 2-fold higher

likelihood of preterm births (OR, 1.97; 95% CI, 1.22-3.16), 4-fold higher likelihood of stillbirths (OR, 4.04; 95% CI, 1.60-10.20), and a 5.7-fold higher likelihood of neonatal mortality (OR, 5.65; 95% CI, 2.20-14.49).

Conclusions: AKI rate during pregnancy is 0.5%. AKI during pregnancy is associated with a higher likelihood of preeclampsia, preterm births, stillbirths, and neonatal mortality. This study increases our understanding and need for change in policies for the management of AKI during pregnancy.

Funding: Private Foundation Support

PO2598

Pregnancy Following Kidney Transplantation: Experience of a Tertiary Renal Obstetric Service Between 1996 and 2020

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Background: Compared with dialysis, fertility & pregnancy outcomes are more favourable following transplantation. However, pregnancies post kidney transplant remain challenging with a risk of adverse maternal & obstetric outcomes

Methods: All transplanted patients attending the renal-obstetric clinic were identified from an in-house database. Further data were collected from their health records

Results: We identified 52 pregnancies in 39 women. The mean age at delivery was 33±3 years. 57% were white, 17% black & 21% Asian. The cause of ESKD was glomerulonephritis (46%), reflux(17%), unknown/other(27%) & diabetes(10%). 3 patients (5%) miscarried & are not included in further analysis. The mean time from transplantation to pregnancy was 84±56 months. The mean follow up after delivery is 6±5.2 years. The mean eGFR pre-pregnancy was 50.8; at 6 months, 1, 3 & 5 years it was was 49.4, 47.4, 48 & 52.9 ml/min. 1 graft was lost during pregnancy (pre-pregnancy eGFR 25, PCR 150); None were lost in the year postpartum. 5 women(12%) have subsequently lost their graft(mean of 4 years postpartum). 1 woman was presumptively treated for rejection during pregnancy; 2 were treated for rejection within 1 month post-partum. 6 others(14%) had a rejection episode - mean time of 38.6±42.4 months post-partum. There were no maternal deaths. 3/19 women checked for Donor Specific Antibodies(DSA) postpartum had a DSA- 1 present pre pregnancy & 2 de novo. The mean gestational age was 35.7 weeks, with 43% born at term & 43% pre-term(5 born <34 weeks). 18 women(37%) developed preeclampsia. There was one intrauterine death. 66% delivered by caesarean section. The mean birth weight was 2400±588 grams; 24% were <10th percentile

Conclusions: Pregnancy outcomes in patients with transplants are better compared with those on dialysis(PMID: 27083278). However, complications still occur. The rate of preeclampsia (36%) is representative of the current literature & much higher than for women without transplants. Diagnosing preeclampsia in patients with pre-existing hypertension & proteinuria, as for many of our patients, remains challenging. In our experience, reflected here, there are relatively low rates of rejection & graft loss but high rates of obstetric complications. We believe these patients are ideally managed in a joint renal obstetric clinic.

PO2599

Does Nephrologist Involvement Improve Aspirin Prescribing in Pregnant Women with CKD?

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Background: Since 2014, the U.S. Preventative Services Task Force has recommended the use of aspirin beginning at 12 weeks gestation in women at high risk for development of preeclampsia including those with chronic kidney disease (CKD). A prior study at the authors' institution revealed overall low prescribing rates for women with CKD with only 50.5% taking aspirin according to the recommended guidelines. The authors hypothesized that having a nephrologist involved in patient care would result in higher aspirin prescribing rates.

Methods: The authors reviewed data from pregnancies with delivery between January 1, 2015 and December 31, 2019. Potential pregnancies were identified with diagnostic codes for pregnancies and then included patients who had diagnostic codes for chronic kidney disease and proteinuria. Pregnancies that ended prior to 12 weeks were excluded. Means, standard deviations, medians, and interquartile ranges were used for continuous variables and frequency. Proportions were used for categorical variables.

Results: In total, 91 pregnancies were included. The mean age at due date was 29.7 (std dev 5.3) with 20.9% being of advanced maternal age. The majority were obese (54.9%), with an overall mean BMI of 33.6 (std dev 8.8). During pregnancy, 64.8% (59/91) of patients with known CKD saw a nephrologist. In addition, 20.3% (12/59) of those with known CKD who had previously seen a nephrologist did not see one during pregnancy. Of those who saw a nephrologist during pregnancy, 50.8% (30/59) were prescribed aspirin. In patients who saw a nephrologist at any time before or after pregnancy, 52.1% were prescribed aspirin while of those who did not see nephrologist during pregnancy, 45% were prescribed aspirin. The odds ratio of receiving aspirin if seen by a nephrologist of 2.33 (0.69-7.89) was not statistically significant.

Conclusions: Nearly two-thirds of pregnant women with CKD saw a nephrologist during pregnancy. The involvement of a nephrologist did not significantly increase aspirin prescribing rates among pregnant women with CKD. Further studies should be done to assess attitudes and knowledge of nephrologists and obstetricians to better understand the reasoning for the low prescribing rates and to assess how to improve aspirin prescribing for preeclampsia risk reduction in pregnant women with CKD.

PO2600

Prepartum 1,3-Butanediol Supplementation Does Not Prevent Onset of Superimposed Preeclampsia in the Dahl S Rat

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Background: Chronic hypertension increases the risk of developing superimposed preeclampsia (PE). Previous reports showed that 1,3-Butanediol (BD) lowers blood pressure (BP) in male Dahl salt sensitive (S) rats and female S.SHR(11) rats. The goal of this study was to test if attenuating hypertension before pregnancy through the placentation period via BD prevents the onset of PE and improves kidney function.

Methods: Female Dahl S rats (a spontaneous model of superimposed PE, 11-16 weeks old) were divided into two groups: BD treated (20% via drinking water) and control (ad libitum water). Animals received BD for 7 weeks, baseline BP measurements (telemetry) were taken, and both groups were then mated. On gestation day (GD) 12, treatment was stopped because pilot studies showed that treatment reduced water intake during late pregnancy. Both groups were maintained on normal rodent chow (Teklad 7034, 0.3% NaCl; n=8/group). At GD18 (late pregnancy), uterine artery resistance index (UARI) was measured via Doppler ultrasound, 24h urine was collected on GD19, and tissues were harvested on GD20. Statistical comparisons between groups were done by Student t-test and repeated measures ANOVA used for BP analysis.

Results: Mean arterial pressure was lower in the treated group at baseline (141.9 ± 4.09 vs. 165.7 ± 4.53 mmHg, p= 0.0076), early (135.9 ± 3.42 vs. 168.9 ± 4.55 mmHg, p= 0.0003), mid (142.0 ± 5.16 vs. 170.8 ± 4.61, p= 0.0048) but not late pregnancy (144.9 ± 5.87 vs. 161.9 ± 4.52 mmHg, p= 0.1650). Treated dams had a lower UARI (0.71 ± 0.02 vs. 0.81 ± 0.02, p=0.0077), less fetal resorptions (1.12 ± 0.29 vs. 2.25 ± 0.41, p= 0.0434)) but no differences in pup weight were observed (2.199 ±0.049 vs. 2.199 ± 0.086, p= 0.9938). Proteinuria (39 ± 8 vs. 32 ± 7 mg/day, p=0.5401), blood urea nitrogen (21 ± 0.75 vs. 22 ± 0.78 mg/dL, p=0.2239), creatinine clearance (1.66 ± 0.30 vs. 1.60 ± 0.21 mL/min, p=0.5672) and renal fibrosis (0.55 ± 0.09 vs. 0.75 ±0.08 %, p=0.1382) were unaffected.

Conclusions: In this study, we observed slightly improved placental perfusion and lower fetal demise following prepartum BD treatment; however, the antihypertensive effects of BD were not sustained through late pregnancy when supplementation was stopped at mid-pregnancy. No improvements in renal function were noted.

PO2601

Low Nephron Endowment and Pregnancy-Related Renal Maladaptation in the Pathogenesis of Preeclampsia

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Background: Pre-eclampsia (PE), whose pathogenesis is still unclear, complicates 2-8% of pregnancies and is responsible of significant maternal and/or perinatal morbidity and mortality. Given the following premises: 1.the high frequency of PE in renal patients (including solitary kidney); 2.the majority of patients with PE, are healthy before pregnancy and return to well-being after delivery; 3.the familial recurrence of PE and the increased PE recurrence risk in subsequent pregnancies; 4.the increased risk in PE patients of developing hypertension and CKD later in life; 5.the association between intrauterine poor environment, reduced nephron mass and risk of hypertension and CKD. We hypothesize that PE, in otherwise healthy women, is the expression of poor kidney adaptation to the increased functional requirements of pregnancy in subjects with a reduced nephron endowment.

Methods: To test this theoretical explanation, the changes in serum creatinine (sCr) during pregnancy (31st gestational week), used as marker of renal functional adaptation, were analysed in a cohort of 22 pregnant women (mean age 34.7 years; 36% nulliparous).

Results: The 9 uncomplicated pregnancies showed sCr decrease of 12.6±11.2 µmol/L (-18.8±16.9%) compared to 4.2±12.1 µmol/L (-3.8±17.5%); *p*=0.0361 (van der Waerden test) in the 13 pregnancies later on complicated by PE (or pregnancy-related hypertensive disorder).

Conclusions: In conclusion, women who later on developed PE lack the expected pregnancy-related decrease in sCr. It can be speculated that hypertension and proteinuria are due to sub-optimal renal clearance and accumulation of placental-derived metabolites toxic to the endothelium in otherwise healthy subjects with limited nephron endowment thus reduced renal functional reserve

PO2602

Hyponatremia in Preeclampsia: A Diagnostic and Therapeutic Challenge

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Introduction: A 32-year-old female at 35-weeks gestation with twin pregnancy was admitted for hypertension, proteinuria, and hyponatremia (**Figure 1A**).

Case Description: She complained of nausea, blurred vision, and pain. Physical exam revealed 3+ generalized edema. Her blood pressure improved with conservative management, and medications controlled her nausea and pain. **Figure 1B** shows her hospital serum sodium trend. The physical exam, serum and urine studies suggested

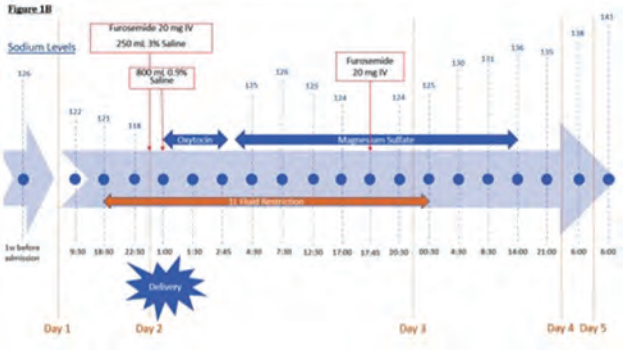
hypervolemic hyponatremia due to nephrotic syndrome. She was placed on fluid restriction. Repeat serum sodium and urine protein to creatinine ratio (UPCR) were 118 mEq/L and 4.4 g/g creatinine, respectively. Her obstetrician decided to perform emergency delivery. Prior to oxytocin induction, she received 3% saline, 0.9% saline, and IV furosemide. Three hours after delivery, serum sodium was 125 mEq/L and UPCR was 0.2 g/g creatinine. Fluid restriction continued for the first 24 hours after delivery and her serum sodium remained stable. Over the next 24 hours, her serum sodium corrected to 138 mEq/L with liberalization of the fluid restriction

Discussion: Hyponatremia in pregnancy may be due to antidiuretic hormone (ADH)-dependent factors, such as "reset" osmostat, diffuse vasodilation, nausea, and pain. Administration of oxytocin, which is structurally similar to ADH, can also reduce serum sodium. In preeclampsia, hyponatremia may occur due to decreased effective circulating volume secondary to antiangiogenic factors or nephrotic syndrome, non-osmotic release of ADH with consequent water retention, or SIADH. Worsening hypertension with end organ damage are severe features of preeclampsia often requiring emergent delivery, but severe hyponatremia is often overlooked as a severe feature. This case illustrates that patients with preeclampsia may develop severe hyponatremia, which improves after delivery. Refined guidelines should consider severe hyponatremia and its management in preeclampsia

Figure 1A

	1 week prior to admission	Day 1
Serum Sodium (mEq/L)	126	121
Serum creatinine (mg/dL)	0.7	0.75
Urine osmolality (mOsm/kg)	-	592
Urine sodium (mEq/L)	-	12
UPCR	0.36	2.97
Blood Pressure (mmHg)	110/60	161/98

Figure 1B



PO2603

Proteinuria in Early Pregnancy: Role of sFLT-1:PlGF Ratio

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Introduction: A 32-year-old nulliparous woman at $20^{5/7}$ weeks gestation by in vitro fertilization was admitted for hypertension (HTN), proteinuria, and acute kidney injury.

Case Description: She reported no home medications other than prenatal vitamins. Exam was notable only for trace leg edema. Given nephrotic syndrome early in pregnancy and unremarkable hemolysis work-up (**Figure 1A**), there was concern for acute glomerulonephritis (GN). Renal biopsy showed signs of thrombotic microangiopathy (TMA) (**Figure 1B**) without evidence of immune-complex mediated GN. As Atypical hemolytic uremic syndrome (aHUS) and Preeclampsia (PEC) were both on the differential, serum was tested for sFLT-1 and PlGF. Based on emerging evidence of alternative complement pathway activation in PEC, Eculizumab use was discussed but not pursued due to uncertain fetal viability, even with pregnancy prolongation. Ultimately, patient chose to terminate the pregnancy and subsequent pathology review revealed maternal vascular malperfusion and early intrauterine fetal demise. Levels of sFLT-1 (95,228 pg/ml), PlGF (139.3 pg/ml), and sFLt-1: PlGF ratio (683.6) were all consistent with severe PEC (**Figure 1C**). At 2-month follow-up, proteinuria had resolved and HTN was controlled with Nifedipine.

Discussion: Patients presenting with nephrotic syndrome and hypertension ≦ 20 weeks gestation pose a diagnostic dilemma. Renal biopsy is necessary to distinguish PEC from GN but pathological diagnosis of TMA can lead to persistent diagnostic uncertainty. Measurement of circulating angiogenic factors can be useful, with sFLT-1:PlGF ratio > 38 supporting a diagnosis of PEC. Further validation and widespread availability of such testing is needed to assist in management of early pregnancy complications.

Figure 1A	Initial laboratory values
Serum creatinine (mg/dL)	1.18 (baseline 0.8)
24-hour urine collection (g/d)	9
Urine protein/creatinine (g/g)	10.7
Urinalysis with microscopy	>300 protein, 0-3 RBCs/hpf, 51-100 WBC/hpf
Serum Albumin (g/dL)	2.7
AST, ALT (Unit/L)	15, 11
Uric Acid (mg/dL)	9.9
Hemoglobin (g/dL)	11.8 with normal differential
Platelets (K/UL)	237
LDH (U/L)	252
Haptoglobin (mg/dL)	77
Peripheral blood smear	No evidence of hemolysis
ANA	1:80
C3, C4 (mg/dL)	121, 22
Lupus Anticoagulant	Negative
Anticardiolipin antibody	Negative
Beta-2-Glycoprotein	Negative

Figure 1B

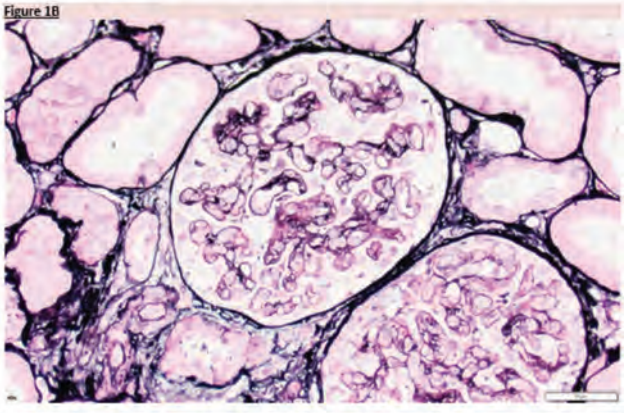

Figure 1C	1 week after discharge
Serum creatinine (mg/dL)	0.9
Urine protein/creatinine (g/g)	3.5
ADAMTS 13 activity	56%
sFLT-1 (pg/ml)	95,228 (5 to 10 x ULN)
PlGF (pg/ml)	139.3 (2 to 3 x LLN)
sFLT-1: PlGF ratio	683.6

Figure 1: Clinical data & Jones stain showing glomerular basement membrane duplication, characteristic of TMA.

PO2604

Hyperemesis Gravidarum-Induced Acute Tubular Necrosis: A Case with More Than Fivefold Rise in Serum Lipase Level Above the Upper Limit of Normal

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Introduction: Hyperemesis gravidarum (HG) occurs in 0.3 to 10 percent of pregnancies with only 0.8 percent requiring hospitalization. HG usually starts within 4^{th} to 6^{th} week of gestation, peaks around 9^{th} week and fades away between 16^{th} to 20^{th} gestational weeks. In some cases, HG may last until the third trimester. Here we are reporting such a case which was associated with serious complication like acute renal failure. Co-incidentally the patient was also found to have serum lipase level 5 times above the upper limit of normal (ULN). Since HG exerts multisystemic manifestations, the unusual pattern of raised serum lipase is often due to associated renal impairment.

Case Description: A 25-year old primigravida at 16^{th} week of gestation was admitted for severe dehydration and acute kidney injury (S. Creatinine 5.1 mg/dl). She was suffering from HG since the beginning of her pregnancy. A month prior to this admission, the patient was hospitalized on multiple occasions for extreme nausea and blood-tinted vomiting. Her initial labs were suggestive of high anion gap metabolic acidosis (anion gap 31.9mmol/L). Urine electrolytes (Na^+<20mEq/day, K^+ 29mEq/day, Cl^- <20mEq/day) with $FeNa^+$<0.1% indicated pre-renal etiology and urine microscopy showed muddy brown casts suggestive of ATN. Patient's serum ALT (134 IU/L) and AST (93 IU/L) were raised >3 and >2 folds of ULN respectively whereas serum lipase (921 U/L) and amylase (309 U/L) levels were raised >5 and 3 folds of ULN respectively. Patient was treated conservatively with IV 0.9% NaCl saline. Eventually, her serum AST, ALT, lipase and amylase started decreasing with spontaneous recovery of renal function overtime (S. Creatinine 0.5mg/dl). Patient's HG persisted until 32^{nd} week of gestation when symptom subsided completely without medication.

Discussion: In acute pancreatitis, the sensitivity and specificity of serum lipase above 3-times of the ULN range 64%-100% and 99%-100% respectively. More than 3-folds rise of serum lipase above the ULN can also be seen in a variety of other conditions including renal failure. Even in 15% cases of HG with normal renal function, serum Lipase can rise by 5-folds. Therefore, clinical and biochemical co-relation is necessary to rule out acute pancreatitis in pregnancy.

PO2605

Outcomes of Delivery Hospitalizations Among Pregnant Women with Kidney Transplant in the United States

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Background: Outcomes of delivery hospitalizations, including acute kidney injury, obstetric and fetal events among pregnant women with kidney transplants (KT) compared to those with no known kidney disease and chronic kidney disease (CKD) stage 3-5 are unclear.

Methods: Hospitalizations for delivery were identified using the enhanced delivery identification method in the National Inpatient Sample dataset from the years 2009 to 2014. Diagnoses of CKD stage 3-5, KT along with obstetric events, delivery methods, and fetal events were identified using ICD-9-CM diagnosis and procedure codes. Logistic regression accounting for the survey weights and matched regression were conducted to investigate the risk of maternal and fetal complications in women with KT as compared to women with no kidney-related diagnosis and compared to women with CKD stage 3-5.

Results: A total of 5,408,215 hospitalizations resulting in delivery were identified, including 405 women with CKD stage 3-5, 295 women with functioning KT, and 5,405,499 women with no kidney diagnosis., Pregnant KT recipients were at higher odds of pregnancy-induced hypertension (OR = 3.11, 95%CI [2.26, 4.28]), preeclampsia/eclampsia/HELLP syndrome (OR = 3.42, 95%CI [2.54, 4.60]), preterm delivery (OR = 2.46, 95%CI [1.75, 3.45]), fetal growth restriction (OR = 1.74, 95%CI [1.01, 3.00]), and acute kidney injury (OR = 10.46, 95%CI [5.33, 20.56]) as compared to women with no kidney-related diagnosis. There were no significant differences in rates of gestational diabetes and cesarean section. Pregnant women with KT had 1.30-time longer length of stay and 1.28-time higher cost of hospitalization. However, pregnant women with CKD stage 3-5 were at higher odds of AKI, preeclampsia/eclampsia/HELLP syndrome and fetal death, and had longer hospital stay and cost of hospitalization compared to pregnant women with KT.

Conclusions: Pregnant women with KT were more likely to experience adverse events during delivery when compared to women with no known kidney disease. However, pregnant women with advanced CKD were more likely to experience serious complications than KT recipients. Women with advanced CKD who wish to conceive might consider conception after transplantation for better pregnancy-related outcomes.

PO2606

Successful Pregnancy in a Patient with Congenital Renal Dysplasia After Initiation of Dialysis

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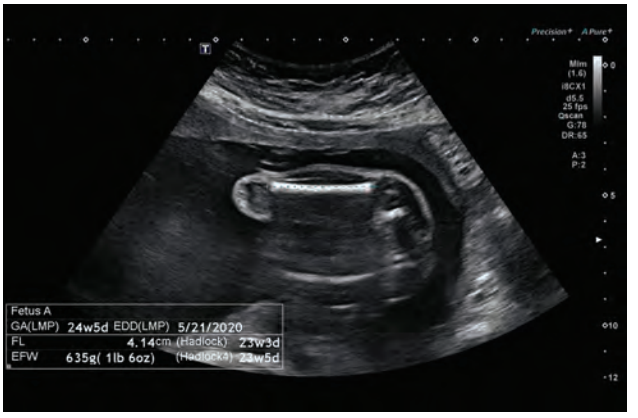
Introduction: Chronic kidney disease (CKD) is a well-known risk factor for adverse maternal and fetal outcomes including preeclampsia and fetal growth restriction. For those on dialysis, increasing the frequency and duration of dialysis has shown to optimize outcomes. However, it remains unclear if and when pregnant patients with CKD should start dialysis to improve outcomes. We present a patient with congenital renal dysplasia who successfully gave birth after starting dialysis.

Case Description: A forty-one-year-old female with an intrauterine pregnancy of 25 weeks and a history of two miscarriages, preeclampsia, and congenital renal dysplasia presented to nephrology clinic. Patient was unaware of her kidney dysfunction and had residual renal function with a creatinine of 3.76 and urine pr/cr ratio of 1.18. A fetal ultrasound revealed a fetal weight in the 12th percentile, head circumference in the 2nd percentile, and biparietal diameter (BPD) in the 33rd percentile. Therefore, the patient started daily dialysis with longer sessions to optimize fetal outcomes. A repeat ultrasound two weeks later revealed interval growth with a fetal weight in the 24th percentile and BPD in the 45th percentile but with abnormal umbilical artery Doppler findings, an indicator of small gestational age. The patient was admitted at 31 weeks due to concern for preeclampsia and continued daily dialysis. Due to labile blood pressures and fetal decelerations, the patient underwent a C-section at 32 weeks and delivered a newborn with an APGARS score of 6/8. Both the patient and her baby were eventually discharged home without complications.

Discussion: Initiation of dialysis resulted in significant interval fetal growth and this patient's first viable infant. Further research is warranted to assess if starting dialysis earlier in pregnant patients with CKD may improve fetal outcomes.



Fetal ultrasound prior to dialysis with a femur length in the 6th percentile and an estimated fetal weight of 635 grams in the 12th percentile.

PO2607

The Ethics of Caring for Pregnant Patients with CKD: A Scoping Review

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Background: Physicians must consider many ethical principles when managing patients with chronic disease before and during pregnancy. An ethical framework could guide joint decision making between physicians and their patients, but does not currently exist.

Methods: We performed a scoping literature review to explore the ethical considerations associated with pregnancy in patients with chronic disease. We searched for articles published between 1975 and 2019 using the terms "Ethics" and "High risk Pregnancy/Pregnancy" along with 29 chronic disease-specific MeSH terms (e.g. scleroderma, diabetes, cystic fibrosis).

Results: We identified 968 articles and excluded 947 based on their title or abstract. 12 full text articles were included in the final scoping review representing discussions, case reports, and literature reviews on the ethics of high-risk pregnancy in 8 chronic diseases. The extracted data were examined and integrated into analyses of clinical cases in order to develop recommendations for ethically caring for this patient population.

Conclusions: Physicians have an ethical duty to their patients to facilitate autonomous decision-making and informed consent. Secondarily, they have a duty to protect the fetus and to use resources judiciously as long as it does not negatively impact the care they provide to their patient.

PO2608

Anti-Glomerular Basement Membrane Disease in Pregnancy

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Introduction: Anti-glomerular baseline membrane (anti-GBM) disease is a rare cause of renal failure due to the production of IgG antibodies against type IV collagen. Its occurrence during pregnancy is even less common and can lead to poor maternal and fetal outcomes.

Case Description: A 23-year-old female with history of depression presented at 15 weeks 3 days gestation with weakness, nausea and vomiting for one week and anuria for 24 hours. Labs were significant for a creatinine of 19.8 mg/dL, BUN 113 mg/dL and potassium 7.1 mmol/L. Labs six months prior were normal. Nephrology was consulted and the patient was transferred to the intensive care unit for urgent hemodialysis. Further serologic investigation revealed elevated anti-GBM antibodies. A kidney biopsy was performed which demonstrated 100% cellular crescents on light microscopy and linear deposits on immunofluorescence, confirming the diagnosis. In addition to daily hemodialysis, the patient underwent plasmapheresis and immunosuppression with pulse dose steroids followed by a steroid taper as well as azathioprine and tacrolimus. The patient returned to the hospital with hypoxic respiratory failure due to parainfluenza virus further complicated by pre-term premature rupture of membranes at 24 weeks 4 days. As the patient had no signs of renal recovery, her immunosuppression was discontinued. The patient remained inpatient receiving daily hemodialysis until 28 weeks 0 days when the patient developed uncontrollable hypertension requiring an emergent cesarean section. The patient gave birth to a live male weighing 1.1 kg. Her post-partum course was uncomplicated, though the patient remains dialysis dependent.

Discussion: The treatment of choice in anti-GBM disease is plasmapheresis to remove circulating antibodies and immunosuppression to reduce antibody production. However, pregnancy presents a unique challenge in choosing immunosuppressive agents as both maternal and fetal effects need to be considered. The involvement of high risk obstetrics as well as neonatology in the care of these patients is imperative to ensure the best possible outcomes.

PO2609

Identification of Renal Disease in Women with Hypertensive Pregnancies

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Background: Hypertension in pregnancy can be associated with renal injury, which may be masked by gestational change. Additionally, pregnancy affords an opportunity to diagnose asymptomatic renal disease. Postpartum assessment enables detection of on going renal abnormalities. We aimed to determine prevalence of renal disease in postpartum women with chronic hypertension, pregnancy induced hypertension or pre-eclampsia in a previous or current pregnancy.

Methods: Women with singleton pregnancies seen in a specialist clinic for hypertension with estimated GFR (CKD-EPI) below 90mls/min/1.73m^2 and/or proteinuria at six-weeks postpartum were offered specialist renal midwifery clinic follow-up.

Results: 143/341 women offered follow-up attended renal clinic (Median 185 (IQR 246.25) days after delivery). 82 (57.3%) women had proteinuria and/or low eGFR. Subgroup analysis according to hypertensive group is shown in Table 1.

Conclusions: Over half of women with proteinuria and/or reduced eGFR at six weeks postpartum had sustained evidence of renal disease regardless of hypertensive diagnosis. Postpartum assessment may afford an opportunity to detect renal disease.

Table 1

	Chronic Hypertension (N=33)	PIH in current pregnancy (N=20)	PE in current pregnancy (N=80)	History of PE/PIH (N=10)
Six Week Postpartum Visit				
Systolic BP (mmHg)	132.8 (14.5)	129.3 (13.3)	129.0 (21.6)	120.6 (8.9)
Diastolic BP (mmHg)	85.1 (9.0)	80.25 (11.8)	81.7 (14.9)	71.8 (7.8)
eGFR (mL/min/1.73m2)	101.4 (22.1)	108.0 (18.3)	109.4 (22.2)	82.3 (25.5)
PCR >15mg/mmol or ACR >3mg/mmol n(%)	24 (72.7)	14 (70.0)	63 (78.8)	3 (30.0)
Longer-term follow-up n(%)				
ACR (mg/mmol)				
A1: <3	23 (69.7)	18 (90.0)	29 (58.0)	6 (60.0)
A2: 3-30	9 (27.3)	2 (10.0)	41 (51.3)	2 (20.0)
A3: >30	1 (3.0)	0	10 (12.5)	2 (20.0)
eGFR (ml/min/1.73m2)				
G1: ≥ 90	26 (78.8)	17 (85.0)	68 (85.0)	4 (40.0)
G2: 60 – 89	5 (15.2)	3 (15.0)	11 (13.8)	5 (50.0)
G3a: 45 – 59	1 (3.0)	0	1 (1.2)	0
G3b: 15 - 29	0	0	0	1 (10.0)
G4: <15	1 (3.0)	0	0	0

BP: Blood Pressure PE:Pre-eclampsia; PIH: Pregnancy induced hypertension; PCR: Protein Creatinine Ratio; ACR: Albumin Creatinine Ratio

PO2610

Senescence Markers in Women with Preeclampsia Pregnancies

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Background: Preeclampsia, a hypertensive disorder of pregnancy, is characterized by impaired angiogenesis and inflammation. Data indicate that preeclampsia is mechanistically related to cellular senescence, an irreversible cell-arrest mechanism which has been increasingly associated with accelerated aging. The aim of this study was to determine if senescence plays a role in the pathophysiology of preeclampsia. To that end, we compared SASP components in blood and fat tissue sections between preeclamptic and normotensive pregnancies, as well as p21 and p16 expression in the fat and kidney tissue samples.

Methods: Blood samples from preeclamptic and normotensive patients at the time of delivery were used to study circulating senescence-associated secretory phenotype (SASP) components. Plasma SASP components were tested using Luminex 200 system. Fat tissue explants (3-5 g) were obtained during the surgery from pregnant women who were clinically indicated for C-section. Kidney sections originated from the autopsy material from patients who died from preeclampsia. Upon protein isolation from fat tissue, SASP components were measured. Fat and kidney tissue sections were immunostained for p16 and p21. Preeclamptic and normotensive participants were matched for age and BMI.

Results: Significant increase of senescence markers were found in blood of preeclamptic pregnancies for NGF (1.30±0.82 vs. 0.77±0.19, p=0.032), MCP1 (316.95±163.95 vs. 207.53±84.78, p=0.047), TNFa (2.79±1.08 vs. 2.06±0.64, p=0.043) and Pai1 (58.03±18.85 vs. 38.12±20.86, p=0.023). Similarly, significant increase in senescence markers was found in preeclamptic pregnancies for MCP1 and TNFa. Expression of p16 was significantly increased in fat tissue, whereas the difference in p21 expression between preeclamptic and normotensive patients was not observed. Expression of p16 in preeclamptic renal sections was significantly higher (p=0.02) than in sections from normotensive pregnancies. The p21 expression did not differ between preeclamptic and normotensive kidney sections.

Conclusions: Women with preeclampsia have higher senescent burden compared to normotensive pregnant women at the time of delivery. Senolytic agents that target senescence may offer the opportunity for mechanisam-based therapies.

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PO2611

Sexual Dimorphism and Hard Outcomes in AKI: Is Female Sex Protective? The Jury Is Still Out

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Background: Many studies focus on sex dimorphism and it's influence on hard outcomes when suffering an AKI episode. Some report that women, while others report that men are protected against adverse clinical events. In a real world cohort of individuals suffering from AKI, we compared hard outcomes between sexes with a novel approach: paired-matched study.

Methods: Retrospective paired-matched study of in-patients with AKI diagnosis; cases were matched based on sex, age and Charlson's Index. We used KDIGO-2012 criteria to define AKI, analyzed clinical variables, and compared the hard outcomes: length of hospital stay, need for acute HD, HD dependence at discharge, and in-hospital mortality.

Results: We included 383-paired matches. Male individuals suffered from peripheral arterial disease and COPD, and were hospitalized in surgical wards more frequently than women. We found no statistically significant difference between groups regarding to the prevalence of common comorbidities and admission to ICU (Table 1A). The distribution in global KDIGO-AKI Stages was similar, but when analyzing every sub-criterion of the classification we found that women fulfilled the serum creatinine (SCr) increment ≥1.5-1.9x more frequently, and men fulfilled reaching a SCr >4 mg/dl more commonly. We found no statiscally significant differences in hospital stay, need for acute HD, HD dependence at discharge, and in-hospital mortality (Table 1 B).

Conclusions: To our knowledge, a paired-matched design regarding to this topic has not been previously published. Although experimental studies find differences in clinical outcomes between sexes when suffering an AKI episode, in this real world study, we did not observe a clear distinction in the incidence of adverse outcomes between sexes. We conclude that sex (either female or male) may not be protective against AKI's hard outcomes.

	Women (383)	Men (383)	P value
A. Features			
Age - ys	78 (68-83)	77 (68-82)	0,56
Charlson's Index	4 (2-6)	4 (2-6)	0,42
Hypertension	339 (89)	333 (87)	0,51
DM	152 (40)	142 (37)	0,46
CKD	233 (61)	234 (61)	0,94
CAD	96 (25)	113 (30)	0,17
CHF	157 (41)	139 (36)	0,18
PAD	**59 (15)**	**126 (33)**	**<0,001**
Cerebrovasc Dis	62 (16)	52 (14)	0,31
COPD	**75 (20)**	**133 (35)**	**<0,001**
Hepatic Dis	21 (6)	19 (5)	0,75
Autoinmm Dis	56 (15)	48 (13)	0,40
AIDS	2 (1)	0 (0)	0,16
Medical Service	**266 (70)**	**240 (63)**	**0,05**
ICU	71 (19)	69 (18)	0,85
Comm-Acq AKI	269 (70)	265 (69)	0,75
KDIGO Stage			
1 (global)	149 (39)	148 (39)	0,94
SCr ≥1,5-1,9x	**89 (23)**	**60 (16)**	**0,008**
SCr ≥+0,3 mg/dl	149 (39)	148 (39)	0,94
2	61 (16)	49 (14)	0,22
3 (global)	173 (45)	186 (49)	0,35
SCr ≥3x	118 (31)	113 (30)	0,69
SCr ≥4 mg/dl	**126 (33)**	**166 (43)**	**0,003**
Acute RRT	48 (13)	48 (13)	1
B. Results			
Hospital Stay	11 (7-21)	12 (7-22)	0,24
HD Dependence	5 (1)	11 (3)	0,13
Mortality	84 (22)	91 (24)	0,55

PO2612

Effects of Veverimer on Serum Bicarbonate and Physical Function in Women with CKD: A Subgroup Analysis from a Randomized Controlled Trial

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Background: More women than men have CKD. However, women have been under-represented in clinical trials. Veverimer is an orally administered, non-absorbed polymer that treats metabolic acidosis by binding and removing HCl from the GI tract. In Phase 3 randomized, double-blind, placebo-controlled trials, veverimer significantly increased serum bicarbonate and improved physical function in acidotic patients with CKD (Wesson et al. *Lancet*, 2019). Here we analyzed efficacy and safety among the women in these studies of up to one year.

Methods: Physical function was assessed using the Kidney Disease and Quality of Life Physical Function Domain (KDQOL-PFD) which quantifies limitations on daily activities and by performance on the repeated chair stand (RCS) test.

Results: Of the 217 pts randomized, 83 (32%) were women, of whom 81% were post-menopausal (≥55 yrs). Select comorbidities included hypertension (95%), diabetes (64%), and congestive heart failure (30%). At Baseline, mean eGFR in women was 28.4 mL/min/1.73m^2 and mean serum bicarbonate was 17.3 mEq/L. More women receiving veverimer met the primary study endpoint, had a significant increase in serum bicarbonate and improved both KDQOL-PFD scores and RCS time (**Table**) compared with placebo. The effects of veverimer exceeded the minimal clinically important difference for both KDQOL-PFD (+3 to +5 points) and RCS (-1.7 seconds). Rates of serious, non-serious and GI adverse events were similar in the groups; none required treatment discontinuation.

Conclusions: Given their lower bone and muscle mass, women with CKD may be particularly vulnerable to the adverse effects of metabolic acidosis. We found that in women with CKD and metabolic acidosis, treatment with veverimer significantly improved how women felt and functioned. The safety of veverimer was similar to placebo.

Funding: Commercial Support - Tricida, Inc.

Efficacy Endpoints	Placebo (N = 33)	Veverimer (N = 50)
Primary Endpoint: proportion increasing serum bicarbonate by ≥ 4 mEq/L or achieving normalization at Week 12	28%	63% P<0.0001
Change from baseline in Serum Bicarbonate (LS mean, mEq/L) at Week 12	+2.0	+4.9 P< 0.0001
Patient-Reported Physical Function (KDQOL-PFD Mean [SD] Total Score at Week 52)*	-5.16 (20.27)	+13.15 (26.11) P = 0.0031
Objective Measurement of Physical Function	+0.77	-4.16 (15.43)

P-values are vs. placebo; An ANCOVA rank-based method was used for physical function endpoints

*Based on evaluable patients enrolled in controlled extension study (placebo, n=31; veverimer, n=46)

PO2613

Dietary Magnesium Intake, Risk of Kidney Stone, and Survival in the Women's Health Initiative (WHI)

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Background: The effect of dietary magnesium intake (DMI) on the risk of stone is controversial, and its effect on survival among kidney stone formers is unknown.

Methods: We examined participants enrolled in WHI, a prospective, longitudinal, multicenter study investigating the health of postmenopausal women, and used Cox regression analyses to determine the independent effects of DMI on the risk of incident kidney stone and survival amoungst the stone formers.

Results: 145,942 participants were identified free of kidney stone history at baseline. 83% were Caucasian, mean age was 63. Among them, 6024 (4%) developed incident kidney stone during 1,601,750 person-years of follow up. The mean daily DMI was 318 mg, with 26% in tertile 1 (<241 mg), 41% in tertile 2 (241-348 mg) and 33% in tertile 3 (>348 mg). The incidence of kidney stone disease was 3.1, 3.3, and 3.9 per 1000 person-year in high, moderate and low DMI groups, respectively. The corresponding multivariable-adjusted hazard ratios were 0.82 (95% CI: 0.71-0.94) for high vs low DMI when dietary oxalate intake (DOI) is high, and 1.01 (95% CI: 0.81-1.26) for high vs low DMI when DOI is low. Among incident stone formers, 82% were Caucasian, 23% were above age 70. Mean daily DMI was 304 mg, 32% in tertile 1, 38% in tertile 2, and 30% in tertile 3. Subsequently, 1346 (22%) died. Older age, histories of hypertension, diabetes and heart disease, low serum vitamin D, cigarette smoking, and hormone replacement associated significantly with mortality, p<0.05. However, DMI had no impact on mortality after adjusting for demographics and potential confounding factors, hazard ratio (HR) 0.91, 95% CI 0.73-1.14, p=0.4 when compared high DMI vs low DMI groups, HR 0.90, 95% CI 0.73-1.11, p=0.3 when compared medium DMI vs low DMI groups.

Conclusions: Our study suggests that higher DMI is associated with lower risk of incident kidney stone disease and this effect is modified by DOI. DMI does not appear to affect survival among post-menopausal women with incident kidney stone disease.

Funding: Clinical Revenue Support

PUB001

Consequences of Improper Interpretation of ANCA

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Introduction: Antineutrophil cytoplasmic antibodies (ANCA) is important in suspected vasculitis. False positive or atypical ANCA (A-ANCA) can lead to erroneous interpretation of immunofluoresence (IF) causing disastrous consequences. We present a patient who was initally reported as Perinuclear-ANCA (P-ANCA) positive and was therefore treated with steroids rendering him adrenal insufficient (AI).

Case Description: A 79-yr-old man with history of CKD, A Fib, protein C deficiency, prostate cancer and ANCA positivity that was treated with steroids, presented to the ER with dizziness, bradycardia and hypotension. He was weak, fatigued, and unarousable. In the ER, he was started on vasopressors and methylprednisolone. His creatinine rose from 2.6 to 3.1 mg/dL. RPGN was suspected and kidney biopsy was performed that showed acute interstitial nephritis or pyelonephritis, due to presence of neutrophils in clumps. His AM cortisol level was 3 ug/dL (10-20). Because of hypotention, polyuria and natriuresis, hydrocortisone and fluticortisone were started. His serum K level decreased and fludrocortisone was stopped. Over next few days, he became normotensive and his mentation improved with increasing dose of hydrocortisone. Hypokalemia slowly resolved with potassium supplements.

Discussion: ANCA are a group of antibodies that bind to antigens of neutrophils, causing systemic vascular inflammation. These autoantibodies can be found in the serum of patients with systemic, small vessel vasculitis and is a biomarker for ANCA-associated vasculitis. A positive staining of ANCA can be classified as: Cytoplasmic, Perinuclear, and Atypical, based on the pattern of IF. In cases with C-ANCA, the staining is diffuse throughout the cytoplasm and the cause of staining is due to antibodies directed against Proteinase 3 (PR3). In cases with P-ANCA, the staining is around the nucleus and it is due to antibodies directed against myeloperoxidase (MPO). A-ANCA can be found in conditions other than vasculitis and does not require immunosuppressive steroids for treatment. A-ANCA can be reported erroneously as P-ANCA or C-ANCA and patients can receive aggressive treatment with high dose steroids. Therefore, we suggest to confirm the ANCA results with MPO or PR3 before initiating aggressive therapy for vasculitis to avoid disatrous cosequences.

PUB002

Lymphoma of a Normal Kidney Size

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Introduction: Renal injury has been reported in the setting of hematolymphoid neoplasms. The kidneys can be affected by a variety of mechanisms such as acute tubular necrosis (ATN), paraneoplastic glomerulopathy, and lymphocytic infiltration of kidney parenchyma (LIK). Diagnostic evaluation is important in differentiating mechanism of kidney injury, which will affect management and prognosis. LIK is suggested with clinical findings of bilateral kidney enlargement, acute kidney failure (AKI), or proteinuria.

Case Description: 50-year-old male with new diagnosis of high-grade lymphoma found to have severe kidney failure. Initial work up was unable to explain the underlying process of kidney failure. The patient was managed with volume replacement to alleviate the pre-renal component. Kidney ultrasound had no evidence of enlargement. Kidney function worsened over days and a decision to initiated dialysis was determined. After establishing dialysis access, kidney function demonstrated an improvement trend without dialysis initiation. Kidney biopsy revealed infiltration by atypical lymphoid cells consistent with the Double-Hit Diffuse Large B-Cell Lymphoma (DLBCL). Patient's kidney function spontaneously recovered. Patient was discharged with plan to start chemotherapy as an outpatient.

Discussion: Our patient was diagnosed with DLBCL. This type of lymphoma accounts for approximately 25 percent of all Non-Hodgkin Lymphomas in the developed world. Clinical presentation of renal involvement includes AKI, proteinuria, or enlarged kidneys on imaging studies. Location of lymphocytic infiltration determines the extent of renal dysfunction, whether interstitium or glomerulus. Renal involvement incidence is 2% at time of diagnosis. Extranodal renal involvement is diagnosed either by biopsy or imaging. Renal involvement can be diagnosed by imaging in 65% of patients. Cases presenting with AKI of interstitial type of lymphomatous infiltration show bilaterally enlarged kidneys in about 95% of patients. Renal involvement in patients with non-Hodgkin's lymphoma remains uncommon. The presence of acute renal failure, proteinuria, or enlarged kidneys should be suspicious of lymphocytic infiltrate of the kidneys. Nevertheless, absence of radiologic changes or proteinuria, similar to our patient, should not rule out kidney involvement. We recommend a low threshold for kidney biopsy to assist in the diagnosis of renal lymphocytic infiltration.

PUB003

Metabolic Encephalopathy due to AKI in a Patient with Recent Infusion of Intravenous Immunoglobulins (IVIg)

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Introduction: IVIg induced AKI is extremely rare (1% of cases). We present a case of AKI requiring hemodialysis secondary to recent IVIg administration.

Case Description: A 61-year-old woman presented with acute onset altered mental status (AMS) for 2 days. Her past medical history included CKD G3, HTN, COPD, PVD, and CAD. A week prior, she received 3 doses of sucrose-containing IVIg for chronic inflammatory demyelinating polyneuropathy. Shortly thereafter, the patient developed a facial rash, poor oral intake, low urine output, and AMS. Labs showed BUN 71 mg/dL, SCr 10.62 mg/dL, baseline SCr 2.6 mg/dL. ABG showed pH 7.07, pCO2 30 mm Hg and HCO3 8 mmol/L. Toxicology screen was negative, CPK and lactic acid were normal. No NSAIDs use was reported. She required only 1 session of hemodialysis with the recovery of renal function and mental status. AIN due to IVIg and/or IVIg induced osmotic nephropathy was thought to be the culprit for her presentation.

Discussion: IVIg can produce adverse reactions thought to be caused by activation of the complement cascade by the aggregation of IgG. To avoid this, a variety of stabilizing agents, including sucrose, are used. Sucrose is absorbed into proximal convoluted tubular cells and is followed by water due to the changed osmotic pressure. This results in cytoplasmic vacuolization and degeneration of the proximal cells. CKD, HTN, DM, advanced age, dehydration, hyperviscosity, use of sucrose stabilizers, high dose IVIg therapy (400–2000 mg/kg), high rate of IVIg administration, or treatment with other nephrotoxic medications increase the risk of AKI. About 30% of cases require dialysis. The mortality rate is 10%. Adverse renal outcomes usually occur within 10 days of initiation of IVIg, and the duration of renal failure lasts between 3 and 45 days. Most cases resolve spontaneously. Early recovery of renal function can be achieved by dialytic removal of sucrose from the circulation. To make a diagnosis, a temporal association must be established with the administration of IVIg. A clinical diagnosis is made after ruling out other causes and is confirmed with a renal biopsy. Measures to prevent AKI include using sucrose-free IVIg or amino-acid-stabilized formulations, adequate hydration, avoiding other nephrotoxins and diuretics, reductions in dose, concentration (<5%), and/or rate of administration (<3mg sucrose/kg/min) of IVIg.

PUB004

A Patient with a Record High Blood Urea Nitrogen Value Surviving Without Dialysis

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Introduction: The blood urea nitrogen (BUN) has limited value as an index of glomerular filtration rate to access kidney function. It can be increased not only in the setting of acute or chronic renal failure but also in hypovolemic state, gastrointestinal tract bleeding, high catabolic states, and by certain medications. Dialysis is the effective treatment for uremia. However, there is no consensus on when to initiate the dialysis for high BUN in acute kidney injury.

Case Description: A 64-year female with history of hypertension, hypothyroid, hyperlipidemia, alcohol use disorder, chronic kidney disease (CKD) with baseline creatinine of 1.5 mg/dl was admitted for head trauma after fall. Patient had poor intake and was noticed to be confused lately by family. No history of analgesic or herbal supplements usage was present. Laboratory results were significant for BUN of 298 mg/dl, Creatinine (Cr) of 13.5 mg/dl, serum potassium of 5.4 mEq/L, phosphate of 6.1 mEq/L and severe metabolic acidosis with serum bicarbonate of 10 mEq/l, anion gap of 33 mEq/L, lactate acid of 4.6 mmol/L. Creatine kinase level was 253 U/L. Urine studies showed no proteinuria, mild hematuria, without crystals. Urine electrolytes showed sodium of 23 mmol/l and chloride of less than 20 mmol/l. Corona virus disease 2019 (COVID-19) was negative both by polymerase chain reaction and antibody test. All the sepsis work up, urine toxicology and blood alcohol level were negative. Renal ultrasound showed normal bilateral kidney sizes. Patient was aggressively resuscitated with intravenous fluid including bicarbonate and her cognitive function improved without dialysis. Her BUN eventually decreased to 30 mg/dl and Cr to 1.26 mg/dl.

Discussion: CKD patients are susceptible to infection, dehydration and develop multiple episodes of acute on chronic renal injury, subsequently resulted in end stage renal disease. Our patient was taking metoprolol, lisinopril and hydrochlorothiazide for hypertension which could also have prompted her into hypovolemic state without adequate hydration. Early detection of the underlying cause is crucial and can prevent the unnecessary complications from dialysis. A few cases of strikingly high creatinine up to 61.3 mg/dl have been reported and survived with dialysis. Based on the review of literature, this is the highest reported BUN in acute on chronic renal failure patient who improved without dialysis.

PUB005

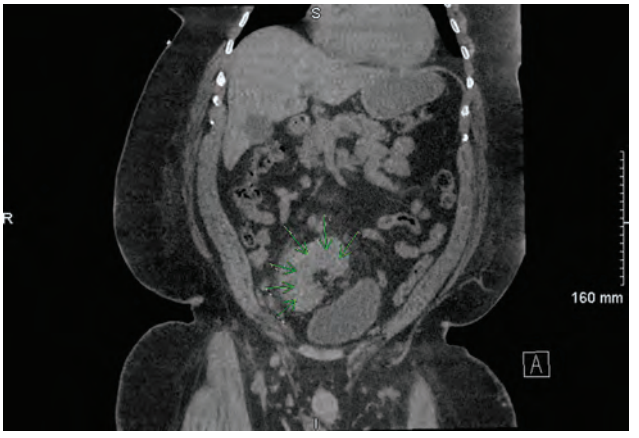
Spontaneous Page Phenomenon in a Pelvic Kidney

Yahya R. Ahmad, William L. Wilson, Megan M. Robinson, Taha Ayach. *University of Kentucky, Lexington, KY.*

Introduction: Page kidney or Page phenomenon refers to compression of the renal parenchyma by subcapsular hematoma. Here we report the first case of spontaneous Page phenomenon in a native pelvic kidney.

Case Description: A 64-year old male with a diagnosis of diabetes mellitus, essential hypertension, chronic kidney disease stage 3b, stage 3 obesity with a body mass index of 53, congenital right-sided pelvic kidney, presented to the emergency room with acute-onset, severe, right lower quadrant abdominal pain. Patient denied having any recent trauma and had no urinary or gastrointestinal complaints. He was not on any antiplatelet or anticoagulation medications. CT angiogram of the abdomen and pelvis was performed which demonstrated a subcapsular hematoma around the right pelvic kidney. He had AKI with a peak creatinine of 4.2 mg/dL from a baseline of 2.2 mg/dL. He remained non-oliguric, with gradual improvement of his renal functions and never required renal replacement therapy or any intervention for Page kidney. He presented with markedly elevated blood pressure of 190/110 mmHg and his hospital course was significant for sustained elevated blood pressure requiring addition of four new anti-hypertensive medications by discharge. Subsequent imaging showed marked decrease in the subcapsular hematoma in a week.

Discussion: Page phenomenon is a rare but potentially fatal condition that can result from trauma, tumor, vasculitis, renal cyst rupture, or procedures like kidney biopsy. External compression of renal parenchyma can result in interstitial ischemia, tubulointerstitial nephritis and compression of intrarenal vessels thus activation of renin angiotensin system (RAS), resulting in AKI and hypertension associated with Page kidney. Persistently elevated blood pressure unresponsive to medical therapy or gradually enlarging hematoma with worsening renal functions might require percutaneous drainage, capsulotomy or even nephrectomy. Optimal medical management of Page kidney includes medications targeting the RAS pathway.



PUB006

Transient Anuric AKI Secondary to Parkinson Disease

Sabine Karam. *Saint George Hospital University Medical Center, Beirut, Lebanon.*

Introduction: Parkinson's disease is a progressive neurodegenerative disease with diverse motor and neuropsychiatric manifestations. At the urological system level, it can cause neurologic dysfunction of the bladder but to our knowledge, no dysfunction of the upper collecting system has been described so far.

Case Description: A 67-year-old Lebanese female with a PMH of Parkinson's disease, HTN, DL, DM II, HF, CKD (1.7), Hypothyroidism, recurrent pyelonephritis and nephrolithiasis was admitted on multiple occasions with a chief complaint of "decreased urination". Physical examination showed no general abnormalities & the patient was afebrile. Upon each admission, a Foley catheter was inserted but with no urine output as she had an empty bladder. Adequate IV fluid hydration did not improve her urine output. The anuria would resolve after a few days with no clear explanation. Renal Scintigraphy using MAG3 technique along with furosemide was performed twice, seven days apart, the first away from an anuric episode and the second during. The first study showed slow cortical emptying into the collecting system but with complete emptying after furosemide while the second study showed accumulation of the tracer in the cortex with minimal spontaneous excretion into the collecting system even after addition of furosemide. There was no evidence of mechanical obstruction or vascular etiology in both studies. An abdominal CT showed no hydronephrosis or evidence of obstructive uropathy. An abdominal MRI showed third spacing and small atrophic kidneys with cortical scarring but no hydronephrosis, calculi, masses, or retroperitoneal fibrosis. The patient had her Parkinson's treatment optimized and the frequency and severity of the episodes decreased.

Discussion: Our findings allow us to speculate that Parkinson's disease could cause neurogenic dysfunction of the upper collecting system that manifests by episodes of intermittent anuria leading to acute kidney injury.

PUB007

Cholesterol Crystal Embolism with End-Stage Renal Failure and Refractory Gastric Ulcers After Abdominal Angiography

Naoki Yamamoto, Koichi Sato, Hisayuki Ogura, Taro Miyagawa, Shinji Kitajima, Tadashi Toyama, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Takashi Wada. *Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan.*

Introduction: Cholesterol crystal embolism is a systemic disease with various clinical manifestations after intraarterial interventions and vascular surgeries. Here we report a case complicated with acute kidney injury requiring hemodialysis and refractory gastric ulcers after transfemoral angiography of celiac and superior mesenteric arteries.

Case Description: A 78-year-old male with coronary artery disease, hypertension, hyperlipidemia and chronic obstructive pulmonary disease was diagnosed as hepatocellular carcinoma by transfemoral angiography of celiac and superior mesenteric arteries. He was admitted to the hospital for an operation of hepatocellular carcinoma. Serum creatinine level gradually increased from 1.17 to 5.87 mg/dL with eosinophilia (4440/μL) and high C-reactive protein (CRP) level (4.96 mg/dL). He started hemodialysis ten weeks after angiography and had been suffering from nausea. Endoscopy showed multiple gastric ulcers. Treatment with proton pump inhibitor started, but did not improve. Cyanosis was present in his bilateral toes and skin biopsy showed cholesterol crystal clefts. He was diagnosed with cholesterol crystal embolism and treated with intravenous prednisolone (PSL) 20 mg/day, resulting in decrease of eosinophil, CRP levels and improvement of gastric ulcers. However, he was unable to withdraw from dialysis and developed disseminated cutaneous herpes zoster. Finally, he died of sepsis. Autopsy showed severe erosion of atherosclerotic plaques at the level of celiac artery. Cholesterol clefts were present in the vessels of kidney, stomach, intestines, liver, spleen, pancreas, diaphragm, adrenal glands and testes. The distribution of cholesterol crystal embolism was consistent with the site of angiography performed from celiac and superior mesenteric arteries.

Discussion: Cholesterol crystal embolism is caused by not only percutaneous coronary interventions and vascular surgeries, but also preoperative transfemoral angiography. We need to consider cholesterol crystal embolism when acute kidney injury and refractory gastric ulcers after transfemoral angiography. Although PSL is administered for cholesterol crystal embolism, tapering strategies is important for patients on dialysis.

PUB008

Hyperkalemia in Community-Acquired AKI: Associated Factors and Clinical Consequences

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Background: Hyperkalemia (hyperK) frequently occurs in the context of acute kidney injury (AKI). We know little about the associated factors and the clinical consequences in patients with community-acquired acute kidney injury (CA-AKI). The aim of present study was to analyze it.

Methods: The present study is based on a cohort of patients with CA-AKI admitted to the our Nephology Service from January 2010 to February 2015. Hyperkalemia was defined as potassium levels above 5.1 meq / L

Results: A total of 308 patients were included. The mean age was 73,22±13,95 years. 58,4% were men. Charlson comorbidity index (CCI) was 7,16 ±2,7 points. The mean of drugs ingested daily was 7,81±3,66 and the length of stay 12,25±11,69 days. In view of the Etiology of AKI, 69,5% prerenal AKI and 30,5% non-prerenal ones. 212 patients had previous chronic kidney disease (CKD) (68.8%). Hemodialysis (HD) was required in 54 patients (17.15%). 38 patients (12.3%) died during hospital stay. HyperK occurred in 173 cases (56,2 %). Mean potassium was 5,45±1,41 meq/L. There was a significant correlation between potassium and pH as well as between K and CCI. There was an association between hyperK and intake of potassium-sparing diuretics (p<0,001); ACEI/ARB (p=0,003) and beta blocker (p<0,001). Using a multiple linear regression model the equation that predicted serum potassium was: K = 36,44 – (4,4 x pH) + 0,98 (if intake of potassium-sparing diuretics) + (0.10 x CCI). Potassium level did not influence the length stay. Patients with HyperK required HD in a higher proportion (23.7 vs. 9.6%; p 0.01) and also had higher mortality during hospital stay (15.6 vs. 8.1%; p 0.048). After a follow-up of 971±702 days after hospital discharge, Kaplan-Meier survival curves showed a significant difference (Log Rank (Mantel-Cox): p< 0,001) between patients with hyperK and patients that did not present it.

Conclusions: HyperK occurred in just over half of our patients. The potassium level was significantly determined by the previous comorbidity, pH and the intake of potassium-sparing diuretics. HyperK patients required HD and died in a greater proportion during hospital stay. Mortality after discharge was higher in patients who presented hyperK. Appropriate measures must be taken to correct hyperK early in patients with CA-AKI.

PUB009

A Case of Anti-Tubular Basement Membrane Antibody-Associated AKI

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Introduction: We report here a case of idiopathic anti-tubular basement membrane (TBM) antibody-related acute interstitial nephritis (AIN).

Case Description: Our patient was a 44 years man and had no history of renal disease. He was pointed out renal dysfunction of serum Cr 1.50 mg/dL in the health checkup 2 months prior to admission. The patient was admitted to our hospital because of worsening of renal function of Cr 2.89 mg/dL. Because renal dysfunction progressed (Cr 10.36 mg/dL), hemodialysis was started on the 8th hospital day. Urine abnormalities such as proteinuria or hematuria was not apparent, however, he showed remarkable elevation of urine NAG and β2-microglobrin excretion, bilateral kidney enlargement, and renal accumulation was shown by Ga scintigraphy. Based on those findings, AIN was suspected and renal biopsy was performed on the 2nd hospital day. Light microscopy revealed diffuse inflammatory cell infiltration in the tubulo-interstitium, and immunostaining showed linear deposition of IgG and C3 in the tubular basement membrane. Similar findings were observed in the tissue sections of other patient with no tubular disorder by the treatment of the serum of this patient, and we diagnosed AIN due to TBM antibody. Prednisolone (PSL) 40 mg/day (0.8 mg/kg/day) was started from the 13th day and methyl PSL 500 mg/day for 3 days was added on the 21st day. Renal dysfunction and inflammatory reaction tended to be improved, however, steroid treatment could not continue because of steroid psychosis. Cyclophosphamide 375-500 mg/day and multiple plasma exchange was added thereafter, however, finally he was shifted to the maintenance dialysis.

Discussion: Cases of TBM antibody-related AIN are very rare, and most of the reported cases are those induced by drugs and those developed after kidney transplantation, and few cases are considered to be idiopathic. Antigen of TBM antibody are thought to be a non-collagen protein that interacts with type-4 collagen, laminin and integrin, which is present in the proximal tubular basement membrane, but the mechanisms and clinical course that cause AINs are unknown. Accumulation of cases including this case is considered necessary.

PUB010

A Triple Threat? Baclofen Toxicity and Posterior Reversible Encephalopathy Syndrome in the Setting of AKI

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Introduction: This is a case of apparent baclofen toxicity and posterior reversible encephalopathy syndrome (PRES). Both conditions are seen in patients with kidney dysfunction but direct association between the two conditions has otherwise been defined. The case highlights areas of special consideration in the evaluation and management of mental status changes in patients with acute kidney injury (AKI). No other reported cases of the combined diagnoses were found on literature review.

Case Description: A 71-year-old female admitted with sepsis due to ESBL E. coli bacteremia and pyelonephritis became unresponsive on her 7th day of hospitalization. There were no abnormal neurologic findings prior to the episode. The patient had been given baclofen 10 mg x 2 doses for back pain within 24 hours of her acute change in mental status. She was non-verbal but opening eyes and withdrawing to pain. The initial presenting signs of infection had been improving with ceftolozane and tazobactam. Serum creatinine was 4.2 mg/dL on admission and had improved to 2.2 mg/dL (baseline 1.5 mg/dL). AKI was attributed to prerenal physiology and sepsis-associated ATN. Mental status changes were attributed to baclofen neurotoxicity. She then developed evidence of partial complex seizures and subsequent imaging revealed findings of PRES. Levetiracetam, antihypertensives, and continued antibiotic therapy were provided. Systolic blood pressure increased to 180 mmHg with a MAP of 115 during the hospitalization. After several days, the patient recovered completely. Creatinine stabilized at 2.0 mg/dL.

Discussion: Medications are a leading cause of acute mental status changes, especially in patients with impaired kidney function. Our case highlights the risks of baclofen toxicity in improving but impaired kidney function. The clinical-radiopathologic diagnosis of PRES may have been missed without imaging. The varying presentations of this condition are a reminder the importance of an expanded differential diagnosis and the need for a better understanding of the pathology. There is no reported association between PRES and baclofen. The role of AKI in the development of PRES is not entirely understood; however, the hypertension-hyperperfusion theory remains a leading consideration in our patient. Management decisions in our patient included forgoing dialysis, blood pressure control, and the use of anti-seizure medications.

PUB011

Renal Zygomycosis: A Rare Presentation in an Immunocompetent Patient

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Introduction: Zygomycosis is a broad term which refers to the infections caused by bread mold fungi belonging to zygomycota phylum. It is an agio-vascular opportunistic infection which can usually present in four different ways including pulmonary, gastrointestinal, renal and disseminated disease. Like other opportunistic infections it has predilection for immunocompromised patients however very rarely, it has been reported in immunocompetent patients.

Case Description: Here we report a case of an immunocompetent patient who was affected by renal zygomycosis and presented as a picture mimicking rapidly progressive glomerulonephritis (RPGN). The patient presented with hematuria, proteinuria and high creatinine and was suspected as a case of RPGN initially. CT scan abdomen showed bilateral smoothly tapered distal ends of the renal arteries with non-perfused enlarged kidneys. These findings were consistent with the diagnosis of Zygomycosis which has angio-invasive nature. Bilateral nephrectomy was done and diagnosis was confirmed on histopathology report as well. Post operatively, the patient was extubated from ventilator, recovered from shock and improved a lot. He was doing fine on maintenance hemodialysis until two weeks later he developed septic shock due to Acinetobacter Baumannii which could have triggered the re-activation of disseminated zygomycosis due to metabolic acidosis and the patient could not survive.

Discussion: Isolated renal zygomycosis is very rare, although few cases have been described in literature. In our case, patient was referred to us as glomerulonephritis as his clinical picture initially resembled rapidly progressive glomerulonephritis. We want to highlight that isolated renal zygomycosis can have presentation mimicking glomerulonephritis, so young nephrologists should rule out infections like zygomycosis before embarking on the diagnosis of Acute glomerulonephritis as misdiagnosis can be catastrophic.

PUB012

Light Chain Cast Nephropathy in an African-American Woman with Waldenström Macroglobulinemia

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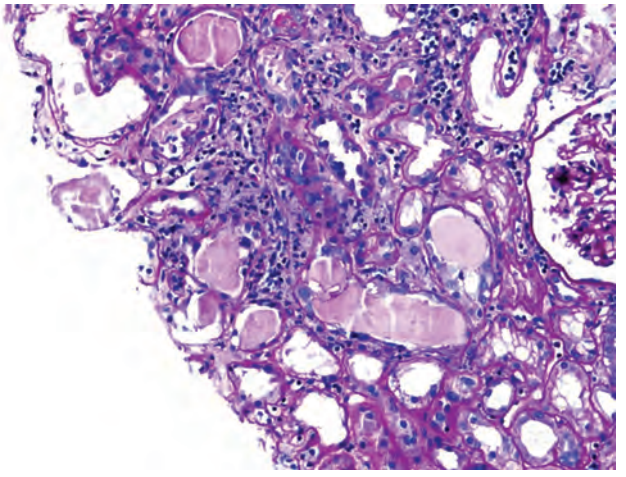
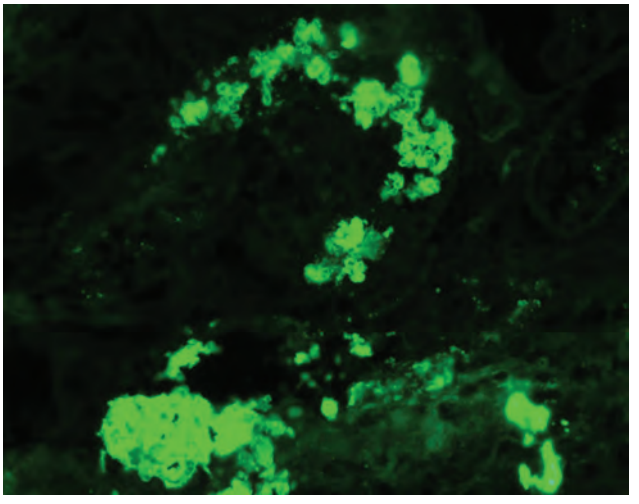
Introduction: Waldenström's macroglobulinemia (WM) is a rare cancer of the lymphatic system due to excess IgM monoclonal protein with a rare renal involvement. Renal involvement is rare with an incidence of 3 cases per million people per year. We describe a case of MW presenting with acute renal failure.

Case Description: A 63-year-old female who admitted to our hospital for influenza B complicated by acute renal failure during the hospital stay, with creatinine up to 6 mg/dL, despite adequate hydration. Electrophoresis revealed a monoclonal component in the gamma region, which classified as an IgM k. A kidney biopsy was performed, showing light cast chains suggested the possibility of myeloma kidney. Furthermore, bone marrow histology was performed, revealing lymphoplasmacytic lymphoma. The patient was treated with bortezomib, dexamethasone, and cyclophosphamide, with complete recovery of renal function.

Discussion: Overall, renal manifestations are not commonly seen in Waldenström's macroglobulinemia. Approximately one-third of patients are asymptomatic at the time of diagnosis. Like our patient who did not have renal symptoms and acute kidney injury discovered serendipitously. Moreover, reported rates of full renal recovery following adequate treatment are almost more than 50 percent. Patients with reversibly renal failure had longer median survival compared with patients who did not restore renal function.





PUB013

AKI in a Patient with Erythema Elevatum Diutinum

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Introduction: Erythema elevatum diutinum (EDD) is a rare cutaneous small vessel vasculitis with dapsone being the drug of choice. EED has been associated with hematological disorders, autoimmune diseases and cancer in <5% of cases. Drug-induced acute interstitial nephritis (DI-AIN) represents 20% of patients with unexplained AKI. The classic triad of rash, fever, and eosinophilia occurs in <10% of patients, and onset may be delayed by weeks or months after drug initiation

Case Description: 55-year-old male with history of EDD admitted for infected lower extremity lesions Vital signs and remainder of physical exam was normal. Patient was on dapsone in the past for over 10 years, however in the last 6months was not taking any medications. Vancomycin, zosyn and dapsone 200mg BID were started on admission. By day 3 only dapsone was continued as imaging was without evidence of deep infection. On day 4 he developed AKI, creatinine (Crt) 4.44mg/dL from 0.7mg/dL on admission. Labs also included Hb of 8.8g/dL, WBC 9.2 k/uL with 5% eosinophils, ESR 118mm/hr. Urinalysis with 3 wbc/hpf, UPCR of 0.18 and urine microscopy showed 1-2 WBC casts/LPF. Serum immunofixation revealed IgA-kappa in the beta region and a faint IgA-kappa monoclonal protein in the gamma region. Autoimmune and infectious serologic work-up negative. Dapsone was stopped on day 5 and renal biopsy was performed due to ongoing rise in Crt on day 8. Biopsy confirmed diffuse active interstitial nephritis with prominent eosinophilic inflammation along with low grade membranous nephropathy favoring secondary, PLA2R negative. Patient started on IV solumedrol followed by oral prednisone taper over 6 weeks. Creatinine improved to 1mg/dL at 3 month follow-up.

Discussion: DI-AIN was attributed to dapsone. Despite withholding this medication, the Crt continued to rise prompting renal biopsy. Studies suggest that early corticosteroid initiation is associated with better outcomes and be considered in patients with no prior kidney dysfunction. In patients with suspected DI-AIN where a biopsy cannot be performed, a trial of empiric steroid therapy may be considered. The finding of secondary membranous nephropathy (MN) was unexpected as to date there has not been any reports of renal disease and EDD. We report a case of secondary MN in a patient with EDD now undergoing a full malignancy investigation.

PUB014

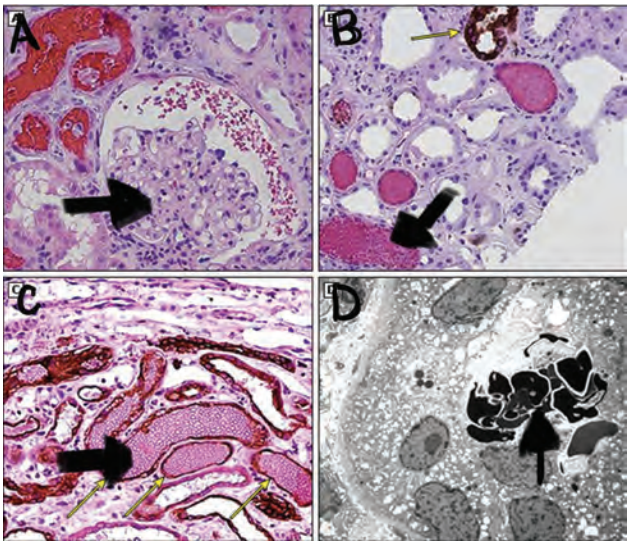
AKI from Tubular Bleeding from Rivaroxaban (XARELTO)

Aamir Zuberi,[1] Fatima Zuberi,[3] Nabia A. Syed,[2] Marissa L. Henderson,[1] Safi Ahmad,[4] Hafsa Zuberi.[5] *[1]Aamir Zuberi MD PA, Decatur, TX; [2]University of Texas at Austin, Austin, TX; [3]University of Texas Southwestern Medical Center at Dallas, Dallas, TX; [4]Wake Forest University, Winston-Salem, NC; [5]Texas Tech University System, Lubbock, TX.*

Introduction: Anticoagulation induced acute kidney injury

Case Description: 68-year-old male with history of 7kg weight gain in the preceding 3- 4 wks. & fatigue. History of CAD, COPD and Pulmonary Embolism treated with Rivaroxaban Exam essentially negative except for edema Creatinine 8.4, ultrasound negative, previous creatinine normal, UA positive for blood & protein Dialysis initiated. All serologies negative IVC filter was placed, anticoagulation stopped, and kidney biopsy performed Biopsy showed diffuse intratubular red blood cells, red cells casts, acute tubular epithelial injury, mild interstitial fibrosis, few eosinophils and negative for crescents or vasculitis (images shown below) On follow-up, Pt. regained kidney function in 2 months and creatinine remained normal at 1 year

Discussion: Warfarin related nephropathy is a rare but well-recognized phenomenon, which has also been reported with other anti-coagulation like Dabigatran (Predaxa), however has not been reported with Rivaroxaban (Xarelto). Warfarin related nephropathy (WRN) and acute kidney injury is sometimes caused by excessive anticoagulation. A biopsy is needed to confirm this condition. Pathogenesis of anticoagulant related nephropathy is glomerular injury, obstruction of renal tubules by RBC casts, and tubular epithelial injury. Histologically, WRN and the biopsy from the patient receiving Rivaroxaban appeared very similar.



A.Normal glomerulus, no crescentsB.& C. Blood in tubules

D. Fragmented RBCs in tubules (Electron Microscopy)

PUB015

Misleading Serologies in Thrombotic Microangiopathy due to Malignant Hypertension

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Introduction: Nephrologists use autoimmune panels to screen for glomerular disease. Some of these markers cause false positives in other systemic diseases which leads to misdiagnosis. We report a rare case of false positive MPO-ANCA and ANA in patient with thrombotic microangiopathy (TMA) due malignant hypertension.

Case Description: A 65 year old African American patient with a history of hypertension, breast cancer s/p right mastectomy, and CKD with baseline creatinine of 1 was admitted hypertensive urgency with pressures of 239/123. She had Acute Kidney Injury with creatinine of 6.6 and her work-up revealed new pericardial effusion, thrombocytopenia (platelets of 90), and anemia (hemoglobin of 9). Autoimmune panel was positive for ANA (1:320, speckled) and positive RNP (>8). The presumptive diagnosis was mixed connective tissue disease. Pericardiocentesis was negative for malignancy and infections. She began dialysis but her renal function never improved. She was discharged dialysis dependent. The patient refused outpatient dialysis and her medications. She was re-admitted few weeks later with uremia and hypertensive urgency with pressures of 209/104. A repeat evaluation showed a newly positive MPO-ANCA (13.4), ANA (1:640, speckled), and a low C3 (72.8). Given the concern for vasculitis, a kidney biopsy was performed. Her biopsy was significant for global glomerulosclerosis, glomerular ischemia, and severe interstitial fibrosis with tubular atrophy. There was extensive arteriolar onion skin intimal fibroplasia with red blood cell fragments. Based on her clinical history, patient had TMA secondary to hypertension. Her biopsy lacked findings of vasculitis due to an absence of necrotizing crescentic glomerulonephritis and negative immunofluorescent stains. The patient was maintained on hemodialysis and hypertension medications.

Discussion: Diseases associated with TMA can have false positive autoimmune markers and they require early recognition. There are cases that show Thrombotic Thrombocytopenic Purpura can produce MPO-ANCA and anti-DNA markers. The markers were correlated to intensity of the disease because the patients with active disease had higher tighters. These markers are created secondary to immune dysfunction during TMA. This case also emphasizes the importance of kidney biopsy in order to distinguish between active vasculitis and non-vasculitic diseases.

PUB016

AKI, Diplopia, and Altered Psyche: One Rare Case of Extrapulmonary Sarcoidosis

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Introduction: Sarcoid is a multi-organ system disease primarily affecting the lungs. Pathological diagnosis requires the presence of non-caseating granulomas. Sarcoidosis is a genetic associated autoimmune disease more prevalent in African Americans. Renal sarcoidosis manifests in about 5-20% of patients with hypercalcemia, hypercalciuria, and nephrocalinosis on normal screening. Renal parenchymal involvement is typically granulomatous tubulointerstitial nephritis. Neuro-sarcoid also occurs in about ¼ of patients, affecting primarily the cranial nerves. CNS involvement can present with visual and occasionally behavioral changes. Ocular sarcoid presentations include uveitis and retinal lesions.

Case Description: 63-year-old white male with a history of rheumatoid arthritis, pulmonary nodules, glaucoma, presented with one year of blurry vision and weird psyche. He was referred to nephrology after an ophthalmologist found intermittent diplopia, transient optic disc swelling and intraretinal hemorrhage. Abnormal labs from 5/2019 with 11/2018 in parenthesis: Scr 2.73 (1.51 mg/dL), BUN 27 (22), Egfr naa 28 (49ml/min), Ser Calcium 8.6 (9.2 mg/dl) ACE 73 U/l, A1c 5.4. Given the worsening CKD IV; the following were drawn: ANA-IFA: positive, speckled pat 1:640, UA bld 10, fn gran cast; 0-5, crs gran cst 0-5, ur prot rand 24. Renal biopsy demonstrated noncaseating granulomatous interstitial nephritis, numerous noncaseating granulomas with giant cells. He was referred to Cleveland Clinic Sarcoid Clinic and started on 40mg prednisone for renal sarcoid. CXR with prior noddles, no hilar or parenchymal changes. CC Ophthalmology clinic's fundal exam revealed peripheral hypo-pigmented lesions possibly consistent with ocular sarcoid. Vision had resolved. At 1 month, steroids were tapered with plans to start Azathioprine. The patient's Scr improved on tapering steroids.

Discussion: Less than one in ten patients present solely with extrapulmonary sarcoid. This case demonstrates a rare presentation of neuro-ocular and renal sarcoidosis in the absence of lung findings. Sarcoidosis ought to be considered in AKI or new chronic kidney disease, particularly if a patient presents with other atypical findings such as retinal or optic nerve changes representing a syndrome of multi-organ involvement. Multiple system involvement is a predictor of progression to ESRD. Glucocorticoids are first-line therapy. Most cases respond to steroids.

PUB017

Dynamics of Tissue Injury mRNA Expression to Bilateral Renal Ischemia-Reperfusion Injury

Samuel J. Pfaff,[1] Toni L. Richards,[2] Kenneth Minor,[2] Yan Zhang,[1] Craig F. Plato,[2] Kristopher Kuchenbecker.[1] *[1]Silver Creek Pharmaceuticals, San Francisco, CA; [2]Plato BioPharma, Inc., Westminster, CO.*

Background: Acute kidney injury (AKI) secondary to acute renal ischemia is associated with high mortality and morbidity with few effective treatments. The bilateral renal ischemia reperfusion injury (IRI) model is commonly employed in rodent studies of AKI. While disease progression is well characterized at the organism level, the dynamics of the molecular responses are less well understood. To improve the translational potential of compounds, the current study sought to temporally and mechanistically define the tissue mRNA expression profiles following discrete durations of IRI.

Methods: Rats underwent sham or warm, bilateral renal ischemia (30' or 40') surgery using PBI's proprietary vascular clamps. Subsets of rats were sacrificed at 8 timepoints following reperfusion (0-48hr), with blood and kidneys harvested at each timepoint for subsequent analyses. Plasma BUN and creatinine were assessed via clinical chemistry. The expression of 100 mRNA transcripts surveying genes across apoptosis, kidney injury, and inflammation/fibrosis pathways were measured by Quantigene.

Results: Plasma creatinine, the classical index of renal dysfunction in AKI was ischemia- and reperfusion time-dependently increased upon inception of reperfusion. Concomitantly, kidney injury and inflammation genes were upregulated early (<4hr) and remained elevated compared to shams throughout study duration. Upregulation of pro-apoptotic genes occurred ≥4hr post-reperfusion, indicating the initiation of programmed cell death. Last, pro-fibrotic genes were upregulated 24-48hr post-reperfusion indicating onset of remodeling. The information content provided by each mRNA expression profile and clinical parameter was determined using a novel statistical framework to identify measures best able to distinguish disease state over 48hr of reperfusion.

Conclusions: This study demonstrated the temporal dynamics of response to renal IRI in rats. The early injury phase (<4hr) was defined by mild, but significantly increased plasma creatinine indicating promptly reduced renal function along with upregulated injury response genes. Induction of pro-apoptotic and pro-fibrotic genes occurred during the later phase, in line with exacerbated renal function. Our novel statistical method identified "high information" genes/parameters that can serve as reliable, mechanistic indicators of AKI in future studies.

Funding: Commercial Support - Silver Creek Pharmaceuticals

PUB018

Antioxidant Ameliorates Pulmonary Renal Injury in an Experimental Model of COVID-19 Organ Failure

Firoozeh Farahmand. *Saint Louis University, Saint Louis, MO.*

Background: Since the outbreak and rapid global spread of COVID-19 multi-organ involvement has largely influenced prognosis and severe AKI has been an ominous clinical predictor with high mortality. The hyperinflammatory response of the body, associated with oxidative stress is a key player in mechansim of multiple organ failure.

Methods: In an experimental model of multiple organ failure of Covid 19 similar to human disease with single injection of Toxoid (TOX) rats were treated with antioxidant carvedilol started daily 1wk pre-TOX-injection and continued for 1 wk post-TOX injection. At 1-week post injection in both TOX+ Antioxidant and TOX groups lungs wet/dry weight ratios were measured to assess edema and lungs and kidneys from both group were analyzed for antioxidant enzyme activities including superoxide dismutase, glutathione peroxidase, catalase and oxidative stress. After sacrificing the animals, kidney and the lung were removed for histology

Results: Antioxidant treatment attenuated TOX induced lung and kidney injury and there was histopathological evidence of its beneficial effects. This was associated with decreased oxidative stress and increased activities of SOD and GSHPx in the lung and the kidney.

Conclusions: In this experimental model that mimics human Covid 19 multiorgan failure, antiooxidant improved survival, lung and kidney injury and also oxidative stress in the kidney. This suggest the beneficial effects of antioxidant as a kidney–lung protective strategy in patients with COVID-19.

PUB019

SRP14 Regulated Renal Tubular Apoptosis Induced by Ischemia-Reperfusion Injury via Interaction with RPS7

Yun Tang, Yanmei Wang, Guisen Li, Li Wang, Yi Li. *Department of Nephrology, School of Medicine, Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China.*

Background: AKI could easily progress to CKD with increased incidence and mortality. Due to the complex pathogenesis, there is a lack of effective early warning to intervene in AKI.

Methods: We performed LFQ proteomic analysis in HK_2 renal tubular epithelial cells after Hypoxia/Reoxygenation to find SRP14 as novel molecule target to prevent AKI upon apoptosis in renal tubular epithelial cells. This study will further study the role and mechanism of SRP14 in regulating MDM2-p53 pathway in apoptosis of renal tubular epithelial cells in AKI. Then analyze the clinical correlation of SRP14 in AKI and explore the possibility of SRP14 as a potential therapeutic target for AKI.

Results: We identified that SRP14 could be involved in apoptosis of renal tubular epithelial cells induced by IRI. SRP14 could regulate the MDM2-p53 loop through RPS7 in renal tubular epithelial cells to regulate apoptosis of renal tubular epithelial cells induced by IRI. The AUC value of SRP14 ($AUC_{[SRP14]}$ = 0.774) was close to serum creatinine ($AUC_{[creatinine]}$ = 0.796), suggesting the potential prognostic value of serum SRP14 to AKI.

Conclusions: This study found that SRP14 regulated renal tubular apoptosis induced by ischemia reperfusion injury via interaction with RPS7 involving MDM2-p53 loop. This finding could provide some novel targets and ideas for AKI control in the future.

PUB020

A Case of Masked AKI

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Introduction: Despite wide recognition of pitfalls, changes in serum creatinine (Cr) and/or a decline in urine output (UO) remain the mainstay of AKI diagnosis. We report a patient whose extremely low Cr and preserved UO demonstrate the problem in reliance on these parameters.

Case Description: 57 F was admitted for respiratory failure due to COVID-19. Her management included tocilizumab, mechanical ventilation, vasopressors, ECMO, and antibiotics. On entry she weighed 54kg and Cr was 0.5 mg/dL. After 5 days, Cr nadired at 0.1 then gradually rose to 0.6 where it remained (day 15). Net fluid balance was 20L. By Cr, her eGFR was 110 ml/min/1.73m^2 but by cystatin C (CysC) it was 56.

Discussion: AKIN defines AKI by an absolute rise in Cr 0.3mg/dl within 48 hrs, a relative increase 150% of baseline within 1 week, or reduction in UO to <0.5mL/kg/hr for at least 6 hrs. Cr is a flawed AKI biomarker due to uncertainty of the baseline, variability in rate of generation, and elimination by secretion and filtration. Cr generation falls rapidly with critical illness. The impact of volume expansion resulting in hyperfiltration or hemodilution are underrecognized. Antibiotics, diuretics, glucose, ketones and bilirubin may interfere with measurement. UO too is flawed since oliguria may occur in the absence of AKI due to antidiuretic hormone or conversely, UO may be maintained despite AKI due to osmotic diuresis, failure of tubular function or diuretic use. The choice of baseline Cr influences our patient's diagnosis. If 0.5 is chosen, she fails to meet AKIN criteria, but based on nadir Cr, she has severe stage III AKI. AKI can also be demonstrated by adjusting Cr for volume expansion: measured Cr x (initial total body water [TBW] + cumulative fluid gain) ÷ initial TBW = 1.4 in our patient. Our patient received tube feeds, suffered hyperglycemia resulting in high osmolar load driving an osmotic diuresis. Also, periodic furosemide was given to mitigate her positive fluid balance. Below normal Cr is generally seen in myopathies, cirrhosis or with drug interference, but hyperfiltration can occur with volume expansion contributing to low Cr. In his case, we believe a baseline small muscle mass, critical illness sarcopenia, and marked volume expansion conspired to mask significant AKI in our patient. Documentation of AKI by measuring CysC led to adjustments in drug dosing.

PUB021

Online Medical Education Significantly Improves Nephrologists' Knowledge and Confidence for Intravenous (IV) Iron Use in Patients with Iron-Deficiency Anemia (IDA) in CKD

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Background: Purpose: To determine if online medical education for nephrologists (Neph) could improve their evidence-based knowledge and confidence to use iv iron to treat IDA in non-dialysis (ND) and dialysis dependent CKD patients

Methods: Participants completed a 3-item questionnaire plus confidence assessment before and after watching a 30-minute online video series of 4 expert interviews with slides. A matched pair design was used pre-/post-assessment, with scores compared to assess changes in the proportion of correct responses. A chi-square test assessed statistical significance at the P <.05 level. Launch 01/29/20; data through 04/13/20. Total Neph learners (n=572), Neph assessment completers (n=122)

Results: At baseline, 20% of Neph (n=122) answered all 3 questions correctly, increasing to 61% (P < .001) post-assessment. An average of 61% of all responses were correct pre-assessment increasing to 83% post (P <.001). 36% of Neph had a measurable increase in confidence using iv iron therapies to manage IDA. The activity significantly increased knowledge on the differences between iv and oral iron in delaying the need for erythropoiesis-stimulating agents when treating IDA in ND-CKD patients (pre: 64%, post: 85%, P <.001) and using a pro-active high dose iv iron strategy in CKD patients on dialysis to reduce cardiovascular risk versus a low dose approach (pre: 29%, post: 71% P <.001). Neph already chose to start iv iron therapy in an IDA patient on hemodialysis currently on ESA but not meeting their hemoglobin goals in adherence to KDIGO guidelines (pre: 91%, post: 93% P =.641). Polling showed 1 in 4 Neph to start IDA treatment with iv iron in <50% of CKD patients.

Conclusions: Online medical education can significantly improve data recall from pivotal clinical trials on iv iron therapy to treat IDA in CKD patients with or without dialysis. This activity was also successful to facilitate application of such evidence into clinical practice and boost confidence using iv iron therapies, specifically with regards to iron repletion before ESA initiation in ND-CKD patients and using higher iv iron doses to mitigate cardiovascular risk in HD-CKD patients. Further nephrologist education on iv iron use in earlier IDA stages could be helpful to optimize patient outcomes.

Funding: Commercial Support - Developed through an independent educational grant from Vifor Pharma

PUB022

Predicting PTH and Calcium Trajectories for ESKD Patients on Intravenous Calcimimetics

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Background: Patients with End-Stage Kidney Disease (ESKD) often experience secondary and tertiary hyperparathyroidism leading to increased fracture risk, vascular calcification, and increased cardiovascular risk. Traditional pharmacotherapy includes phosphorus binders, Vitamin D analogues, and oral calcimimetics. Despite this, many ESKD patients still have elevated parathyroid hormone (PTH) levels. Etelcalcetide is an intravenously delivered calcimimetic approved to treat hyperparathyroidism. Advantages include a long half-life and IV administration which guarantees drug delivery. Despite this, response of PTH and calcium levels to etelcalcetide remains difficult to predict. A predictive algorithm could assist clinicians in assessing the potential effect of a given dose. As a first step in developing a dosing decision support tool, we present a predictive model that forecasts the 1-, 2-, and 3-month PTH and calcium values for patients receiving etelcalcetide.

Methods: We used tree ensemble (RandomForest) models for their ability to model the data non-linearities. Model inputs were historic data (calcimimetic dosing, labs, dialysis records, demographics, and phosphorus binder orders) and future calcimimetic dosing.

Results: The Mean Absolute Error (MAE) is 205, 227, and 249 pg/mL for the 1-, 2-, and 3-month PTH predictions, respectively. In addition, for the 1-, 2-, and 3-month predictions, 70%, 65%, and 59% of the predictions, respectively, lie within ±250 pg/mL of the actual PTH value. The MAE for the 1-, 2-, and 3-month calcium predictions is 0.410, 0.458, and 0.496 mg/dL, respectively. In addition, for the 1-, 2-, and 3-month predictions, 71%, 65%, and 63% of the predictions, respectively, lie within ±0.5 mg/dL of the actual calcium value.

Conclusions: The error distribution of the predictions is such that they 1) may be clinically meaningful as part of an effort to better control PTH, while potentially reducing excessive up-titration of etelcalcetide (and thus cost) and 2) may serve as a benchmark for future modeling efforts. Limitations include: a relatively small data set which precluded the use of other models (e.g., recurrent neural networks) and the dialysis program's strict criteria for receiving etelcalcetide which led to a study population with significantly higher PTH values than may be encountered in the general dialysis population.

Funding: Private Foundation Support

PUB023

A Rare Case of Staghorn Calculi Complicated by Bilateral Xanthogranulomatous Pyelonephritis

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Introduction: Staghorn calculi are usually unilateral and typically occur in women. Chronic obstruction and infection of staghorn calculi can cause xanthogranulomatous pyelonephritis (XGP), a rare destructive granulomatous process of renal parenchyma. We describe a case of bilateral staghorn calculi in a man complicated with XGP and worsening renal function.

Case Description: A 64-year-old man with bilateral staghorn calculi and chronic kidney disease (CKD) stage 4 was admitted for fatigue and worsening renal function. He tested positive for COVID-19 by nuclei acid-based test. Serum creatinine increased from 3.5 (2 months ago) to 6.2 mg/dL. Renal ultrasound showed dilated left calyces and large shadowing calculi without hydronephrosis. History was notable for persistently alkaline urine (urine pH >6.5), 100% carbonate apatite (dahllite) on stone analysis, and urinary tract infection with *Proteus mirabilis.* CT imaging revealed bilateral staghorn calculi with "bear paw" signs (left > right), a typical appearance of XGP [Figure]. Compared to a CT scan completed 10 months ago, the left kidney was enlarged with greater low-attenuating spaces indicating worsened XGP; the right kidney decreased in size with less stone burden corresponding to the right percutaneous nephrolithotomy performed 7 months prior. AKI was thought to be related to COVID-19, and surgical intervention was deemed unnecessary. Bilateral XGP likely increased his risk of AKI and hampered renal recovery, and he was subsequently initiated on hemodialysis.

Discussion: In this rare case of staghorn calculi progressed to bilateral XGP, we observed the detrimental effects of staghorn calculi on the kidneys. More research on staghorn calculi is needed to improve the high morbidity and mortality associated with this disease.

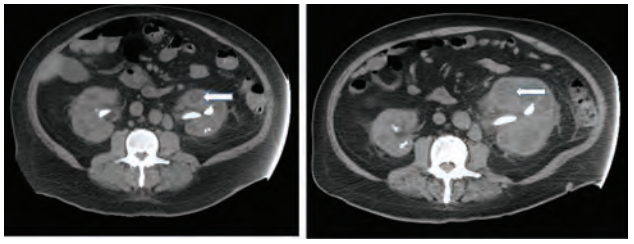

Figure. Abdominal CT- 10 months prior (left): bilateral staghorn calculi with rounded areas of low-attenuation replacing renal parenchyma representing "bear paw" signs (white arrows). Present (right): interval enlargement of left kidney with larger low-attenuating spaces consistent with worsened XGP; smaller right kidney with less stone burden.

PUB024

Factors Associated with Serum Concentrations of 25-Hydroxyvitamin D (25D) and 1,25-Dihydroxyvitamin D (1,25D) in Stable Hemodialysis Patients

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Background: Serum 1,25D, an active form synthesized from 25D, is present in CKD patients (Ishimura, Kidney Int 1999; Wolf, Kidney Int 2007). However, factors associated with 1,25D and 25D are not well known. The aim of the present study is to examine the relationship between 1,25D, 25D and clinical parameters in hemodialysis patients.

Methods: Serum 1,25D and 25D were measured by a RIA2-Ab method and an ECLIA method, respectively, in 108 stable maintenance hemodialysis patients (72 ± 10 years, 64 males, hemodialysis duration: 6.9 ± 7.5 years, 45 diabetics) from December 2019 to February 2020, i.e., in the winter.

Results: Serum 1,25D were 14.6 ± 8.0 pg/ml, demonstrating that 77 patients showed values less than reference ranges of healthy subjects (30-60 pg/mL). Serum 25D were 12.0 ± 4.8 ng/mL, demonstrating that 101 patients showed vitamin D deficiency of < 20 ng/mL. There was no significant correlation between serum 1,25D and 25D in maintenance hemodialysis patients in the present study, although 1,25D and 25D had been reported to show significant, positive correlations both in pre-dialysis CKD patients (Ishimura, Kidney Int, 1999) and in incident dialysis patients (Wolf, Kidney Int 2007). There were no significant correlations between 25D and clinical parameters. However, there were significant, negative correlations between 1,25D and intact PTH ($r = -0.344$, $p < 0.001$) and between 1,25D and ALP ($r = -0.309$, $p < 0.02$), although no significant correlations were seen between 1,25D and other parameters, such as Ca and P. In multiple regression analyses, 1,25D was significantly, independently associated with intact PTH and with ALP after adjustments of several clinical parameters ($R^2 = 0.345$, $p < 0.001$: $R^2 = 0.256$, $p < 0.001$, respectively).

Conclusions: In maintenance hemodialysis patients, all patients showed hypovitaminosis D, in terms of serum 25D. 1,25D, even in low serum levels, correlated significantly and negatively with intact PTH and ALP. These results indicated that even low levels of serum active vitamin D, 1,25D, affect the status of CKD-MBD. The results may further indicate that the metabolism of vitamin D should be considered in the pathogenesis and treatment of CKD-MBD.

PUB025

A Case of Parathyroid Hyperplasia with Single Explosive Growth

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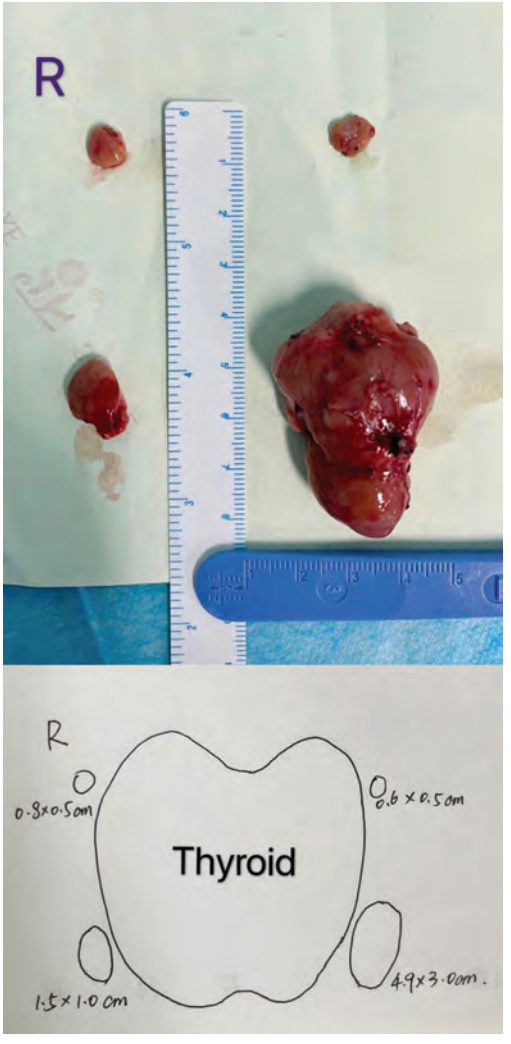
Introduction: Exploration of parathyroid hyperplasia with single explosive growth

Case Description: A 46.Y.O Asian man with ESRD has been undergoing regular hemodialysis for 20 years due to glomerulonephritis. The patient has had bone and joint pain for 10 years. In 2018, the measurement of his serum iPTH was elevated and the value was over 1000pg/ml (no data about serum calcium and phosphate levels), and he didn't have regular treatment. Serum calcium, phosphate and alkali phosphatase were 2.46mmol/L, 2.4mmol/L and 380u/L respectively, and serum iPTH was 2205pg/ml in this admission examination. The ultrasonography showed two hyperplastic parathyroid glands. They are 13*5mm on the right lower side of thyroid gland and 43*18mm on the left lower side. Parathyroid nuclide scanning showed three hyperplastic parathyroid glands. That is located in bilateral hypothyroidism and left upper sternum,consider parathyroid development, Total parathyroidectomy was successfully carried out with the general anesthesia in May 15, 2020. Four parathyroids were excised, which were 0.6*0.5cm in the upper left, 4.9*3.0cm in the lower left, 0.8*0.5cm in the upper right, and 1.5*1.0cm in the lower right (the maximum diameter and length). Pathological diagnosis showed that there was parathyroid nodular hyperplasia in the upper left, lower left, upper right and lower right. PTH values a week after surgery was less than 1.2pg/ml, serum calcium 2.13mmol/L, phosphate was 0.85mmol/L, Patient bone pain disappeared. Patient has been discharged and will be close followed up.

Discussion: Total parathyroidectomy is effective in uremic patients with secondary hyperparathyroidism which has explosive hyperplasia with parathyroid glands.



Thyroid and parathyroid

PUB026

Acute Changes in Plasma Phosphate After Phosphorus-Standardized Meals in Peritoneal Dialysis: A Randomized Cross-Over Trial

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Background: Hyperphosphatemia is associated with increased morbidity and mortality in patients with chronic kidney disease. The aim of this study was to assess whether a meal with high phosphorus content affects plasma phosphate in the hours following such a meal among subjects with end-stage kidney disease on peritoneal dialysis.

Methods: This was a single-blinded randomized cross-over trial of 12 subjects on maintenance peritoneal dialysis, in which subjects were randomized to consume a meal with either high or low phosphorus content on two separate trial days. On each trial day plasma phosphate was measured immediately before consumption of the standardized meal, and after one, two, three and five hours.

Results: The mean fasting plasma phosphate at baseline was 1.69 ± 0.22 mmol/L. Plasma phosphate was similar between the two meals at baseline, as well as at one, two, three, and five hours after consumption. The largest observed difference in plasma phosphate between the two meals was 0.15 mmol/L, which occurred five hours after consumption (high phosphorus meal 1.75 ± 0.32 mmol/L versus low phosphorus meal 1.60 ± 0.14 mmol/L ($p = 0.06$)). Using summary analyses for repeated measures we observed a significant difference in the plasma phosphate between the two meals ($p = 0.03$).

Conclusions: Our results show that in subjects with end-stage kidney disease a meal with high phosphorus content has only a negligible effect on plasma phosphate compared to a meal with low phosphorus content. Thus, large increases in plasma phosphate cannot be accounted for by a high intake of phosphorus in the hours prior to blood sampling.

Funding: Private Foundation Support

PUB027

A Rare Case of Severe Tertiary Hyperparathyroidism in a Patient with ESRD

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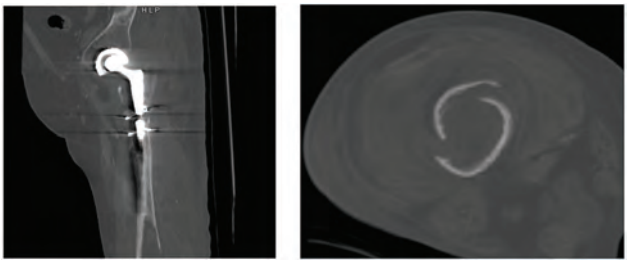
Introduction: Refractory tertiary hyperparathyroidism is defined as severe, persistent & progressive elevation of PTH which cannot be lowered by medical management & associated hypercalcemia, hyperphosphatemia, bone/joint pain and/or fracture, extra skeletal calcification, calciphylaxis & pruritus.

Case Description: A 43-year-old undocumented Hispanic male with PMH of uncontrolled DM, HTN, ESRD (HDX 3/week) & persistent tertiary hyperparathyroidism (on Cinacalcet) presented with multiple bone fractures, bilateral leg weakness, soft tissue calcification & severe renal osteodystrophy. Significant lab findings included PTH 3518pg/mL, phosp 6.7mg/dL, Ca+ 10.9mg/dL & ak phosp 804 IU/L were all above goal. X-ray of lower ext. revealed diffuse osteopenia with chronic fracture in distal fibula, midfoot, distal tibia & dislocation of talonavicular joint as well as extensive atherosclerotic vascular calcification & multiple punctate soft tissue calcification. CT spine reported demineralized appearance of vertebral bodies & sacrum, wide erosion of sacroiliac joints bilaterally & calcified atherosclerotic disease of abdominal aorta & bilateral interiliac arteries. Patient was diagnosed as refractory tertiary hyperparathyroidism & treated with doxercalciferol, phosphate binders & advised for parathyroidectomy on multiple previous encounters but was unable to do due to health care access issue.

Discussion: Parathyroidectomy which has mortality benefit is indicated in the setting of severe & sustained PTH value above 800-1000 pg/mL, refractory to medical treatment & associated to others indicators like hypercalcemia, refractory hyperphosphatemia, bone pain/fractures & our case has majority of the above mentioned indications. Various other factors including immigration, insurance issues and post-operative intensive care requirements complicated the potential for parathyroidectomy in this patient. Although with advancement of medical field, the symptoms of severe hyperparathyroidism are rarely observed but the manifestations are real if not treated on time as per guideline recommendations.



Figures showing pathological fractures & muscular atrophy

PUB028

Progression of CKD Stage G3a Among African Americans

Yelyzaveta Prysyazhnyuk, Isha Puri, Jie Ouyang, Ernie Yap. *SUNY Downstate Health Sciences University, Brooklyn, NY.*

Background: Chronic kidney disease (CKD) stage 3 represents the most of all CKD patients. Stage G3 is divided into G3a (GFR 45–59 ml/min/1.73m^2) and G3b (30–44 ml/min/1.73 m^2) based on findings that showed differential kidney outcomes. Stage G3a has several unresolved paradigms. Firstly, it does not always imply kidney damage. It is recommended that cystatin C be used to confirm in people without manifestations of kidney damage to avoid over-diagnosis. Secondly, it primarily comprises of the elderly, and most will not progress to advanced CKD before succumbing to other causes of death. Thirdly, in people with manifestations of kidney damage, stage G3a becomes an important predictor of disease progression. The influence of ethnicity on eGFR in delineating these aberrancies in CKD G3a is unclear. In this study, we sought to analyze the progression of CKD G3a patients in a predominantly African American cohort.

Methods: We performed retrospective chart reviews of patients at our CKD clinic. GFR was estimated based on the MDRD formula. Continuous variables are presented as mean±SD. Comparison of continuous variables were performed using one-way ANOVA. Univariate and age and body mass index (BMI)-adjustment analyses was performed by Cox proportional hazards model. IBM ***SPSS*** v. 25 was used.

Results: 319 patients were analyzed. Median follow-up was 79.7 months (IQR: 93.1). 259 (81.2%) patients had at least 2-years follow-up. In these patients, the mean annual GFR declines were 4.4±3.8, 2.3±2.1, 1.6±2.7 and 1.4±2.2 ml/min/1.73 m^2 for stages G2, G3a, G3b and G4 respectively (p<0.001). Univariate Cox proportional hazard analysis showed that CKD G3a, Gb and G4 had relative risks (RR) of progression to G5 of 1.0 (95% CI: 0.5-2.2; p=0.98), 3.8 (1.6-9.1; 0.003) and 19.4 (8.7-43.0; <0.005) respectively. When adjusted for age and BMI, risks of progression to G5 were: RR=1.3 (0.6-3.0; 0.5), 5.8 (2.3-14.7; <0.005) and 29.6 (12.1-72.2; <0.005) for CKD G3a, G3b and G4 respectively.

Conclusions: In our cohort of predominant African Americans, CKD G3a does not predict disease progression.

Characteristics	All (n=319)	CKD Stage G2 (n=162)	CKD Stage G3a (n=92)	CKD Stage G3b (n=41)	CKD Stage G4 (n=24)
Age, years±SD	62.6±13.6	59.9±13.7)	65.6±11.8)	64.9±14.9	66.2±13.9
Female sex, %	61.1	64.2	58.7	56.1	58.3
Ethnicity AA, %	94.0	90.7	100	92.7	95.8
BMI, kg/m^2 ± SD	29.8±6.7	29.8±6.8	30.1±6.7	30.5±6.9	27.7±6.3

CKD- chronic kidney disease; AA- African American; BMI- body mass index

PUB029

Is Routine Screening with Serum and Urine Protein Electrophoresis in Evaluation of CKD Justified?

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Background: Current guidelines for the evaluation of chronic kidney disease (CKD) in Ontario, Canada do not include routine screening with serum and urine protein electrophoresis (SPEP and UPEP). Previous studies suggest that M-spike is more common in CKD compared to the general population (1,2). This study aims to examine the use and cost of screening SPEP and UPEP in the evaluation of CKD pts.

Methods: This is a retrospective study of 149 sequential incident pts referred to a teaching General Nephrology clinic for evaluation of CKD between Jan and Nov, 2018. The SPEP and UPEP testing frequency, and proportion with M-spike were obtained by chart review, along with the routinely performed clinical, blood and urine tests, imaging, as well as reports of any Hematology consultation, renal and bone marrow biopsies performed.

Results: Screening SPEP and UPEP tests were done in 104 (70 %) pts, mean age 72.2 yrs, 42 (40 %) female, 52 (50 %) DM, and Caucasian majority. M-spike was present in 11 pts (10.6 %, 96 % CI 5.4 – 18.8 %), 2 IgG-κ, 5 IgG-λ, 1 IgA-λ, 2 LC-κ, and 1 LC-λ. Eight had Hematology consultation, 6 had bone marrow biopsy, and 3 had renal biopsy. Diagnoses were 7 MGUS, 2 myeloma (MM), 1 amyloid (AL), and 1 both MM + AL. There were no differences in clinical, demographic, CBC, serum calcium, urine albumin to creatinine ratio, urinalysis, or renal imaging among pts with and without M-spike but sample size did not allow multivariate analysis.

Conclusions: In this study, the prevalence of M-spike in CKD is higher than has been reported in the literature in the general population (5.4 - 18.8 % vs. 3 – 4 %). The cost for testing and interpretation fees for SPEP and UPEP are CDN $ 25.53 and $ 32.99 respectively, with detection costs of $ 553.28 per M-spike and $ 1,521.25 per myeloma or amyloid. These costs are consistent with previous studies controlled for inflation (1,2). Routine screening with SPEP and UPEP in the evaluation of CKD may be useful and cost-effective. Larger prospective studies are needed to identify subgroups with higher likelihood of M-spike to target testing. 1. Al-Hwiesh et al. J Am Soc Nephrol 2003 14:295A. 2. Chew et al. Am J Kidney Dis. 1999 Jul;34(1):135-9.

PUB030

Is Yakima County a CKDu Hot Spot? A Case Series of CKD in Latino Agriculture Workers

Mark D. Baldwin, Katherine Ackerman, Tara L. Kronen, Polly Wiltz, Lizzie Lamb. PNWU CKDu Investigative Task Foce *Pacific Northwest University of Health Sciences College of Osteopathic Medicine, Yakima, WA.*

Introduction: The first case series of chronic kidney disease of unknown etiology (CKDu) was described in 2002 in sugar cane cutters in El Salvador. This unique diagnosis presented in relatively young men without any of the traditional risk factor associated with renal disease. The common feature amongst cases was strenuous work in extremely hot environments. Yakima, Washington, an agricultural community in the Pacific Northwest, has had the highest average temperature increase in the Pacific Northwest at 3°F over the past 30 years. Average summer temperatures for July and August are 88°F and 89°F, respectively. Yakima County is 49.5% Latino and 27.5% (29,331) of the total population is involved in agriculture. The majority of labor-intensive agriculture jobs are performed by Latino workers, drawing attention to Yakima as an unexpected hotspot for CKDu.

Case Description: We describe three Latino agricultural workers seen by a nephrologist (MDB) in a local free clinic in the span of 8 months. The ages ranged from 58-68 and all worked ten years or more for local farms. Each patient had at least Stage 3 CKD (<60 ml/min/m^2), hypertension, hyperuricemia, without proteinuria nor albuminuria; there was no history of diabetes mellitus. Renal ultrasounds were unremarkable. Treatment was focused on controlling hypertension and hyperuricemia, however little disease modifying interventions are available.

Discussion: These cases, collected over a relatively short period of time, demonstrate that CKDu is more common than previously thought amongst agricultural workers in

northern regions. At 46.6021° N latitude, Yakima is closer to the North Pole than the Equator, and much farther north than other areas where CKDu has been documented. With increasing global temperatures, agricultural workers are on the frontline of climate-related health issues. Further study is necessary to develop awareness, earlier risk factor detection, and effective interventions for these essential and vulnerable members of our communities.

PUB031

The Correlation Among Management of the Comorbidities and Progression of Renal Dysfunction or Adverse Events for CKD Patients

Takahiro Kuragano, Takeshi Nakanishi. *Hyogo college of Medicine Kidney and dialysis, Nishinomiya, Japan.*

Background: It is well established that several factors including anemia, hypertension, hyperuricemia, metabolic acidosis, and CKD-MBD are associated with progression of CKD or adverse events of these patients. However, the significant factors which associated with progression of CKD or adverse events under the condition of appropriate control which according to guidelines have not been cleared.

Methods: The study was an observational study in a single center for a period of 3 years. In 88 patients with various stages of CKD (not on dialysis) who were treated by nephrologists, Hb, ferritin, iron and albumin and high sensitive C reactive protein (hCRP), β2microglbulin (MG), $HCO3^-$, and intact-parathyroid hormone (iPTH), in addition to urinary sodium, potassium, calcium, phosphorus protein, and β2MG levels, were measured. All patients were treated according to the clinical practice guideline for CKD. A time-dependent Cox hazard model was applied to evaluate the association between clinical parameters and adverse events.

Results: In multiple regression analysis, baseline of lower Hb (β=0.497, P<0.001) and vitamin D 125 (β=0.258, P=0.006), and higher int-PTH (β=-0.334, P=0.001), urinary phosphorus (β=0.328, P=0.001), urinary β2MG (β=-0.225, P=0.031) and urinary protein (β=0.280, P=0.02) levels were selected as significant predictors of decline of estimated glomerular filtration rate (eGFR) or 1/ creatinine(Cr) at the end of the study. In the Cox hazard model, low calcium (HR: 0.37, P=0.026), high phosphate (HR:5.90, P<0.001), low 125 vitamin D (HR: 0.94, P=0.013), high int-PTH (HR:1.02, P<0.001) level, use of a phosphate binder (HR: 4.95, P=0.012), and use of vitamin D analogs (HR:3.75, P=0.014) are selected as risks for adverse event including initiation of dialysis.

Conclusions: In this study, we found that among several factors, anemia and CKD-MBD related factors (phosphate, calcium, vitamin D, int-PTH) were selected as significant predictors for the progression of renal dysfunction. Furthermore, although phosphate binder or vitamin D analogs were administered appropriately, CKD-MBD factors were associated with dialysis initiation or adverse events of these patients. From these results, we presumed that the early intervention or strict control for CKD-MBD factors might attenuate the risk for adverse events of CKD patients.

PUB032

Association of Anion Gap with the Risk of CKD Progression

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Background: Increased anion gap is a marker of acid retention most reflected in patients with CKD. This study's objective is to assess whether a higher anion gap is a risk factor for CKD progression.

Methods: This prospective cohort study assessed 4131 participants with CKD stage 2 to 4, who enrolled in a chronic renal insufficiency cohort study. Three types of anion gap were used as exposures, traditional anion gap (AG1), Albumin corrected anion gap(AG2), full anion gap(AG3). Multivariable adjusted Cox proportional hazard models were built using the lowest tertile as the reference of all three anion gaps for the composite outcome (50% decline in eGFR or ESRD) and ESRD. Models were adjusted for relevant covariates and baseline eGFR.

Results: This study included 4131participants [mean (SD) age, 60.48(10.21) years; 1788 (43.28%) female]. During 26673.46 person years of follow up, 805 participants reached ESRD and 1138 participants reached a composite outcome of a 50 % decline in GFR or ESRD. In a multivariable adjusted model each SD increase in AG1, AG2 and AG3 were independently associated with 10%, 10% and 12% increased risk for CKD progression: [hazard ratio (HR) 1.10; 95% CI (1.01-1.21): HR 1.10 ; 95% CI (1.02-1.20), HR 1.12 ;95% CI (1.03-1.21)], however each SD increased in AG2 and AG3 was independently associated with a 11 % increased risk for ESRD [HR 1.11; 95% CI (1.02-1.21), HR 1.11; 95% CI (1.02-1.22)]. In multivariable adjusted models compared to tertile 1 (<10) those in tertile 3 (>12) had a 33% and 41% higher risk for CKD progression [HR 1.33;95% CI (1.09-1.62), HR 1.41;95% CI (1.16-1.71)] and 32% and 60% higher risk for ESRD [HR 1.32; 95% CI (1.06-1.64), HR 1.60;95 %CI (1.28-2.01)].

Conclusions: Higher albumin corrected and full anion gap may be a risk factor for CKD progression and ESRD.

Table 1| Associations between AGs and ESRD [T1 as reference]

Continuous		AG1				AG2				AG3			
		HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value
Crude		0.9512	0.8883	1.0190	0.1520	1.3870	1.2490	1.4310	<0.0001	1.3280	1.2370	1.4250	<0.0001
Multivariable adjusted		1.0901	0.9876	1.2031	0.0857	1.1358	1.0222	1.2179	0.0142	1.1181	1.0208	1.2248	0.0163
Tertiles (T1 as reference)		HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value
Crude	Tertile1	Reference				Reference				Reference			
	Tertile2	0.7423	0.6287	0.8764	0.0004	1.1750	0.9806	1.4080	0.0805	1.2480	1.0390	1.5000	0.0180
	Tertile3	0.9307	0.8475	1.1835	0.9878	1.9750	1.6686	2.3430	0.0000	1.9890	1.6710	2.3680	<0.0001
Multivariable adjusted	Tertile1	Reference				Reference				Reference			
	Tertile2	0.7245	0.5873	0.8937	0.0026	0.9882	0.7955	1.2347	0.9362	1.0486	0.8336	1.3190	0.6850
	Tertile3	1.0216	0.8242	1.2663	0.8452	1.3261	1.0696	1.6442	0.0101	1.6092	1.2880	2.0104	<0.0001

Table 2 | Associations between AGs and composite outcome [ESRD or 50% declines in eGFR]

Continuous		AG1				AG2				AG3			
		HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value
Crude		0.9877	0.8897	1.0093	0.0977	1.2710	1.1490	1.3550	<0.0001	1.2090	1.0960	1.3270	<0.0001
Model 2		1.1091	1.0124	1.2149	0.0260	1.1095	1.0236	1.2023	0.0112	1.1265	1.0318	1.2169	0.0068
Tertiles (T1 as reference)		HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value	HR	2.50%	97.50%	p-value
Crude	Tertile1	Reference				Reference				Reference			
	Tertile2	0.7593	0.6547	0.8805	0.0003	1.1850	1.0130	1.3860	0.0343	1.2500	1.0620	1.4710	0.0073
	Tertile3	0.9805	0.8393	1.1455	0.8039	1.7590	1.5060	2.0530	<0.0001	1.8430	1.5690	2.1600	<0.0001
Multivariable Adjusted	Tertile1	Reference				Reference				Reference			
	Tertile2	0.8003	0.6483	0.9875	0.0211	0.9819	0.8087	1.1921	0.8535	1.0047	0.8237	1.2255	0.9631
	Tertile3	1.0161	0.8341	1.2377	0.8744	1.3333	1.0960	1.6221	0.0060	1.4132	1.1620	1.7187	0.0005

Figure one shows the crude and the multivariable Cox proportional hazard models using anion gap as tertiles.

PUB033

Childhood Risk Factors for Adulthood CKD

Michal Stern Zimmer, Asaf Vivante. *Sheba medical center, Ramat Gan, Israel.*

Background: Chronic Kidney Disease (CKD) is a demographic health challenge, affecting - as much as 8 to 18% of the world population. Identifying childhood risk factors for future CKD may help clinicians make early diagnoses facilitating complication monitoring and initiation of preventive interventions for CKD and its accompanying comorbidities. We aim to describe these childhood risk factors that may predict development of overt kidney disease later in life.

Methods: PubMed publications (January 2009 - January 2019) were searched for publications by using terms and synonyms for chronic kidney disease (CKD) and specific childhood kidney related risk factors. We also manually searched the reference lists of key articles, reviews and meta-analyses.

Results: There are a multitude of childhood risk factors associated with future onset and progression of CKD. These risk factors can be grouped into five categories: genetic factors (e.g. monogenic or risk alleles), perinatal factors (e.g. low birth weight and prematurity), childhood kidney diseases (e.g. congenital anomalies, pyelonephritis, glomerular diseases and acute kidney injury), childhood onset of chronic conditions (e.g. cancer, diabetes, hypertension, dyslipidemia and obesity) and different lifestyle factors (e.g. physical activity and diet).

Conclusions: The available published information suggests that the lifelong risk for CKD can be attributed to multiple factors which appear already during childhood. However, results are conflicting on the effects of childhood physical activity, diet and dyslipidemia on future renal function. On the other hand, there is consistent evidence to support close monitoring for high risk populations.

Risk Factors for chronic kidney disease in childhood and adulthood
Category
Genetic factors
Ethnicity
Family history of kidney diseases
Monogenic kidney diseases
Risk alleles
Perinatal Factors
Prenatal exposure to nephrotoxins
SGA
Prematurity
Major childhood kidney disease and their impact in adulthood
CAKUT
Glomerulopathies
Cystic kidney diseases
Tubulointerstitial disorders and other childhood kidney conditions
Acute Kidney Injury of any cause
Childhood onset of chronic conditions conferring future risk for CKD
Diabetes
Hypertension
Hyperlipidemia
Obesity
Cancer
Lifestyle factors
Diet
Lack of physical activity
Socioeconomic status

PUB034

Therapeutic Interventions to Assess Outcomes and Disparities in Chronic Kidney Disease Among Veterans (TRI-CKD)

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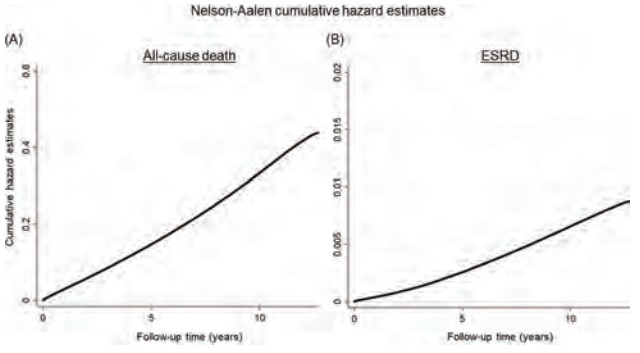
Background: There continues to be a large unmet need in the management of CKD, due in part to a lack of effective intervention strategies to prevent CKD progression or decrease morbidity/mortality in patients with CKD. There is also a lack of race-specific application of clinical interventions, despite evidence suggesting racial differences in response to various therapies. High quality, large observational studies are essential to provide preliminary results in support of future clinical trials, and to offer large-scale, widely applicable evidence to inform clinical practice in this population when clinical trials are not feasible.

Methods: We established a cohort of 3,565,367 individuals with stable eGFR >60 mL/min/1.73m^2 during October 1, 2004-September 30, 2006, using an algorithm based on repeated serum creatinine measurements. Data about patients' demographics, socioeconomic characteristics, comorbid conditions, administered medications, labs, vital signs, vital status, incident CKD and ESRD outcomes were obtained from various VA databases, from Centers for Medicare & Medicaid Services, and from USRDS.

Results: The mean (SD) age of the cohort is 59 (14) years; 93% are male; 16% are African-American; and 24% are diabetic. The mean baseline eGFR is 84 mL/min/1.73m^2. Individuals are followed longitudinally for up to 13 years. Overall, the crude rates of all-cause death and ESRD are 31 and 0.63 per 1000 patient-years (**Figure**).

Conclusions: We established a large nationwide cohort of US veterans with normal eGFR. Studies from this cohort will generate a wealth of information to examine therapeutic interventions used to treat various conditions associated with poor outcomes in patients with all levels of kidney function, potentially providing significant clinical, social, and policy implications for the care of US veterans and also for patients with kidney diseases in general.

Funding: Veterans Affairs Support



PUB035

Treatment Response in Patients with Uncontrolled Gout Co-Treated with Pegloticase and Leflunomide

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Background: Many patients with CKD develop gout with a prevalence ≤36% in later stage disease. Though oral urate-lowering therapies are used in CKD patients, some may not respond to or cannot tolerate them. Uncontrolled (refractory) gout can be treated with pegloticase (PEGylated uricase enzyme), however, anti-drug antibodies (ADAs) can cause loss of therapeutic efficacy. Compared with pegloticase alone, recent case series show markedly higher response rates with methotrexate/pegloticase co-therapy (42% vs. 80-100%). However, certain considerations with methotrexate use including significant renal or hepatic disease may not be as restricting with leflunomide. This study examined pegloticase response rate in patients co-treated with pegloticase and leflunomide.

Methods: This chart review study included uncontrolled gout patients treated with pegloticase (biweekly 8 mg infusions) and oral leflunomide (20 mg/day). Patient, disease, and treatment parameters were examined, along with safety data. Patients receiving ≥12 pegloticase infusions with a serum uric acid level (sUA) <6 mg/dL at infusion 12 were considered responders.

Results: 10 patients were identified and included (5 men, 72.7±12.5 years, pre-therapy sUA: 7.1±2.4 mg/dL). Common comorbidities were CKD (90%), hypertension (70%), diabetes mellitus (60%), obesity (60%), congestive heart failure (50%), and coronary artery disease (20%). 7 patients (70%) met responder criteria (26.6±14.0 infusions, sUA at infusion 12: 0.9±1.5 mg/dL). 3 patients were lost to follow-up or discontinued therapy. Gout flare (1 patient, 3 flares), wooziness/loss of consciousness (1 patient; before pegloticase infusion, deemed solumedrol related), worsening of kidney/cardiac issues (1 patient, deemed unrelated to treatment), and mild, transient ALT/AST increases (2 episodes, 1 patient) were observed. All treatment-related AEs were known effects of pegloticase or leflunomide.

Conclusions: These findings suggest that leflunomide/pegloticase co-therapy can increase the proportion of pegloticase responders, likely due to attenuation of ADAs. While methotrexate has been shown to increase pegloticase response rates, many gout patients have advanced CKD and leflunomide potentially represents an alternative option for minimizing ADAs.

Funding: Commercial Support - Horizon Therapeutics

PUB036

A Double-Blind, Randomized, Placebo-Controlled with an Open-Label Rollover Extension Phase 2/3 Clinical Trial to Evaluate Safety and Efficacy of US-APR2020 in Subjects with CKD Stage IV

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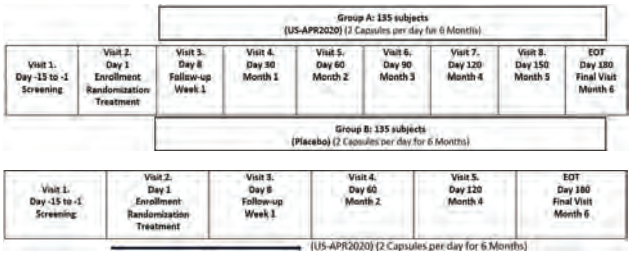
Background: CKD patients experience poor quality of life due to high levels of uremic toxins in the blood. Renadyl™, a Pro/Prebiotic dietary supplement has been in the market since 2010. It is proven to reduce several uremic toxins in 3 pilot clinical trials with no adverse outcomes. The product is now awaiting FDA-IND approval for a drug trial. This will be a large scale 12-month RCT to validate US-APR2020 as a Live Bio-Therapeutic drug product (LBP) under CBER guidelines.

Methods: (A) 6-month randomized placebo-controlled parallel design in an outpatient setting followed by (B) 6 month Open-Label Rollover Extension which will enroll all patients from study A.

Results: Study end points: As compared to placebo**; Primary**: 1: Less than 10% adverse event in the study population. 2: Arrest the decline of eGFR as per NKF-USFDA guidelines. **Secondary**: 1: Improvement in any of the basic blood uremic metabolic markers. 2: Improvement in any of the complete blood count (CBC) and hematology parameters. 3**:** Reduction in C-Reactive Protein (CRP) levels. 4: Percent change from baseline in rating scale (Modified SF36 QOL questionnaire) at the end of 6 and 12 month. **Tertiary (IN FEW SELECTED SITES):** Blood levels of Kidney Injury Molecule (Kim-1), Neutrophil Gelatinase-associated Lipocalin (NGAL), gut microbiome derived uremic toxins: Indoxyl Sulfate (IS), para-cresyl sulfate (pCS) and Trimethylamine-N-Oxide (TMAO).

Conclusions: This is the first-ever clinical trial proposed using Pre/probiotics US-APR2020 as a Live Bio-Therapeutic drug product (LBP) for CKD IV patients. Being noninvasive the intervention avoids any possible infection. The addition of US-APR2020 with standard care of therapy may possess excellent potential towards CKD applications worldwide. Formal IND process under CBER/US FDA in progress. Seriously interested clinical PI's please contact: rangan@kibowbiotech.com



PUB037

Effects of Tolvaptan on Long-Term Prognosis in CKD Patients

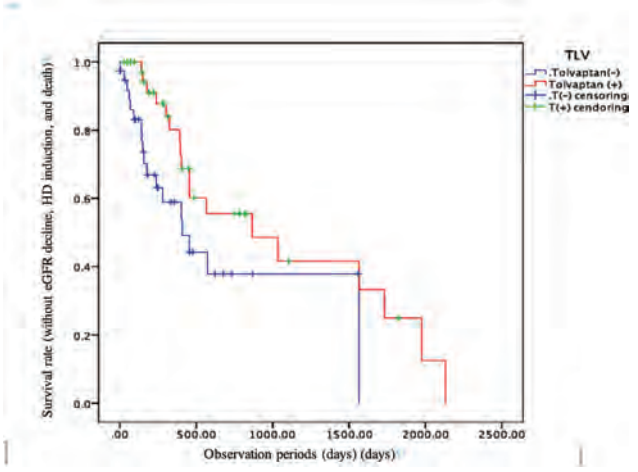
Kazuhito Fukuoka, Yuko Shibata, Shinya Kaname. Kyorin University School of Medicine, department of Nephrology and Rheumatology *Kyorin Daigaku, Mitaka, Japan.*

Background: Tolvaptan is a novel diuretic agent used for the treatment of intractable edema and SIADH in Japan, as well as polycystic kidney disease. Purpose: To determine whether tolvaptan prevent worsening renal function or prolongs the time to dialysis induction in pre-dialysis CKD patients.

Methods: A retrospective observational study (case-control study). Eligible patients were CKD patients treated with tolvaptan more than 30 days at our hospital between 2012 and 2018. The control patients were selected from CKD patients without the use of tolvaptan at our hospital that matched base line characteristics using the generated propensity variables. The endpoints were a decline in eGFR of more than 30%, introduction of dialysis, and death. The logistic regression analysis was performed on the indicator of the presence or absence of tolvaptan. Survival analysis was analyzed by the Kaplan-Meier method and tested with log rank, generalized Wilcoxon, and Rarone-Ware. The software for the statistics was IBM® SPSS® Statistics ver. 24.

Results: A total of 106 patients received tolvaptan during the study period, including 52 who met the study criteria. The median age was 65 years, the mean duration of treatment was 533 days, and the dose was 8.16 mg/day. Of these, there were 15 cases of diabetes and 6 cases of nephrosis. The normal patient group matched to these cases was selected from 63209 cases. Tolvaptan was administered after hospitalization, with an 82.1% increase in urine output and a weight of -4.2% at discharge. The tolvaptan combination group had a significant prolongation of days to endpoint: control group (746.0, p=0.013; 95% CI 479-1012) vs Tolvaptan group (1076.3, 95% CI 761-1391).

Conclusions: Tolvaptan is expected to improve prognosis because of its ability to improve edema even in advanced CKD cases. Tolvaptan has been shown to improve edema in advanced CKD as well as inhibit the deterioration of renal function with long-term use.



PUB038

Serum Calcium Changes and Renal Function: A Dual Path Track

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Background: Although hypercalcemia is associated with an impairment of renal function, the literature is scarce in demonstrating this relationship in clinical practice. We hypothesized that fluctuations in serum total calcium (tCa) may impact renal function in patients with chronic kidney disease (CKD).

Methods: This is a retrospective study which enrolled 148 patients with at least 2 clinical appointments with concomitant tCa and estimated glomerular filtration rate (eGFR) measurement in the period between January-2017 and December-2019. We collected demographic, clinical, and biochemical data. Up to 3 consecutive measurements were analyzed.

Results: Patients were mostly Caucasian women, aging 66 ± 15 years. Mean eGFR was 45.1 ml/min/1.73m^2. Hyperparathyroidism (parathyroid hormone > 65pg/ml) was associated with a 2.8-fold increased risk for hypercalcemia (p=0.030). There was a non-linear relationship between change in tCa and change in eGFR, so that when tCa increased above the normal limit, there was a reduction in eGFR. Patients with hyperparathyroidism seem to present a significant lower risk of impairment in eGFR in the consecutive measurements when compared to other causes of hypercalcemia.

Conclusions: The development of hypercalcemia in patients with CKD is associated with a deterioration of renal function. Therefore, the strict control of serum calcium is advised in these patients.

PUB039

The Tri-POCUS Approach for Assessment of Volume Status in Critically Ill Patients with COVID-19

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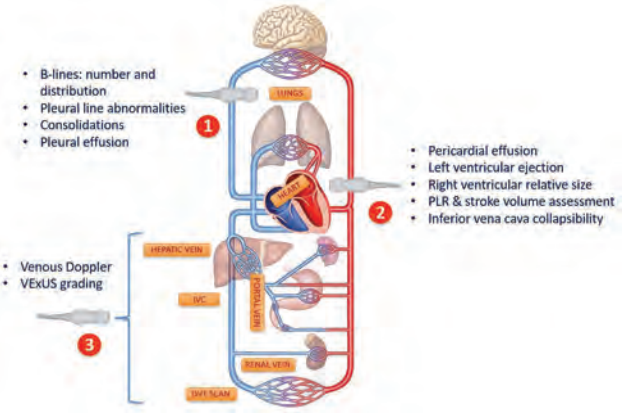
Background: The volume status of patients with coronavirus disease 2019 (COVID-19) is dynamic and can range from severe hypovolemia (on initial presentation) to overt hypervolemia (after fluid resuscitation) due to its distinct clinical features such as cytokine storm. While lung point-of-care ultrasound (POCUS) is established as an invaluable bedside tool in assessment of volume status of the critically-ill, its use in this setting is limited by expanding lung infiltrates and a tendency for acute respiratory distress syndrome (ARDS).

Methods: We developed a combinational bedside ultrasound program to overcome the limitations of the individual methods of POCUS and provide a more precise evaluation of the volume status in critically ill patients with COVID-19. The Tri-POCUS approach represents concurrent bedside assessment of the lungs, heart (focused cardiac ultrasound [FoCUS]), and the venous system (blood flow pattern in the hepatic, portal and intra-renal veins) (Figure-1).

Results: In patients with COVID-19, distinguishing ARDS from cardiogenic pulmonary edema by lung POCUS alone is challenging due to several overlapping features. FoCUS allows for both static measures of preload as well as dynamic assessment (e.g. volume responsiveness to passive leg raise maneuver). Evaluation of blood flow pattern in the hepatic, portal and intra-renal veins not only can gauge fluid status but it also allows for direct assessment of the congestive state in end organs hence monitoring response to therapy.

Conclusions: The Tri-POCUS program is an extension of our previously published work on focused renal POCUS curriculum. The components of this combinational approach have been selected based on their ability to cover the limitations of each individual method and provide a synergistic effect, especially in clinical settings such as COVID-19 where there is a tendency for rapidly changing volume status confounded by distracting features (e.g. expanding lung lesions).



PUB040

New-Onset Nephrotic Syndrome in a Child Associated with COVID-19 Infection

Siddharth A. Shah. *University of Louisville, Louisville, KY.*

Introduction: The COVID-19 outbreak has turned into worldwide public health emergency. The renal histo-pathological features of acute tubular necrosis or thrombotic microangiopathy are-reported in adults previously with severe COVID-19 infections. In children, the renal manifestations associated with COVID-19 infection are not widely reported. Here, we describe a case report of a child with new onset nephrotic syndrome associated with COVID-19 infection.

Case Description: 8-year-old boy with no previous significant medical history presented with bilateral eye and facial swelling soon after his parents were-diagnosed with COVID-19 infection. He had diarrhea but no fever or shortness of breath. One week after onset of swelling, the boy was also tested positive for COVID-19 infection. Based on clinical findings of significant proteinuria (Urine protein and creatinine ratio of 11.4), hypoalbuminemia (serum albumin of 2 g/dL) and hypercholesterolemia (Total Cholesterol of 384 mg/dL), he was diagnosed having nephrotic syndrome. He responded well to standard-dose prednisone treatment for nephrotic syndrome. In one week of starting prednisone treatment, he went into clinical remission. Lymphopenia continued to be present for 2 weeks after onset of symptoms. There were no complications related to clot formation or secondary infections with this presentation.

Discussion: This is the first case report to our knowledge of pediatric patient presenting with new-onset nephrotic syndrome associated with COVID-19 infection. Although, the burden of disease from COVID-19 is less severe in children, they can present with immune system related kidney disease like nephrotic syndrome. The patient responded well to standard-dose prednisone treatment used typically for new onset nephrotic syndrome.

PUB041

Recurrent Arteriovenous Graft Thrombosis in COVID-19

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Introduction: COVID-19 has been associated with increased risk of hypercoagulability. We report a case of COVID-19-associated coagulopathy leading to recurrent arteriovenous (AV) graft thrombosis in an end-stage renal dialysis (ESRD) patient.

Case Description: 84 yo African American female with ESRD on dialysis via lower extremity AV graft, diabetes and atrial fibrillation on warfarin who was diagnosed with COVID-19 came back again 1 week later and was admitted due to hypoxemia. COVID-19 PCR was again positive. INR was 1.4, D-dimer 3.28mcg/mL, platelet count 114K/mm^3, mildly prolonged PT, aPTT. She had elevated venous pressures during dialysis. Doppler suggested AV graft thrombosis. Heparin drip was started. Angiography and intravascular ultrasound (IVUS) showed thrombosed AV graft. (Figure 1a,1b) Thrombectomy was successful (Figure 1c,1d) with uneventful hemodialysis afterwards. She was discharged. Next day, she came back again with diarrhea. Coronavirus PCR was still positive. INR was 1.9. She again had high venous pressures. Doppler found recurrent thrombosis. Heparin drip was started. Vascular surgery placed dialysis catheter and held thrombectomy till her coronavirus PCR turns negative.

Discussion: Incidence of venous thromboembolism (VTE) can be as high as 58% in patients with COVID-19. All categories of 'Virchow's triad' are involved, endothelial injury (increased cytokines and complements), stasis (immobilization) and hypercoagulable state (changes in prothrombotic factors). Risk factors are males, obesity, heart disease, hypertension, diabetes and ESRD. High D-dimer, mildly prolonged PT, aPTT and thrombocytopenia are common. Full-dose anticoagulation is recommended for documented VTE.

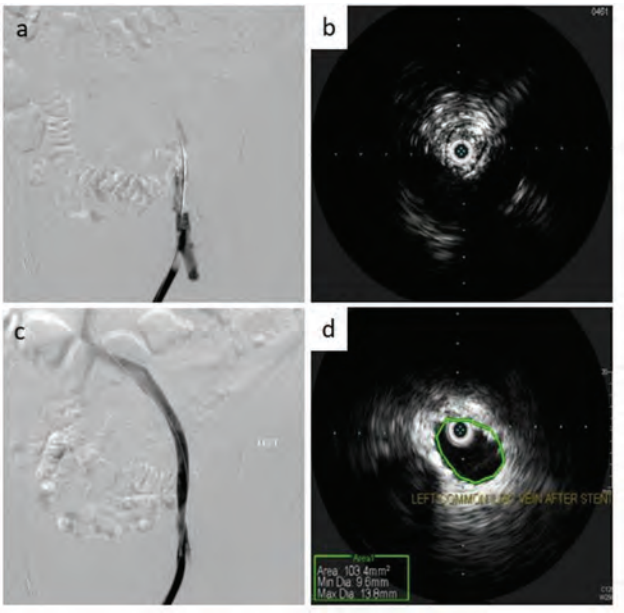

Figure 1 a, Angiography showing occlusion of graft; **b**, IVUS showing occluding thrombus; **c**, Angiography after successful thrombectomy; **d**, IVUS showing successful revascularization.

PUB042

Manage of a Peritoneal Dialysis Unit During the COVID-19 Pandemic

Ana T. Domingos, Roberto C. Marques, Anabela M. Guedes, Céu Laranjo, Idalécio Bernardo, Pedro L. Neves. *Centro Hospitalar do Algarve EPE, Faro, Portugal*.

Background: Peritoneal Dialysis (PD) patients are special, as they are mainly independent in a "life-support technique" but susceptible to various potential complications related. This pandemic brought new challenges and PD Units had to be reorganized considering their specific population, human and material resources. We aimed to understand the impact of our restructuration and discuss some lessons learned.

Methods: We retrospectively reviewed the activity and intercurrences at our Unit during the COVID-19 state of emergency declared by our Government, from 19th March to 2nd May (6 weeks), and compared it to the correspondent past two years (table 1). In a normal period, most of our patients are evaluated in a monthly basis. Simple descriptive and Student's paired T-test analysis were performed.

Results: We managed 34 patients in the correspondent period of 2018, 36 in 2019 and 38 in 2020. Clinical appointments in this 2020 period were realized by phone. Necessary dislocations to the Unit in 2020 included peritonitis, exit-site infections and catheter malfunctioning. No dropouts occurred. There were no positive cases of COVID-19. Student's paired T-test analysis between 2020 and 2019, plus 2020 and 2018, showed no statistically significant differences in every evaluated phenomenon (except for non-presential appointments; this discrepancy is justified by the Unit's dynamic, without clinical implications).

Conclusions: Despite the restructuring, we were able to provide more teleassistance and the mean of complications/hospital admissions weren't statically worse. Some activities were postponed, but its true impact isn't yet clear. Will suboptimal care bring long-term complications? Nonetheless, PD technique stands out for favorably, mainly if all the necessary support from medical and nurse staff is guarantee.

Activity and intercurrences at our PD Unit.

	2018 (N) MEAN ± SD	2019 (N) MEAN ± SD	2020 (N) MEAN ± SD
CLINICAL APPOINTMENTS	50 1.51±0.8	53 1.47±0.77	67 1.76±0.94
NECESSARY DISLOCATIONS TO THE UNIT	7 0.21±0.48	6 0.17±0.51	7 0.18±0.51
NON-PRESENTIAL APPOINTMENTS (material requisition)	12 0.36±0.55	10 0.28±0.57	42 1.11±0.73
HOSPITAL ADMISSION	3 0.09±0.29	2 0.06±0.23	3 0.08±0.27
PERITONITIS	1 0.03±0.17	3 0.08±0.28	3 0.08±0.27
EXIT-SITE INFECTION (ESI)	2 0.06±0.24	2 0.06±0.23	2 0.05±0.23
PERITONEAL EQUILIBRATION TEST (PET)	8 0.24±0.43	6 0.17±0.38	Postponed
CATHETER PLACEMENT	0	3	Operating rooms closed
NEW TRAINING/TRANSITION	1 patient	2 patients	Postponed

PUB043

Exploration on Renal Protective Compounds and COVID-19-Induced Renal Injuries Based on Network Pharmacology and Molecular Docking

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Background: The fullscreen of COVID-19 is getting revealed as some of the infected patients had developed severe renal complications. Natural compounds may have protective effects against COVID-19-induced renal injuries. The aim of this study is to explore the interactions and underlying mechanisms between active compounds and COVID-19-induced renal injuries.

Methods: The interaction network of 8 collected natural compounds (Hederagenin, β-sitosterol, Luteolin, Quercetin, Kaempferol, Jaranol, Formononetin and Calycosin) and COVID-19-related target proteins was established by using the pharmacological database. GO and KEGG pathways were also analyzed. Molecular docking was run by AutoDockTools and Discovery Studio.

Results: 259 target genes are potentially related to COVID-19, AKI and CKD. Active compounds may improve COVID-19-induced renal injuries by alleviating the inflammatory response, vascular abnormal changes, cell apoptosis and necrosis in kidneys. The docking results had indicated that 8 compounds may show great possibilities to interact with SARS-CoV-2 main protease 3CL and ACE2 by showing significant binding energy.

Conclusions: Our study may provide molecular evidence and support on compounds from herbal medicines or dietary supplements may serve as potential perspective drugs to protect kidneys from COVID-19-induced renal injuries.

Funding: Government Support - Non-U.S.

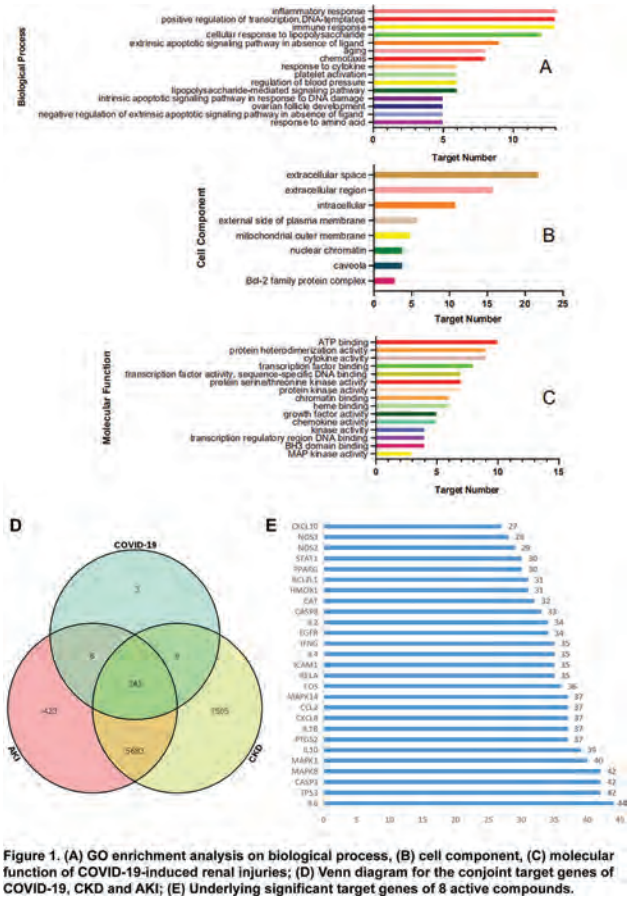


Figure 1. (A) GO enrichment analysis on biological process, (B) cell component, (C) molecular function of COVID-19-induced renal injuries; (D) Venn diagram for the conjoint target genes of COVID-19, CKD and AKI; (E) Underlying significant target genes of 8 active compounds.

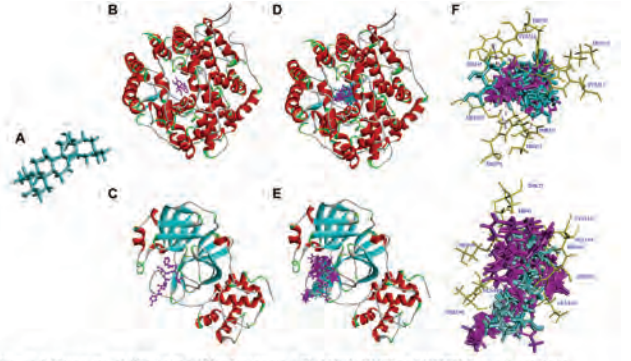


Figure 2. Diagrams of interaction of Hederagenin with ACE2 (1R42) and COVID-19 main protease 3CL (6LU7); (A) the 3D structure of Hederagenin in lake blue; (B) the human ACE2 crystal structure, an endogenous ligand in the active binding site of 1R42 was shown in dark pink; (C) the human COVID-19 main protease 3CL crystal structure, an endogenous ligand in the active binding site of 6LU7 was shown in dark pink; (D) the potential interactions between Hederagenin with human ACE2; (E) the potential interactions between Hederagenin with human COVID-19 main protease 3CL; (F) the π-π interactions and H-bonds of related amino acid in active binding site of Hederagenin in 1R42; (G) the π-π interactions and H-bonds of related amino acid in active binding site of Hederagenin in 6LU7.

PUB044

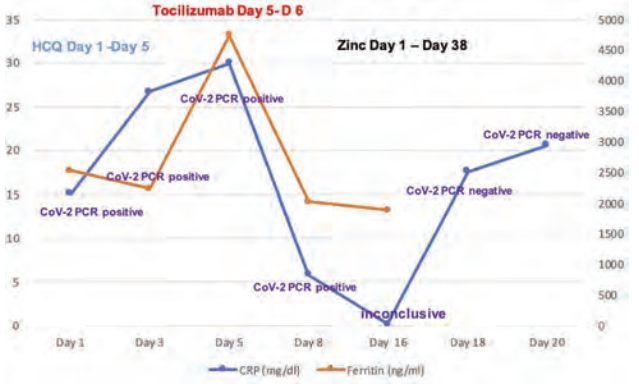
Complete Recovery from COVID-19 Infection in an ESRD Patient

Ravi K. Thimmisetty,[1] Zeenat Y. Bhat,[2] Noreen F. Rossi.[2] *[1]Nephrology Associates, Cape Girardeau, MO; [2]Wayne State University, Detroit, MI.*

Introduction: We report a hemodialysis case having both influenza and COVID-19 who presented without respiratory symptoms and recovered fully with treatment by Interleukin-6 (IL-6) inhibitor

Case Description: 68-year-old Caucasian woman with history of hypertension, diabetes mellitus, obesity, sleep apnea, atrial fibrillation, and ESRD on hemodialysis came to hospital with fever of 102°F. Her symptoms were fatigue, mental status changes, and decreased energy levels. There was no travel history and no contact with COVID positive or suspected COVID patients. On arrival to ER she had temperature of 99.4 f, bp 117/63, HR 102, RR 18, oxygen saturation of 99% on 2liters of oxygen. Examination revealed normal breathing sounds, no wheezing, and functional left forearm arteriovenous fistula. Rest of the exam was with in normal limits. Laboratory results showed sodium 138, potassium 5.7, chloride 96, bicarbonate 24, blood urea nitrogen 71, creatinine 13.5, C-reactive protein 15.06, ferritin 2532, She was positive for both influenza and SARS COV-2 PCR. Blood and urine cultures showed no growth. Imaging showed prominent interstitial vascular prominence; underlying pneumonia could not be excluded. Patient was admitted to COVID-19 isolation unit and empirically started on oseltamivir, Hydroxychloroquine, Zinc sulfate, vancomycin and, piperacillin-tazobactum for influenza, possible COVID and bacterial infection. Maintenance hemodialysis was resumed with challenging fluid removal because of pulmonary vascular congestion. She was positive for SARS COV-2 PCR on four subsequent tests. She developed progressive hypoxia. Oxygen requirements increased to 15 liters salter oxygen consistent with acute respiratory distress syndrome. Two doses of Tocilizumab (IL-6 inhibitor) were given. Patient improved significantly and discharged home with two SARS CoV-2 PCR negative results

Discussion: Our case is unique of having both influenza and COVID-19 infection and improved. More studies are warranted to evaluate clinical benefit of the above therapies



PUB045

AKI with Minimal Pulmonary Pathology in SARS-CoV2 Infection

Yasnowski Frank,[2] Rajeev Rohatgi.[1,2] *[1]Northport VA Medical Center, Northport, NY; [2]Stony Brook University Renaissance School of Medicine, Stony Brook, NY.*

Introduction: SARS-CoV2 transmission occurs through infection of the upper airway epithelial cells. Though many cases are asymptomatic or mild, a significant fraction require hospitalization that is associated with morbidity and mortality. Primarily a pulmonary illness causing hypoxia and an acute respiratory distress syndrome (ARDS), SARS-CoV2 is also associated with AKI and other life-threatening systemic disorders. Generally, AKI occurs late in the course of SARS-CoV2 infection after severe pulmonary manifestations.

Case Description: 49 year old African American male presented to the emergency department with 3-4 days of nausea and vomiting. He was diagnosed 10 days prior with SARS-CoV2. His past medical history is significant for pulmonary interstitial fibrosis, lupus nephritis diagnosed in 2017 with baseline serum creatinine of 3 mg/dL, and hypertension. His outpatient medications included lisinopril and hydroxychloquine. On admission his serum creatinine 28.9 mg/dL, blood urea nitrogen was 230 mg/dL, Na 133 meq/L, K 7.4 meq/L, Bicarb 11 meq/L, Cl 96 meq/L, and albumin 2.9 g/dL. His serum aldosterone 2.3 ng/dL, ACE 6 U/L, procalcitonin 1.29 ng/mL, and D-Dimer 2055. His urine dipstick showed 500mg /dL protein with moderate blood. On arterial blood gas, he had a compensated metabolic acidosis, a partial pressure of oxygen of 92.6 mm Hg on room air, and no respiratory distress. No hypotension was observed. CXR showed hazy patchy bilateral opacities, most pronounced in the lower lungs. A dialysis catheter was placed, and the patient dialyzed. The patient's pulse oximeter remained between 96-100% on room air, D-Dimer 2055-2613, and procalcitonin < 1.29 ng/mL during his 12 day hospitalization. He was discharged on TIW hemodialysis.

Discussion: AKI due to SARS-CoV2 usually occurs in the setting of severe pulmonary disease with hypoxemia and is likely related to multiple factors including hypotension, activation of coagulation and complement cascades, and cytokine storm. On the other hand, other evidence points to renal specific tropism due to abundance of TMPRSS2 and ACE2 in renal epithelia and autopsy findings of SARS-CoV2 nucleocapsid in renal epithelia. Though the case is confounded by (1) chronic kidney disease and (2) hydroxychloroquine use, this case illustrates pure kidney failure in a patient with minimal pulmonary disease and suggests a renal specific disease due to SARS-CoV2.

PUB046

Dialysis Care During the COVID-19 (C19) Pandemic: A Large Urban Academic Dialysis Center Experience

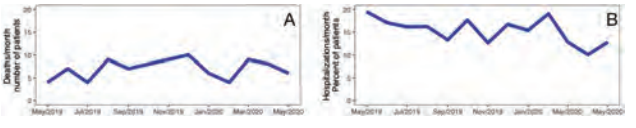
Jose E. Navarrete,[1] Kathy Oliver,[2] Tomiwa Ishmail,[2] Harold A. Franch,[1] Ibironke W. Apata.[1] *[1]Emory University School of Medicine, Atlanta, GA; [2]HSM dialysis services, Atlanta, GA.*

Background: Effective dialysis care during the C19 pandemic has required implemetation of new policies and procedures to ensure adequate care, to avoid contagion in dialysis centers and to minimize unnecesary expossure to medical personnel.

Methods: Emory dialysis program provides dialysis care for ~ 750 patients in 4 hemodialysis centers and 3 home dialysis locations in the metro Atlanta area. The first cases of C19 in Georgia were reported on March 2, 2020 and plans to contain the spreading of the disease were implemented in our dialysis units, including mask use, triaging of patients and personnel based on symptoms, telemedicine rounds, cohorting of C19+ patients in a single shift in a designated unit, and physical isolation of nursing home residents while receiving hemodialysis. This report describe the clinical outcomes related to these interventions.

Results: Until May 30/2020, 106 patients had been tested (14%). 22 patients were positive for C19 (2.9%) of which 20 were on HD and 2 on PD. Five C19+ patients died (mortality 23%). Patients that tested positive were older (65±13 vs 60±13y/o), mainly African-Americans (90%) with a higher BMI (29 vs 26), more likely to be diabetics (51% vs 44%) and to reside in a Nursing Home (20 vs 10%), with higher prevalence of cardiovascular disease (45 vs 30%). Dialysis-related parameters (albumin, hemoglobin, phophorus, PTH, Kt/V and blood pressure) were similar between those that tested positive vs negative. 4% (31 patients) of our entire dialysis population resides in Nursing Homes. 12 of them have been tested and 8 were C19+ (26%). The dialysis patients that expired were older (69 vs 57y), all were African-Americans and had higher BMI (30 vs 26) and time on dialysis (12.3 vs 5.6 y) than those that survived. We did not observe an increase frequency of hospitalizations or deaths compared to previous months (Figure 1).

Conclusions: In our dialysis population the incidence of C19 infection was 2.9% with 14% of patients tested. Mortality was 24%. Deceased patients were older, had a higher BMI and were on dialysis for longer time compared to those that survived. We did not observe an increase rate of hospitalizations or deaths during initial 3 months of the pandemic.



PUB047

A Case of Severe Rhabdomyolysis Associated with COVID-19 Infection Without AKI

Genta Uehara, Keisuke Okamoto, Tibor Fulop. Division of Nephrology *Medical University of South Carolina - College of Medicine, Charleston, SC.*

Introduction: We present a case of severe rhabdomyolysis associated with COVID-19 infection without acute kidney injury (AKI).

Case Description: A 43 year-old African American male with a history of medication-induced rhabdomyolysis 6 years ago, renal cell carcinoma status post partial right nephrectomy, hypertension, type 2 diabetes, and morbid obesity presented to emergency department with upper respiratory symptoms, myalgia and discoloration of urine for one week. He reported taking atorvastatin and diltiazem for a long time but has never

developed myalgia. There was no family history of myopathies, or binge alcohol intake beforehand. On physical examination, patient was hypertensive, euvolemic, and afebrile, with normal oxygenation. Chest x-ray showed subtle increased interstitial reticulation in the perihilar regions and COVID-19 rapid test returned positive. Laboratory data showed very high creatine kinase (CK) (208,456 U/L). Urinalysis showed trace proteinuria, large blood but only few red blood cells and confirmed myoglobinuria. However, his creatinine was normal (0.8 mg/dL), as well as serum calcium (8.4 mg/dL), phosphate (3.9 mg/dL), and uric acid (5.2mg/dL) levels. Patient was admitted for treatment of assumed severe rhabdomyolysis. COVID-19 was treated conservatively with oxygen supplementation. Atorvastatin and diltiazem were held, and normal saline and isotonic sodium bicarbonate fluids were administered. CK continued to rise with a peak of 499,020 U/L on day 3, but decreased steadily to 58,745 U/L on day 7. Renal function remained stable all the time during the treatment (serum Cr 0.68 – 0.82 mg/dL), with maintained urine output and well-preserved electrolytes and uric acid levels throughout.

Discussion: There are increasing number of reports of COVID-19-associated rhabdomyolysis, but risk factors and characteristics are fairly known. The clinical and laboratory manifestations are suggestive of COVID-19 associated rhabdomyolysis rather than statin-induced. We are not aware of any other reports documenting such extreme CK values – with a proper rise and fall of CK – without impacting renal function. As far as we know, this is the first case of COVID-19 associated rhabdomyolysis with peak CK of 499,020 U/L, without AKI and concurrent electrolyte abnormalities. The relationship to COVID-19 vs. individual genetic susceptibility remains to be explored.

PUB048

CKD Patients on Hemodialysis (HD) with COVID-19 Infection: Characteristics and Outcome

Suresh Sankarasubbaiyan, Mallikarjuna Gowda B. Gowda, Mohammad S. Husain, Satyanarayana R. Puvvada, Vikram A. Sonawane, Kaparaboina K. Kumar, Guruvulu Venkata, Kamal D. Shah. *Nephroplus, Hyderabad, India*.

Background: The COVID-19 pandemic has special significance for Chronic Kidney Disease patients on HD. Clinical characteristics and outcome from low resource settings are not well known

Methods: From March 15 2020 until May 20, 2020, quality managers reviewed all patients with confirmed COVID-19 infections in 200 HD centres among MHD patients. For patients with COVID-19 infections: age, gender, geographical zone, type of Insurance, continuity of care was noted, HD characteristics and outcome were reviewed. Comparison of median was done with Mann Whitney/Wilcoxon 2 sample test and proportion with Fisther exact test. All patients were transferred to public hospital for regulatory compliance limiting follow up of HD sessions.

Results: 39 out of 18402 patients developed COVID-19 infection. M: F: 28: 11, Age; 54.62 + 14.92 years. Geographically: East zone:3(7%), North:12(31%), South:5(12%), West:19(50%). Payers: self pay:19(49%), government insurance:15 (38%) and private Insurance:5(13%). 32(82%) hypertensives, 23(59%)diabetics. Outcome: 8(20%) expired, 18(46%) discharged, 12(31%) in hospital and 1 at home. Mean Hb (77%) : 9.81 ±1.71 g%, Adequacy (74%): 1.30 ± .44, Vascular access (72%): 75% permanent access, 7% temporary catheter, 18% tunneled catheter, Albumin (64%): 3.69 ±.31.

Conclusions: Maintenance HD patients have increased mortality as compared to reports in normal population and is associated with need for intensive care, steroid use and ventilatory support.

Comparison of survivors and non-survivors in maintenance HD patients with COVID-19 infection

	Survivors n = 31	Non-Survivors n= 8	p value
Age (yrs)	63	67	.06
M/F (%)	67.7/32.3	87.5/12.5	.39
DM(%)	58	62	1.0
Htn(%)	75	100	.30
Intensive care unit(%)	48	100	.01
Ventilator need (%)	3	97	.000
Antivirals Rx(%)	51	87	.10
Steroid Rx(%)	22.6	100	.001
Zonewise East North South West	 9.7 29 12.9 48.4	 0 37.5 12.5 50	
Length of stay (days)	14	8.5	.36

PUB049

Starvation-Induced Metabolic Acidosis in a COVID-19-Infected Pregnant Patient

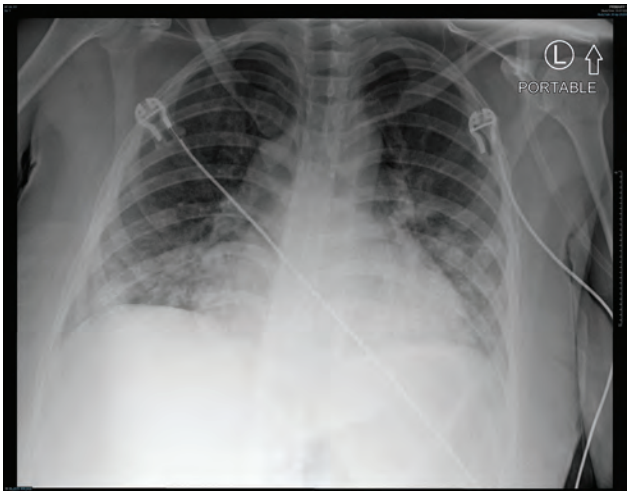
Muhammad R. Mustafa. *Stony Brook University, Stony Brook, NY*.

Introduction: Suffolk County in NY was hardest hit with COVID 19. We present a case of a pregnant female with COVID 19 infection and high anion gap acidosis.

Case Description: 34 yo female, 33 weeks twin pregnancy, a/w fever, SOB and polyuria. Her oral intake was poor. She was positive for COVID 19. Her T - 100 F,O2 sat 99% with O2 by NC at 2 L. She had bibasilar crackles. Both babies were moving. CXR showed multifocal pneumonia. Nephrology was consulted for metabolic acidosis. A diagnosis of starvation ketosis of pregnancy was made due to anion gap acidosis, high serum beta-hydroxybutyrate and ketonueia. Dextrose 5% with sodium bicarbonate was given. She had C section, remained intubated for 24 hours, recovered well and was discharged on hospital day 7.

Discussion: Almost 15% of pregnant patients develop server COVID 19, Pregnant patients with COVID infection are a higher risk group.

Test	Day 0	Day 4
Sodium	141	136
Potassium	3.7	3.9
Chloride	107	100
Bicarbonate	15	25
BUN	4	4
Cr	0.58	0.49
Anion gap	19	11
Beta Hydroxybutyrate	2.1	Normal
Urine ketones	Moderate	Negative
CRP	6.4	5.4
pH	7.38	7.40
pCO2	28	30
HCO3	16	19



PUB050

Slow Low-Efficiency Dialysis (SLED) Implementation During the COVID-19 Pandemic Surge

Richard L. Barnett, Kenar D. Jhaveri, Bessy Suyin Flores Chang, Azzour D. Hazzan, Shamir Hasan, Steven Fishbane, Mark A. Finger. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY*.

Background: The high rate of ARF in COVID-19 hospitalized patients increased the demand for critical care renal replacement therapy 2-3 fold at Northwell Health (NW). At the 2 largest hospitals, Long Island Jewish (LIJ) and North Shore University Hospital (NSUH), bedside HD was provided by HD RNs and continuous renal replacement therapy (CRRT) by critical care (CC) RNs. RN workload in these hypercatabolic patients soared as HD treatments more than doubled and CRRT increased from 9 to 30,. Shortages of CRRT fluid and filter sets ensued. SLED, a technique utilizing standard HD dialysate and filters, combined with a collaboratiive approach between CC and HD RNs was considered.

Methods: In late March, a cohort CC bedside HD program, was initiated. Based on this success, a leadership panel of CC/HD RN and Renal/CC MDs created a SLED project plan. Details were reviewed with stakeholders on Friday prior to the Tuesday "Go-Live." 3 patients previously treated with HD or CRRT via a Shiley catheter were selected as a pilot for three 6-8 hour sessions, Fresenius 2008T, Revaclear 300 filters with dialysate flow rate 300 cc/min and blood flow rate 200-300 cc/min were ordered. HD RN initiated treatments and available throughout, while clinical stability was monitored by CC RN.

Results: NSUH pilot involved 5 patients over 3 sessions. Suboptimal cohorting required remote tablet monitoring and frequent presence of several HD RNs. One patient was terminated in one session due to persistent hypotension. Clearances and UF goals were achieved throughout. A week later the LIJ pilot used the design and advantage of NSUH experience with a 3 bed "SLED Room" model. The same 3 patients participated in all 3 sessions supervised by a single HD RN with no discontinuation. CC RN satisfaction with SLED was ranked "high" at both sites and by LIJ HD RNs but "Spread SLED" rated only "fair" by NSUH HD RNs. Pilots were extended 10 days. During this period SLED was initiated at 2 other NH sites. Future SLED programs will be focused on NH hospitals lacking CRRT.

Conclusions: SLED is an efficient alternative to CC HD and CRRT. The challenges of effective cohorting in a pandemic surge relegate its role to a piece of a comprehensive renal critical care program. It imay be particularly valuable for hospitals lacking CRRT options.

PUB051

Kidney Transplantation in the United States During the Coronavirus Disease 2019 Pandemic: An Interrupted Time Series Analysis

Ekamol Tantisattamo,[1,2] Natnicha Leelaviwat,[3] Sakditad Saowapa,[3] Natchaya Polpichai,[4] Busara Songtanin,[5] Possawat Vutthikraivit,[6] Chawit Lopimpisuth.[5] *[1]Division of Nephrology, Hypertension and Kidney Transplantation, Department of Medicine, University of California Irvine School of Medicine, Orange, CA; [2]Multi-Organ Transplant Center, Section of Nephrology, Department of Internal Medicine, William Beaumont Hospital, Oakland University William Beaumont School of Medicine, Royal Oak, MI; [3]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [4]Faculty of Medicine Songklanagarin Hospital, Prince of Songkla University, Songkla, Thailand; [5]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [6]Phramongkutklao College of Medicine, Mahidol University, Bangkok, Thailand.*

Background: The number of kidney transplant (KT) in the United States (US) has decreased during COVID-19 pandemic; however, the magnitude of this impact is unclear.

Methods: A period from January 5 to April 18, 2020 was divided into pre- and post-COVID-19 periods by assigning March 1, 2020 as the first day of the post-COVID-19 outbreak in the US. The number of waitlist candidates (WLC) and new KT every 7 days were obtained from OPTN/SRTR. An interrupted time series analysis was performed to examine an incidence rate ratio (IRR) between pre- and post-COVID-19 period by using multiple Poisson regression.

Results: Compared to pre-COVID-19 period, the average number of new KT during post-COVID-19 period decreased (479±33 vs 318±119 cases/week, mean difference±SEM 161±44, 95%CI 67, 255). The number of WLC was relatively stable (mean±SD 65,937±959 cases/week); whereas, it decreased during post-COVID-19 period (61,759±2203 cases/week). Mean incidence rates (IR) of new KT during pre- and post-COVID-19 periods were 727±58 and 511±176 cases/10^5 WLC-week, respectively (Figure1). The IR of new KT during post-COVID-19 period was 29% lower than those during pre-COVID-19 period(IRR 0.71, 95%CI 1.96, 2.11) and each one additional week was associated with a 4% decrease in the new KT (IRR 0.96, 95%CI 2.60, 2.63). After adjusted by age group, transplant areas, and time-study period interaction term, the IR of new KT was 3% increase for every one more week during pre-COVID-19 period (IRR 1.03); whereas, there were 12% decrease for every one more week after March 1, 2020(IRR 0.88). Compared to pre-COVID-19 period, the IR of new KT during post-COVID-19 period was 9% lower for every additional week for each corresponding period (IRR 0.91).

Conclusions: COVID-19 outbreak in the US since March 2020 is an independent factor of a significant decline in the number of new KT. Further information regarding ability of control COVID-19 may direct KT.

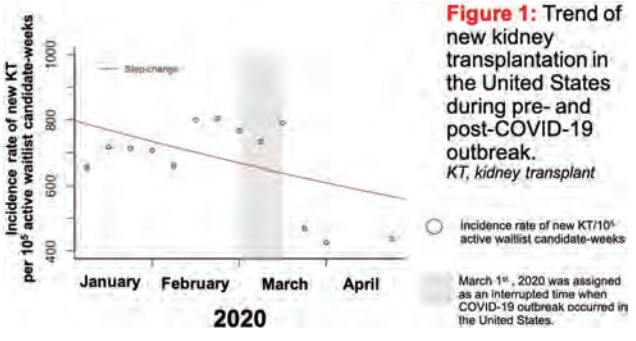


Figure 1: Trend of new kidney transplantation in the United States during pre- and post-COVID-19 outbreak.
KT, kidney transplant

PUB052

Spectrum of AKI in Patients with COVID-19 Infection

Irtiza Hasan, Vishal Jaikaransingh, Abdalagani A. Abakar Baher, Jose S. Reyes Oliva, Charles W. Heilig. *University of Florida College of Medicine - Jacksonville, Jacksonville, FL.*

Introduction: With the gradual unfolding of the full spectrum of COVID19 manifestations, Acute Kidney Injury (AKI) is emerging as a frequent association & a predictor of disease severity & mortality. We present 3 cases of AKI in COVID19 patients & illustrate the clinical course, management & outcome.

Case Description: The first case was a 50-yr old male with DM, HTN, & obesity, admitted with pneumonia, dyspnea & diarrhea, developed hypotension, arrhythmia, & required intubation on day 31 of admission. The next case was a hypertensive, obese 57-year old female, admitted with pneumonia, worsening dyspnea & respiratory failure without hypotension, was intubated on day 30 of admission. Both of the cases developed AKI with oliguria & progressed to anuria 24 hrs post-intubation. Case 3 was a 72-year old female with hypothyroidism admitted with pneumonia, dyspnea, diarrhea, & AKI, was intubated on day 12. All cases had bilateral pneumonia on chest radiograph & significantly raised inflammatory markers (CRP, LDH, Procalcitonin, Ferritin, ALT/AST, d-Dimer, & INR). Peak S. Creat. was 4.1, 6.6, & 3.07 for cases 1, 2, & 3 respectively. Urinalysis for all cases revealed proteinuria, hematuria, plus 4+ budding yeast & signs of UTI for cases 1 & 2. Ultrasound revealed structurally normal kidneys for all cases. Case 1 & 2 were diagnosed as stage III AKI & Case 3 with stage II AKI. All cases received some form of antibiotics, hydroxychloroquine, & heparin for COVID19 and CVVHD for renal support & later iHD for case 2. Glomerulonephritis specific workup could not be done due to the patient's clinical status. Among the cases, case 2 made full recovery & discharged, case 1 was stable but hospitalized, case 3 expired on day 14 of hospitalization due to multiorgan failure.

Discussion: Our cases highlight the inherent variability in causation & clinical course for AKI in COVID19. Interestingly, all 3 cases had the full spectrum of kidney involvement from proteinuria, hematuria to AKI. Although difficult to discern in the absence of biopsy, some potential causes of AKI in these patients include ischemia (respiratory failure, hypotension) (cases1 & 2), cytokine storm syndrome (case 3), or direct COVID19 induced acute tubular injury. Increased vigilance is required to recognize probable causes for AKI and to develop adequate management protocols to limit AKI–related morbidity or mortality.

PUB053

COVID-19 Infection in Renal Transplant Patients

Azm U. Hussain, Kashif Eqbal, Rafeea Shah, Mary Dutton, Miriam Berry. *University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: The SARS CoV-2 pandemic has disproportionately affected vulnerable patient populations including kidney transplant recipients (KTR).

Methods: Our transplant centre covers a large multi-ethnic urban population with high rates of co-morbidity and social deprivation, and provides follow-up care for approximately 1500 kidney transplant recipients. In line with national guidance, COVID-19 testing was largely restricted to those patients presenting to secondary care. Where COVID-19 was confirmed or suspected, anti-proliferative drugs were stopped, maintenance corticosteroids increased, and calcineurin inhibitor was stopped in patients requiring admission. We performed a retrospective analysis of clinical presentations and outcomes in kidney transplant recipients with confirmed COVID-19 between 20th March and 10th May 2020.

Results: 25 patients (approximately 1.6%) had confirmed COVID-19. 11 (44%) were female and 14 (56%) male. The median age was 61 years (range 33 – 84 years). 11 (44%) were White - British, 12 (48%) Asian and 2 (8%) Afro-Caribbean. Median time post-transplant was 84 months (range 6 – 360), and more recently transplanted patients were not at increased risk. Respiratory symptoms were the predominant presenting complaint in 19 patients (76%) followed by GI symptoms in 4 (16%). Acute kidney injury (stages 1-3) occurred in 15 patients (60%) with 7 patients (28% of whole population 46% of patients with AKI) requiring renal replacement therapy. 6 patients (40%) recovered renal function at a median follow up period of 26 days (range 10 - 51). 4 (16%) were admitted to ITU for ventilation. 10 patients (40%) died (although one death was not related to COVID-19). Among the patients who died, median age was 65 years and 6 (60%) were male with ethnicity proportionate to the study population.

Conclusions: The strategy of performing COVID-19 testing only in patients requiring secondary care likely i) underestimates the incidence and ii) overestimates the disease severity. However, our data show that COVID-19 confers significant morbidity and mortality in kidney transplant recipients despite prompt reduction of immunosuppression. These data will inform a revised consent process for those patients awaiting kidney transplantation. Follow up studies are required to assess longer term outcomes, and potential complications in KTRs who have recovered from COVID-19.

PUB054

COVID-19 Induces a Wasting Syndrome in Hemodialysis Outpatients: Outcomes in Rochester, New York

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Background: COVID-19 (COV) has infected 2852 residents of Monroe County with a death toll of 218 to date. Hemodialysis (HD) patients (pts) are at high risk for developing COV due to multiple comorbidities. Many patients also reside in Skilled Nursing Facilities (SNF) which have high infection rates. One single Fresenius Medical Care (FMC) dialysis facility in the Rochester, NY area with no Tues/Thurs/Sat (TTS) shifts became the designated unit to provide maintenance HD for all COV positive (+) pts in our region until they had 2 negative COV tests. This is a quality improvement review of our patients.

Methods: The study included all 18 pts thus far who received at least one HD treatment in our COV + unit. Demographics and labs ~ 2 months prior to their first COV + test and during the first month in our COV unit were analyzed and compared with data from the 33 COV negative (-) Mon/Wed/Fri (MWF) patients in the same facility. Paired and unpaired T tests were used to determine the statistical significance of observed differences in weight (wt) and labs pre and post COV+ and between COV + and - pts.

Results: Of our 18 pts, 50% were African American and 50% Caucasian American. Mean age 67, BMI 29.2. 50% resided in SNF prior to COV. All had ESRD. 3 initiated HD in the last 2 months. 8 pts were on HD ≤ 1 yr. 11 were hospitalized, 3 were intubated and 2 died. 78% had DM. Compared to 2 months prior to COV + testing, pts lost a mean wt of 8.6 (± 1.8) kg in the first month in our COV + unit (p= 0.0002). Albumin decreased from 3.75 (± 0.60) to 3.33 (± 0.54) (p= 0.0005) and ferritin rose from 753 (± 512) to 1526 (± 1147) (p = 0.0019). Potassium and Phos did not change. COV - pts lost no wt. Ferritin was higher in COV+ pts (1526 vs 993, p = 0.026). Mean time to first neg COV test was 26 days (range 13 - 55). Importantly, no MWF pts or any staff became COV + during the 2 months of caring for COV+ TTS pts.

Conclusions: While respiratory symptoms of COV are often stressed we noted few symptoms other than anorexia and substantial wt loss in the 89% of pts that survived COV. This was associated with a significant decrease in albumin and increase in Ferritin consistent with inflammation and malnutrition. On average it took ~ 4 weeks for pts to test negative once infected. With good infection control practice and PPE, nurses and COVID - pts remained free of COVID in our facility.

PUB055

AKI in Hospitalized Patients with COVID-19: A Mexican Population

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Background: Although severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection is primarily a respiratory disease, other organs are also affected. Several pathological studies confirm that SARS-CoV-2 invades kidney tissue causing endothelial damage, glomerular and vascular changes, extensive acute tubular injury and podocyte viral infection. AKI in COVID-19 appears to be frequent, with an AKI incidence of up to 46%, and a 20% requirement for renal replacement therapy (RRT). Patients with AKI show a trend towards worse outcomes and increased mortality. Information on Latin-American population is scarce.

Methods: We created a cohort to describe the incidence, risk factors, and outcomes associated with AKI in hospitalized patients with COVID-19 in Mexico City, excluding patients with a known chronic kidney disease. AKI was defined and classified according to KDIGO guidelines.

Results: We included 127 patients. 11 patients (8.66%) met the criteria for severe COVID-19, and were more likely to have AKI (81.82% vs. 54.31%, p=0.078). Of the 72 (56.69%) patients that had AKI, 48% were diagnosed at the time of admission. Patients with AKI were more likely to be men (61.7% vs. 42.42%, p=0.043) and older (55.68 years vs. 48.89 years, 0.018). With regards disease severity, 72% of them had a grade 1 AKI. 7 patients (9.72%) had grade 3 AKI, 4 of which needed renal replacement therapy. Overall length of stay was longer in patients with AKI (12 days vs. 7 days, p=0.003). A nonsignificant trend towards stay in critical care units was observed. 3 out of 127 patients died, all 3 had AKI.

Conclusions: Amongst our studied population, AKI was associated with a longer length of stay and with a trend towards a more use of critical care services. The lack of association of AKI with mortality could be due to the low overall in-hospital mortality of COVID-19 patients (2.40%).

PUB056

AKI Lingering in a Patient with Novel Coronavirus

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Introduction: Renal manifestations of the novel Coronavirus infection has been reported during the actual pandemic. While the renal injury was more pronounced in critically ill patients, the levels of AKI, proteinuria and hematuria predicted the severity of the infection. We are reporting a severe case of AKI and proteinuria with SARS-CoV- 2 infection out of proportion of its clinical manifestation.

Case Description: This is a 55 year old African American male patient with PMH of hypertension, aortic valve replacement on Warfarin anticoagulation and CKDIII-b with baseline eGFR of 50 ml/min/1.73m2 (creatinine of 1.5 mg/dL) and recent diagnosis of COVID-19 related gastroenteritis 10 days prior to presentation, was admitted with general malaise and decreased intake. He had no cardiac nor respiratory symptoms. He was afebrile and physical examination was non remarkable. His labs were significant for BUN level of 129 mg/dL and creatinine of 22.0 mg/dL. His blood glucose was 88 mg/dL. Urinalysis showed glucose 100 mg/dL, 0-3 RBCs, 3-10 WBC with a protein/creatinine ratio of 12.8 g/g. His renal ultrasound showed increased cortical echogenicity with edema. His serological workup was unrevealing with negative hepatitis B and C testing, low ASO levels, negative ANA, Anti-PR3, Anti-MPO and Anti-GBM antibodies. He had normal C3, C4 and negative serum immunofixation with free Kappa/lambda ratio of 1.7. His Alb was 1.7g/dL with triglycerides levels of 184 mg/dL. A kidney biopsy was deferred for its high complication risk. Repeatedly, the patient tested positive for SARS-CoV-2 on reverse transcription polymerase chain reaction assay with a nasopharyngeal swab. During the hospital stay, the patient was non-oliguric and afebrile and was treated with supportive medical care. On day 8 of hospitalization, his labs showed creatinine of 14 mg/dL and BUN of 99 mg/dL with persistent proteinuria estimated at 14 g/g. At present, he continues to asymptomatic and is being monitored outpatient for his kidney recovery.

Discussion: Variable histopathological lesions (FSGS, collapsing glomerulopathy, podocytopathy and tubular interstitial disease) has been described in the renal manifestations of the novel coronavirus. While its physiopathological mechanisms remain unclear, the severity of proteinuria and renal injury observed in this clinically asymptomatic patient highlight an unusual infection-driven mechanism.

PUB057

Patients with COVID-19 and Kidney Disease: Who Fared Best?

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Background: COVID-19 poses the greatest global challenge in modern day healthcare. Chronic Kidney Disease (CKD) patients are classed as 'high risk' in terms of the morbidity and mortality associated with COVID-19. We present data from a large centre encompassing a 24-bed inpatient renal ward, 2 in-centre haemodialysis (HD) units and a large ITU. We aim to compare and contrast clinical outcomes for COVID-19 patients with renal disease.

Methods: Observational analysis was performed on 61 patients (mean age 65y), all positive for COVID-19. Patients were stratified according to their renal status at the point of contracting the virus (table 1).

Results: Acute Kidney Injury (AKI) (n=24; mean age 67y) – 23 of 24 patients were intubated and ventilated in ITU. 18 died. 4 remain on haemofiltration (1 patient transferred for Extracorporeal Membrane Oxygenation). Only 1 patient required no ventilatory support and survived with resolution of the AKI. 1 patient requiring invasive ventilation survived with recovery of renal function. **Chronic HD (n=20; mean age 60y)** – 20 prevalent adult HD patients tested positive for COVID-19. 10 recovered and remain on HD. 10 died. **Kidney Transplant Recipients (KTR) (n=4; mean age 59y)** – 3 were managed as outpatients and have recovered with functioning grafts. 1 died. **Peritoneal Dialysis (PD) (n=2; mean age 68y)** – 1 was managed as an outpatient and has made a good respiratory recovery. 1 patient died. **CKD (without renal replacement therapy (RRT)) (n=11; mean age 72y)** - 11 patients with pre-existing CKD (stages 3-5) contracted COVID-19. 5 made a recovery with no progression to RRT. 2 died without RRT. 2 received acute HD and subsequently died. 1 remains on acute HD and 1 has progressed to chronic HD.

Conclusions: AKI patients had the poorest outcomes in terms of need for ventilatory support and mortality. 50% of chronic HD patients with COVID-19 died. Despite immunosuppressants, only 4 KTRs (total cohort of 352) contracted COVID-19. The introduction of virtual transplant clinics, minimisation of face-to-face contact and effective shielding may have influenced this. These data aim to reinforce the international collaborative against this global pandemic.

Table 1: Outcomes for people with kidney disease infected with COVID-19

At time of COVID-19 diagnosis			Outcome (post treatment for COVID-19)										
Status	n	Mean age (years)	CKD without RRT	Functioning transplant	Chronic HD	PD	Acute HD		Filtered (CVVHD/CVVHF)			AKI-not filtered	Died
							Ongoing HD	Died	Recovered function	Died	Ongoing	Recovered function	
AKI	24	67	0	0	0	0	0	0	1	18	4	1	0
Transplant	4	59	0	3	0	0	0	0	0	0	0	0	1
CKD without RRT	11	72	5	0	1	0	1	2	0	0	0	0	2
Chronic HD	20	60	0	0	10	0	0	0	0	0	0	0	10
PD	2	68	0	0	0	1	0	0	0	0	0	0	1
Total	61	65	5	3	11	1	1	2	1	18	4	1	14

PUB058

COVID-19: Angiotensin Receptor Blocker to the Rescue?

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Background: An unusual suspect has been incriminated in the Coronavirus outbreak, Renin-angiotensin-aldosterone system (RAAS). RAAS is an intriguing system that holds many mysteries that are still waiting to be unraveled and explored.

Methods: Angiotensin-II (Ang II) is well known for its proliferative and vasocontrictive effects and we have been using ACE1 inhibitors (ACEI) to prevent Ang II formation and angiotensin receptor blockers (ARB) for inhibition of Ang II receptor binding. Angiotensin 1-7 (Ang 1-7) along with ACE2, in the other hand, proven to have vasodilatory, antiproliferative and overall protective effects. Given the beneficial effects of ACE2 and Ang 1-7, it would make sense to potentiate this pathway for our sake, especially in the setting of lung injury.

Results: In the recent years, it's been shown that Coronavirus is not only using the ACE2 to enter the cell, but also decreasing ACE2 expression at the same time. This is detrimental. ACE2 expression seems to be decreased in elderly and elevated in obese. It is very interesting to see that COVID severity varied among these individuals, likely due to the precarious balance between the amount of viral entry and activity of ACE2/ Ang 1-7. If we can upregulate the expression of ACE2 by some mechanism, this would in turn increase the production of beneficial Ang 1-7. But with upregulated ACE2, one must make sure that there is a competitive substrate for ACE2, in order to make the Coronavirus binding of ACE2 difficult. A suitable candidate for that substrate, is Ang II. ARB, as opposed to ACEI, would seem to increase the levels of Ang II, while upregulating the expression of ACE2. Theoretically, we can reap the benefits of enhanced ACE2 expression while competitively inhibiting Coronavirus binding to ACE2, by the increased levels of Ang II. Titrating up ARB dosing as tolerated by the patient, will be necessary for the above mechanism to work effectively.

Conclusions: Individual variability in expressing ACE2 and Ang 1-7 receptor binding, will determine the degree of benefit of ARBs in diminishing Coronavirus infectivity and severity. Tolerability to ARBs, will also be a limiting factor when treating the patients. Studying ACE2 levels, Ang 1-7/Mas receptor activity in different patient populations and the correlation between Coronavirus infection and severity, would be of great value in the outbreak and provide more insights into the world of RAAS.

PUB059

COVID-19 Financial Ramifications on the Pediatric Nephrology Workforce

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Background: The adverse impact of the COVID-19 pandemic on state and federal budgets, coupled with widespread lockdown measures, and reduced non-COVID-19 clinical volume has forced healthcare and academic organizations to adapt to declining revenues. We examined the financial ramifications of the pandemic on the pediatric nephrology workforce.

Methods: Online survey distributed to active members of the American Society of Pediatric Nephrology (n=897) over 2 weeks in May 2020.

Results: Response rate was 16% (n=144). Most respondents (34%) were 35-44 years old, followed by 45-54 years old (24%). Most were White (65%) followed by Asians (24%). Respondents resided in the South (31%) followed by the Northeast (29%) and Midwest (22%). Most were faculty (92%) in early career stage (Assistant Professor, 31%), affiliated with a free-standing children's hospital (55%) or a children's hospital within an adult hospital (36%), working full time (79%) with an average of 60% effort dedicated to clinical activities. Most acknowledged feeling worried about the long-term financial ramifications of COVID-19 on their employer (88%) and their own financial future (75%). **Figure 1** summarizes the financial repercussions reported. The majority (47%) were unclear whether they will be expected to assume increased clinical duties once stay-at-home orders are lifted, however, 44% reported new childcare or eldercare responsibilities.

Conclusions: Overwhelming concern regarding employee and employer financial security exists among practicing pediatric nephrologists in the context of the COVID-19 pandemic. Uncertainty, institutional hiring freezes, compensation reduction, and increased duties in one's personal life all pose additional threats to a specialty with an already looming workforce shortage. Comprehensive strategies to prevent attrition and burnout are required to sustain the pediatric nephrology workforce during recovery from the COVID-19 pandemic.

Figure 1. Financial repercussions reported by U.S. pediatric nephrologists as a consequence of COVID-19 pandemic

PUB060

Not All Coronvirus a Patients Are Dying from Broncho-Pneumonia: Most Might Be Dying from Cerebro-Neurologic-Vascular Diseases and Cardiovascular Complications

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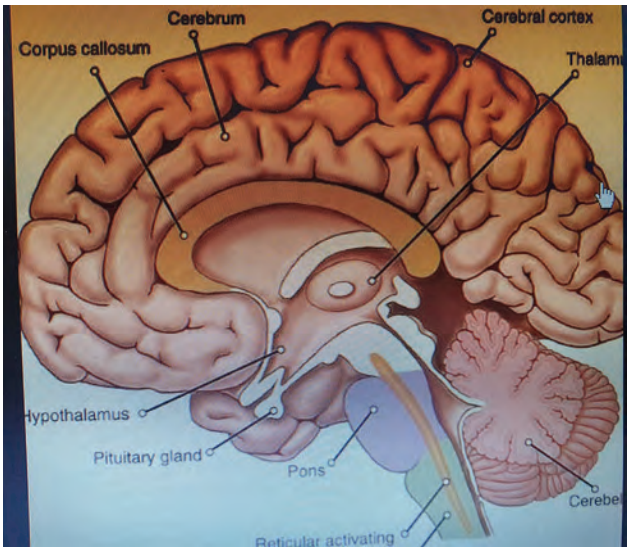
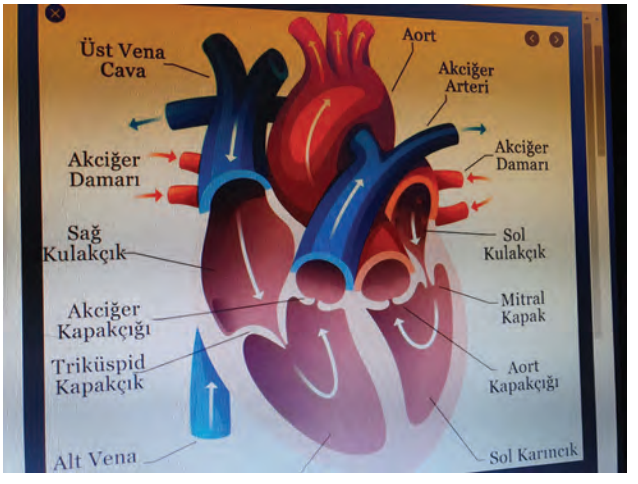
Introduction: Acute bronchopneumonia is not sufficient to explain deaths. Lungs, brain-nerves - hearth- cardiovascular system might be playing for key roles. Three are playing togethers. In last days, lungs and brain and heart suddenly are stopping.

Case Description: Key places are neurological conjunction systems between **brain, lungs and cardiological systems. All o**rgans are being regulated by last two systems. All mentioned activities are being regulated in those systems. All decisions and functions of human are giving there

Discussion: A neurologist and a cardiologist must be involved in treatment in late stages. This is vital. 1-Pulmonologists are following lungs. 2-Pulmonary-toracal surgeons shoul think two sided bronchial tubes from outside. 3-Cardiologist must follow EKG continiously. Echocardiography must be performed every day..They must know well inside of hearth and must question which drugs are taking. 4-Neurologists must perform MRG for **brain**, **back lower brain** and should make EEG, every day. AFFECTION-REACTION-EFFECTING-INFORMING BACK rules must be controlled. They must detect nerotransmission system is **from top to bottom** as I have written above like so called **zig-zag-zig system** or **reverse neutransmission system is occuring as zag-zig-zig system** to destroy body. If it is so this strange system can be called from now on '' **SAGLIKER'S REVERSE NEUROLOGICAL WORKING SYSTEM.".**





PUB061

A Case of Novel Coronavirus Disease 19 in a Chronic Hemodialysis Patient with Severe Cardiovascular Disease

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Introduction: Patients on maintenance hemodialysis (MHD) are vulnerable to COVID-19. MHD individuals are usually old with chronic comorbidities while these features are all risk factors of poor prognosis.

Case Description: Our patient was a 79-year-old female with ESRD and had been on MHD for 12 years in Wuhan. She had a history of severe coronary heart disease. The patient firstly reported fever, chest tightness and cough. One week later, she developed diarrhea and the chest CT indicated "viral pneumonia". Her COVID-19 testing was reported positive, and she was admitted to the hospital with SpO2 of 92% and high level of hs-CRP, cardiac troponin I (TNI) and creatine kinase MB isoenzyme. She was prescribed oxygen therapy, methylprednisolone, intravenous immunoglobulin, prophylactic anticoagulation and CRRT therapy. Her respiratory condition improved gradually and COVID-19 testing showed negative. However, on admission day 19, the patient presented psychiatric symptom, and was considered as secondary higher-level cognitive impairment since she received regular CRRT therapy without using drugs which could cause mental disorders. Two days later, her chest X-ray showed lung infection advanced with increased hs-CRP and PCT indicating bacterial infection. We prescribed meropenem and vancomycin. Meanwhile, there was an increasing trend of TNI, and electrocardiogram indicated acute coronary syndrome (ACS). Clopidogrel, aspirin and atorvastatin were prescribed immediately. Unfortunately, on admission day 22, the patient suffered cardiac arrest and was declared dead after active rescue. The cause of death was considered as cardiogenic shock and ACS.

Discussion: To our experience, personalized immunomodulation therapies against "cytokine storm" including steroid, intravenous immunoglobulin and CRRT might play

important role in treating severe COVID-19 patients with MHD. Cardiovascular disease is the leading cause of death in ESRD patients. The cardiovascular events of this patient might be combined with COVID-19 associated heart injury and worsen of pre-existing CHD. We suggested lack of family support during quarantine might be a reason of psychiatric symptom. In conclusion, personalized immunomodulation therapies might be helpful in treating severe COVID-19 patients with MHD. Cardiovascular events were associated with poor outcome.

PUB062

Clinical Presentation of Hemodialysis Patients with COVID-19: A Single-Center Study with 18 Patients

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Background: SARS-CoV-2 has affected every nation around the world. The 1st case in the Dominican Republic was reported in early March, with the most affected being the elderly and patients with comorbidities like cardiovascular diseases. Most hemodialysis patients share these comorbidities, in addition to a weaker immune system and health care facility exposure, it is thought to be a vulnerable population. The aim is to describe the clinical manifestation, main laboratory abnormalities, imaging findings at the moment of presentation, and the clinical course of patients on hemodialysis diagnosed with COVID-19

Methods: Exploratory study on 18 dialysis patients with Covid-19 in a renal replacement therapy facility. Demographics, symptoms, laboratories, CTscan, hospital course, ventilation requirement, treatment and complications were described

Results: With a population of 204 patients, 18 were diagnosed with Covid-19 in the first 2 months of the outbreak in our facility. 77.8% were males, mean age was 60 years, and 44% had known contact with infected people outside the facility. All patients had cardiovascular disease and 12 had diabetes. Cough was the most common manifestation 77.8%, dyspnea 66.7%, fever 55.6%, and malaise 44.4%, among others manifestations. Oxygen therapy was required in 66.7%, with 11.1% needing mechanical ventilation. All presented abnormal CTscan findings, 60% with a COVID-RADS grade 3. Three patients were positive and asymptomatic on a round RT-PCR test taken for all facility patients, 2 of them with CTscan graded COVID-RADS 3. Only symptomatic patients were admitted, 3 were directly admitted to the ICU, and 2 were later transferred from inpatient floor to ICU. The mean duration of hospitalization was 11 days and just 1 lethal outcome. At the moment of admission, 22.2% presented negative results on RT-PCR but had clinical and imaging findings consistent with Covid-19, with serologic conversion later

Conclusions: Even with the increased risk of exposure, comorbidities, and a weaker immune system, these didn't necessarily determine a higher probability of infection. We have found a high incidence of respiratory symptoms, in contrast to other case reports. Asymptomatic cases had imaging with COVID-RADS grade 3, this made us consider that the COVID-RADS grade on CT scan its a helpful tool for diagnosis of Covid-19

PUB063

Pink Urine in a Patient with COVID-19

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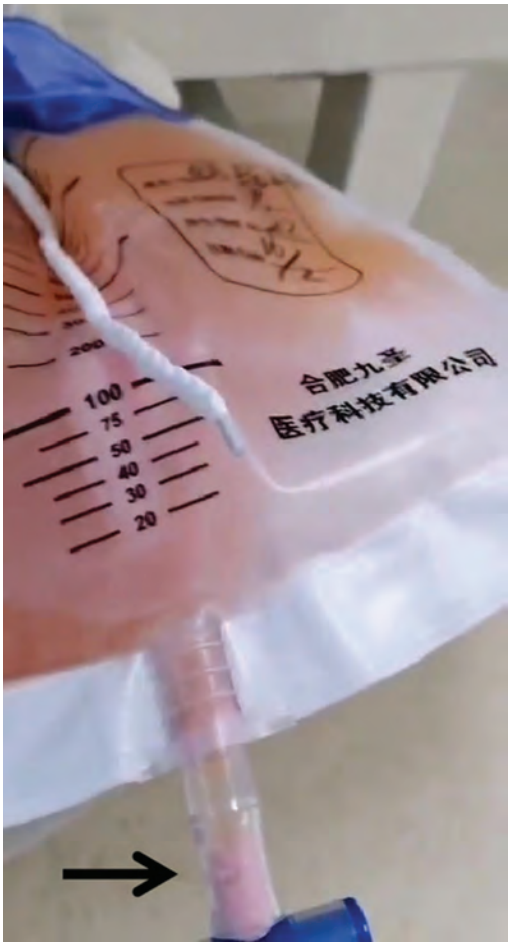
Introduction: Pink urine syndrome has been reported as a rare symptom described after surgery and propofol anesthesia. COVID-19 is not only manifested as a respiratory disease characterized by viral pneumonia, but also damage such as kidney, heart, blood and nervous system especially in severely ill patients.

Case Description: A 56-year-old man was diagnosed as severe COVID-19. He was admitted to ICU and underwent the tracheal intubation. During this treatment, propofol was used to sedate. He suddenly excreted cloudy pink urine on that day (Figure 1). There were some pink crystals in the urine bag and pink sediment at the bottom of the urine bag (Figure 2, Figure 3). His urine dipstick showed a specific gravity of 1.02, pH 5.5, blood (1+) and protein (1+). He had no urinary tract symptoms and his urine cultures were normal. His blood gas analysis showed pH was 7.3. His colour of urine gradually returned to normal when the patient was given intravenous Sodium bicarbonate injection.

Discussion: Pink urine syndrome is a phenomenon in which uric acid precipitates into the urine due to reduced urinary pH. Propofol can increase the excretion of uric acid in the urine. Lower urine pH will reduce the solubility of uric acid, promoting the formation of amorphous uric acid crystals, which exhibit a characteristic pink color. At the same time, metabolic acidosis may aggravate this phenomenon. COVID-19 has been reported to invade cells mainly through ACE2 receptors. ACE2 receptor is strongly expressed in the proximal tubule of the kidney, causing acute tubular necrosis. It has suggested that the kidney is one of the main targets of COVID-19. While considering the pink urine syndrome might caused by propofol, we speculate that COVID-19 could damage the renal tubule which affect its reabsorption of uric acid, which may worsen the uric acid crystallinity.



Pink urine deposits observed.

PUB064

Telemedicine in the Care of Kidney Transplant Recipients with COVID-19

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Introduction: Kidney transplant (KT) recipients with COVID-19 symptoms are bringing challenges to providers given the risk of COVID-19 exposure to health care workers, patients, and the public.

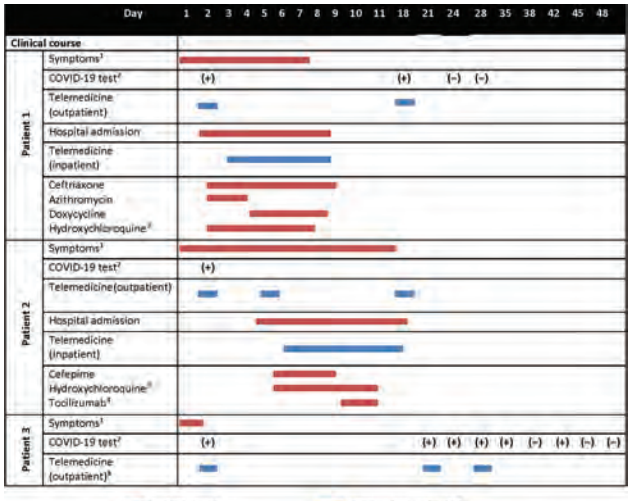
Case Description: Three KT recipients with COVID-19 were managed using telemedicine via synchronous video visits integrated with an electronic medical records system, from home to inpatient settings (Figure 1-2). Patient 1 is a 53-year-old male s/p KT in 2012; Patient 2 is a 56-year-old female s/p KT in 2019; and Patient 3 is a 53-year-old female s/p simultaneous liver-kidney transplant in 2014. Patients 1 and 3 had follow-up COVID-19 NAT testing: Patient 1 converted to be negative at 24 & 28 days, whereas Patient 2 converted to be negative at 45 & 48 days.

Discussion: Telemedicine helped assess, diagnose, triage, and treat patients with COVID-19 while avoiding an ER or outpatient clinic visit. We highlight the value of telemedicine in the maintenance of uninterrupted follow-up care for immunosupressed patients with prolong viral shedding.

	Patient 1			Patient 2			Reference range(unit)
Hospital Day	Day 1	Day 3	Day 5	Day1	Day 4	Day 7	
White blood cells	4.58	4.73	4.39	4.37	3.88	4.69	4.50-11.0 (K/cu mm)
Absolute lymphocyte count	0.31	0.24	0.42	0.22	0.20	0.37	1.10-4.80 (K/cu mm)
Hemoglobin	12.0	11.6	12.3	12.6	11.4	12.0	13.9-16.3 (g/dL)
Platelets	151	188	300	278	311	400	150-350 (K/cu mm)
Serum sodium[1]	122	127	138	140	138	143	135-148 (mmol/L)
Serum potassium	4.8	4.7	4.9	4.7	4.6	5.4	3.5-5.1 (mmol/L)
Serum calcium	8.4	8.5	9.0	8.7	8.4	8.9	8.4-10.5 (mg/dL)
Serum bicarbonate	20	20	23	26	25	24	21-31 (mmol/L)
Serum creatinine	1.6	1.4	1.3	0.9	0.8	0.9	0.6-1.3 (mg/dL)
Urea nitrogen (serum)	19	15	18	14	13	16	7-22 (mg/dL)
Albumin	3.8	3.6	3.6	4.4	3.5	3.9	3.5-5.3 (g/dL)
Aspartate aminotransferase	66	-	78	22	19	22	0-37 (U/L)
Alanine aminotransferase	46	-	113	15	14	17	0-40 (U/L)
Alkaline phosphatase	72	-	81	75	58	63	30-120 (U/L)
C-Reactive protein	6.8	-	1.9	6.1	6.2	0.7	<0.5 (mg/dL)
Tacrolimus trough level	5.1	7.0	5.7	7.0	6.6	6.3	5.0-20 (ng/mL)
D-Dimer	0.63	-	0.51	0.27	0.28	0.24	0.00-0.49 (mg/L)
Lactate dehydrogenase	307	-	289	182	-	-	118-273 (U/L)
Serum ferritin	548	-	603	1103	990	1268	30-400 (ng/mL)
Interleukin 6	43.77	-	-	9.9	-	-	<0.5 (pg/mL)

[1]Patient 1 had mild acute kidney injury (AKI) and acute hyponatremia on admission; his spot urine sodium was 22 mmol/L and serum osmolarity was 258 mosm/Kg suggestive of volume depletion. Hence, his home lisinopril was stopped, and he received ringers lactate intravenous (IV) fluid replacement carefully.

Table 1: Patients 1 and 2 laboratory test results during hospitalization. Patient 3 was not hospitalized.



[1]Patient 1: dry cough, low-grade fever, chills, nausea and vomiting, watery diarrhea, and loss of the sense of smell. During hospitalization, patient developed shortness of breath and hypoxia.
[2]Patient 2: dry cough, rhinorrhea, and chest tightness, and subsequently developed high-grade fever and diarrhea. During hospitalization, patient developed shortness of breath and hypoxia.
[3]Patient 3: mild headache, rhinorrhea and fatigue; symptoms were improving gradually without specific treatment.
[4]Naso-oropharyngeal swab, nucleic acid test (NAT) was used to detect COVID-19 RNA by polymerase chain reaction (PCR): (+) COVID-19 RNA detected, (–) COVID-19 RNA not detected.
[5]Hydroxychloroquine 400 mg twice daily for 1st day, then 400 mg once daily for days 2, 3, 4, and 5.
[6]Tocilizumab 4 mg/kg per dose once daily for a total of two doses.
[7]Patient was also followed by a transplant coordinator via telephone calls twice weekly.

Table 2: Clinical course of the three patients with COVID-19 who were managed via telemedicine

PUB065

Urinary Abnormalities and Urinary Sediment Findings in COVID-19 Patients

Alejandro Garcia Rivera, Luz Y. Villegas, Ríos C. Katia yuritzi, Arantxa K. Aguilar, Marcos Adrian E. Lopez, Jesús A. Rico sánchez, Carlos A. Villavicencio López, Ernesto Ojeda, Luis A. Salazar Soltero, Rafael A. Ayala cortés, Carolina R. Alvarez, Jesús A. Vega López de Nava, Nidia Rodriguez Plascencia, Renato Parra Michel. *Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Hospital General Regional No.46, Instituto Mexicano del Seguro Social, Guadalajara, Mexico.*

Background: Coronavirus disease 2019 (COVID-19) is a new disease of pandemic proportions. There are only a few reports about urinary abnormalities in this disease, and to our knowledge there are no reports about the usefulness of urinary sediment on prognosis. Our aim was to describe the urinary abnormalities in COVID-19 and to assess the utility of urinary sediment on prognosis in COVID-19.

Methods: Prospective, single-center study, in patients diagnosed with COVID-19 (with a positive RT-PCR test), who were admitted in our hospital, from April 2020 to date, and whose urine sample could be obtained at admission to the isolation wing.

Results: 22 patients were included; 17 (77.3%) had proteinuria, 12 (54.5%) had microscopic hematuria, and 9 (40.9%) had leukocyturia. Granular casts (with a Chawla cast scoring index greater than 3) were present in 8 (36.4%) patients. Of the 8 patients with granular cast, 6 developed an AKI (75%), 2 required Hemodialysis (25%) and 3 died (37.5%). Of the 14 patients whose urinary sediment was classified as bland, 5 developed an AKI (35.7%), none of them required hemodialysis, and 2 subsequently died (14.2%). There was a statistically significant difference between a bland urinary sediment and a sediment showing granular casts for the need of hemodialysis or death (p=0.02), with a positive LR of 3.5.

Conclusions: The urinary sediment is a cheap, available tool for the prognosis of need for hemodialysis or death in patients diagnosed with COVID-19, and should be taken into consideration in the assessment of these patients by the Nephrology department.

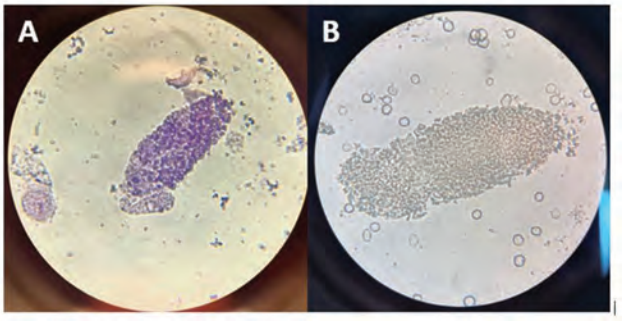


Figure 1. Urinary sediment slides showing: A) a granular cast with a renal tubular cell within; B) a granular cast with several isomorphic erythrocytes.

PUB066

Repurposing Baby Monitors in COVID-19

Sobia N. Khan, Sandeep K. Mallipattu. *Stony Brook University, Stony Brook, NY.*

Introduction: As of May 2, total of 1,130,075 confirmed cases resulting in 65,605 deaths were reported in US. Nearly 3.2% of individuals with COVID-19 develop AKI and have been reported to require dialysis. Initial reports from Wuhan, the burden of acute kidney injury was relatively low, about 3% -9%, subsequent analysis have demonstrated increase in the incidence to 15%

Case Description: In February, 376 hemodialysis and 59 CRRT while in March, 273 hemodialysis and 30 CRRT offered in our hospital. During pandemic bed capacity doubled from 650 to 1317 beds. Physical space gained by converting ambulatory surgical center and ambulatory locations. In April, observed 1,811 COVID-19 patients admitted to the hospital with 50 chronic hemodialysis patients, 30 were COVID positive. 334 hemodialysis treatments while 136 continuous renal replacement therapy offered 12.8% therapy given in February increase surgency of 27.9% in April for CRRT whereas the number of hemodialysis treatments offered stayed stable at average of 355 hemodialysis treatment.

Discussion: To minimize the risk of exposure in COVID-19 isolation rooms we implemented telemonitoring strategy. We identified baby monitors could serve "read-to-go" telemonitoring. VTech Baby Monitor 7" display. HD camera uses WiFi connection to capture movements and sounds which helps in monitoring the patients in real-time. The camera ability to pan 360 degrees, tilts 82-degrees and zooms ten times to enable viewing of the dialysis monitor and patient. Two-way voice communication allows easy communication between patient and nursing. Before hemodialysis nurse sets up camera by the patient's bedside (1 camera facing the dialysis monitor other camera facing patient and the dialysis access). Dialysis nurse visualize through the handheld monitor. Telemonitoring system COVID19 patients undergoing hemodialysis we observed zero positive COVID-19 dialysis staff

PUB067

Impact of Ethnicity on COVID-19 Infection and Mortality Amongst In-Centre Haemodialysis Patients

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Background: It is reported that patients of BAME origin are at greater risk of infection and death due to COVID-19. We describe outcomes in an inner city, ethnically diverse in-centre haemodialysis (HD) population during the pandemic.

Methods: A total of 1253 patient electronic records were analysed retrospectively. 207 infections were recorded -197 patients tested positive for Sars-Cov-2 on validated nasopharyngeal PCR analysis and 10 patients included due to high clinical suspicion. Ethnicity data is self-reported. All COVID-19 positive patients were isolated for subsequent dialysis sessions. Whole-cohort screening confirmed the rates of infection.

Results: Overall rate of infection amongst the group was 16.5% (n=207), hospitalisation 7.5% (n=94) and death 3.5% (n=44). Within COVID-19 infections, hospitalization rate was 45% and mortality 21%. Seven patients received critical care and two were intubated. Ethnicity data are shown in table 1: There was no significant difference in rates of COVID infection between ethnic groups. The risk of infection in BAME patients was not significantly greater than in white patients (p=0.24, OR 0.79, 95%CI 0.55-1.14). The mean age of those who died from COVID did not differ from the entire cohort (62 vs 63.2 years). Males made up the majority of both the baseline cohort (61.2%) and those infected with COVID (58.5%). 71% of those who died were male. Body mass index did not differ between the group as a whole and those infected with COVID. Rates of diabetes mellitus did not differ significantly between those infected with COVID and those who died.

Conclusions: We have defined COVID infections and outcomes within a real-life, large haemodialysis population. Hospitalisation and mortality rates were high, and patients self-reporting as black or Asian were over-represented in the infected group compared to the baseline prevalent HD population. Higher rates of death were observed in black and asian groups but conclusions are limited by small numbers. Larger collaborative studies are required to expand on these findings.

Ethnic breakdown of HD cohort and COVID cases

Ethnicity	Baseline HD Cohort (% of total population (n))	COVID Cases (% of cases (n))	COVID Deaths (% of deaths (n))
Black	23.9 (300)	28.5 (59)	31 (13)
Asian	27.5 (345)	31.9 (66)	35.7 (15)
White	23.9 (300)	23.2 (48)	23.8 (10)
Other	24.6 (308)	16.4 (34)	9.5 (4)

PUB068

COVID-19 Management in New York City Kidney Transplant Recipients: Before and After the Apex

Michelle L. Lubetzky, Rebecca Craig-Schapiro, Meredith J. Aull, Thalia Salinas, John R. Lee, Samuel Sultan, Jun B. Lee, Choli Hartono, Sandip Kapur, Thangamani Muthukumar, Manikkam Suthanthiran, Darshana M. Dadhania. *Weill Cornell Medicine, New York, NY.*

Background: Kidney graft recipients receiving immunosuppressive therapy may be at heightened risk for Covid-19 and adverse outcomes. We aimed to study how practice patterns and outcomes changed before and after the peak incidence of cases in New York City.

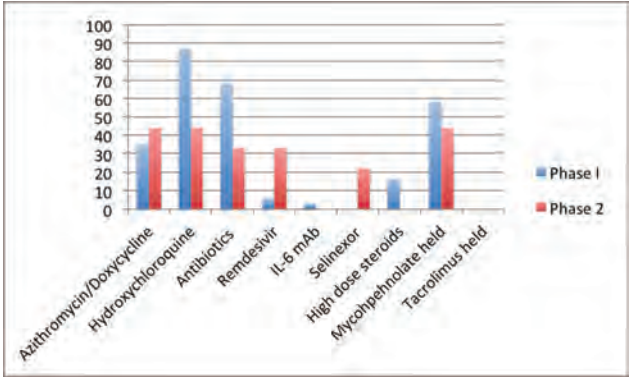
Methods: We reviewed 68 consecutive adult kidney graft recipients from our center diagnosed with SARS-CoV-2 from March 13, 2020 to May 25, 2020. We compared outcomes of those treated from March 13 until the apex of infections on April 14 (Phase 1), and those treated from April 15th to May 25, 2020 (Phase 2).

Results: Characteristics of both Phase 1 and Phase 2 patients are described in Table 1. Inflammatory markers were lower in the second phase as was patient mortality. Changes in management strategies between the two phases are highlighted in Figure 2. Graft loss occurred in 4 patients (6%) and there were 5 deaths (7%).

Conclusions: Data from our study suggest that management strategies of immunosuppressed patients changed over the course of the Covid-19 Pandemic in New York City, including less use of hydroxychloroquine, and increased use of novel agents such as remdesivir. Additional data are needed to better understand if the decrease in patient mortality during the second phase is attributable to better management or lower inflammatory response in the setting of Covid-19 illness.

	All Patients		Hospitalized Patients at NYP/WC	
Patient Characteristics	Phase 1 (N=48)	Phase 2 (N=20)	Phase 1 (N=31)	Phase 2 (N=9)
Age (mean+/-DS)	54.7 ±14.8	53.2 ±9.9	56.5 ±15.9	55.4 ±11.8
Gender: Female, N (%)	15 (31)	6 (30)	5 (16)	2 (22)
Ethnicity: N (%)				
Caucasian	15 (31)	4 (20)	9 (29)	2 (22)
Black	13 (27)	4 (20)	9 (29)	2 (22)
Hispanic	17 (35)	6 (30)	11 (35)	2 (22)
Asian	2 (4)	6 (30)	2 (6)	2 (22)
Living Donor, N (%)	32 (67)	12 (60)	21 (68)	7 (78)
Comorbidities, N (%)				
Smoking	10 (21)	4 (20)	7 (22)	2 (22)
Diabetes	11 (23)	7 (35)	8 (26)	4 (44)
Cardiovascular Disease	15 (31)	4 (20)	12 (39)	3 (33)
Pulmonary Disease	8 (17)	1 (5)	6 (19)	1 (11)
Cause of ESRD, N (%)				
Hypertension	8 (17)	8 (40)	6 (19)	5 (56)
Diabetes	11 (23)	7 (35)	8 (26)	2 (22)
Induction, Anti-thymocyte globulin, N (%)	35 (73)	18 (90)	24 (77)	6 (67)
Baseline Immunosuppression. Steroid Maintenance, N (%)	19 (40)	8 (40)	13 (42)	5 (56)
Time from Transplant to Diagnosis, median (range)	5 (0.4, 35)	2 (0.2, 15)	4 (0.4, 6)	0.8 (0.3, 15)
Less than 1 year after Transplant, N (%)	6 (13)	7 (35)	4 (13)	5 (56)
Time from Symptoms to Diagnosis, median (range)	7 (0, 31)	10 (1, 21)	7 (0, 31)	14 (1, 21)
Admission Vitals Signs				
Temperature (°C)			37.8±0.9	37.5±0.6
Systolic Blood Pressure (mmHg)			129±20	120±20
Heart Rate (bpm)			95±16	95±13
Respiratory rate			22±6	19±2
Oxygen Saturation			94±5	94±5
Admission Laboratory Values				
Creatinine (mg/dL)			3.3±3.6	2.8±2.2
White Blood Cell Count (*10^3/uL)			6.5±3.7	4.3±3.1
Absolute Lymphocyte Count			0.8±0.4	0.3±0.3
Inflammatory Markers*				
Ferritin (ng/mL)*			1646±1743	2426±1088
C-reactive protein (mg/dL)*			50.0±68.7	7.3±5.0
Procalcitonin (ng/mL)*			0.6±0.9	0.4±0.4
D-Dimer (ng/mL)*			937±1238	368±132
Interleukin-6 (pg/mL)*			60±101	5±1
Outcomes				
Graft Lose, N (%)	3 (6)	1 (5)	3 (10)	1 (11)
Case Fatality, N (%)	5 (10)	0 (0)	5 (16)	0 (0)

* Data available for Phase 1 out of 31 patients: 29 for procalcitonin, 24 for Ferritin and CRP, 21 for d-dimer and 8 for IL-6. For Phase 2: 9 patients had d-dimer, procalcitonin and CRP, 7 had ferritin and 3 had IL-6



PUB069

Effect of COVID-19 Infection in Three Patients Treated with Rituximab

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Background: Rituximab (RTX), a monoclonal antibody against the CD20 antigen found on B lymphocytes, is widely used for glomerular diseases. It may be advantageous in COVID19 given the exaggerated immune response and cytokine storm elicited by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or could be detrimental given the impaired response to infections in immunocompromised patients.

Methods: We examined the clinical presentation and outcomes of 3 patients undergoing treatment with RTX who were infected with SARS-CoV-2.

Results: 2/3 patients had complication of severe hypoxemia with evidence of pulmonary infiltrates on imaging. Both had underlying ANCA vasculitis with a history of pulmonary involvement. Both were treated with remdesivir and one received convalescent plasma. The patient who received convalescent plasma was SARS-CoV-2 RNA negative at 3 weeks. The patient who received remdesivir but not plasma remained positive for SARS-CoV-2 RNA at 7 weeks and was negative for IgM and IgG antibodies at 4 weeks. The third patient recovered without hospitalization and had a first negative RNA test at 3 weeks and was positive for IgG antibodies when tested at 7 weeks despite a confirmed zero B cells by flow cytometry.

Conclusions: 3 out of 3 patients who developed SARS-CoV-2 infections while on RTX recovered. A larger review of individuals on RTX therapy infected with SARS-CoV-2 should be examined to study the association between B cell depletion and COVID19.

Patient Characteristics and Outcomes

Age /gender /race	Underlying disease	Comorbidities	Duration of RTX therapy	B cells	SARS-CoV-2 Infection					
					Presenting symptoms	Complications	Treatment	Time from 1st positive test to 1st negative test	SARS-CoV-2 Antibody	Disposition
62/F/C	PR3-ANCA vasculitis*	HTN, COPD	6	Absent	Fevers, cough, diarrhea, vomiting	Hospitalization for severe hypoxemia (not intubated)	- HCQ - Held azathioprine - Remdesivir	>7 weeks	Not detected	Home
39/F/C	MPO-ANCA vasculitis¶	Rheumatoid arthritis, morbid obesity, HTN,	5	Absent	Fevers, fatigue	Hospitalization for severe hypoxemia requiring high flow O2 in	- Remdesivir - Convalescent plasma	3 weeks	N/A	Home

*PR3-Anti Neutrophil Antibody (ANCA): Patient with eye, ENT, lung and kidney involvement

¶ MPO-ANCA: Patient with ENT, lung and joint involvement

HCQ: Hydroxychloroquine

FSGS: Focal segmental glomerulosclerosis

C: Caucasian, H: Hispanic

PUB070

AKI Following Hemolysis Related to Hydroxychloroquine Treatment for COVID-19 in a G6PD-Deficient Patient

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Introduction: COVID-19 is associated with significant morbidity and mortality. As a potential treatment, Hydroxychloroquine (HCQ) is actually widely used. Concern has arisen about side effects of HCQ. Here, we describe severe AKI following HCQ administration for COVID-19.

Case Description: A 65-year-old patient has been admitted for fatigue. His treatment was gliclazide, lercanidipine for T2DM and arterial hypertension. Initial evaluation revealed: SpO2 91%. Blood tests are detailed in the table1. COVID-19 pneumonia was diagnosed. HCQ and azithromycin were given, including a loading dose of HCQ. Patient developed severe acute hemolytic anemia (AHA) and AKI (table1, Day7). Blood tests were consistent with acute hemolytic anemia (AHA). Glucose-6-phosphate dehydrogenase (G6PD) activity showed <0.2IU/g hgb (7.0-17.0) consistent with AHA triggered by HCQ in a G6PD deficient patient, and further complicated with AKI. Given the ongoing oliguria, hemodialysis was commenced. 23 days later, recovery of kidney function allowed him to stop dialysis. There remains a slight impairment of kidney function tests (table1, Day72).

Discussion: The residual enzyme activity of G6PD deficiency determines the severity of clinical manifestations which are usually triggered either by fava bean ingestion or drugs, and are dose-dependent. This patient had a severe deficiency and he received a loading dose of an at-risk drug. Both induced hemolysis crisis. AKI is a rare complication of AHA related to G6PD deficiency. The need for renal replacement therapy seems exceptional. Renal recovery could be incomplete. Severe G6PD deficiency can manifest late in life. HCQ should be used with caution given potential severe side effects. We then recommend early monitoring of hemolysis parameters.

	Day1	Day7	Day 72	Units
Hemoglobin	15,1	6,7	12,7	g/dl
Platelets	160	388	259	x10³ G/L
White Blood Cells	4,09	12,96	4,8	x10³ G/L
CRP	78,3	380	1,6	mg/L
Na	134	135	140	mmol/L
K	4,1	4,7	3,9	mmol/L
Cl	95	98	105	mmol/L
HCO3	26	22	25	mmol/L
Creatinine	0,83	4,75	1,03	mg/dl
LDH (<210)	274	1956	235	U/L
Bilirubin (6.8-17.1)	6,8	83.8	6,8	µmol/L
Haptoglobin (30-200)	-	<10	88	mg/dL

Table 1: Selected blood tests

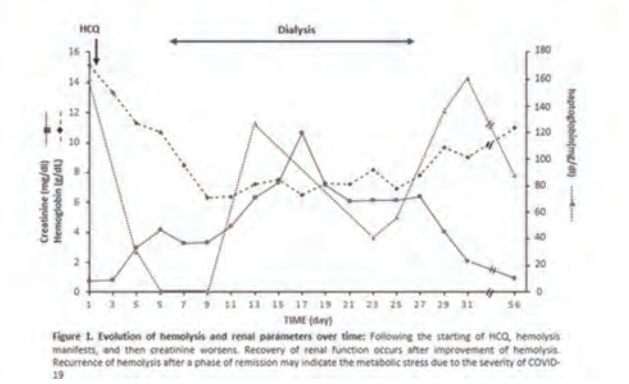

Figure 1. Evolution of hemolysis and renal parameters over time: Following the starting of HCQ, hemolysis manifests, and then creatinine worsens. Recovery of renal function occurs after improvement of hemolysis. Recurrence of hemolysis after a phase of remission may indicate the metabolic stress due to the severity of COVID-19

PUB071

Pragmatic Approach Toward Nephrology Practice in the COVID-19 Era: Shared Learnings and Experiences Toward Consensus Through a Virtual Educational Platform Involving 404 Nephrologists

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Background: COVID19 rapidly spread globally, imposing the need for change in nephrology practices guided by the recommendations, issued by scientific associations

Methods: We conducted a nationwide virtual educational initiative with an inbuilt technological platform to enable live sharing of experiences of new modes for nephrology practice during COVID 19 pandemic, based on the adoption of current recommendations and evidences to enable indigenous, adaptive experiences of 404 nephrologists with approximately 8,000-man hours of cumulative clinical experience. The four zones across the country were represented by an individual educational task force member

Results: There was a uniform consensus that suspected patients need to be treated similar to a COVID 19 positive patient, with dialysis facility provided in isolation area, to mitigate direct risk to both healthcare providers and patients and indirect risk of contamination of the hospital system. Multiple screening procedures and prohibition of eatables in dialysis area is the new mandate. Role and importance of CRRT, PIRRT and peritoneal dialysis was highlighted. Femoral catheterization is the preferred route. The experience of Tenckhoff catheter technique in peritoneal dialysis in 38 patients was discussed. Higher dose of anticoagulants is being utilised for extracorporeal procedures to reduce risk of enhanced risk of thrombus formation in COVID 19. The varied, emerging clinical presentation, including asymptomatic cases has made COVID 19 testing compulsory at most of the institutions. The nephrologists were informed about the emerging evidence for the need to continue the ongoing ARBs or ACE inhibitors. Renal transplantation with careful precautionary practice is being performed with modulation of dose of immunosuppressive agents in COVID 19 positive patients

Conclusions: Safe and efficient delivery of nephrology care practices needs a uniform acceptance. Even minor liberties and deviations from established safe practice protocols could compromise the safety of the health care workers

PUB072

COVID-19 in Kidney Transplant Recipients

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Background: Coronavirus disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Kidney transplant recipients are at a higher risk for complications due to comorbid conditions and concurrent immunosuppression. We like to describe a small cohort of kidney transplant recipients with COVID-19

Methods: A single-center, retrospective observational cohort study describing short term outcomes of COVID-19 infection in kidney transplant recipients.

Results: A total of 8 kidney transplant recipients were diagnosed with COVID-19 with a mean age of 58 yrs (26-78), predominantly African American (7/8), mean duration

from transplant 3.5 yrs (1.5-11 yrs). All patients have HTN (8/8), half the patients have Diabetes mellitus-2 (4/8). Common presenting symptoms are fever and shortness of breath. 6/8 patients required hospitalization. 8/8 patients were managed with a reduction of immunosuppression, primarily by decreasing the dose or holding the anti-proliferative agent. 1/8 patients died, 4/6 discharged from hospital, 1/6 still admitted to the hospital with respiratory failure. 5/6 patients required supplemental oxygen. 2/6 patients required ICU stay and 1/6 required mechanical ventilation and renal replacement therapy. 3/6 hospitalized patients received hydroxychloroquine/ Azithromycin combination and 1/6 received Remdesivir. Median hospital stay is 5 days with a mean of 9 days. The patient who required mechanical ventilation and renal replacement is the only recipient who died from COVID-19 at our transplant center.

Conclusions: COVID-19 is a novel infection primarily presenting with fever and shortness of breath. The course of illness appears to be severe with the majority of patients requiring supplemental oxygen and a third of hospital admitted patients required ICU stay. Reduction of immunosuppression appears to be helpful, however, no control group available. COVID-19 affected population is predominantly African American (7/8) and older recipients with age > 50 yrs (7/8).

Recipient #	1	2	3	4	5	6	7	8
Age in years	78	50	26	76	56	55	67	57
Race	AA	AA	C	AA	AA	AA	AA	AA
Sex	F	M	M	M	M	M	F	M
Years from transplant	11	1.5	8	1	10	2	3	2
HTN	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DM-2	No	Yes	No	Yes	Yes	No	Yes	No
Presenting complaints	Fever, SOB	Cough	Fever	SOB	Fever	Fever, SOB	Fever, SOB	Cough
Hospitalization	Yes	Yes	No	Yes	No	Yes	Yes	Yes
ICU Stay	Yes	No	No	No	No	No	Yes	No
Supplemental Oxygen	Yes	Yes	No	Yes	No	Yes	Yes	No
Treatment	HCQ/AZ	-	-	HCQ/AZ	-	HCQ/AZ	Remdisivir	
Reduction of Immunosuppression	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hospitalization duration in days	25	5	-	3	-	5	10 (ongoing)	7
Outcome	Deceased	Alive	Alive	Alive	Alive	Alive	Alive	Alive

PUB073

Cases of COVID-19 Reported in a Predominantly White Rural Hemodialysis Cohort

Ravi K. Thimmisetty. *Nephrology Associates, Cape Girardeau, MO.*

Background: COVID-19 is a novel coronavirus disease causes by the severe acute respiratory syndrome coronavirus 2. Because of its high infectivity rate, WHO described the disease as a Pandemic on March 11th 2020. Severe infections were reported in adults with underlying comorbid conditions, therefore hemodialysis patients are not an exception. We are reporting COVID-19 cases in a rural hemodialysis center predominantly Caucasian patients

Methods: We reviewed the cases of confirmed and suspected COVID-19 infections in our dialysis center. Precautions were taken promptly after COVID-19 infection become Pandemic. All patients were taken temperature check at the entrance door, surgical face mask was provided, sanitizers were provided, and social distance was followed. All physicians and dialysis staff followed the same guidelines. All suspected and confirmed cases should get two negative SARS CoV-2 PCR tests for acceptance at our dialysis center.

Results: Out of 71 dialysis patients, men and women were 56% and 43%. 73.2% of them were Caucasians and 23.9% were African Americans. There were one confirmed COVID-19 disease who was hospitalized for about a month. She acquired from a community spread. She improved and resumed schedule after two negative SARS CoV-2 PCR results. Four people were sent to hospital for having cough, fever, dyspnea, all of them were negative for COVID 19 infection. In our dialysis unit, 55.7% of patients have diabetes, 83% have hypertension, 47.8% of them have both diabetes and hypertension. Patient with confirmed COVID-19 fall into age group of 65-79 yrs. 35.2% of the patients fall into this category. Octogenarians constitute 15.4%. 29.5% of patients were of 50-64 yrs. 19.7% of the patients were less than 50 yrs. of age. There is only one patient got infected with COVID-19, representing around 0.01% of our dialysis population which is very low. There were no deaths from COVID-19. None of octogenarians and African American patients were infected in our dialysis center

Conclusions: Immune status is impaired in dialysis patients and may explain to some extent how body response to COVID-19 infection. And because of same reason, even antibody testing may also not helpful in dialysis patients. It is early to come to conclusion, need further observations from large scale studies once we have full spectrum of pathophysiology and management of COVID-19 disease in hemodialysis patients.

PUB074

Severe AKI in COVID-19: Not Irrecoverable

Latoya N. Gayle, Gene C. Otuonye, Nia Flemming, Deborah A. Fein. *Englewood Hospital and Medical Center, Englewood, NJ.*

Introduction: COVID-19 infection has varied presentations inclusive of pneumonia(PNA), gastroenteritis(GE) & AKI. Prompt identification with aggressive therapy is needed to reduce morbidity & mortality. This is a case of COVID-19 infection with septic shock & severe AKI, successfully treated.

Case Description: 65-year-old female presented with 7-days of vomiting, diarrhea, fever, dry cough, fatigue & confusion. Multiple household members recently positive for SARS CoV-19. She had a history of HTN & CKD3a. Baseline creatinine(Cr) 3 months ago was 1.2. On exam, BP 86/48,T95F,RR 27. She had dry mucous membranes, bilateral coarse breath sounds & rales on auscultation, confusion & flapping wrist tremor. Labs showed Cr of 21.5,BUN 162, CO2 9,D-dimer >20,CRP 55.ABG on 3L nasal cannula showed PH 7.21,PO2 104,PCO2 30.CXR noted right upper lobe infiltrate. CT head & EEG were unremarkable. SARS-CoV-2 PCR was positive. She was taken to ICU for septic shock from COVID-19 PNA & GE with severe AKI. She required phenylephrine for pressor support. She received IV D5 ½ NS with bicarbonate, doxycycline, ceftriaxone & vancomycin. Dialysis was considered but renal function rapidly improved:within 24 hours phenylephrine was weaned off & Cr decreased to 12. She recieved Enoxaparin due to high D-dimer & low PO2. In 5 days she had complete return of mentation, improved ventilation & resolution of asterixis. On discharge day 10,Cr was 1.0,BUN 17,D-dimer 8.5 & CRP 24. She was discharged on Apixaban.

Discussion: The Covid-19 global pandemic has resulted in significant mortality. Prompt identification & aggressive treatment of the critically ill is paramount to prevent multi-organ failure. AKI occurs in up to 23% of patients & confers increased mortality especially when associated with septic shock. In our patient, with severe AKI, uremia with encephalopathy she had marked improvement & resolution with supportive therapy. Renal recovery with this degree of impairment is unusual as a majority of patients with similar characteristics have poor outcomes. This recovery may be attributed to aggressive fluid resuscitation, correction of metabolic acidosis & early initiation of anticoagulation. It is well known that AKI in critically ill Covid-19 patients is associated with high mortality. This case shows that renal & overall clinical recovery is still possible. More research is needed to identify predictors of prompt recovery.

PUB075

A COVID-19 Patient with AKI

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Introduction: Patients with COVID-19 typically present with respiratory illness. AKI is a common complication of COVID-19. Although the etiology of AKI remains unclear, it is thought to be secondary to hemodynamic changes, cytokine release and/or direct viral (SARS-CoV-2) cytotoxicity. The following case describes a patient who presented only with GI symptoms, which led to the diagnosis of COVID-19 and AKI.

Case Description: 71 year-old white male, a nursing home resident, has DM2, HTN, CKD stage 3 and dementia/cognitive impairment. His baseline serum Cr was 1.49 in 2019. He was brought to our hospital for a new diagnosis of AKI and COVID-19. Three days ago, he started to have nausea/vomiting, and was treated with Zofran. No improvement the next day. Bp 96/63, P 107, Temp 97.7. COVID-19 test was positive. On the following day he was brought to a local ER after 3 large projectile emesis. Labs revealed BUN/Cr 80/9.4. He was given1 liter IVF and was transferred to our hospital. He had watery brown-greenish stools, although he denies diarrhea or abdominal pain. Meds included Insulin, statins, heparin, SSRI, and donepezil. At our ER, the patient was awake, alert, orietented to self and year. T 98.3, BP 119/71, P 119, RR 18, SpO2: 95% on RA. PE was unremarkable. Blader scan: 150 ml. Lab: WBC 10.9, Hb 13.3, Plt 207. Na 130, K 4.0, Cl 97, bicarb 17, BUN 85, Cr 8.6, Ca 7.3, Phos 6.6, Alb 3.2. LFT was normal. FeNa = 1.5%. UA: pH 5, prot 1+, Glu 50, RBC 5, WBC 4, with amorphous sediments. CXR: lungs were clear. Renal ultrasound: kidneys with normal size and echogenicity. No obstruction. Patient was admitted to the COVID ward. Patient's nausea and vomiting stopped upon his admission, although his watery stools lingered. He was treated with iv fluid to optimize his hemodynamics. Over the next 5 days patient's serum Cr decreased to 2.0mg/dL.

Discussion: Since the COVID-19 pandemic, GI symptoms and AKI are often regarded as complications of the overall respiratory illnesses. Patients with only GI symptoms were often not suspected for COVID-19. The causes of this patient's AKI include hemodynamically mediated +/- ATN +/- possible cytokine release. Regarding direct viral cytotoxicity, postmortem data has shown the presence of coronavirus-like particles in podocytes and tubule cells. While the direct viral effect to the kidneys is still not understood, treatment with conventional approaches may significantly improve renal outcome.

PUB076

De-Differentiation of Human Urine-Derived Stem Cells to SIX2+/ CITED1+ Cells by 3D Tubuloid Culture

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Background: In contrast to pluripotent stem cell-derived organoids which take nearly one month to derive for kidney, adult stem cell (ASC) derived organoids can be derived within 7 days of culture without needing tedious direction through embryonic development. Protocols have been generated to derive organoids or spheroids of intestine, liver, prostate, pancreas, stomach, salivary gland, breast, colon and taste buds from ASCs. These 3D cultures have been used for disease modeling and personalized medicine approaches. Recent work from the Hans Clevers lab showed that cells derived from the urine of a patient with cystic fibrosis could be made into kidney epithelial tubular organoid structures termed "tubuloids."

Methods: These tubuloids cultures developed quickly and exhibited many of the hallmark features of an intact tubular epithelium. The tubuloid culture media includes Wnt signaling enhancers, EMT inhibitors, and fibroblast growth factors which are all reported to be essential for kidney development. We applied this tubuloid 3D culture protocol [MOU1] to our cultures of human urine-derived stem cells (USCs). USCs are hypothesized to be the pariental epithelial cells lining the glomerulus that are shed into the urine. The USCs from healthy adult donors were grown on 96 well U-bottom suspension culture plates in tubuloid media for 10 days. The 3D tubuloid-like structures harvested at Day 10 were stained for both early nephron progenitor markers and tubular precursor markers.

Results: Tubuloid-like spheres derived from USCs expressed both nephron progenitor markers SIX2 and CITED1 as well as tubular cell precursors PAX2 and PAX8.

In contrast, the starting USCs lack PAX2, SIX2 and CITED1. [MOU1] We will next quantify the expression of these and other nephron progenitor markers over the time course of 3D culture.

Conclusions: Our results suggest a new method to derive patient-matched SIX2+/CITED1+ cells from non-invasive urine samples.

Funding: Private Foundation Support

PUB077

Comparative Evaluation of Orthostatic Hypotension in Patients with Diabetic Nephropathy

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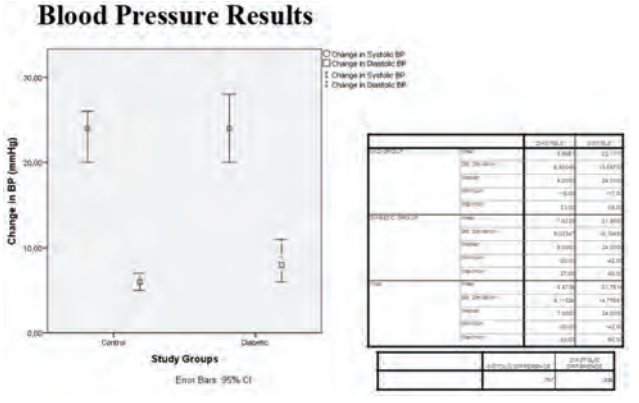
Background: Orthostatic Hypotension (OH) affects 5-20% of population. Our study investigates the presence of OH in diabetic nephropathy patients (DNP) and the factors affecting OH in comparison with other chronic kidney disease patients (CKDP).

Methods: Patients presented to the nephrology clinic and consented were included in the study. DNP were defined by renal biopsy and/or clinical criteria. CKDP of same sex, age and eGFR were matched to DNP. Demographic parameters and medications were obtained from the records. OH was determined by mayo clinic criteria. Same researcher used the electronic device to measure the blood pressures (BP). All samples were taken and analyzed the same day for biochemical and hematologic parameters and albuminuria. Statistical analyzes were performed with IBM SPSS22.0 program.

Results: 112(51F,61M, mean age:62,56±9,35 years) DNP and 94(40F,54M, mean age:62,23±10,08 years) CKDP were included. 70.5% DNP vs 61.7% CKDP had OH (p=0,181). The mean change in systolic BP in DNP was 21,50+16,10mmHg and it was 7,63+9,03mmHg in diastolic BP. In CKDP mean change in systolic BP was 22,1+13,09mmHg and it was 5,96+6,80mmHg in diastolic BP. There was no difference between the groups in systolic BP (p=0.797), but it was present for diastolic BP (p=0.025). 60.0%F and 74.7%M patients had OH (p=0.026). Uric acid levels were 7.18mg/dl in OH patients and 6.36mg/dl in nonOH (p=0,017). Blood albumin level was not different in two groups (p=0,902). 73.7% of patients on calcium channel blockers developed OH (p=0,015) and OH developed in 80.6% of 36 patients on alpha blockers (p=0,049).

Conclusions: Our study demonstrated OH is frequent among DNP and there was no difference compared to CKDP. It is important to check OH in all CKDP as it is more common than thought.



PUB078

Clinical Practice Gap Analysis of CKD in Type 2 Diabetes from Identification to Diagnosis to Management

Amy Larkin,[1] Kelly L. Hanley,[1] George L. Bakris.[2] *[1]Medscape LLC, New York, NY; [2]UChicago Medicine, Chicago, IL*.

Background: Understanding clinical practice gaps in the identification, diagnosis and management of CKD in patients with T2D can inform development of tools to improve physician practices.

Methods: A survey instrument of 25 multiple choice, knowledge- and case-based questions allowed participants to assess their knowledge, attitudes, and confidence with regard to CKD in T2D. The survey was available online to physicians across the globe without monetary compensation or charge. Respondent confidentiality was maintained and responses were de-identified and aggregated prior to analyses. Initial data collection occurred from February 26, 2020, to April 20, 2020.

Results: To date, 193 nephrologists completed the full assessment. Physicians demonstrated gaps in the following areas. When asked how satisfied nephrologists were with current treatment approaches for managing CKD in patients with T2D, 10% selected very satisfied, 74% selected moderately-mostly satisfied, and 16% slightly-not satisfied.

Topic	Incorrect Responses to Knowledge and Clinical Decision-Making Questions (%)
Assessment to diagnose kidney disease stage	38%
Evidence-based strategies to delay progression of CKD in patients with diabetes	73%
SGLT2 inhibitors CVOT data comparisons	89%
Results from CREDENCE trial	36%
Mechanism of cardiorenal syndrome	87%
Link between diabetes, kidney disease, and the cardiorenal syndrome	48%
Fibrosis as a component of progression of CKD	66%
Knowledge of billing procedure for CKD screening	65%
Comparison of safety profiles for approved MRAs	49%
Differences in emerging MRAs compared to traditional MRAs	62%
Clinical trial data for emerging MRA	35%

Conclusions: This educational research on assessment of physicians' clinical practices yielded important insights into clinical gaps related to identification, screening, diagnosis, and management of CKD in patients with T2D. Further studies are planned to assess the effect of medical education on decreasing these clinical practice gaps.

Funding: Commercial Support - Bayer Global

PUB079

Practice Patterns of SGLT2 Inhibitor and GLP-1 Agonist Treatment in Eligible Type 2 Diabetic Patients Before and After the Publication of the 2018 ADA/EASD Position Statement

Bijin Thajudeen, Wei Xiang Wong, Saeed Bidar, Sevag C. Boyadjian, Wina Yousman, Amy N. Sussman, Frank C. Brosius. *Banner University Medical Center Tuscon, Tucson, AZ*.

Background: The ADA/ EASD published a position statement in October, 2018 on the prevention of atherosclerotic CVD events in diabetic patients focusing on the use of SGLT2 inhibitors (SGLT1I) and GLP-1 agonists(GLP1A). The objective of this study is to determine the practice patterns of endocrinologists and nephrologists in implementing current societal recommendations for use of SGLT2I and GLP1A.

Methods: This study had two phases, a retrospective phase and prospective phase to determine use of SGLT2I/GLP1A before and after the publication of ADA/EASD position statement. All subjects with type 2 diabetes and CVD/CKD who were at least 18 years of age and who were followed at the endocrinology and/or nephrology clinics were included in the study. Eligible patients had a minimum of two clinic visits in either endocrinology and/or nephrology clinics during either the retrospective phase (October 2017- September 2018) or prospective phase (October 2018 – September, 2019). Information collected included utilization of SGLT2I/GLP1A, HbA1c, eGFR, new CVD events and adverse effects of SGLT2I/GLP1A therapy. Primary outcomes measured was the change in percentage of eligible patients treated with an SGLT2I/GLP1A.

Results: A total of 113 charts were reviewed. Only 18 patients(15.9 %) were on either SGLT2I/GLP1A at the end of retrospective phase. By the end of prospective phase, 25 patients (22.1%) were on one of these agents. Out of 28 patients with Hba1c more than 8 at the end of restrospective phase, percentage of patients on SGLT2I/GLP1A at the end of prospective phase remained the same. Utilization of SGLT2I/GLP1A ranged 11% to 28.9%. There was no statistically significant difference between the groups treated with SGLT2I/GLP1A compared to group not treated with these agents in terms of HbA1c (P value 0.94) or eGFR (P value 0.35).

Conclusions: Despite the new recommendations, a substantial number of patients are not on SGLT2I/GLP1A even if the diabetes is not controlled adequately. However this lack of adherence to protocol doesn't seem to affect the diabetes control or change in renal function. We need larger studies to further explore the practice patterns of physicians and its impact on outcomes.

PUB080

A Study on an Early Marker of Renal Damage in Known Diabetics Living in an Urban Slum of Hyderabad, India

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Background: India is the nation with the second largest prevalence of type 2 diabetes mellitus in the world, with an estimated 69.2 million people having the condition as of 2015. In the surrounding as a whole, 78.3 million people live with type 2 diabetes, out of which 52.1% are undiagnosed. 44% of all cases of nephropathy are caused by type 2 diabetes mellitus.

Methods: There are two goals for this cross-sectional study: i) to measure the prevalence of microalbuminuria and albuminuria in type 2 diabetic patients and ii) to determine associated factors that elevate a diabetic's risk for kidney disease. The study was done with 100 type 2 diabetics from Adda Gutta, Hyderabad, India. We performed urinalyses to measure urinary albumin, and gave a modified WHO STEPS questionnaire to assess lifestyle risks.

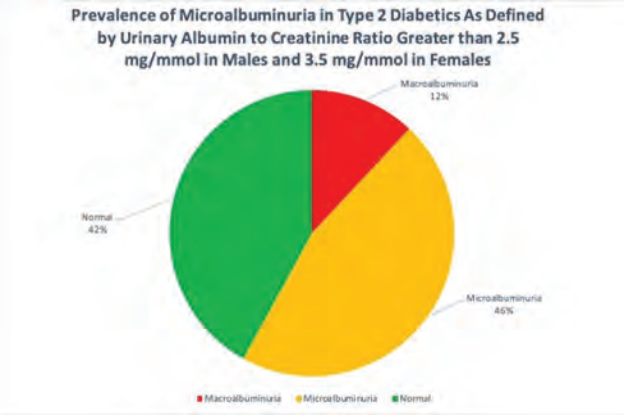
Results: 42 of the 100 patients surveyed were normoalbuminuric, 46 were microalbuminuric, and 12 were albuminuric. Significant risk factors were: being older than 44, having type 2 diabetes for longer than 6 years, drinking alcohol, and smoking.

Conclusions: The prevalence of microalbuminuria in type 2 diabetic people is quite a bit higher than it was in previous studies. Primary prevention needs to be emphasized in this population so that future generations don't get type 2 diabetes mellitus. If patients get their serum creatinine checked, then should nephropathy arise, then it will be detected earlier, and treatment could start earlier. Future studies could ask questions regarding stress on the questionnaires, as well as check the patients' serum creatinine, blood pressure, and lipid profiles.

Funding: Private Foundation Support, Government Support - Non-U.S.

Table 1. Summary of the status of the patients' kidneys. Patients, based on the ACR, were classified into three groups: normoalbuminuric, microalbuminuric, and macroalbuminuric. (n=100)

Status:	Number (n=100)
Normoalbuminuric:	42
Microalbuminuric:	46
Macroalbuminuric:	12



PUB081

The Miraculous Shrinking Kidney

Alonso R. Diaz, Shubha Ananthakrishnan, Joshua B. Crane. *University of California Davis, Davis, CA.*

Introduction: Glomerular hyperfiltration is common in conditions such as diabetes and obesity and can result in glomerular hypertrophy and organ growth as well as corresponding GFR increase. When hyperfiltration results in proteinuria this is a poor prognostic sign for ckd progression and needs to be managed appropriately. With this case report, we document dynamic progressive reduction in sizes of almost 18 and 16 cm kidneys, associated with resolution in proteinuria, after weight loss.

Case Description: A 70-year-old man with type II diabetes mellitus with retinopathy, hypertension and morbid obesity was referred to nephrology for very enlarged kidneys and proteinuria. Of note, two weeks prior he had undergone a gastric bypass surgery. Prior to gastric surgery his BMI had been as high as 41.6 kg/m2. Kidneys measured 17.7 cm on the right and 15.9 cm on the left. His spot protein to creatinine ratio pre-gastric bypass was 2,388 mg/g. Due to the significant growth of the kidneys, concern was initially for an infiltrative process and kidney biopsy was considered. However, the patient had just had gastric bypass surgery for weight loss, so the decision was made to serially monitor kidney sizes as hyperfiltration was high on the differential. With weight loss surgery and dietary changes, within six months, the patient had lost sixty pounds and decreased his BMI to 32.5 kg/m2. His A1c had decreased from 8.1 to 6.9. He was able to stop insulin and was maintained on metformin 1000mg bid and sitagliptin 100mg. His urine protein to creatinine ratio dramatically reduced from around 2388 mg/d to normal level of 78 mg/g Twenty-nine months post-surgery he has lost roughly ninety pounds and his BMI has decreased to 30. Remarkably his kidneys have decreased in size to 14.7 and 13 cm in size.

Discussion: This case illustrates dynamic change in kidney size by imaging with large weight loss as well as successful remission of sub-nephrotic range proteinuria following gastric sleeve surgery, extensive weight loss and glucose control.

PUB082

Multiple Targets on Sodium Excretion with SGLT2 Inhibitors, Furosemide, and Spironolactone Improves Diuretic Resistance in Patients with Diabetic Nephropathy on CKD Stage 3-4: A Pilot Study

Wei Liang. *Renmin Hospial of Wuhan University, Wuhan, China.*

Background: At stage 3-4 of chronic renal disease, patients with diabetic-induced renal dysfunction are not sensitive to the conventional diuretic therapy based on loop diuretics and thiazide diuretics, leading to the earlier renal replacement at stage CKD 3-4. The lower sodium excretion could contribute to the development of diuretic resistance. The protective effects of SGLT2 inhibitors on cardiovascular is contributed by metabolic regulation and osmotic diuretic effect of glucose due to extra excretion of Glucose. The present study aims to investigate the efficacy and safety of SGLT2 inhibitors on the diuretic resistance of diabetic nephropathy at CKD 3-4 stage.

Methods: Patients with Diabetic nephropathy at CKD3-4 stage were administrated with furosemide + hydrochlorothiazide for 3 days with urine volume <1000ml, urine sodium excretion <90mmol followed by Dapagliflozin/Canagliflozin once a day for 7 days.

Results: 3 male and 7 female patients with diabetic nephropathy were included, aged 51-80 years, with eGFR 60-4.6ml/min, and 3 patients presented with cardiac insufficiency. Urine volume was 800±300ml/24 hours before treatment and 2000±500ml/24 hours after treatment. Sodium excretion in urine was 80±20mmol/24 hours before treatment and 150±50mmol/24 hours before treatment. The average net weight change was -3.5±2.2kg. The Scr increased by 30%±5% before and after treatment, and the renal function in 2 patients increased by >30% after 7 days of treatment, and returned to the level of Scr before treatment after 7 days of withdrawal of Dapagliflozin/ Canagliflozin. Electrolyte levels were comparable before and after treatment.

Conclusions: The diuretic regimen based on SGLT2i could significantly improve the resistance of diabetic nephropathy patients to loop diuretics, increase urinary sodium excretion, and slightly elevate renal function in the short term without affecting blood electrolyte level. The efficacy and safety of long-term use of SGLT2i in diabetic nephropathy patients at CKD3-4 stage need further investigate in larger sample size.

PUB083

Peripheral Neuropathy in a Hemodialysis Patient with a Normal Serum Vitamin B12 Level: Possible Vitamin B12 Deficiency in Target Tissues

Yadanar W. Lei,[1] Thinn E. San,[2,1] Htun M. Aung,[3,1] Aye M. Thida,[4,1] Myat E. Mon,[1] Kyaw M. Thein,[5,1] Kyaw Hla,[1] Alexander M. Swan.[1,6] *[1]Nephrology Hypertension Renal Transplant & Renal Therapy, LLC., Avenel, NJ; [2]Icahn School of Medicine at Mount Sinai Elmhurst Hospital Center, Elmhurst, NY; [3]Interfaith Medical Center, Brooklyn, NY; [4]Woodhull Medical and Mental Health Center, Brooklyn, NY; [5]South East Regional Health Authority, Kingston, Jamaica; [6]Rutgers New Jersey Medical School, Newark, NJ.*

Introduction: Many hemodialysis patients suffer from vitamin B12 deficiency, usually due to inadequate nutritional intake. Besides, food sources of vitamin B12 contain high concentrations of electrolytes, which are harmful to these patients. Thus, they are restricted to foods with low vitamin B12 content. Moreover, high-flux dialyzers remove vitamin B12 molecules from circulation, leading to vitamin B12 deficiency. We report a hemodialysis patient presenting with peripheral neuropathy and a normal serum vitamin B12 level whose symptoms improved with monthly vitamin B12 injections after excluding other differential diagnoses of peripheral neuropathy.

Case Description: An 86-year-old man with a history of ESRD on hemodialysis for 3 years along with HTN and CAD presented with fatigue, muscle weakness, and numbness of his extremities for 3 weeks. He was taking aspirin, dipyridamole, finasteride, tamsulosin, and pravastatin. His dietary history was significant for poor nutritional intake. Laboratory findings showed Hb 10.6 g/dL, MCV 102 fL, RBS 87 mg/dL, potassium 4.6 mmol/L, and BUN 42 mg/dL. Common causes of peripheral neuropathy in ESRD patients, such as uremic neuropathy, diabetic neuropathy, and hyperkalemia were excluded. Further evaluation revealed a normal serum vitamin B12 level of 421 pg/dL and a normal folic acid level of 11.4 ng/mL. Given his risk factors for possible vitamin B12 deficiency in target tissues, he was treated with monthly vitamin B12 1000 mcg injections and followed up regularly. His symptoms improved significantly after four months of injections.

Discussion: In hemodialysis patients, chronic inflammation impairs uptake of circulating vitamin B12 by peripheral tissues leading to decreased production of transcobalamin II, increased synthesis of transcobalamins I and III with further accumulation of vitamin B12 in blood. In addition, despite normal or high serum vitamin B12 levels, these patients may suffer from vitamin B12 deficiency in target tissues and show symptoms such as fatigue and peripheral neuropathy. Therefore, it seems reasonable to consider vitamin B12 supplementation in these patients after excluding other causes of peripheral neuropathy. Further studies are highly recommended.

PUB084

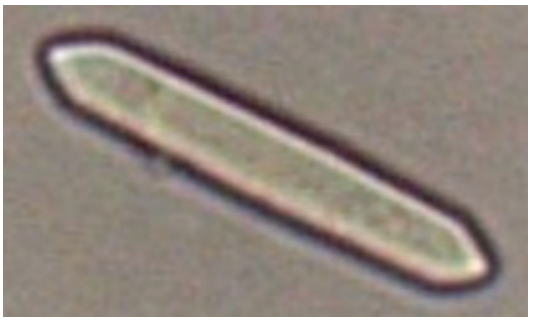
Hemodialysis Prescription in Ethylene Glycol Overdose: A Mathematical Approach

Muhammad T. Shakoor, Jie Tang. *Warren Alpert Medical School of Brown University, Providence, RI.*

Introduction: The timely management of Ethylene glycol (EG) overdose is essential. Hemodialysis (HD) is indicated for rapid elimination of its toxic metabolites. We introduce a case diagnosed shortly after presentation prior to the availability of the blood EG level and share calculations that were used to precisely and accurately estimate the clearance of EG through HD.

Case Description: A 61-year-old male presented with unresponsiveness. Labs were notable for anion positive metabolic acidosis with anion gap 28, osmolal gap 57, along with stage 2 AKI. His whole blood lactate was >17.1 meq/L, with a venous lactate of 0.5 meq/L. EG intoxication was diagnosed based on high lactate gap (16.6) and calcium oxalate monohydrate crystals in his urine sediment. He was given fomepizole and emergently hemodialyzed. We calculated HD prescription based on a simple calculation which we have been using reliably to calculate HD duration and post HD EG level. His predialysis EG level was 71 mg/dl. To calculate the EG removal via HD, we need patient's weight and EG clearance (Cl_{EG}) for specific filters used in HD. Our patient weighed 98kg (TBW 59L) and Cl_{EG} for the F200 filter under Qb400 ml/min and Qd 800 ml/min is 147 ml/min. We decided to dialyze him for 4 hours. His post HD EG level was estimated to be: Kt of EG= 240 min (HD time) * 147ml/min (Cl_{EG})= 35L Kt/V of EG = 35L/59L= 59% Post HD EG level = 71 mg/dl (pre-HD EG level) x (1-59%) = 29 mg/dl After HD was completed, the post HD EG level was 30 mg/dl.

Discussion: Generally, the diagnosis of EG intoxication is delayed and calculation of HD prescription remains a challenge due to lag in obtaining serial EG assays in clinically useful time frame. We present a case of EG toxicity that we were able to diagnose promptly without having to wait for EG blood levels, and we present a simplified approach to determine the duration of HD based on a single EG assay. This calculation can be used to individualize HD treatments and avoid over or undertreatment of intoxication.



Calcium Oxalate Monohydrate Crystal

PUB085

The Estimation Formula of Phosphorous, Potassium, and Salt Amounts Excreted into Urine in Hemodialysis Patients

Momoko Fukazawa,[1] Shunichiro Urabe,[1] Motoko Kato,[1] Yukie Kitajima,[2] Akihiro C. Yamashita,[3] Toru Hyodo.[1] *[1]Eijin Clinic, Hiratsuka, Japan; [2]Tokyo University of Technology School of Health Sciences, Shinagawa, Japan; [3]Hosei University, Koganeishi, Japan.*

Background: We elucidated the contribution of residual renal function (RRF) to the phosphorous, potassium and salt excretion and established the estimation formula of these amounts which are excreted into urine by RRF of hemodialysis patients.

Methods: We collected the 24 hours urine from 22 hemodialysis patients (mean age: 73.1±12.1 years old, dialysis history: 31.1±29.3 months, 15 males, 12 diabetics). The urine volume, phosphorous, potassium and salt amounts in the 24 hours urine and creatinine clearance were determined. The correlation coefficients among the urine volume, amounts of phosphorous, potassium and salt, creatinine clearance (Ccr).

Results: The mean urine volume was 862±421mL/day. The mean phosphorous amounts in the urine was 114.5±55.9 mg/day, potassium 418.2±212.4 mg/day, and salt 4.7±2.6 g/day. Ccr was 3.7±1.8 mL/min. There was a significant positive correlation: urine volume vs phosphorous amounts ($r=0.759$, $p<0.001$), urine volume vs potassium amounts ($r=0.662$, $p<0.001$). (Phosphorous amounts in the urine=101× [24 hours urine(L)]-28) (Potassium amounts in the urine=334× [24 hours urine(L)] +130). There was a significant positive correlation between urine volume and salt amounts excreted into urine ($r=0.915$, $r^2=0.84$, P,0.001).(Salt amounts in the urine=5.7×[24 hours urine(L)–0.2].

Conclusions: As for phosphorous and potassium, if 24 hours urine volume is known, the amount of urinary excretion of phosphorous and potassium can be roughly estimated. As for salt, if 24 hours urine volume is known, the amounts of urinary excretion of salt can be estimated with 84 % accuracy. Measuring urine volume in hemodialysis patients can estimate solute excretion roughly.

PUB086

Treatment of Uremic Tumoral Calcinosis in Maintenance Hemodialysis Patients

Guibao Ke, Fengxia Zhang, Xueqin Chen, Hong Zhang, Shuai C. Dou, Zhiwen Liang, Shi Wei, Xinling Liang, Shuangxin Liu. *Department of Nephrology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.*

Background: Uremic tumoral calcinosis (UTC) is a rare disease with metastatic tissue calcification in maintenance hemodialysis (HD) patients. However, limited data are available on treatment of UTC in HD patients. This article mainly discusses the diagnostic findings and efficacy of treatment in HD patients with UTC.

Methods: A retrospective analysis was conducted on the data of 13 cases of UTC, including their clinical features, biochemical indicators, imaging findings, diagnosis, therapeutic methods and follow-up results. Parathyroidectomy (PTX) or drug treatment were determined based on intact parathyroid hormone (iPTH) levels and clinical symptoms.

Results: All of 13 patients were diagnosed as UTC definitely by imaging examination. The predominant areas involved were the buttocks (4 cases, 30.77%), shoulders (4 cases, 30.77%), and elbows (3 cases, 23.08%). Based on the levels of iPTH, cases were categorized into two different groups: PTX treatment group was associated with high levels of iPTH, while drug treatment group (lanthanum carbonate or sevelamer with STS) was lower iPTH. After PTX treatment, there was a significant decrease in serum iPTH, calcium (Ca), phosphate (P) and alkaline phosphatase (ALP) levels ($p<0.05$). In drug treatment group, the serum P levels was decreased significantly, along with a finding that hemoglobin levels was increased ($p<0.05$). All the UTC had lessened or even disappeared after treatment 4 to 6 months.

Conclusions: Although most UTC patients have an increased iPTH, a small number had lower iPTH levels. Based on iPTH levels and clinical symptoms, the patients were treated with PTX or drug therapy. With proper treatment, UTC disappeared without the need for surgery to remove calcinosis tissue.

Funding: Government Support - Non-U.S.

PUB087

Survival Analysis of Hemodialysis Patients: Impact of Uremic Toxins

Mari Sargsyan,[1] Juan Robles bauza,[1] Sheila Cabello Pelegrin,[1] Joana M. Ferrer,[1] Miguel Uriol Rivera,[1] Juan Rey Valeriano,[1] Sonia Jimenez,[1] Cristina Egea,[1] Tania Villagrasa,[1] Gonzalo Gómez marqués,[1,2] Bernardino Barcelo,[1,2] Joan M. Gasco.[1,2] *[1]Hospital Universitari Son Espases, Palma de Mallorca, Spain; [2]Universitat de les Illes Balears, Palma de Mallorca, Spain.*

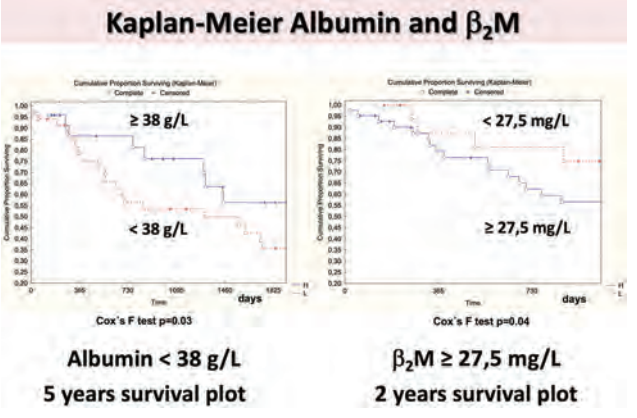
Background: HEMO study showed that β_2M serum level over time was predictive of mortality in hemodialysis (HD) patients (p). The aim of the study was to analyse β_2M and indoxyl sulfate (IS) as predictor factors of mortality.

Methods: 5 years follow-up of 60 prevalent HD p. Baseline midweek pre-HD serum β_2M by nephelometry and total IS levels by HPLC connected to a UV detector. High serum β_2M group ≥ 27,5 mg/L. As to IS, p were divided into quartiles (1q <9,7 mg/L, 2-3q ≥9.7-26.5mg/L, 4q>26.5 mg/L). Kaplan–Meier analysis at 1,2,3 and 5 years in univariate analysis for albumin (≥38 g/L or lower), β_2M, and total IS groups. Multivariate analysis by proportional hazards Cox's model.

Results: 60 prevalent p with mean vintage of 46,8 months (range 3-299 months). 60±20 years. Females 46,6%. 35% diabetic. 51,6% HD, 48,3% post-dilution haemodiafiltration, with mean convective volume of 23,8±2,8L. Mean eKt/V 1,67±0,4, mean nPCR 1±0,27g/kg/day. 8,3% of p had urine volume>500cc/24 hours. Mean β_2M level 5,6±1,9mg/L (X±SE). Mean total IS level 18,9±1,6mg/L. Overall mortality at 5 years was 57%. Albuminemia lower than 38g/L was associated with mortality at 2, 3, and 5-years in univariate analysis (Cox's F test p=0.03, figure). No difference in survival rate between p with high or low serum β2M levels at 3 or 5 years analysis (Cox's F test p=0.27). At 2 years analysis, p in the lower β_2M group had better survival (Cox's F test p=0.04, figure). There was no statistically significant association between albumin, β_2M, IS level and mortality on multivariate analysis. We observe no statistically significant associated between IS levels and all-cause mortality.

Conclusions: β_2M < 27,5 mg/l was associated with better survival at 2 years univariate analysis. IS had no statistically significant association with all-cause mortality in our cohort.

Funding: Government Support - Non-U.S.



PUB088

A Novel Optimised Approach to Flow Balance and Fluid Removal During Haemodialysis

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Background: Fluid management is an integral component for managing patients to correct abnormalities in plasma composition and maintain fluid balance. Consequently, accurate fluid removal during treatment is a critical design element of haemodialysis machines. The SC+ haemodialysis system developed by Quanta Dialysis Technologies, is a compact, simple-to-use dialysis system designed to improve patient access to self-care and home haemodialysis. This paper describes the design, evaluation and performance of the flow balance and ultrafiltration module of SC+ to deliver specified fluid removal in accordance with the international technical standards for haemodialysis defined in IEC 60601-2-16 using a number of unique proprietary technologies.

Methods: SC+ uses volumetric flow balancing chambers contained within a single use disposable cartridge. During normal operation, dialysis fluid flows through the cartridge in discrete packets achieved by the application of pneumatic pressure and vacuum to manipulate a flexible PVC membrane that, in turn, opens and closes a sequential series of valves and pump cavities that constitute the flow balance chambers. Proof of system performance was undertaken using a range of dialysers and venous pressures, with and without ultrafiltration, to quantify the net fluid removal error, in order to simulate a range of patient conditions in typical clinical practice.

Results: In total, the tests comprised 22 separate runs on multiple machines, with 88 individual 30-minute measurement samples, taken over a range of environmental conditions, dialyser types (with differing KuF), dialysate flowrates, and venous pressures. Across all results, there was a mean error of 7.4g/hour rate error, (max allowed is 100g/hr) of positive flow from the blood to the dialysate side with a standard deviation of 19.88g/hr.

Conclusions: It has been demonstrated that flow balance error and fluid removal attainable with SC+ lies well within the acceptable standards permitted for haemodialysis machines, demonstrated across a range of clinically relevant parameters at dialysate flow rates of up to 500ml/min.

Funding: Commercial Support - Quanta Dialysis Technologies

PUB089

Clinical Performance of the Optiflux® F160NR Dialyzer

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Background: Subjects in the clinical trial (NCT# 03536663), *An Open-Label Clinical Study to Assess the Performance of the Dialyzer with Endexo™ in End-Stage Renal Disease Subjects*, were dialyzed with the Optiflux® F160NR dialyzer, followed by the new dialyzer with Endexo. This sub-analysis reports the safety and performance of the Optiflux® F160NR dialyzer.

Methods: Subjects prescribed thrice-weekly HD for at least 30 days at three US study sites were enrolled in the study. The Optiflux F160NR dialyzer study period included 12 HD treatments. Performance and safety assessments included URR, spKt/V, serum albumin and ß-2-microglobulin levels with removal rates measured pre and post HD, complement activation, and Adverse Events (AEs).

Results: Twenty-six subjects were screened. Twenty-three subjects were enrolled in the study (median age 64 years, females 73.91% and white 73.91%) and completed 268 HD treatments with the Optiflux F160NR dialyzer. Four subjects discontinued the study due to missed visits, not related to adverse events. 19 subjects completed all 12 HD treatments per protocol (n =228 dialysis sessions). Delivered HD parameters are presented in Table 1. No SAEs were reported during the study. Four subjects reported at least one adverse event not device related. Mean (SD) reported for enrolled subjects were: 80.5% (4.5) for URR, 1.9 (0.3) for spKt/V, 47.1% (7.4) for corrected ß-2-microglobulin removal rate and an increase of 8.3% (8.2) post HD for serum albumin. Complement activation was measured Pre HD and 30 min Post HD start and showed no overt activation for C3a, C5a and sC5b-9.

Conclusions: HD treatments were well tolerated and URR and spKT/V were high with Optiflux® F160NR dialyzer. Serum albumin levels increased post HD. Complements showed no overt activation.

Funding: Commercial Support - Fresenius Medical Care North America

Table 1. Delivered HD for completed subjects (n=19, 228 HD sessions)

HD	Mean (SD)
Dialysis Duration(min)	205.2 (18.0)
Blood flow rate (mL/min)	445.6 (32.4)
Dialysate flow rate (mL/min)	695.0 (62.7)
Blood volume processed (L)	82.2 (7.9)
Ultrafiltration volume (mL)	2253.8 (666.6)

PUB090

Dialysis Disequilibrium Syndrome: Severe Irreversible Brain Injury Following Hemodialysis

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Introduction: Dialysis disequilibrium syndrome (DDS) is a clinical complication of hemodialysis (HD) characterized by neurological symptoms attributed to cerebral edema that rarely occurs in ESKD patients following their first HD treatment. Treatment is primarily preventative, aimed at decreasing the rate of urea clearance to reduce subsequent osmotic fluid shifts. We describe a case of DDS with severe neurological sequelae in a patient with acute on chronic kidney disease.

Case Description: A 39 yo man with CKD 4 presented with dyspnea, lethargy and confusion. Initial labs showed a Na 133 mmol/L, K 7.9 mmol/L, BUN 281 mg/dl and creatinine 38.6 mg/dL. HD was initiated for treatment of uremia and hyperkalemia. Two hours after the start of HD, the patient had a tonic-clonic seizure followed by cardiopulmonary arrest. Lab data post-arrest showed a Na 133 mmol/L and BUN of 112 mg/dL (Fig 1). In the subsequent days, the patient remained in a comatose state. MRI of the brain revealed cortical restricted diffusion in both cerebral hemispheres and bilateral basal ganglia, concerning for hypoxic-ischemic injury. His clinical status did not improve over 3 months. He required a tracheostomy and PEG tube placement with HD dependency on discharge.

Discussion: DDS remains a rare clinical phenomenon which typically occurs with initiation of HD in those with severe azotemia and advanced CKD. Risk factors include pre-existing neurological conditions, hyponatremia, and higher starting BUN levels. While the pathogenesis remains debated, DDS is believed to be due to a reverse osmotic effect that occurs due to a faster decline of urea within the blood versus the brain creating osmotic disequilibrium with subsequent movement of water into the brain causing cerebral edema. Idiogenic osmoles may also be involved. Recognition of patients at high risk is crucial as it provides an opportunity to implement preventative strategies including reduced HD treatment time with lower blood flows aimed at more gradual clearance of urea.

Figure 1: Patient's clinical course

PUB091

Sustained High-Dose Chronic CRRT Fails to Attenuate Severe Lactic Acidosis in an Immunotherapy-Resistant Case of Malignant Melanoma with Liver Visceral Crisis

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Introduction: Lactic acidosis is the most common cause of metabolic acidosis in hospitalized patients. Though of little proven benefit, continuous renal replacement therapy (CRRT) has been suggested as treatment in some patients. We describe a rare case of a patient with lactic acidosis who received nineteen days of high dose CRRT.

Case Description: A 60-kg young Chinese female with melanoma and extensive liver metastasis presented in a visceral crisis. She was given combination of nivolumab and ipilumab which was projected to take 1 month to work. She had severe lactic acidosis with serum lactate of 17mmol/L on admission despite normal renal function. After a failed trial of medical therapy, CRRT was started purely for lactic acidosis. A spot measurement of effluent lactate was 15mmol/L while the corresponding plasma lactate was 16.3mmol/L, suggesting sieving coefficient of 0.92. Switching to a lactate free dialysis fluid multiBic did not help. Despite uninterrupted CRRT for 19 days, and repeated increase of effluent dose to peak of 5L/hour, giving lactate clearance of 76.7ml per minute, there was no improvement. She eventually demised 4 days after cessation of CRRT.

Discussion: We describe an unfortunate case where 2 specialties tried hard to save this young patient from the fatal complications of her aggressive tumor. Type B lactic acidosis is better described in hematological malignancies but there are increasing reports in solid organ tumors, most with extensive hepatic involvement. We present the first case of melanoma causing lactic acidosis reported in literature till date. While CRRT, convective therapies, bicarbonate-based dialysis fluids have been suggested as treatment for lactic acidosis, there is little proven benefit. In our case, we combined all 3 strategies, persisted at high dose for 19 days with no success. 2 learning points: Firstly, lactic acidosis in the absence of hypoperfusion (Type B) is not uncommon and equally dangerous. Secondly, while dialysis removes lactate to some extent, it is at best a temporizing measure. Addressing the underlying cause takes priority. Dialysis, regardless of dose, modality and timing is less likely to affect outcome.

PUB092

Primary Caregiver Burden in a Hemodialysis Clinic in Mexico: Prevalence and Caregiver-Related Risk Factors

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Background: Dialysis treatment is defined as a family disease. Primary caregiver is the main person who takes the responsibility for and supports the patient; caregiver burden can be defined as the strain or load borne by a person who cares for a chronically ill family member. The Zarit survey is a psychometric instrument designed to grade caregiver burden, recommended and validated among caregivers of patients in hemodialysis.

Methods: A descriptive study was conducted among primary hemodialysis caregivers from a dialysis clinic in Guanajuato, Mexico. Zarit Scale (A validated 22-item questionnaire with five item ranged from 0=never to 4=always) was applied in order to identify presence and level of caregiver burden. Caregivers of patients less than 3 months were excluded. Social and demographic data related were also collected. Data was analyzed for descriptive statistics using T-test and Chi square for comparation between groups.

Results: A total of 86 primary dialysis caregivers answered the survey via personal interview with one of the investigators. Most responders were female (77%) with a mean age of 47±15 years old. Seventy seven percent were married and almost all had an occupation (95%): homemaker (43%) was the most common. We found that couples take care of patients in 42% of cases, followed by parents (27%). Interestingly, 46% of responders did not take own recreational time and some of them (38%) were diagnosed with some chronic illness. More than half (56%) usually take care of 1 to 3 more persons along with the patient and meantime of life spent caring was 2 years. Any level of caregiver burden was identified in 67%, most of them (86%) in a slight level. There were not statistical differences between groups with none and any burden.

Conclusions: ESRD affects not only patients but also the people who takes care of them. Caregivers burden is prevalent in our clinic. Caregivers are predominantly female

partners who have to cope with patients care along with attendance of other relatives and often the need to work for economic support of their families. These results should be added to the public health burden of ESRD in Mexico.

Burden Level	
None (0 - 20)	28 (33)
Mild (21 - 40)	40 (46)
Moderate (41 - 60)	14 (16)
Severe (61 - 88)	4 (5)

PUB093

Within-Patient Relationships Between Ultrafiltration and Fluid Gains in Haemodialysis Patients

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Background: Despite the now-widespread use of haemodialysis treatment, optimal fluid management in long-term dialysis patients remains challenging. Whilst the between-patient factors affecting target weight and ultrafiltration have been well studied, little is known regarding the within-patient factors affecting these relationships.

Methods: Dialysis data for a group of stable haemodialysis patients, from 4 dialysis units, were analysed over a period of one year. All weights and volumes are expressed as percentage of target weight.

Results: From 100 patients (aged 28–89, mean 65.4, 54% male) observed over a year, complete data were available for 15530 dialysis sessions, and 13027 combinations of dialysis session plus the following inter-dialytic interval. Mean arterial pressure dropped by 3.5(+/-14.6)mmHg during dialysis, with a significant correlation ($p<0.05$) between pressure drop and ultrafiltration volume in 26 patients (mean R=0.09, mean regression gradient 3.2). In 87 patients, inter-dialytic fluid gain correlated strongly ($p<0.05$) with the previous dialysis session's ultrafiltration volume (mean R=0.37, mean regression gradient 0.20) suggesting a significant role of ultrafiltration volume in driving subsequent fluid intake behaviour (thirst). Unsurprisingly, more fluid was gained over longer inter-dialytic intervals: mean(sd) weight at the start of dialysis was 103.2(1.0)% after a 3-day gap and 102.5(1.0)% after a 2-day gap, with this difference being significant ($p<0.05$) in 87 patients. However, fluid gain was non-linear, diminishing during longer inter-dialytic intervals: mean(sd) daily inter-dialytic fluid gain was 1.13(0.38)% during the 3-day gap vs 1.21(0.53)% during the 2-day gap ($p<0.05$ in 36 patients), implying that at least a third of patients consume less fluid during the 3rd post-dialysis day.

Conclusions: Inter-dialytic fluid gain is strongly dependent on ultrafiltration during the previous dialysis session, and diminishes during the inter-dialytic interval. Large ultrafiltration volumes, which have historically been perceived as the inevitable result of large fluid intakes, are actually a cause of thirst and large fluid intakes in haemodialysis patients. These data, derived from within-patient analyses, strongly challenge our conventional understanding of dialytic fluid management.

PUB094

Medical Waste Management: How Industry Can Help Us Protect the Environment and Money

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Background: The global climate change and it's consequences force us to remodel our processes and rething current model of providing the HD treatments. One of the crucial point, which have massive impact on the environment and the economy is the waste management. Every HD session produce above 1 kg of medical waste, which should be properly stored and destroyed. Well thought out processes and our choices can improve dialysis unit budget as well as decrease CO2 emission nascented during the waste incineration.

Methods: The weight of dialyser is one of the crucial components of the medical waste produced during dialysis session. The authors checked the weight of different dialysers regulary used in dialysis centers in Poland. The Kern CM 320-IN scale was used for the measurement. The measurement accuracy was 0,1 g. Also the filling volume of each dialyser has been taken into consideration.

Results: The the weight difference between dialyser produced by different manufacturers is 95 grams from the heaviest to lightest ones. The ligthest dialysers are Fresenius FX class filters, the heaviest ones are Baxters Polyflux. that it's mass should be taken into consideration, when we are choosing the type of the filter. Of course the most important are still the medical parameters of the dialyser but in case of comparable performance data, the weight can be tip the balance during decision making. The dialysis center, treated 100 patients can save 1.482 kilos of medical waste yearly only by using the lightest dialysers, in comparison with the heaviest ones. In global perspective the saving are much more noticeable. Authors also noticed the difference in priming volume of checked dialyser. The biggest one was in Elysio dialysers, the smallest in FX series and Leoceed ones.

Conclusions: Everyone of us should be aware how our daily activity influence on the environment. Both, medical industry and nephrologists are responsible for decreasing the quantity and weight of medical waste produced during dialysis treatment. Careful proceeding with the disposables (proper procedures, medical staff training and awareness) will directly help to make the HD treatment more cost-effective and help to protect our planet.

PUB095

Early Intervention of Continuous Hemodialysis Filtration Is Effective to Improve Acute Kidney Injuries and Mortality in Patient with Propofol-Related Infusion Syndrome

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Introduction: Propofol related infusion syndrome (PRIS) is a fatal syndrome that often develops under the long-term propofol infusion at high doses. The main features of the PRIS consist of cardiac failure, rhabdomyolysis, acute kidney injury, and severe metabolic acidosis. High dose propofol, but also supportive treatments with catecholamines and corticosteroids, act as triggering factors. Propofol is usually administered at 0.3~4.0 mg/kg/hr or less to the sedation of adult patients, and is not administered beyond 7 days to prevent PRIS. We report here a case of PRIS developed rhabdomyolysis, acute kidney injury, and severe metabolic acidosis under the dose of propofol within the safety dose.

Case Description: A 41-year-old woman was operated cervicothoracic posterior longitudinal ligament ossification. After the operation, maximum 3.5 mg/kg/hr of propofol was used for sedation for treatment of severe pneumonia under the mechanical ventilator. Catecholamines was also used to support hemodynamics. However, unidentified hyperthermia and impaired blood pressure were prolonged, then administration of propofol was discontinued on POD6. Acute kidney injuries (sCr2.3mg/dl), metabolic acidosis and high serum CK (79300U/L) due to rhabdomyolysis were observed on POD8. Continuous hemodialysis filtration (CHDF) therapy was initiated, and hyperthermia, oxygenation, impaired hemodynamics and renal dysfunction were gradually improved. Finally, cardiac failure and renal function were totally recovered.

Discussion: Propofol impairs free fatty acid utilisation and mitochondrial activity. Imbalance between energy demand and utilisation is a key pathogenetic mechanism, which may lead to cardiac and peripheral muscle necrosis. CHDF may effective to maintain renal function and acid-base equilibrium through removal of metabolites induced by mitochondrial damage, such as lactate and creatine kinase. PRIS particularly when combined with catecholamines can be lethal and we suggest early intervention of CHDF is effective to improve renal injuries and mortality.

PUB096

The Conduct of Sponsored Trials Has No Association with Dialysis Facility Clinical Quality Outcomes

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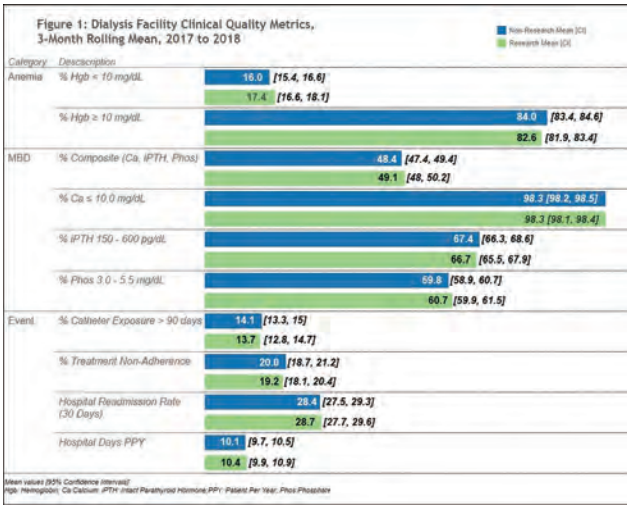
Background: There is a paucity of clinical trials conducted in nephrology vis-à-vis other fields (Baigent, et al. 2017). The lack of knowledge on impacts of trial conduct on dialysis facility operations can create barriers between stakeholders. We aimed to assess clinical quality target achievement in dialysis facilities conducting trials versus matched facilities with similar attributes that were not involved in research activities.

Methods: We used data from adult (age ≥18 years) hemodialysis patients treated at a dialysis provider network in the United States during 2017 to 2018. Facilities that did not participate in trials were matched to research facilities using 1:1 matching on logit of propensity score for patient years of follow-up, years of certification, % of Medicare patients, % of ESCO facilities and geographical region. We cross-sectionally compared mean facility-level quality metrics for: anemia (% Hgb ≥10 & <10g/dL), mineral bone disorder (% calcium ≤10.0mg/dL, % phosphate 3.0-5.5mg/dL & % iPTH 150-600pg/dL), and event outcomes (% catheter exposure >90 days, % treatment non-adherence, 30 day readmission rates, hospital days/patient year).

Results: We found no significant differences between mean facility-level quality metrics in dialysis facilities that conducted trials versus matched facilities not involved in research (**Figure 1**).

Conclusions: We found the conduct of trials in dialysis facilities had no association with achievement of quality targets, as compared to matched facilities not participating in trials. These insights are of importance to providers and stakeholders participating in/considering nephrology research activities that are necessary for advancing the state of the art.

Funding: Commercial Support - Fresenius Medical Care



PUB097

The Kt/V Measurement Provides Little Useful Information to Help Manage a Patient

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Background: We measure KT/V monthly but to what purpose? Does this reflect adequate dialysis? Can one predict needed information such as albumin, calcium phosphorus product or potassium?

Methods: To this end we reviewed our montly May 2020 dialysis laboratory studies to see if there was any meaningful relationship with the standard pooled KT/V measurement. We indexed albumin. calcium phosphorus product and whether thes parameters correlated with KT/V.

Results: Our population consisted of 106 patients of which 61 were males with an average age of 64 ± sd 12 years and on dialysis an average of 1785 ± sd 1713 days and 45 females of average age 65 ± sd 17 years on dialysis 1137 ± sd 979 days. The median time on dialysis was 842 days for males and 846 days for females. The mean albumin was 3.7 ± 0.36 g/100 ml. The mean hemoglobin was 9.6 g /100 ml ± sd 1.4, Th mean calcium phosphorus product was 48 ± sd 16. Th calcium averaged 9.2 ± sd 0.7 mg/100 ml and phosphorus 5.3 ± sd 1.7 mg/100 ml. The mean KT/V was 1.48 ± sd 0.30. Using Excel a correlation coefficient was calcuated between albumin and KT/V = 0.28, hemoglobin versus KT/V = -0.03, calcium and phosphorus product versus KT/V = -0.19 and potassium versus KT/V = 0.05. Vintage of dialysis corelated poorly with albumin = 0.09 and with potassium 0.09.

Conclusions: In summary KT/V as a standalone measurement has minimal if any relationship to the parameters investigated and its continued use should be reconsidered.

PUB098

Impact of Major Surgical Operations on Clinical Outcome in Dialysis Patients

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Background: We aimed to study the impact of major surgical operations on clinical outcome in patients with haemodialysis (HD) or peritoneal dialysis (PD).

Methods: We retrospectively evaluated the records of all patients on HD and PD, who had been treated for at least 3 months at our outpatient clinics between January 1, 2014 and December 31, 2018. In addition to clinical and laboratory parameters, data on all major surgical operations were recorded.

Results: Among the 202 patients, 133 (66%) were on HD and 69 (34%) on PD. The mean age (±SD) was 58.3±14.5 years, 48% were female and 28% had diabetes mellitus. Forty-seven patients (23%) had a major surgical operation. The operation types were cardiovascular in 14 patients, orthopaedic in 11, gastrointestinal in 8, genitourinary in 6, parathyroidectomy in 5 and brain, pulmonary and breast in 1 patient each. Operations were emergent in 10 patients (21%) and elective in the others (79%). Among the whole study population, 59 patients (29%) died during the study period. In Kaplan-Meier analysis (Figure), mean (95% CI) survival time in operated patients was 43 months (37 to 49 months), while it was 49 months (46 to 52 months) in the others (p=0.023). Fifteen out of 23 deaths (65%) among the operated patients occurred in the first month after surgery. Severe perioperative complications (arrhythmias, hypervolemia, hypotension, bleeding, acute coronary syndrome, respiratory failure and cerebrovascular event) were recorded in 17 (36%) of the operated patients, of whom 16 died (p=0.001). Although did not reach a significant level, mortality rate tended to be higher after emergent operations than that after elective operations. Cox regression analyses revealed that age (RR 1.033, 95% CI 1.010-1.057, p=0.005), diabetes (RR 2.581, 95% CI 1.474-4.521, p=0.001), preoperative C-reactive protein level (RR 1.005, 95% CI 1.002-1.007, p<0.0001) and having a major surgical operation (RR 1.868, 95% CI 1.068-3.268, p=0.028) were the independent predictors of mortality.

Conclusions: Although prospective studies with a higher patient number are needed to confirm, our study shows that, in addition to age, diabetes and inflammatory status, having a major surgical operation is an independent risk factor for mortality in dialysis patients.

PUB099

Outcomes of Ceftolozane/Tazobactam Recommended Doses in Treating Multidrug-Resistant Bacteria in Critically Ill Patients Using Renal Replacement Therapy

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Background: Ceftolozane/tazobactam (CEF/TAZ) is a new broad spectrumn cephalosporin effective against Multi-drug Resistant (MDR) bacteria. The clinical outcomes of the recommended dose of CEF/TAZ in patients utilizing renal replacement therapies are lacking. The purpose of this study was to evaluate the clinical and microbiological efficacy of CEF/TAZ in treating MDR in pateints utlizing continous venovenous hemofiltraion (CVVH) and intermittent hemodialsyis (IHD).

Methods: A retrospective cohort study was conducted at our quaternary care hospital between May 2015 and December 2019. We reviewed all hospitalized adults who had MDR *Pseudomonas aeruginosa* or MDR *enterobacteriaceae* treated with CEF/TAZ while utilizing CVVH or IHD

Results: We identified 11 patients who met the inclusion criteria with a mean age of 63.0 ± 17.8 years and a mean weight of 63.8±15.7 kg. All patients were critically ill, needed mechanical ventilation, and used vasopressors. All 11 patients had pneumonia, one of them developed secondary bacteremia and two had decubitus ulcer. Nine patients had MDR *pseudomonas aeruginosa* while two had MDR *E. coli* and *Klebsiella Pneumonia.* Six patients were on IHD, while the remaining 5 patients were on CVVH. The most commonly used dose for CVVH was 450 or 750 mg intravenous (IV) every 8 hours (only one received 1500 mg at the same frequency). For IHD, the common dose was 450 mg IV every 8 hours. Of the 7 pateints who had repeated cultures, three had microbiological cure and four had clinical cure. Two pateints expired within 30 days and 3 more expired within 90 days. Two of the patients who had clinical cure, had recurrence within 4 weeks.

Conclusions: The efficacy of the recommended CEF/TAZ dose in patients utilizing RRT is uncertain. Pharmacokinetics and pharmacodynamics studies are urgently needed to determine the adequacy of CEF/AVI dosing in this population

PUB100

Does Dialyzer Surface Area Alone Adjusted to Body Surface Area Have Any Clinical Impact on Adequacy: A Single-Center Observation Study in Saudi Arabia

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Background: Dialysis adequacy using sp Kt/V is a standard KPI in HD units, determined by dialyzer clearance(K), Volume of distribution urea(V) and treatment time(t). Increase in larger dialyzer size (t, V being constant) is a norm to improve Kt/V during HD as the patients gradually lose residual kidney function. However initial and subsequent dialyzer prescription using Body Surface Area(BSA) instead of Weight(V) is less well studied. We looked into effect of BSA and DSA on Kt/V.

Methods: 163(n=) patients receiving in-center HD on Gambro dialyzers (Polyflux, Revaclear) studied. Demographic and clinical data collected. Patients were stratified into 4 groups based on their dialyzer surface area (DSA) as 1.4, 1.7, 1.8 and 2.1 m^2. For each group, we then calculated BSA(Du Bois method), HD vintage, treatment time(hours), Access type, sp Kt/V (Dougirdas) and % pts with inadequate sp Kt/V, <1.2. Hemoglobin for each group was compared too.

Results: Our patients were representative of any HD center in terms of demographics; age 57.8 ±18.3, 50.9%Males, 28.2% DM, vintage 59.3±51.2 m, BMI 25.1±6, BSA 1.7±0.3 and Kt/V 1.7±0.4. The use of dialyzer with DSA's 1.4, 1.7, 1.8 and 2.1 were 63.2%, 5.5%, 8.6% and 22.1 %. Among 4 groups, there was no significant difference in terms of age, treatment time, vascular access and hemoglobin, Image 1. But when DSA and BSA were stratified for adequacy, there was a modest linear trend of decreasing Kt/V with increasing BSA among 4 increasing DSA groups. Although all met the minimum spKt/V of 1.2, the proportion of patients with inadequate Kt/V were increasing despite their increasing dialyzer sizes. Factoring for equilibrated Kt/V, adequacy could just be borderline for larger patients.

Conclusions: Dialyzer size change in itself may not be effective in achieving target Kt/V as BSA increases; attention must be paid to increasing dialysis time. Dialyzer prescription, adjusting for BSA may be more appropriate, particularly in large patients.

Table 1 . Dialysis variables

DSA M²	AGE, YEARS	HOURS/ SESSION	FISTULA (%)	HEMOGLOBIN G/DL
1.4	57.2±20.3	3.86±0.2	47.6	11.0 ±1.8
1.7	60.9±14.5	3.88±0.2	55.6	11.2±0.8
1.8	60.9±14.0	3.92±0.17	61.5	11.3 ±0.8
2.1	58.3±14.2	3.86±0.25	48.6	11.0 ±1.4

Table 2 . Dialyzer, Body Surface Area and Adequacy

DSA (M2)	BSA (M2)	Δ SA (BSA-DSA)	SP KT/V	SP KT/V <1.2 (%)
1.4	1.55 ±0.23	0.15±0.2	1.74±0.39	3.9
1.7	1.59 ±0.13	-0.11±0.1	1.68 ±0.37	11.1
1.8	1.68 ±0.21	-0.12±0.2	1.66 ±0.22	14.3
2.1	1.94 ±0.19	-0.10±0.4	1.48±0.35	13.5

PUB101

High Ultrafiltration Rate: Is It Bad? A Case Report of a Patient on Hemodialysis for 29 Years with High Ultrafiltration Rate

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Introduction: High ultrafiltration on Hemodialysis stresses cardiovascular and could have negative effect on survival. This is the notion of many studies done in line with High ultrafiltration. However, are we missing the other side of coin, cumulated effect of fluid overload on cardiovascular system?

Case Description: We present a case 60 year male develop protein urea lost follow up, presented with CKD 5, started on hemodialysis which he is on for 29 years now. He was hypertensive to start with later became normotensive. His intradialytic weight gain is 4.5 to 5.5 liters, which he tolerates well without any episode of intradialytic hypotension.

Discussion: Except Carpal, tunnel Syndrome for which he had surgery, clinically stable, normal biochemical parameters and acceptable cardiovascular status with this entire very remarkable journey.

PUB102

The Influence of Different Hemodialysis Frequency on Maintenance Hemodialysis Patients

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Background: To investigate the effects of different dialysis frequencies on anemia, nutritional status, calcium and phosphorus metabolism, renal function indicators in patients.

Methods: The general data of MHD patients in our center from 2017 to 2019 and annual laboratory monitoring indicators (including HGB, SF, Bun, Scr, Ca, P, iPTH, ALP, ALB), urine volume and eGFR, were used to compare in patients with different hemodialysis frequency groups (Group A: 2 times/week, B: 5 times/2 weeks, C: 3times/ week).

Results: There were 269 patients (163 males, 106 females), with an average age of 52.650±14.982 years. There were statistical differences among HGB, Ca and ALB, but no statistical differences among SF, P, iPTH, ALP, Bun and Scr. The three-year overall compliance rate evaluation found that the overall compliance rate of HBG and Ca significantly increased. It was found that the compliance rates of HGB and Ca at the dialysis frequency of 2 times a week were significantly lower than those of the other two groups, but there is no difference for P, iPTH and ALB.

Conclusions: Different from western countries countries or developed areas, the the frequency less than 3 times is more than two-thirds in the western region in China. In this study, the average of HGB and Ca in patients with dialysis 3 times a week is significantly higher than other groups with low-frequency, and the compliance rate of HGB and Ca in group with the dialysis 3 times a week increased significantly. The results suggested that the higher frequency group was better in anemia and calcium correction.

the compliance rate of HGB, Ca, P, iPTH, ALB (%)

		HGB	Ca	P	iPTH	ALB
2017	Group A	21.277	25.532	45.745	63.83	82.979
	Group B	42.478	41.593	43.363	53.982	86.726
	Group C	45.161	51.613	33.871	62.906	90.323
	X2	6.561	11.654	2.224	0.171	1.422
	P value	0.038	0.003	0.329	0.918	0.491
2018	Group A	35.106	31.489	46.809	61.702	87.234
	Group B	53.982	41.592	36.283	55.752	90.265
	Group C	69.355	52.548	32.307	72.581	93.548
	X2	18.169	5.642	3.710	0.798	1.669
	P value	0.000	0.043	0.156	0.671	0.434
2019	Group A	47.872	40.426	45.055	27.660	87.234
	Group B	60.176	48.673	43.363	29.203	87.612
	Group C	67.741	58.065	32.258	30.546	95.162
	X2	7.315	4.697	2.486	0.166	2.965
	P value	0.026	0.031	0.288	0.920	0.227

PUB103

Achromobacter Xylosoxidans, Subspecies Denitrificans, Exit Site Infection, and Aeromonas Hydrophilia Peritonitis: Rare Infections in Peritoneal Dialysis Patients

Akshay Verma, Faisal N. Khan. *Victoria Nephrology Associates, Victoria, TX*.

Background: Achromobacter xylosoxidans, subspecies denitrificans, exit site infection in peritoneal dialysis patient is rare and will be reported. A second case of rare peritoneal infection caused by Aeromonas hydrophilia peritonitis will also be reported. Both are gram-negative micro-organisms and are usually found in wet environments, causing infections in immunocompromised patients. Both cases occurred in the same rural city and in the same dialysis facility.

Methods: The cases involved conducting interviews with patients and documenting each visit. All observations and visitations were assessed in the dialysis center of a rural area. Previous data of cases with similar rare pathogen caused peritonitis were also analyzed.

Results: The patient with exit site infection, Achromobacter xylosoxidans, was treated with oral ciprofloxacin for 3 weeks resulting in a slow improvement of the exit site. During treatment the patient experienced erythema, discomfort, and discharge. At the end of the treatment, repeat cultures drawn from the exit site were negative. The patient with Aeromonas hydrophilia peritonitis is currently being treated with intraperitoneal Gentamicin.

Conclusions: Achromobacter xylosoxidans and Aeromonas hydrophila are both rare bacterial infections that have a history of causing infections in immunocompromised individuals exhibiting multiple risk factors. We reported exit site infections and peritonitis in end stage kidney disease patients. Both infections have been treated without any adverse effects or removal of peritoneal dialysis catheters.

PUB104

Bicarbonate-Rich Peritoneal Dialysis as Salvage Therapy for Metabolic Acidosis

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Introduction: Use of peritoneal dialysis (PD) in ICUs in developed nations is limited. The need for emergent dialysis is often considered a contraindication for peritoneal dialysis and the large peritoneal surface area is often neglected in the resuscitation of critically ill patients. We report a case of successful emergent PD with high bicarb dialysate in an actively dying patient not tolerating standard renal replacement therapies.

Case Description: A 36 yo male with no medical history sustained multiple gunshots. He was found to have multiple injuries in the small bowel including the duodenum. Two 15-french drains were placed at the time of surgery. While initially stable, he gradually developed worsening hypotension and developed abdominal compartment syndrome requiring a bedside laparotomy that evening. A severe metabolic acidosis remained refractory to standard therapy. CRRT was started briefly but he was unable to tolerate due to worsening hypotension. His pH worsened (pH 6.97) with bicarb 6mmol/L and lactate (LA) 26.9mmol/L. Family said their goodbyes and he was made DNR. Methylene blue was given without hemodynamic change. Given his young age, inability to tolerate CRRT and intraperitoneal access already available, decision was made for emergent PD as a final effort to control refractory acidosis. Approximately 1L of 1.5% peritoneal dialysate with an additional 300 mEq sodium bicarb/2L bag was instilled for a 30 minute dwell time. Within an hour, his labs showed pH 7.12, bicarb 15mmol/L, LA 16mmol/L and his vasopressor requirements decreased. After four exchanges, CRRT was initiated. His acidosis resolved within 24 hours and he was vasopressor free by 36 hours. He was extubated, dialysis dependent and continues to recuperate.

Discussion: PD in developed nations is often a forgotten modality for acute renal failure. We found only 2 published reports since 1980 using PD in the ICU for metabolic control. Our case describes successful use of high bicarbonate PD in the ICU to control refractory acidosis and achieve hemodynamic control. Data is lacking on the use of emergent PD in trauma patients and within ICUs despite its relative ease and low cost. High bicarbonate PD is an option for refractory acidosis in the critically ill.

PUB105

Myoclonic Seizures and Altered Mental Status in a Patient on Peritoneal Dialysis Treated with Piperazine

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Introduction: Here we present the case of a man on automated peritoneal dialysis (APD) with altered mental status and myoclonus after the self-administration of piperazine, an anthelmintic. This case illustrates how dangerous self-medication can be in patients with chronic kidney disease. Additionally, it shows that neither peritoneal dialysis nor hemodialysis appear effective methods for piperazine clearance in patients on renal replacement therapy (RRT).

Case Description: A 66-year-old man was brought unresponsive and with myoclonus to the ER. His past medical history included diabetes mellitus, with diabetic nephropathy that lead to ESRD. He was started on RRT 1 year before presentation; initially hemodialysis but later APD. He had no history of seizures or any other neurological disease. Physical examination on admission revealed a dehydrated, ill-looking patient. He was unresponsive to verbal commands. Myoclonus predominantly in his left arm was noticed. Initially we

suspected bacterial infection as the cause of the altered mental status, empirical antibiotic treatment was initiated. However, the patient's symptoms persisted, requiring care at the ICU and intubation. Further interrogation of the patient's family revealed that he had self-administered a full bottle of piperazine hexahydrate. An infectious cause was ruled out and no clinical improvement was achieved with antiepileptics. At this point piperazine intoxication was our most likely diagnosis. After a week of APD we decided to switch RRT to sustained low efficiency hemodialisys (SLED). He received two sessions. Gradually the patient's mental status improved and was discharged with his usual APD.

Discussion: The most common symptoms of piperazine intoxication are myoclonus, decreased level of consciousness and ataxia. Few data is available regarding the dializability of this medication, and neither PD nor HD seem effective treatment options. Hemoperfusion seems a suitable alternative. Clinical improvement in this case may be due drug metabolism, independent of treatment. We want to highlight the importance of education in renal patients, specially in the dangers of self-medication. Fortunately, our patient had a full recovery. But that may not be the case of other patients who inadvertently poison themselves with "safe" medications; like piperazine.

PUB106

Two-Year Follow-Up of Quality Indicator Compliance in a Large International Peritoneal Dialysis Institution

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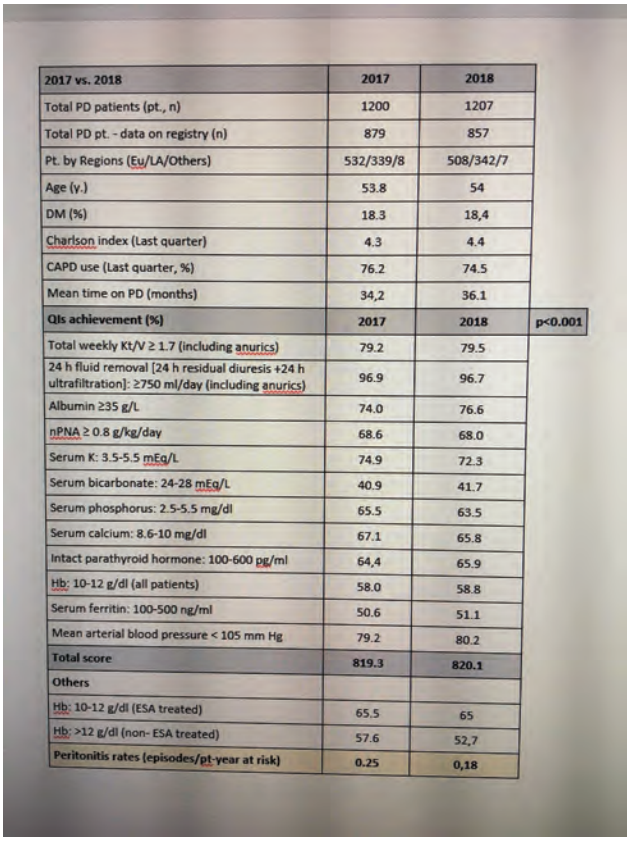
Background: Peritoneal dialysis (PD) practice is not universally homogeneous, best clinical practices are not completely understood as reference values are often obtained from small sized populations and/or frequently based on chronic kidney disease (CKD) and/or hemodialysis data. **Objectives:** To evaluate two years of follow up of compliance with PD-related quality indicators (QIs) following definition of new targets in an international PD network.

Methods: All English and Spanish language CKD and PD guidelines were reviewed. Twelve Qis were considered being of significant relevance and targets for these QIs were defined (see table). Retrospective data analysis

Results: Achievement of QI targets for years 2017-2018 is shown in table (image). Variability among countries not shown.

Conclusions: There was a significant increase in QIs achievement in 2018 vs. 2017. ≥75% of patients met the target for the following variables: total weekly Kt/Vurea, 24 h fluid removal, mean arterial blood pressure and serum albumin. Peritonitis rates are clearly over International objectives and were improving. Due to the lack of referral source data, these series may help to understand PD practice and outcomes in a global setting.



2017 vs. 2018	2017	2018	
Total PD patients (pt., n)	1200	1207	
Total PD pt. - data on registry (n)	879	857	
Pt. by Regions (Eu/LA/Others)	532/339/8	508/342/7	
Age (y.)	53.8	54	
DM (%)	18.3	18,4	
Charlson index (Last quarter)	4.3	4.4	
CAPD use (Last quarter, %)	76.2	74.5	
Mean time on PD (months)	34,2	36.1	
QIs achievement (%)	**2017**	**2018**	**p<0.001**
Total weekly Kt/V ≥ 1.7 (including anurics)	79.2	79.5	
24 h fluid removal [24 h residual diuresis +24 h ultrafiltration]: ≥750 ml/day (including anurics)	96.9	96.7	
Albumin ≥35 g/L	74.0	76.6	
nPNA ≥ 0.8 g/kg/day	68.6	68.0	
Serum K: 3.5-5.5 mEq/L	74.9	72.3	
Serum bicarbonate: 24-28 mEq/L	40.9	41.7	
Serum phosphorus: 2.5-5.5 mg/dl	65.5	63.5	
Serum calcium: 8.6-10 mg/dl	67.1	65.8	
Intact parathyroid hormone: 100-600 pg/ml	64,4	65.9	
Hb: 10-12 g/dl (all patients)	58.0	58.8	
Serum ferritin: 100-500 ng/ml	50.6	51.1	
Mean arterial blood pressure < 105 mm Hg	79.2	80.2	
Total score	**819.3**	**820.1**	
Others			
Hb: 10-12 g/dl (ESA treated)	65.5	65	
Hb: >12 g/dl (non- ESA treated)	57.6	52,7	
Peritonitis rates (episodes/pt-year at risk)	**0.25**	**0,18**	

PUB107

Acyclovir-Induced Encephalopathy in a Patient on Peritoneal Dialysis

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Introduction: Acyclovir is an antiviral agent that is used for treatment of diverse viral pathologies. The regular pharmacokinetics for acyclovir is altered with kidney dysfunction. At present, our knowledge regarding treatment of acyclovir neurotoxicity in patients undergoing peritoneal dialysis (PD) is limited, as only few case reports have been published. We describe a case of acyclovir induced encephalopathy in a PD patient that was successfully treated with hemodialysis.

Case Description: 34F with a history of systemic erythematous lupus (on prednisone, cellcept and plaquenil), ESKD on peritoneal dialysis (PD), subclinical hypothyroidism, anemia and hypertension was admitted for herpetic lesions of her lips and right eyelid. She was initiated on intravenous acyclovir at a dose of 500mg daily. 24 hours later, she developed acute confusion which progressed to include myoclonus, lethargy and coma. Labs on admission revealed hemoglobin 10, Na 137, K 4.6, Cl 92, CO2 22, BUN 64, Cr 20.85. CT head was negative. EEG did not reveal any epileptiform activity. Lumbar puncture and brain MRI did not show any evidence of viral encephalitis. Acyclovir neurotoxicity was considered as the etiology for her severe encephalopathy. Acyclovir was held and her CCPD prescription was increased but she continued to remain encephalopathic. A decision to initiate hemodialysis (HD) was made. After the first HD session, her mentation slightly improved. She received a total of 3 HD sessions, after which her mental status completely returned to baseline. Given that she improved after discontinuation of acyclovir and with HD this confirmed her diagnosis of acyclovir induced neurotoxicity. She was switched back to PD after recovery.

Discussion: Dose adjustment for acyclovir is recommended in patients with ESKD. Even when the acyclovir dose is adjusted for these patients, it can still cause neurotoxicity. This complication seems to be more common in those on PD likely due to the slower removal of the medication with PD. Clinicians need to be aware of this potential adverse event, as this diagnosis needs prompt recognition and treatment. Clearance of acyclovir with PD is not completely understood and in fact PD was not adequate to help with clearance in our patient despite increasing her prescription. The modality of choice for clearance of acyclovir in toxicity is hemodialysis.

PUB108

The Analysis of Risk Factors for the Patients with Venous Needle Dislodgment and Bleeding During Hemodialysis

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Background: A puncture of vascular access is commonly used in clinical treatment, such as hemodialysis or central venous catheters. Leakage or infection associated with Venous needle dislodgement (VND) is a high risk of fatality. However, only a few studies are focusing on patient disease, medication, and other risk assessments. Therefore, this study aims to explore the risk factors of patients with venous needle dislodgment and bleeding and hope to establish the risk classification.

Methods: This study was a prospective study conducted in the hemodialysis unit of Tainan Regional Hospital. During the three months from July 2019 to Sep 2019, we collected clinical data, including patient sex, gender, diseases, records of dialysis access leakage, anti-coagulant dose, and a risk assessment form. We compared the data between the two groups of patients who have at least one risk in the risk assessment form. We analyzed the data with STATA™. P<0.05 was defined as significant.

Results: In the study period, seventy-one patients were included in this study, with an average age of 63.0 (± 1.19 years) and 46 males (64.79%). The patients with any risk in the risk assessment form were considered the high-risk group. There were 72 venous needle dislodgment and bleeding in 32 patients during the study period. In the below feature, gender, high-risk group or not, diabetes, high blood pressure, exposure to Benzodiazepine, the experience of Intradialytic hypotension, exposure to warfarin, or dosage of anti-coagulant, there was no statistic significant between the patients experienced at least one episode of VND and others.

Conclusions: Between patients experience VND or not, we did not find any significant association in not only conventional factors or other factors. However, this study provides a reference for future research.

Funding: Commercial Support - AcuSense BioMedical Technology Corp

	Control (39 patients)	VND (32 patients)	P-Value
Male	28 (71.8%)	18 (56.3%)	0.19[b]
Age	63.28±0.16	62.65±0.17	0.79[a]
Risk assessment	19 (48.72%)	12(37.5%)	0.34[b]
AVF failure s/p PTA	9 (23.09%)	6(18.75%)	0.66[b]
Diabetes	24(61.54%)	23(71.88%)	0.36[b]
Hypertension	24(61.54%)	24(75%)	0.22[b]
Exposure to Benzodiazepine	6 (15.38%)	8(25.0%)	0.31[b]
Intradialytic hypotension	12 (30.77%)	5 (15.62%)	0.17[b]
Exposure to Wafarin	8 (20.51%)	7(21.88%)	0.89[b]
Anti-coagulation dose[c]	1000.0±92.41	1247.5±149.68	0.17[a]

[a] t-test , [b] chi-square test , [c] Innohep Equalibrition dose , * significant

Association between Venous Needle dislodgement and bleeding and other risk factors

PUB109

Catheter Malposition: Unacceptable Reason for Access Dysfunction

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Introduction: In 2017, 80% incident and 20% prevalent patients in the US received hemodialysis (HD) with a catheter (CVC). CVC placement with ultrasonography and fluoroscopy guidance (FG) is an accepted standard of care to avoid early mechanical complications. Early dysfunctional CVC (dCVC), defined as malfunction in <1 week of insertion is often due to a malpositioned tip leading to inadequate HD and a higher risk of bacteremia. We present a series of early dCVC, a preventable complication.

Case Description: Case 1: 42 y/o male had left IJ non-tunneled CVC placed for continuous dialysis therapy. Encountered multiple episodes of circuit clotting soon after initiation of therapy despite heparinization. The dCVC tip was found to be abutting against the innominate vein wall preventing adequate blood flows. An attempt to place a tunneled right subclavian vein catheter at bedside, without fluoroscopy was unsuccessful. Chest XR showed the CVC tip in the left IJ. **Case 2:** 30 y/o male with a pre-existing right portacath presented with several episodes of non-sustained ventricular tachycardia, 2 days after a newly placed left dialysis CVC. Chest XR showed portacath had disconnected and migrated to the right ventricle. Removal of the dislodged portacath led to resolution of arrhythmia. Dialysis CVC was preserved. **Case 3:** 49 y/o obese female had poor blood flows (300 ml/min) in catheter and frequent alarms that failed to improve despite tPA and port reversal. dCVC resulted from tip retraction from right atrium into SVC requiring replacing with a longer CVC. **Case 4:** 65 y/o female with left IJ tunneled CVC, placed under FG, had poor blood return 2 days after placement. The CVC tip had migrated to the right innominate vein. Catheter was replaced successfully. **Case 5:** 70 y/o male encountered clotting of the continuous dialysis circuit soon after initiation with a left IJ CVC, requiring replacement of circuit to continue with therapy. Evaluation showed a short CVC with tip abutting against superior vena cava (SVC) wall and required replacing with a longer CVC.

Discussion: Recognizing and troubleshooting early dCVC is an essential learning milestone for a nephrology trainee. Evaluation of a dCVC includes chest XR, forceful saline flush and appropriate use of tPA. Most of these mechanical complications are preventable with proper training and utilizing imaging tools during the procedure.

PUB110

Percutaneous Transluminal Angioplasty in Arteriovenous Fistula Dysfunction Secondary to Vascular Stenosis

Mohammed Shoeb Ahmed Khan, Vinod Kumar. Aster Medcity *Aster Medcity, Kochi, India*.

Background: Arterio-venous fistula (AVF) is the lifeline of a hemodialysis patient and the number of vascular access sites are limited in a patient. Vascular stenosis necessitates vascular intervention or creation of a "de novo" AVF. In this study we aimed to evaluate the outcome of percutaneous transluminal angioplasty (PTA) in arterio-venous fistula due to vascular stenosis.

Methods: This is a prospective study of two years (02.05.17 to 02.05.19). Records of patients admitted to our hospital were obtained from hospital archives and images from the hospital radiology archive system. Demographic characteristics, duration of dialysis, stenosis or occlusion level, patency rates of AVF were evaluated. All procedures were performed by interventional radiologists in a hybrid cath lab. Antegrade, retrograde, or both antegrade and retrograde punctures were used, depending on the site of the stenosis as deemed on preoperative ultrasound. A complete angiogram from the proximal arteriovenous anastomosis to the central venous outflow was performed in all cases. A successful percutaneous balloon angioplasty was defined when there was no more than 30% residual stenosis (KDOQI). AVF patency rates were assessed at six months and one year.

Results: Total number of patients studied were 16. The average age was 66.6 years. All were hypertensive and diabetics comprised 75% of study group. Coronary artery disease was established in 81.25%, and two patients were known to have chronic liver disease. Most common type of AVF was the left brachio-cephalic (62.5%), followed by radio-cephalic (37.5%). Average dialysis vintage of AVF at the time of procedure was one year. Previously failed AVF was present in two patients. There were 18 vascular stenosis in 16 patients. The most common site of stenosis was the venous cannulation zone (62.5%), followed by anastomotic site stenosis (31.5%) and central vein stenosis (18.75%). Successful PTA was done in 12 patients. There were no complications; hemodialysis was resumed within 24 hours after the procedure. The primary patency rate at three months was 100%, six months was 75% and at one year it was 37.5%. Four patients were lost to follow up. Mean follow up was 9.41 ±6.79 months. None underwent a repeat PTA.

Conclusions: Percutaneous transluminal angioplasty is effective for salvaging arterio-venous fistula in majority of hemodialysis patients

PUB111

A Tale of Two Accesses: The "Less Is More"

Sherif Metwally, Anil K. Agarwal, Khaled Boubes. *The Ohio State University, Columbus, OH.*

Introduction: Well-functioning dialysis access is of utmost importance as the lifeline of those with end stage kidney disease (ESKD). We present 2 patients with 'imperfect' accesses where a conservative approach avoided potentially problematic interventions.

Case Description: Case 1 A 24 year old man started hemodialysis (HD) in 1992 due to IgA nephropathy. He received a kidney transplant in 2000 which failed in 2005 requiring resumption of HD. His vascular access history is complex, including multiple bilateral failed arteriovenous (AV) fistulae and AV grafts requiring numerous access interventions including tunneled HD catheter placements, angioplasties, and thrombectomies. He has also developed severe contrast allergy, making any further endovascular interventions difficult. Since 2005 he has been dialyzing through a right upper extremity AVF complicated by central venous occlusion causing mild right arm swelling. Last resort vascular access options including a femoral AVG and a HeRO graft were contemplated. However, clinical decision making based on the presence of extensive collateral circulation, we opted for a conservative approach instead utilizing low blood flow rates. He has been doing well on this prescription for the last 3 years with adequate dialysis and swelling resolution. Case 2 A 67 year old woman with ESKD started peritoneal dialysis (PD) 2 years ago. PD was complicated by recurrent malpositioning of PD catheter with the catheter tip repeatedly migrating to the right upper quadrant. Changing the catheter insertion site and suturing it to the bladder wall did not prevent tip migration. Transition to HD was contemplated but she was able to continue with PD albeit with position changes to allow for complete drainage of PD fluid. Despite occasional sluggish drainage of PD fluid, the patient continued on PD for a total of 15 months before receiving a kidney transplant.

Discussion: These 2 cases illustrate the importance of dialysis access function as well as the dilemma of both the patient and provider when it becomes dysfunctional. The cases, however, also demonstrate that anatomical perfection is not always necessary to achieve adequate function. In both cases, a conservative approach allowed the patient to optimize dialysis through their existing 'malfunctioning' access and avoided further interventions that could result in worse complications, proving the adage 'Less is More' still true for dialysis access.

PUB112

What Are Nephrologists' Preferences Related to Continuing Medical Education?

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Background: Understanding how clinicians prefer to learn and participate in continuing medical education (CME) can help providers of such education design more engaging and effective activities that can potentially further improve nephrologists' clinical performance.

Methods: Medscape conducted a 10 question, online, incentivized survey in November 2018. Respondents' confidentiality was maintained and responses were de-identified and aggregated prior to analyses.

Results: Most preferred duration for a CME activity: 30 minutes (51%) Followed by 15 minutes (31%) Most preferred format for a CME activity: online (70%) Followed by live events at a medical conference (13%) Most preferred format for an online CME activity: video and text (45% each) For online CME/CE, most preferred instructional design format: case-based (56%) Most important factors in selecting online CME/CE activities: content description (60%) and learning objectives (56%) The most important factors in selecting which symposia to attend at a scientific congress were content description (60%), learning objectives (41%), and faculty (37%) Most common ways of becoming aware of available professional education activities: invitation from online providers (79%) and societies (74%) The majority of participants reported that in the past 12 months they have learned something from CME that changed their practice (86%) Serial learning is more impactful and clinically meaningful than a single activity (80%)

Conclusions: CME activities have an impact on changing clinician practices. Learner preferences for nephrologists related to live and online CME were identified. Most prefer participation in multiple activities that are online, 15-30 minutes, case-based, video and text. Content description, learning objectives, and faculty play an important role in learner participation. These data should inform development of future CME activities that are engaging and impactful.

PUB113

Online Education Effectively Improves Nephrologists' Knowledge, Competence, and Confidence Related to Hyperkalemia Management

Amy Larkin, David R. Anderson, George Boutsalis. *Medscape LLC, New York, NY.*

Background: To improve outcomes for patients, clinicians must be able to implement evolving standards of care and apply relevant data on hyperkalemia management. We sought to determine if an online continuing medical education (CME) curriculum could improve hyperkalemia management.

Methods: The online CME curriculum consisted of 4 activities. Of these, 3 were 30-minute video panel discussions. A repeated pairs pre-/post-assessment study design was used and McNemar's test assessed educational effect for each activity. The last activity comprised two patients presenting in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a 2-tailed paired t-test to determine *P* values. The activities launched in 2019 and data were collected for 4-12 weeks.

Results: Education significantly improved physicians' knowledge, competence, and performance managing and treating hyperkalemia. A 40% relative increase was observed among nephrologists related to knowledge of clinical trial data related to hyperkalemia. Nephrologists also significantly improved their knowledge and competence regarding the use of therapies in practice, with a relative increase of 16% observed. Case based simulation had a strong and significant positive impact on physicians' performance in the treatment of hyperkalemia. The % of physicians who decided to start preferred potassium-binder more than tripled after education.

Conclusions: Some gaps still remain after education. Over 40% physicians are still not equipped with the right information regarding clinical trial data and the use of therapies in practice. In addition, an average of 40% physicians are still not making the right decision to start preferred potassium-binder. As such, further education needed in these areas.

Funding: Commercial Support - independent educational grant from Astrazeneca and Fibrogen

Themes	N	% Correct Pre	% Correct Post	% Relative Change
Knowledge/Competence: Clinical Trial Data	225	38%	53%	40% (P < .001)
Knowledge/Competence: Use in Practice	230	49%	57%	16% (P< .05)
Performance: Initiate Newer Potassium-binder	160	15%	66%	340% (P < .001)

PUB114

Renal Clinic Quality Improvement Education Initiative

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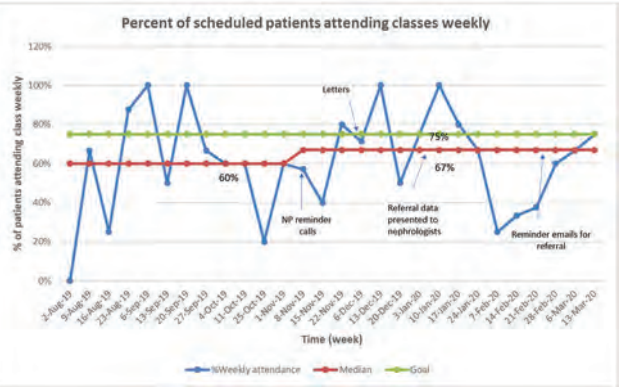
Background: Benefits of timely CKD modality education include increased knowledge and home dialysis. At our centre, attendance of scheduled CKD 4/5 patients to education sessions was low. This quality improvement study was initiated and aims to increase the prevalent percentage of CKD 4/5 patients who received CKD modality education from 40% to 55% over one year.

Methods: Outcome measure was prevalent weekly percentage of CKD 4/5 patients who completed education. Process measures were 1) weekly percentage of scheduled patient education attendance and 2) weekly number of incident CKD 4/5 patient education referrals by nephrologists. Ishikawa diagram was utilized to determine system gaps and develop changes to test in plan-do-study-act (PDSA) cycles. Changes tested were: a) NPs tracking weekly class attendance, b) NP reminder calls, c) information letter mailed to patients, d) referral data presented to nephrologists, e) reminder emails to nephrologists on education eligible patients. Discussion with primary care colleagues and 5-whys tool resulted in developing an information webpage for patient education including NPs' zoom recorded sessions. Median outcome and processes were calculated and plotted on run charts.

Results: Prevalent percentage of CKD 4/5 patients educated decreased from 40.6% to 29.4%. All referred patients have not yet been educated due to COVID19 and number of new patients increased over time. Median weekly session attendance increased from 60-67% with PDSA cycles a-c (Figure 1). Monthly incident education referral number increased from 5-18/month.

Conclusions: Weekly session attendance and incident education referrals increased. Prevalent percent patients educated deceased but number of incident referrals increased. To provide a virtual information option for patients with barriers to attending sessions and for use during COVD19 pandemic, the webpage described is a helpful resource developed as a result this project. We anticipate this tool will increase the outcome and both process measures over time.



PUB115

Optimizing On-the-Go Learning Utilizing Short Modules on Topics Related to Nephrology

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Background: Residents and medical students are expected to formulate evidence-based treatment plans by keeping up with the most recent guidelines but that can be difficult given our schedules. In such circumstances, it is ideal to learn bite-sized pieces on the go.

Methods: We created two modules about Phosphorus Binders and Oral Hypoglycemic Agents using a friendly graphic interface called Prezi. These modules were estimated to take 10-15 minutes and were accompanied by a total of seven content related questions that were compiled from Uworld Step 3 Question Bank, John Hopkins Primary Modules, and hospital courses of patients seen at Stony Brook. Survey monkey was utilized to create the pre and posttest. The modules were sent to third and fourth year medical students. Data was collected for 10 days.

Results: Wilcoxon signed rank test was utilized to evaluate the effectiveness of the modules. Unfortunately, only six students completed the hypoglycemic module of which two had no improvement in scores, so no statistical significance was achieved. However, four of the six students had improvement in posttest scores by at least one point. Improvement in the posttest scores for the phosphorus module was significant as of the nine students who completed the phosphorus module, eight had an improvement by at least 1 point (W 36, p=0.008).

Conclusions: The observation of improved posttest scores for the phosphorus module supports the use of short lessons using a friendly graphic interface such as Prezi.

PUB116

Wabishki Bizhiko Skaanj: A Learning Pathway to Foster Better Indigenous Cultural Competence Within Canadian Kidney Research

Helen Robinson-Settee, Craig Settee. *Can-SOLVE CKD Network, Vancouver, BC, Canada.*

Background: Can-SOLVE CKD is a kidney research network in Canada within which Indigenous patients, caregivers, researchers, and community leaders have created an Indigenous Peoples' Engagement and Research Council (IPERC). A key component of IPERC's work is the creation of a new learning pathway, Wabishki Bizhiko Skaanj ("White Horse" in Anishinaabemowin), that will help researchers build respectful partnerships with Indigenous peoples within the health research setting. Wabishki Bizhiko Skaanj aims to enhance researchers' knowledge of racial biases, Indigenous voices and stories, the impact of colonization, and culturally safe health research practices.

Methods: A working group including members of the Can-SOLVE CKD Network, Diabetes Action Canada, First Nations Health Authority (BC), Provincial Health Services Authority (BC), and First Nations Health and Social Secretariat of Manitoba is leading the pathway's development. Two in-person workshops were held in October 2017 and March 2018 to develop the concept and identity of the curriculum, which consists of interactive learning exercises, facilitated online modules, and webinars. Several components of the pathway have been piloted and feedback is being gathered via surveys, pledges, and stories.

Results: The pathway's content is designed to help participants understand, recognize, and correct the racism that occurs in health care and research, in some cases caused by their own conscious and unconscious biases. Through enhanced knowledge, self-awareness and strengthened cultural competency, Wabishki Bizhiko Skaanj aims to support all partners in health care and research to close the gaps in health outcomes between Indigenous and non-Indigenous communities.

Conclusions: Wabishki Bizhiko Skaanj represents a novel learning platform for Indigenous cultural safety in Canadian health research. While Wabishki Bizhiko Skaanj was developed in the context of kidney health, the learning pathway can be adopted by networks and institutions across Canada, to help reduce and ultimately eliminate the racism that Indigenous people face within the health care system.

Funding: Government Support - Non-U.S.

PUB117

Ethylene Glycol Poisoning with Near-Normal Osmolal Gap: A Diagnostic Challenge

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Introduction: Ethylene glycol poisoning is classically associated with a high anion gap metabolic acidosis (HAGMA). Neurological and gastrointestinal symptoms predominate early while renal failure and death occur if not diagnosed and treated promptly. The diagnosis is usually suggested by HAGMA and an elevated serum osmolal gap in the setting of a suspected ingestion. Rarely, the serum osmolal gap may be close to normal which can delay the diagnosis or lead to a misdiagnosis. We report a case of ethylene glycol ingestion with near-normal serum osmolal gap.

Case Description: An 85-year-old man with a past medical history of Dementia presented to the Emergency Department with altered mental status, restlessness and elevated creatinine of 1.4 mg/dl (baseline 1.2mg/dl). History was difficult to obtain. Vital signs were normal and the physical exam was remarkable only for altered mental status. CT scan of the head did not reveal any acute abnormality. Laboratory workup revealed HAGMA (anion gap = 21 mEq/L, arterial blood pH = 7.26, serum bicarbonate = 9.3 mmol/L, lactic acid = 2.2 mmol/L) with a near-normal serum osmolal gap (12 mOsm/kg). Urinalysis, urine drug screen, blood ethanol, beta-hydroxybutyrate, acetaminophen and salicylate levels were normal. Given a high clinical suspicion for toxic alcohol ingestion, the patient was treated with IV fluids and fomepizole. Over the next few days, his mental status improved, and repeat laboratory workup demonstrated correction of the anion and serum osmolal gaps. Additional history obtained later from his family increased the suspicion for toxic alcohol ingestion. Ethylene glycol level, a send out lab, eventually resulted at an elevated level.

Discussion: The workup for a HAGMA should include evaluation of the serum osmolal gap in the setting of a suspected toxic alcohol ingestion. Although uncommon, the absence of an elevated serum osmolal gap should not prohibit treatment for toxic alcohol ingestion when the clinical suspicion is sufficiently high.

PUB118

A Not-So-Primeval Case Report of Elevated Creatinine Levels Following Work-Out Supplement Ingestion

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Introduction: Creatine is widely used and may be associated with acute kidney injury (AKI). They also may cause elevated serum creatinine (sCr) levels without AKI. We present a case of elevated sCr levels following supplement ingestion in a healthy male. To our knowledge, this degree of sCr elevation following supplement ingestion has not been reported in the absence of AKI.

Case Description: A 26 year old male with no medical history was seen for an elevated sCr (2.9 mg/dL) found on labs 3 weeks earlier. Baseline sCr was 1.3-1.4 mg/dL. He endorsed polyuria for 1 year. He denied ingestion of supplements, but reported working out 6 days per week. His BP and physical exam were normal. On UA, specific gravity was 1020, pH was 6.5, and sediment was unremarkable. He was asked to obtain a renal panel and a cystatin C (CyC), followed by a 24 hour urine collection to document urinary volume clearances. SCr had declined to 1.57 mg/dL that day, but on turning in his 24 hour urine sample, sCr was 16.21 mg/dL. A renal panel was repeated in the ER. He received only one urine collection container and filled it after 12 hours. He also reported taking two exercise supplements with work outs: Primeval Labs EAA Max™ and Protein Whey. BP, examination, and urine microscopy remained unremarkable. See Table for laboratory results. At appointment (apt) 2, the patient had abstained from supplements for 72 hours. He was counseled to continue to avoid these in the future.

Discussion: We present a case of elevated sCr's following ingestion of workout supplements in a healthy male. This case was unique given the degree of sCr elevation. The patient had normal CrCl, CyC eGFR, and a pattern of osmolar and electrolyte free water clearance consistent with a solute diuresis. Cr is usually not considered an effective osmole because it is present in insignificant amounts, but very large amounts of ingested creatine can increase Cr levels and also act as an effective osmole.

Creatinine and Cystatin C Levels

Date	Cr (mg/dL)	CyC (mg/L)
7/19	1.4	
8/19	1.3	
3/20	2.9	
4/20, T0 Apt 1	1.57	0.77
T+7d (submitted 12hrs urine collection)	16.21	0.78
T+8d (ER visit)	3.5	
T+14d Apt 2	0.9	0.69

PUB119

Compensatory Rules for Simple Acid-Base Disorders

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Background: Most acid-base compensatory equations are based on limited numbers of human observations. We searched the literature for all studies addressing the issue of acid-base disorder compensation. We then utilized all the available data to create an acid-base compensation diagram and generate more accurate compensatory equations.

Methods: We used 84 published articles that evaluated the acid-base blood gas parameters of patients with simple acid-base disorders. We extracted the measured bicarbonate and PCO_2 values of the observations in these articles to calculate the most accurate compensatory formulas for simple acid-base disorders.

Results: Our database was comprised of 3806 observations with simple acid-base disorders. Our results generally agreed with the Goldberg acid-base nomogram except for patients with severe metabolic alkalosis (Figure 1). The best proposed formula in the literature for simple acid-base disorders and the compensatory formulas generated by our data are illustrated in Table 1.

Conclusions: Although the formulas described in the literature perform relatively well in predicting the appropriate compensatory response to simple acid-base disorders, more accurate predictive formulas were developed.

Table 1. The best proposed equations in the literature and most accurate formulas for simple acid-base disorders

Primary acid-base disorder	The best proposed formula in the literature	Most accurate formula (Regression line)
Metabolic acidosis	$PCO2 = (1.5 \times HCO3) + 8 \pm 2$ (Winters' equation)	$PCO2 = (1.29 \times HCO3) + 9.82$
Metabolic alkalosis	$PCO2 = HCO3 + 15$	$PCO2 = (0.77 \times HCO3) + 20.41$
Acute respiratory acidosis	$\Delta HCO3 = (0.1 \times \Delta PCO2)$	$\Delta HCO3 = (0.07 \times \Delta PCO2) + 1.26$
Chronic respiratory acidosis	$\Delta HCO3 = (0.4 \times \Delta PCO2)$	$\Delta HCO3 = (0.24 \times \Delta PCO2) + 4.26$
Acute respiratory alkalosis	$\Delta HCO3 = (0.2 \times \Delta PCO2)$	$\Delta HCO3 = (0.33 \times \Delta PCO2) - 1.20$
Chronic respiratory alkalosis	$\Delta HCO3 = (0.5 \times \Delta PCO2)$	$\Delta HCO3 = (0.46 \times \Delta PCO2) - 0.19$

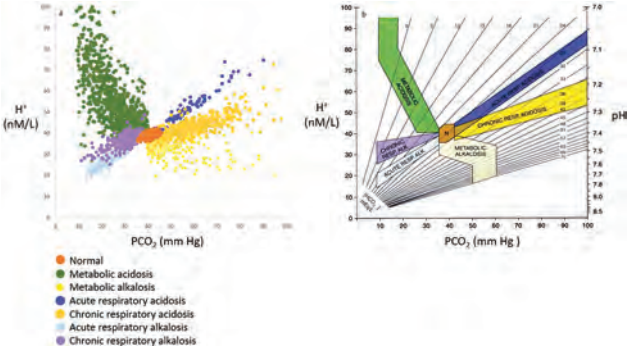

Figure 1. Comparison our data points (a) with acid-base map proposed by Goldberg et al. (b)

PUB120

Hypernatremia Three Ways

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Introduction: Hypernatremia is a disorder commonly seen in hospitalized patients. It is often caused by dehydration from low water intake, GI, or urine losses. We present a case in which there were 3 distinct etiologies of hypernatremia that developed during the same admission.

Case Description: A 55 year old male with Down Syndrome and epilepsy was admitted from his nursing home for altered mental status and a 2 day history of lethargy and low oral intake. On admission, he had hypotension, tachycardia, and altered cognition from baseline but otherwise had unremarkable exam. He was diagnosed with klebsiella UTI, acute kidney injury, and hyponatremia. He was started on ceftriaxone and given 1 L of normal saline for hypovolemic hypernatremia, later switched to a continuous D5W infusion. Pertinent blood and urine chemistry after a liter of saline is shown in table 1. Over the next 4 days, sodium corrected slowly to 144 mEq/L, creatinine returned to baseline, and the D5W infusion was replaced with tube feeds. On day 6, he was again found to be hypernatremic but with polyuria. Urine chemistry (table 1) suggested osmotic diuresis which was attributed to high protein tube feeds. The polyuria and hypernatremia resolved with a change in feeds and D5W infusion. Meanwhile, he was found to be in status epilepticus and intubated for prolonged hypoxia. Despite maximal anti-epileptic treatment, he continued to have frequent seizures. On day 9, he again had polyuria and hypernatremia but this time with lower urine osmolality (table 1). A central DI process was considered due to hypothalamic injury from status epilepticus, which has been reported seldomly. The urine osmolality increased to 413 mOsm/kg 2 hours after desmopressin 2 mcg SQ, confirming the suspicion. His serum sodium and urine volume remained within

normal limits on scheduled desmopressin doses over next week; however, on day 15 family requested withdrawal of care due to ongoing seizures and futility of care.

Discussion: Our patient developed 3 episodes of hypernatremia during same admission, all due to different etiologies. This case highlights the importance of careful ongoing assessment of history and lab parameters since the best treatment strategy may change for the same diagnosis during the same admission.

Admission day	Serum sodium (mEq/L)	24 hr urine output (mL)	Urine osmolality (mOsm/kg)	Urine sodium (mEq/L)	Urine potassium (mEq/L)
1	179	200	514	115	37
6	156	5460	505	115	33
9	150	5125	244	31	23

PUB121

Pyroglutamic Acidosis: A Painful Gap in the MUDPILE

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Introduction: Pyroglutamic acid (5-oxoproline) is a rare cause of metabolic acidosis most often associated with sub-acute or chronic acetaminophen intake in the presence of unique risk factors.

Case Description: A 25-year old female with Crohn's disease presented with one month of worsening abdominal pain, diarrhea, and anorexia with reported 20 kg weight loss. She developed septic shock secondary to sigmoid colon perforation and underwent sub-total colectomy and end-ileostomy. Her hospital course was complicated by stage 2 acute kidney injury (AKI) secondary to acute tubular necrosis with a peak creatinine of 0.8 mg/dL from baseline of 0.3 mg/dL. Her AKI gradually resolved with supportive treatment. Over a 10-day period, she received a total of 20 g of acetaminophen with a total daily dose <4 g/day. Subsequently, a persistent unexplained high-anion gap metabolic acidosis developed with serum bicarbonate levels as low as 11 mmol/L and a corrected anion gap of 26 mmol/L. Further laboratory data showed normal serum osmolality, blood urea nitrogen, beta-hydroxybutyrate, L-lactate, D-lactate, acetaminophen, and salicylate levels. Upon subsequent investigation, a urine 5-oxoproline level was markedly elevated at 26,740 mmol/mol creatinine. The patient's severe metabolic acidosis resolved with discontinuation of acetaminophen and oral bicarbonate supplementation.

Discussion: Pyroglutamic acidosis is an often underrecognized condition requiring a high index of clinical suspicion for diagnosis. Urine or serum 5-oxoproline levels are needed for diagnosis, which may not always be readily available. Chronic acetaminophen use depletes intracellular glutathione resulting in increased levels of 5-oxoproline. Patients, like the one reported here, with malnutrition, female gender, sepsis, and kidney dysfuction are especially susceptible as they have lower glutathione levels leading to faster 5-oxoproline accumulation despite standard dosing of acetaminophen. Prompt recognition is essential for treatment with acetaminophen cessation and bicarbonate supplementation. The use of acetaminophen as an analgesic alternative to opioids is growing, especially in peri-operative and critical care settings. Clinical awareness of predisposing conditions and close monitoring of patient's acid-base and kidney status can help us mitigate this underrecognized complication of acetaminophen use.

PUB122

Amphotericin B Lipid Complex Inducing Distal Renal Tubular Acidosis

Ian J. Da Silva Lugo, Heydee M. Fournier, Carla I. Colon Nunez, Yamiris Rodriguez, Keysha Lopez vega, Alejandra A. Villagrasa Flores, Ileana E. Ocasio Melendez. *Univesity of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico.*

Introduction: Amphotericin B is the drug of choice for most life-threatening fungal infections. Nephrotoxicity is a common adverse reaction of this medication and its lipid complex formulation is an alternative to ameliorate this risk. Renal Tubular Acidosis (RTA) is an uncommon but major complication that can occur, and close monitoring should be performed for rapid identification and management. We hereby present the case of a patient who developed distal RTA secondary to amphotericin B lipid complex.

Case Description: A 59-year-old male patient without known medical history was admitted to Hematology-Oncology Ward with Acute Myeloid Leukemia. Chemotherapy with cytarabine and idarubicin was initiated. The patient developed pancytopenia secondary to chemotherapy nadir and septic shock dependent of vasopressors. In addition, the patient suffered an intractable sinus congestion that lead to a biopsy in which invasive fungal sinusitis secondary to Aspergillus was revealed. Amphotericin B lipid complex was started and resulted in improvement of the infectious process. However, the patient developed a stage three acute kidney injury with associated hypokalemia of 2.9 mmol/L, hyponatremia of 129 mmol/L, and mixed high and normal anion gap metabolic acidosis of 21.4 mEq/L. Noted findings were consistent with distal RTA and high anion gap component due to renal failure. Amphotericin B was changed to another antifungal and potassium and bicarbonate were replaced. Treatment led to resolution of azotemia, electrolyte, and acid-base disturbances.

Discussion: Nephrotoxicity is induced after amphotericin B inserts into tubular cell membranes and creates pores that increase permeability, leading to kaliuresis and back diffusion of secreted hydrogen ions. Although this effect is less common with liposomal amphotericin, it has been described in the literature. In addition, the risk increases in the presence of other nephrotoxic agents or non-modifiable risks such as critical illness. This case highlights the importance of prompt recognition of distal RTA in the at-risk population as it can lead to an early adequate management and prevention of further deterioration.

PUB123

Treatment Pattern of Hyperkalemia Among Patients Presenting Emergency Department in China

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Background: In China, the treatment pattern of hyperkalemia (HK) among patients presenting emergency department (ED) is not well described.

Methods: Data containing hospital information system (HIS) records of 157 hospitals, covering 30 provinces in China were extracted from Beijing Data Center for Rational Use of Drugs. Patients (aged ≥18 years old) in ED with record(s) of HK, defined as serum potassium (S-K) >5.0mmol/L, from 2015.1.1 to 2017.12.31 were included. The diagnosis rate was defined as the proportion of HK episodes that have diagnoses records. Treatment rate was defined as the proportion of HK episodes that have records of any HK treatment including diuretics, glucose injection + insulin (G+I), calcium injection, sodium bicarbonate, potassium binder or dialysis. Retesting rate was defined as the proportion of HK records that have potassium retest record(s) within 1 day.

Results: A total of 36,615 ED patients with at least one S-K record >5.0mmol/L each were included. The overall HK diagnosis rate was 9.2%. Diagnosis rates increased by the severity of HK, patients with S-K ≥7.0 mmol/L showed the highest diagnosis rate of 31%. The overall treatment rate within 2 days was 45.2%, treatment rates increased by the severity of HK. Analyzing the HK episodes with HK treatment, G+I (used in 72.4% of HK episodes), loop diuretics injection (used in 50.36% of HK episodes) were most commonly used, while oral potassium binders, including sodium polystyrene sulfonate and calcium polystyrene calcium, were used in only 0.2% of HK episodes. Combined treatments were observed, among which a combination of G+I and loop diuretics injection was used in 10.4% of episodes and a combination of G+I, diuretics injection, calcium injection and sodium bicarbonate was used in 7.4% of episodes. Subgroup analysis of HK treatment in patients with chronic kidney disease showed that, G+I (used in 71.7% of episodes), loop diuretics injection (used in 61.2% of episodes) were most commonly used. The overall retesting rate within 1 day was 19.36%. Patients with S-K 5.0-5.5 mmol/L were retested less frequently (15%) than those with S-K ≥5.5 mmol/L (22.4-30.6%).

Conclusions: In China, the diagnosis and retesting rates of HK in ED patients was relatively low. Glucose injection + insulin was commonly used to treat HK in ED, while oral potassium binders were rarely used. Combination of treatments was common.

PUB124

Factors Associated with Volume Overload in Pulmonary Arterial Hypertension

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Background: Knowledge about the pathophysiology of volume overload in pulmonary arterial hypertension (PAH), a frequent and early complication, and major contributor to the development of right heart failure, is scant. We aimed to identify factors associated with volume overload in PAH patients.

Methods: We reviewed medical charts of consecutive 32 patients with PAH. Patients on loop diuretic were considered volume overloaded. Repeated measures of clinical and lab variables recorded at the time of each right heart catheterization (RHC) were included for analysis. For comparisons between diuretic and not-on-diuretic groups, we used independent t-test for normally distributed and Mann-Whitney U test for nonparametric variables.

Results: Mean age at last follow up was 51.2 ± 11.6 years, 100% were white, 94% were female, and mean estimated glomerular filtration rate (GFR) was 93 ± 19ml/min. Median follow-up was four years. Fifty-six percent patients were on loop diuretic. These patients on diuretic were significantly more edematous (1.24 ± 1.37 vs. 0.27 ± 0.63 score, p=0.005), had higher BMI (30.5 ± 6.3 vs. 25.1 ± 4.9 kg/m^2, p=0.002) and covered less distance on 6 minute-walk test (360 [300,413] vs. 420 [385,464] meters, p=0.012) than patients not on diuretic. No difference was noted in age, gender, BP, NYHA class, or oxygen saturation. RHC were performed ≥2 times more often in diuretic vs. non-diuretic group (68% vs. 28.6%, p=0.03). On RHC, right atrial pressure (RAP) was significantly higher (7.9±4.2 vs. 3.8±3.2 mmHg, p=0.006) and there was trend towards higher mean pulmonary artery pressure (49 ± 13.3 vs. 42 ± 12.5 mmHg, p=0.08) in diuretic group with no difference in cardiac index or pulmonary vascular resistance. Serum alkaline phosphatase was higher (106.8 ± 34.3 vs. 76.2 ± 35.3 U/L, p=0.02) in diuretic group with no difference in other blood work including BNP and estimated GFR. There was no difference in proportion of patients on PAH-specific therapies. On follow-up, four patients in each group died or were lost to follow-up.

Conclusions: High BMI and RAP, well-known factors associated with volume overload in other edematous disorders were applicable in our PAH cohort as well suggestive of presence of similar pathways of impaired natriuresis despite normal GFR. Further studies are required to confirm these pathways which can guide appropriate early-on therapeutics.

PUB125

A Negative Anion Gap with a Positive Outcome

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Introduction: The utility of an increased serum anion gap (SAG) in clinical practice has long been established. A decreased or negative SAG, however, often remains undiscovered or neglected. Overproduction of paraproteins, such as IgG (cationic) and

IgA (anionic), will cause deviations in SAG. In IgG myeloma, the combination of cationic IgG accumulation as well as hypercalcemia and hypoalbuminemia can lead to a low or negative SAG. We report a patient who presented with an unrelated chief complaint and was found to have a myriad of electrolyte abnormalities causing a negative SAG, eventually leading to a diagnosis of multiple myeloma.

Case Description: A 56 year old woman presented with right knee pain due to septic arthritis. Her admission labs were notable for a sodium of 124 meq/L, Cr 4.76 mg/dL. Her anion gap was -3 and her serum osmolality was measured as 316 mOsm/kg with a 50 mOsm/kg osmolar gap. Her total protein was noted to be 12.6 g/dL, albumin 2.1 g/dL, with hypercalcemia to 11.1 mg/dL and glucose 104 mg/dL. Her blood gas sodium was 137 mEq/L consistent with pseudohyponatremia. UAC and UPC were 187 mg/g and 780 mg/g respectively. SIEP and UIEP ultimately demonstrated monoclonal IgG Kappa. Her total protein increased to 13.7 g/dL; she subsequently became lethargic and developed epistaxis due to hyperviscosity syndrome with a serum viscosity of 9.2 relative to water. She underwent 3 sessions of plasmapheresis and her pseudohyponatremia resolved (Na 139 meq/L) and total protein improved to 8.9 g/dL. SAG increased to 7. Her mental status and epistaxis improved. Subsequent bone marrow biopsy confirmed 65% plasma cells. Patient was started on dexamethasone and bortezomib.

Discussion: This case illustrates the myriad presenting electrolyte derangements of multiple myeloma. The combination of pseudohyponatremia, negative SAG, increased osmolar gap, and high protein gap raised the suspicion of a cationic hyperproteinemia, which eventually led to the diagnosis of IgG multiple myeloma. The hypercalcemia and AKI were also classic features of her myeloma. Her mental status changes, which were thought to be from hyperviscosity, were indications to treat with plasmapheresis. A negative SAG is rare and has a limited differential diagnosis, with IgG myeloma as perhaps its most significant clinical etiology.

PUB126

A Surprising Complication Following Steroid Therapy: Tumor Lysis Syndrome

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Introduction: Tumor Lysis Syndrome (TLS) is a known lethal complication of chemotherapy and radiotherapy in malignancies with high tumor bulk. It is characterized by lysis of malignant cells causing hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and acute renal failure. Few cases have been able to demonstrate the occurrence of TLS following steroid therapy alone in the absence of chemotherapy or radiotherapy.

Case Description: We report a 76-year-old female with Past Medical History of Hypertension, Diabetes Mellitus Type-II and Chronic Kidney Disease that came to our hospital complaining of pleuritic chest pain since 3 days. Vital signs and physical exam were unremarkable. Labs results were remarkable for hemoglobin 7.8 g/dl and serum creatinine 1.60 mg/dl. No evidence of leukocytosis, electrolytes disorders or positive cardiac markers were present. Patient was admitted with diagnosis of symptomatic anemia. During blood transfusion, patient developed an acute allergic reaction evidenced by generalized urticaria and bronchospasm. Single dose intravenous steroid therapy (methylprednisolone 20 mg) was given. After 48 hours post transfusion clinical condition continued to worsen. New labs showed leukocytosis (49.7 $10^3/\mu L$) and lactic acidosis (8.5mmol/L). Severe hypotension led the patient to developed acute respiratory failure requiring mechanical ventilation and vasopressors therapy. Further labs revealed typical findings of TLS including hyperuricemia:15.6mg/dL, hyperkalemia: 6.5mEq/L, hyperphosphatemia: 5.90mg/dL and hypocalcemia: 6.0mg/dL. Due to persistent leukocytosis (103 $10^3/\mu L$) flow cytometry studies were done showing evidence of monoclonal B lymphocytosis consistent with Chronic Lymphocytic leukemia. Treatment was initiated with aggressive hydration, allopurinol and rasburicase. Follow up labs revealed normalization of uric acid: 3.0mg/dl, potassium: 4.3 meq/L, phosphorus: 2.23mg/dl, calcium: 8.0 mg/dl and creatinine: 2.30mg/dl. Despite correction of metabolic abnormalities, patient was pronounced dead at day 15 hospital stay due to multiorgan failure.

Discussion: This case demonstrates the importance of early recognition of TLS following steroid therapy. Prompt prophylactic management prior to the use of steroid therapy is of utmost importance in patients with clinical suspicion of a hematologic malignancy, since this complication caries a high mortality risk.

PUB127

Laxative Use in Acute Hyperkalemia

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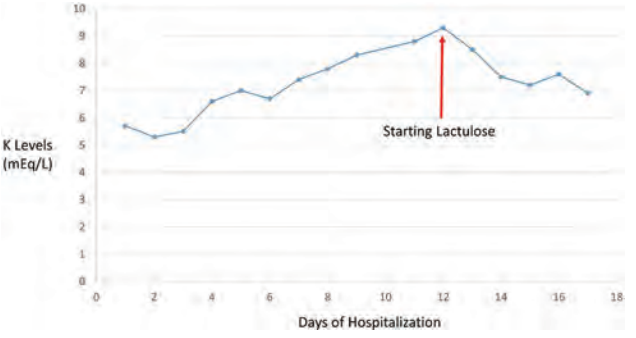
Introduction: The most effective treatment of severe hyperkalemia is hemodialysis. Treatment options for patients who are not candidates for renal replacement therapy are limited. Oral potassium binders, available for treatment of chronic hyperkalemia, are not approved for acute hyperkalemia. We describe a stage 5 CKD patient with severe hyperkalemia who was not a hemodialysis candidate in whom lactulose was used after other measures failed to lower serum potassium (K^+).

Case Description: 66 year old female with stage 5 CKD who was not a candidate for renal replacement therapy due to severe schizoaffective disorder was being managed medically. Her serum K^+ was controlled with patiromer 8.4 mg/day during the previous year. She presented with volume overload and uremic encephalopathy with hyperkalemia (K^+, 5.7 meq/l), high anion gap metabolic acidosis (serum CO_2 10 mEq/L) and serum creatinine, 20 mg/dl. She received 10 units of insulin with D50, 150 mEq of IV sodium bicarbonate, furosemide 60 mg IV daily, and patiromer 8.4 g/day. Her serum K^+ decreased to 5.3 meq/l after 24 hr, but increasesd to 7.0 mEq/L after 72hr. Patiromer dose was doubled to 16.8 g/day, and sodium bicitrate was added. Serum K^+ initially decreased to 6.7 meq/l, but subsequently progressively increased despite improvement of metabolic acidosis, repeated administration of insulin+D50 and albuterol, patiromer, and use of high dose loop diuretics, peaking at 9.3 mEq/L on day 11. Daily lactulose dose of 17 g daily was added, resulting in diarrhea and gradual decline in serum K^+ at an average rate of 0.7 mEq/L/day, reaching a nadir of 6.9 mEq/L after 72 hr. The patient unfortunately passed away on that day due to other uremic complications.

Discussion: Lactulose is a non absorbable disaccharide metabolized by colonic bacteria to noncarbohydrate organic acids, which acts as an osmotic cathartic. In this case lactulose was successfully implemented in treating severe hyperkalemia when all other measures failed. Controlled use of laxatives can be considered as a means to control hyperkalemia in patients who are not candidates for renal replacement therapy.



PUB128

Battling Warburg: Type B Lactic Acidosis in a Patient with Diffuse Large B-Cell Lymphoma

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Introduction: The Warburg effect is a rare paraneoplastic syndrome seen in patients with hematologic malignancy. The metabolism of cancerous cells converts to aerobic glycolysis and results in type B lactic acidosis.

Case Description: The patient is a 62-year-old man with diffuse large B-cell lymphoma and prior hemophagocytic syndrome (HS) diagnosed 6 months prior, on chemotherapy. He presented with several weeks of fever and respiratory symptoms. Clinical exam and diagnostics did not reveal a source of sepsis. Chest radiography and CT chest were without infiltrates. COVID-19 PCR was negative. Labs- WBC 1,500 /mm3, Hemoglobin 8.8 g/dL, Platelets 63,000 /mm3, creatinine 1.1 mg/dL, lactate 2.6 mmol/L, ferritin 417 ng/mL, serum triglycerides 349 mg/dL. Patient was placed on vancomycin and cefepime and volume expanded, but continued febrile with persistent lactic acidosis. Abdominal CT revealed splenomegaly with focal hypodensities, mild descending and sigmoid diverticulosis without diverticulitis. CT mesenteric angiography revealed moderate narrowing of celiac artery and severe narrowing of the inferior mesenteric artery origin. For suspected ischemic colitis, the patient was taken emergently for exploratory laparotomy, but findings did not support ischemia. Creatinine trended up to 2.0 mg/dL with increasing lactate of 11 mmol/L, bicarbonate 13 mmol/L, and serum pH of 7.0. At this point, without septic or ischemic processes identified, the lactate production was attributed to DLBCL, and not HS as ferritin was not substantially elevated. CRRT was initiated for anuric AKI. Lactate continued to trend up to 21.7 mmol/L with bicarbonate 6 mmol/L. Family discussions were held, and the patient was transitioned to palliative care.

Discussion: Type B lactic acidosis should be considered in the differential diagnosis in patients with increased anion gap metabolic acidosis and malignancy. One rare and potentially fatal Type B lactic acidosis is due to the Warburg effect, a rare and potentially lethal paraneoplastic syndrome of hematologic malignancies.

PUB129

An Uncommon Indication for Renal Replacement Therapy in Tumor Lysis Syndrome

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Introduction: Tissue damage in Tumor Lysis Syndrome (TLS) results largely from the precipitation of uric acid and calcium phosphate. As calcium phosphate arises the risk for calciphylaxis increases, which can lead to severe renal failure in addition to other systemic complications. We hereby present a case with an uncommon indication for hemodialysis in a patient with tumor lysis syndrome.

Case Description: A 62-year-old male patient with Mantle Cell Lymphoma presented to the emergency room with a one-day history of hemoptysis, emesis, and fatigue. Laboratory workup revealed severe anemia of 6 g/dL, marked leukocytosis of 265.27 thousand/μL, increased uric acid 15.1 mg/dL, and elevated lactate dehydrogenase of 1,261 U/L. These findings were consistent with active disease, and upon admission, the patient

was started on IV hydration, dexamethasone, rasburicase, and allopurinol. On the fifth inpatient day, chemotherapy regimen was started, and white blood cell count decreased by approximately 50 thousand/μL. Two days after, laboratory values were remarkable for hyperkalemia of 6.1 mmol/L, blood urea nitrogen of 66.2 mg/dL, creatinine of 2.61 mg/dL, hyperphosphatemia of 8.5 mg/dL, and a corrected calcium of 7.1 mg/dL. These findings were suggestive of TLS following chemotherapy, along with the development of a non-oliguric stage three acute kidney injury. The next day, the patient had adequate urine output, stable blood pressures, no signs of volume overload or uremia, but laboratory values revealed worsening renal parameters and an increased calcium-phosphate product above 70 mg^2/dL^2. Consequently, hemodialysis was performed with good tolerance and response to treatment.

Discussion: The criteria for hemodialysis in this case of a non-oliguric euvolemic patient with acute renal failure secondary to TLS was founded on an elevated calcium-phosphate product, as opposed to more common indications such as anuria, fluid overload, or persistent electrolyte disturbances. The prognosis for complete recovery of renal function is excellent if dialysis is initiated early to rapidly reduce serum uric acid and phosphate concentration. This emphasizes the importance of a prompt assessment of the calcium-phosphate product as an indication for renal replacement therapy in the setting of tumor lysis syndrome.

PUB130

Hypomagnesemia and Proton Pump Inhibitors

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Introduction: Proton pump inhibitors (PPIs) are commonly used for GERD. They are associated with acute interstitial nephritis, B12 deficiency, Clostridium difficile infection, gastric malignancy, atrophic gastritis, bone fractures, and rarely, hypomagnesemia. We present a case of hypomagnesemia manifesting with unexplained hypocalcemia, refractory hypokalemia, and neuromuscular disturbances.

Case Description: A 63 year old male with GERD and prostate cancer (scheduled for prostatectomy), was found to have abnormal electrolyte values on routine preoperative evaluation. Two months ago, they were all normal. He had carpopedal spasms, facial twitching, frequency and weak urine stream for two months. He denied diarrhea, nausea, vomiting, fever, chills, medication changes or use of supplements. He drank alcohol socially. Trousseau sign was positive. Labs showed potassium 2.8 mmol/L, bicarbonate 27 mmol/L, BUN 12 mg/dL, creatinine 0.87 mg/dL, calcium 6.1 mg/dL, albumin 4 mg/dL, magnesium 0.9 mg/dL, and phosphorus 3.2 mg/dL. 25-OH vitamin D was 9 ng/mL, with normal 1, 25 (OH)2 vitamin D. PTH was elevated at 122 pg/mL. Fractional excretion of magnesium (measured after changing his PPI to an H2-receptor antagonist) was 2.5%. It was suspected that PPI use may have driven hypomagnesemia (which accelerated renal K+ losses), with associated PTH resistance and vitamin D deficiency (causing hypocalcemia). Symptoms resolved with electrolyte supplementation.

Discussion: Hypomagnesemia can result from gastrointestinal or renal losses. The presumed mechanism for PPI-induced hypomagnesemia involves impaired absorption of magnesium by intestinal epithelial cells caused by PPI-induced inhibition of transient receptor potential melastatin-6 (TRPM6) and melastatin-7 (TRPM7) channels. The aim of treatment is correction of magnesium and vitamin D first, resulting in rapid improvement of potassium and calcium. Our case is unique, as he developed the abnormalities so acutely. He was also restarted back on his PPI, along with magnesium supplements, and repeat electrolytes over the ensuing 4 months have been normal.

PUB131

Rising from Death: A Case of Life-Threatening Hyperkalemia

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Introduction: Hyperkalemia affects the cardiac conduction and can result in fatal consequences. We describe a rare case of life threatening hyperkalemia presenting in setting of hyperglycemia, sepsis and shock and manifesting as new ST elevation in anterior leads, which resolved with correction of hyperglycemia.

Case Description: A 63-year-old male with intellectual disability and diabetes presented in state of shock after refusing his medications for last 5 days. His vitals on arrival were pertinent for hypothermia (T 29.1C) and hypotension (56/30 mm Hg). He had cold and clammy extremities and Glasgow Coma Scale of 5. Cardiovascular and abdominal examination were unremarkable. Laboratory result showed arterial pH of 6.9, serum potassium [K] of 11.1mg/dL, serum bicarbonate level of <6 mmol/L, serum phosphorus of 11.8 mg/dL, serum creatinine of 2.4 mg/dl (baseline 0.6 mg/dl), blood glucose of 1100mg/dL and serum sodium [Na] of 129mg/dL. Chest radiograph showed cardiac enlargement and electrocardiography (EKG) revealed absent P waves, prolonged QRS intervals, ST elevation in anterior leads, marked left axis deviation and tented T waves. The creatine kinase (CK) levels were normal but troponin T high sensitivity were elevated. He was treated with intravenous fluids, sodium bicarbonate, calcium gluconate, insulin drip, broad-spectrum antibiotics and norepinephrine. The blood glucose, potassium and bicarbonate levels improved with conservative management without need for renal replacement therapy. Subsequent transthoracic echocardiogram was negative for acute ischemic changes and repeat EKG showed sinus rhythm and resolution of ST changes.

Discussion: Severe hyperkalemia is dangerous and can result in cardiac arrest. Our patient presented with very high potassium levels, however hypothermic state might have reduced the metabolic demands and prevented immediate cardiac arrest. Hyperkalemia in setting of uncontrolled hyperglycemia usually responds to medical management if the patient is not anuric. Moreover, pseudo infarction as seen in this case is a rare manifestation of hyperkalemia. With the recent emphasis on reducing door-to-balloon times in ST elevation myocardial infarction, it is important to be aware of its association with hyperkalemia as it usually resolves with reduction of the serum potassium levels.

PUB132

Analysis by Bioimpedenziometria of Three Cohorts with Expanded Extracellular Volume: Critically Ill, Nephrotic, and Hemodialysis Patients

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Background: By applying current, bioimpedanciometry provides information on body composition, estimating total body water (TBW) and extracellular water (ECW) with formulas. However, these estimates are imprecise in edematous patients. Fortunately, there are variables that are directly measured: resistance (R), reactance (Xc) and phase angle (AF), which in theory reflect the cells' ability to maintain adequate function. In our work, we mainly wanted to analyze this second group of variables in patients with increased ECV and additionally compare them with a group of healthy volunteers

Methods: Using a multifrequency bioimpedanciometer, we performed measurements on edematous patients in the ICU, edematous patients with nephrotic syndrome (NS), and anuric patients on hemodialysis (HD) before starting a random session. The control group were healthy volunteers (V) of the same age as the studied patients. A *t-test* was performed to compare each group against V and a *pearson's correlation test* was performed to assess correlation between variables

Results: During 6 weeks measurements were made getting data of 14 V, 11 HD, 13 SN and 11 ICU. When comparing against V, significant differences were obtained in R, Xc and AF, ($p<0.05$) in all groups except R in the HD group. When comparing among them the most edematous groups (ICU and NS), surprisingly no differences were obtained ($p>0.05$). In the estimated variables related to water distribution (ECW, TBW and ECW/TBW), the 3 groups show significant differences compared to V, except in TBW of the HD. Finally, when looking for a correlation between measured and estimated variables, we found that Xc has a high negative correlation (r: -0.75) with ECW; AF has a high negative correlation (r: -0.83) with ECW/TBW, while R has a moderate negative correlation (r: -0.67) with ECW and TBW

Conclusions: Our results show, the studied groups have differences in measured and estimated variables compared to V, theoretically reflecting a state of cellular malfunction in addition to the expansion of the ECV. Surprisingly, patients with NS and ICU are "electrically" the same, despite their very different clinical contexts. However, we cannot rule out that it is only due to expansion of the ECV of a similar amount since the measured variables depend to some degree on the estimated variables

PUB133

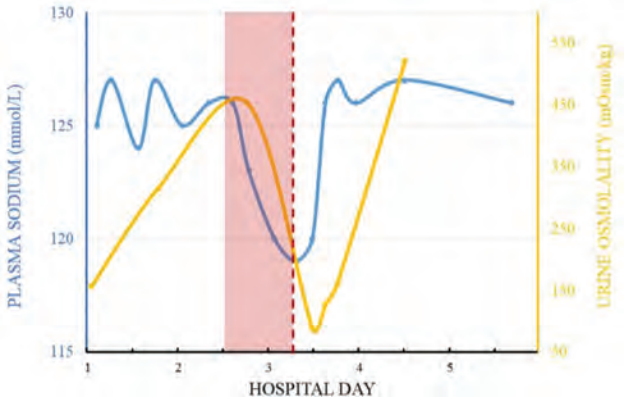
Intractable Hyponatremia, Polydipsia, and the Reset Osmostat: A Case Report

Mohamed T. Hassan Kamel, Ashish Upadhyay, Steven C. Borkan. *Boston Medical Center, Boston, MA.*

Introduction: Water intake in excess of water excretion results in hyponatremia, the most common electrolyte abnormality in clinical practice. Typically, ADH secretion fluctuates to maintain a physiologic serum osmolality, the so called "ADH osmostat". This threshold can be altered by multiple physiologic and pathologic stimuli.

Case Description: A 71-year-old man with severe depression, type II diabetes mellitus and chronic obstructive pulmonary disease presented to the hospital with diffuse weakness, difficulty with focused attention and suicidal ideations. He admitted to drinking more than 15 liters of liquid daily. Home medications included metformin, insulin, lisinopril, amlodipine, metoclopramide, pantoprazole, and trazodone. Physical exam revealed hypertension and truncal obesity, but was otherwise unremarkable. Laboratory investigation revealed a plasma sodium concentration of 120 mEq/L, blood urea nitrogen of 9 mg/dl, creatinine of 0.82 mg/dL, serum osmolality of 263 mOsm/kg and urine osmolality of 155 mOsm/kg with a urine sodium of 38 mEq/L. Because of neurological symptoms and worsening hyponatremia, the patient received 3% hypertonic saline infusion. Serum sodium was noted to fluctuate during periods of unsupervised access to fluid, hypertonic saline infusion and fluid restriction. Urine osmolality was also noted to flucutate, dropping appropriately with worsening hyponatremia and rising with fluid restriction, hypertonic saline and resultant rise in serum sodium. The rise in urine osmolality occured without normalization of serum sodium.

Discussion: In this report, we present a case of symptomatic hyponatremia associated with polydipsia in an elderly patient with psychiatric comorbidities and chronic hyponatremia. We describe the accompanying laboratory findings that support the diagnosis of reset osmostat. We postulate that chronc hyponatremia secondary to polydipsia related to psychiatric illness could have reset this patient's osmostat and discuss potential therapeutic strategies.



PUB134

An Unusual Cause of Rhabdomyolysis

Esilida Sula Karreci, Larissa Kruger gomes, Ruth Schulman, Krishna A. Agarwal, Amar Pandit, Bradley M. Denker. Beth Israel Deaconess *BIDMC, Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Rhabdomyolysis results from muscle cell injury and often leads to AKI. Common causes include trauma, medications, electrolyte abnormalities, and metabolic myopathies. The clinical presentation includes muscle pain, dark urine, and possibly oliguria. Here, we present an unusual etiology of rhabdomyolysis resulting from sustained hyperosmolarity due to severe hyperglycemia and hypernatremia.

Case Description: 23-year-old male with no significant medical history presented with fatigue, poor appetite for 10 days. He denied fever, nausea, vomiting, abdominal pain, diarrhea,. Despite drinking large amounts of fluids, he felt thirsty, with frequent urination. Family history: diabetes. Social history; no alcohol, smoking or drug use. No prescription/OTC medicines, or herbal supplements. Vital signs were notable for a heart rate of 110-120 beats/min. He appeared lethargic. Physical exam showed dry mucous membranes and tachycardia, otherwise unremarkable. Initial laboratory values showed blood glucose of 1132 mg/dL, Cr 3.5 mg/dl, Na 147 mEq/L (see table). Urine showed glucosuria and ketones, sediment was bland. He was started on an insulin drip. Corrected Na was 172 with a free water deficit 10L. Initially given 3L NS bolus followed by1/2NS to correct hypernatremia, with goal correction of 10-12 mEq in the first day. On day 3, he complained of weakness and difficulty getting up but no muscle soreness. He developed a temperature of 101oF and his exam was unremarkable. Creatinine and Na improved (see table), however, ALT/AST continued to rise. Right upper quadrant US showed hepatic steatosis. Repeat UA showed large blood, but no red blood cells on sediment. CPK returned at 111850 IU/L, and peaked at 195380 IU/L on day 5. He was given isotonic fluids at 500cc/h. He remained tachycardic with low grade fevers and on day 9, CTA showed bilateral pulmonary emboli.

Discussion: This case highlights an unusual cause of rhabdomyolysis caused by hyperosmolarity in HHS. Although, the literature suggests that rhabdomyolysis may be present in up to 50% of HHS cases, this is an extreme case and highlights the importance of looking for rhabdomyolysis in HHS. It is unclear why our patient showed such a severe phenotype.

Laboratory findings

	Hgb	Hct	Plt	Gl	BUN	Cr	Na	K	Gap	Ca	P	ALT	AST	CPK
Day 1	17	52	296	1131	96	3.5	147	5.6	41	10	9	103	128	
Day 3	11	36	58	238	22	1.3	153	4	13	8	2.6	254	870	111850

PUB135

An Atypical Case of Hypocalcemia Associated with the Use of Patiromer

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Introduction: Novel potassium (K) binders were approved a few years ago and introduced to the market. With their increased use, more side effects are surfacing. We report an atypical case of hypocalcemia that was associated with the use of patiromer.

Case Description: An 86 year-old male with stage 3 chronic kidney disease secondary to left radical nephrectomy from urothelial cancer, who was on patiromer for chronic hyperkalemia, presented with obstructive acute kidney injury (AKI) that was associated with hypocalcemia (6.3 mg/dL [8.6-10.5 mg/dL]), hypomagnesemia (0.6 mg/dL [1.6-2.6mg/dL]) and metabolic acidosis (CO2 16 [22-30 mmol/L]). Ionized calcium (iCa) was low at 3.34 [4.60 - 5.30 mg/dL] and phosphorus 4.6mg/dL [2.2 - 4.6 mg/dL]. His intact parathyroid hormone (PTH) was elevated at 121 [14.0 - 72.0 pg/mL], however, this was relatively lower than his baseline of 200-250 pg/mL. After adequate magnesium repletion and discontinuation of patiromer, his Calcium improved to 8.4 mg/dL, iCa improved to 4.20mg/dL, and his PTH went back up to his previous baseline at 220 pg/mL. His AKI improved following placement of a ureteral stent.

Discussion: Hypercalcemia is a known side effect of patiromer use since it exchanges calcium ion with potassium. To our knowledge, however, hypocalcemia has never been attributed to patiromer use. In this unique case, hypocalcemia was an indirect side effect caused by severe hypomagnesemia that was probably exacerbated by the use of patiromer. Hypomagnesemia can cause hypocalcemia through suppression of PTH secretion, which was evident in this case, along with increasing PTH resistance. Novel potassium binders have a myriad of useful indications; however, one should be vigilant to their effects on other electrolytes.

PUB136

Hypokalemic Periodic Paralysis

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Introduction: Hypokalemic periodic paralysis (HOKPP) is characterized by transient episodes of muscle weakness and inability of muscle movement associated with hypokalemia. The paralysis typically affects the arms and legs, though the diaphragm and the tongue may also be affected.

Case Description: A 50-year-old female with tobacco use and significant alcohol consumption presented with progressive upper and lower limb weakness, numbness, and paresthesias that worsened over the past 2-3 months. She also reported fever, sweats, and unintentional 40-lb weight loss over the past 3 months. The patient denied use of diuretics and laxatives. Labs revealed serum potassium 1.9 mmol/L (3.5 - 5.2), phosphorous 2.2 mg/dL (2.5 - 4.5), bicarb 43 mmol/L (21-30), and a venous blood gas of 7.61/50/25/50, which is consistent with metabolic alkalosis. EKG demonstrated U waves and ST depressions significant for severe hypokalemia. She was admitted for severe hypokalemia and was given oral and IV potassium. Vitamin D was 16.0 ng/mL (30-100), which is suggestive of hypovitaminosis D. TSH and cortisol were normal, thus ruling out thyrotoxicosis and Cushing's, respectively. Serum aldosterone and renin levels were normal, thus ruling out adrenal involvement. The Transtubular K+ Gradient was calculated to be 4, indicating a renal tubular wasting of potassium. In addition to renal potassium wasting, the cellular shift of potassium in the setting of chronic malnutrition and prolonged alcohol use exacerbated the severe hypokalemia. The patient's potassium was repleted, and she was discharged from the hospital with close outpatient follow up.

Discussion: Hypokalemic periodic paralysis is characterized by transient episodes of muscle weakness in the setting of hypokalemia. HOKPP manifests itself as a sudden onset of weakness ranging from mild transient weakness of the arms and legs to paralysis of the diaphragm and accessory muscles, resulting in lethal respiratory failure. HOKPP can be triggered by a stressor, such as a viral illness or by specific medications, such as insulin or beta-agonists. HOKPP is important to rule out when evaluating a patient with abrupt onset of paralysis or weakness, especially in patients with no history or risk factors of other pertinent disease, such as stroke. The failure to diagnose and properly treat HOKPP can be fatal. It is vital to address the underlying cause of hypokalemia to prevent the recurrence of HOKPP.

PUB137

Screening Fabry Disease in CKD Patients in a Single Center of Middle Taiwan

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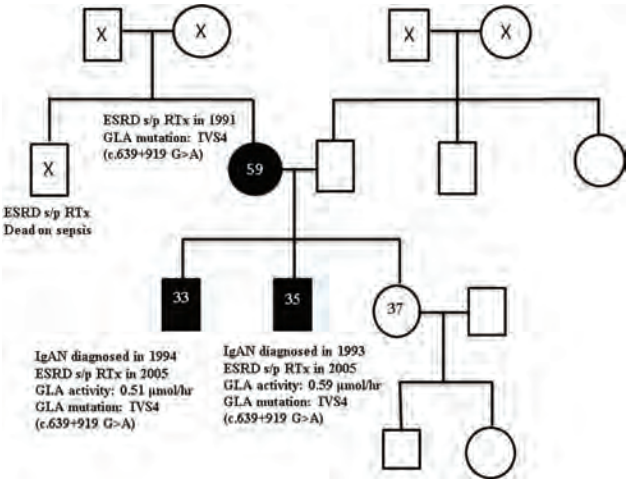
Background: Fabry's disease (FD) is an X-linked inherited rare, progressive, lysosomal storage disorder affecting multiple organs due to the deficient activity of alpha-galactosidase (a-Gal A) enzyme. The prevalence has been reported to be 0.15–1% in hemodialysis patients; however, the information on the prevalence in chronic kidney disease (CKD) is lacking in Taiwan. This study aimed to determine the prevalence of FD in our CKD patients.

Methods: We screen male patients older than 18 years in our dialysis, renal transplantation (RTx) and Pre-End Stage Renal Disease (pre-ESRD) program patients. A total of 611 male CKD patients were screened using an assay of α-Gal A activity by dried blood spots (DBS). A Fabry confirm test by GLA gene analysis was done for those with low enzyme activity.

Results: There were 2 cases with positive (a-Gal A activity <0.6 μmol/hr) and 6 patients with borderline (0.6~1.5 μmol/hr). Interestingly, the 2 positive cases were brothers diagnosed IgA nephropathy (IgAN) in their childhood and received RTx identified as late-onset FD with GLA mutation in c.639+919G>A, a popular mutation site found in studies of male newborns screening for cardiac variant FD in Taiwan, and their mother was the carrier of GLA mutation. We also found 3 cases with borderline of a-Gal A activity with mutation on nonfunctional region. The prevalence of FD is about 0.33 % (2 in 611) in the high-risk population group with CKD. The clinical symptoms of FD patients are nonspecific except in those with various degrees of renal failure. Those patients' correct diagnosis was delayed, taking years and even decades.

Conclusions: FD should be considered in the differential diagnosis of any CKD patients even with knowing their renal disease entities without symptoms and signs suggestive of FD. Clinicians should be aware FD might be not only renal involvement, but also affected heart and brain.



PUB138

A Novel Frameshift Mutation of COL4A5 Identified by Whole-Exome Sequencing in a Chinese Family with Alport Syndrome

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Background: Alport syndrome is an inherited kidney disease caused by the defects in type IV collagen, approximately 80% of which is caused by X-linked mutations in the *COL4A5* gene. This study explores a novel frameshift mutation of *COL4A5* responsible for renal disorder in a 3-generation Han Chinese pedigree.

Methods: We enrolled the proband and his family members from a village in Sichuan province, and collected the family history and clinical data. Clinical examinations were performed to evaluate the phenotypes of the family. Blood samples from the proband and the other eight family members were collected for genetic screen. Whole exome sequencing (WES) was applied in the proband to find out the potential genetic variants, and then the variant within the family was verified by Sanger sequencing.

Results: The 31-year-old male proband and his elder brother had ESRD, binaural sensorineural hearing loss and ocular lesions. Further, his three male cousins received hemodialysis and all died from ESRD between 18 and 25 years old. The 90-year-old maternal grandmother, one maternal aunt and one female cousin had only microscopic hematuria without gross hematuria, proteinuria, impaired kidney function or extrarenal symptoms. Genetic analysis identified a novel deletion mutation (c.422_428del) in exon 7 of *COL4A5* gene which located on the X chromosome in the proband. The c.422_428del variant was also detected in the proband's grandmother and four other affected family members. The proband's farther and three unaffected family members had not found this variant. This mutation was results into frameshift followed by formation of a truncated (p.Leu142Valfs*11) COL4A5 protein product with only 152 amino acids including an aberrant 10 residues. This mutation was not present neither in the Exome Variant Server of the NHLBI-ESP database, ExAC database or in the 1000 Genomes database. According to the variant interpretation guidelines of American College of Medical Genetics and Genomics (ACMG), this novel variant was classified as "likely pathogenic" variant for Alport syndrome in this pedigree.

Conclusions: Our study identified a novel *COL4A5* frameshift mutation in a Chinese family with Alport syndrome, expanding the mutational spectra of *COL4A5* gene, which were significant for screening and genetic diagnosis for Alport syndrome.

Funding: Government Support - Non-U.S.

PUB139

Elevated Ambulatory Blood Pressure Is Associated with a Progressive Form of Fabry Disease

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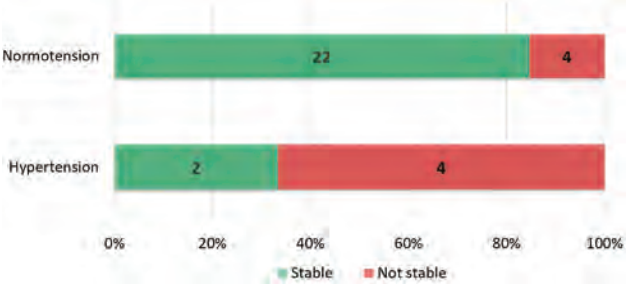
Background: Published data on hypertension incidence and management in Fabry Disease (FD) are scanty and it remains to be shown how much high blood pressure (BP) contributes to organ damage in these patients. Therefore, we have assessed BP values and their correlations with clinical findings in a cohort of FD patients.

Methods: Between January 2015 and May 2019, all adult FD patients (n=32) referred to our institute were enrolled; they were Caucasians (n=24 females, n=8 males) with an average age of 50±12.2 years. Data regarding hypertension were obtained by ambulatory BP monitoring (ABPM), home self-monitoring and office measurements. Patients were defined as hypertensive according to 2018 ESC/ESH Guidelines. The severity and the stability of FD were assessed with the Fabry Stabilization Index (FASTEX). Organ involvement and hypertension risk factors were also evaluated.

Results: The ABPM revealed elevated BP in 18.75% (n=6) of the FD population and 50% (n=3) of this group was diagnosed with masked hypertension. All these patients were females with an average age of 58±9.9 years. They presented a lower (p=0.046) glomerular filtration rate compared with the normotensive patients (77±17.7 and 89.3±21.4 ml/min/1.73m^2, respectively) and a more advanced cardiac hypertrophy with a higher LVPWd (p=0.044) and LVMi (p=0.033). Four of them (66.7%) were classified as progressive by the FASTEX score while the majority of the normotensives (84.6%) were stable (Figure 1). No correlation (p=0.428) was found between the category of GLA mutation and the development of hypertension.

Conclusions: Newly detected hypertension is found in a restricted portion of stable FD patients, while it becomes more prevalent in clinically progressive cases. The use of ABPM is of paramount importance to reveal masked hypertension which can contribute to the progressive worsening of the organ failure. We recommend a standardised ambulatory long-term BP monitoring program and timely antihypertensive intervention to improve the outcome of FD patients.



FASTEX score

PUB140

Digenic Inheritance of Extracellular Matrix Mutations in a Family with FSGS

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Background: Focal and segmental glomerulosclerosis (FSGS) is a histologic pattern of injury that characterizes a wide spectrum of diseases with different pathophysiologies and for which current diagnostic methods often fail to distinguish molecular mechanisms. We have recently reported whole exome sequencing (WES) in an adult FSGS cohort but most disease still remains unexplained.

Methods: In an unexplained family with adult-onset autosomal dominant FSGS, WES was performed in 3 affected relatives to identify candidate genes.

Results: The proband presented with proteinuria in his 20s and a renal biopsy at age 41 demonstrated FSGS (**Figure 1**). His two brothers also had FSGS documented in the 4th and 5th decades of life. The proband and his elder brother developed end-stage renal disease (ESRD) in the 5th decade of life while the youngest brother has stage 3b A3 CKD at age 59. Of the proband's 3 sisters, one developed proteinuria at the time of last follow-up at age 54. Her daughter whose renal biopsy also demonstrated FSGS at age 23, had approximately 3.3 g/d of proteinuria and an eGFR of 48 ml/min at age 30. After WES, five heterozygous rare variants were identified and sequenced in all affected relatives. Two of these variants segregated in affected family members and encoded extracellular mesangial matrix proteins. Renal biopsies showed classic segmental sclerosis/hyalinosis lesion on a background of mild mesangial hypercellularity. One of these genes is already reported to cause an autosomal recessive neurologic disorder.

Conclusions: We postulate that the additive effect of heterozygous mutations in extracellular matrix proteins leads to adult-onset FSGS. The absence of clinically significant extra-renal symptoms is likely as a result of the impact of the mutation which should lead to translated protein rather than complete deficiency seen in autosomal recessive disorders. Our results provide a signal of more complicated genetic inheritance patterns in unexplained families.

Funding: Private Foundation Support, Government Support - Non-U.S.

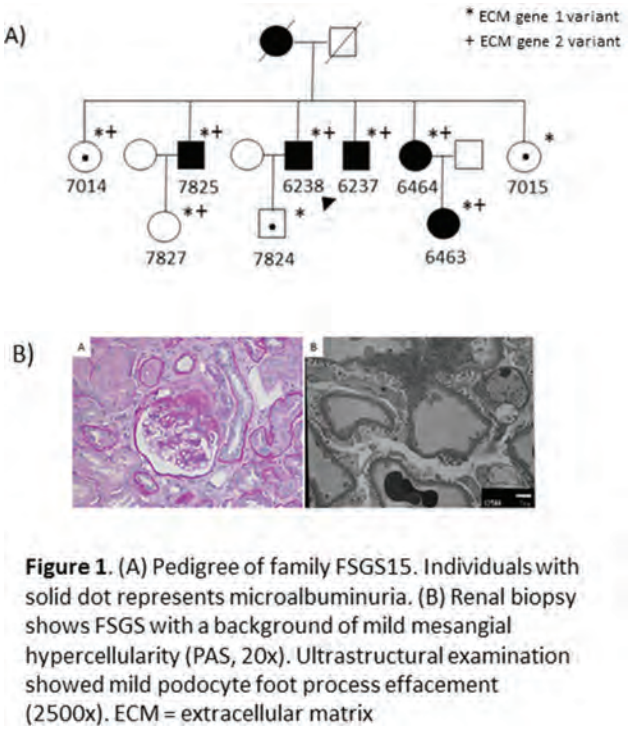

Figure 1. (A) Pedigree of family FSGS15. Individuals with solid dot represents microalbuminuria. (B) Renal biopsy shows FSGS with a background of mild mesangial hypercellularity (PAS, 20x). Ultrastructural examination showed mild podocyte foot process effacement (2500x). ECM = extracellular matrix

PUB141

Findings of Whole-Exome Sequencing in a Tunisian Man with Congenital Anomalies of Kidney and Ureteral Tract and Dilated Cardiomyopathy

Sabra Aloui,[1] Majdi Nagara,[3] Salima Ltaief,[1] Ahmed Letaief,[1] Manel Ben salah,[1] Mouna Hamouda,[1] Meriem Ben salem,[1] Habib Skhiri,[1] Ridha Mrad,[2] Sonia Abdelhak.[3] *[1]Department of Nephrology, Monastir University, Monastir, Tunisia; [2]Department of Human Genetics, Charles Nicolle Hospital, Tunis, Tunisia; [3]Laboratory of Biomedical Genomics and Oncogenetics, Institut Pasteur de Tunis, Tunis, Tunisia*.

Background: Congenital Anomalies of Kidney and Ureteral Tract (CAKUT) is a paediatric concern but can be diagnosed in adults adding challenges in the identification of CAKUT's etiology. To date, there are more than 50 single-gene disorders known to underlie CAKUT. Furthermore, a substantial number of CAKUT causes are extremely rare in the general population. Whole exome sequencing (WES) has been proposed as the solution in some cases.

Methods: Whole exome sequencing and case study of an adulte with CAKUT, cardiomyopathy, factor7 and other anomalies

Results: It is about a 30-years-old Tunisian man. He was referred to our unit for renal failure. His parents are second degree consanguine. He was hospitalized at age 2 years for dehydration. He had a brother with Parkinson disease started early at age of 20 years. He was hospitalised at age 29 in cardiology unit for heart failure. Explorations revealed dilated cardiomyopathy (DCM) and an elevated plasmatic creatinine. Physical examination showed a peculiar facies with crying facial expression when laughing, dental anomalies, mild mental retardation, strabismus, large prominent earlobes, brachydactylia, right cryptorchidism and normal blood pressure. Laboratory exams confirmed kidney failure: creatinine at 900µmol / L without proteinuria or haematuria. Prothrombin level was low to 50%, the exploration revealed a factor VII deficiency. Ultrasound scans showed a single right kidney of reduced size. We concluded at chronic renal failure due to tubulointerstitial nephritis associated with urofacial syndrome, DCM and factorVII deficiency. The diagnosis of a CAKUT with OCHOA syndrome was suspected but heart failure and factor VII deficiency were not explained. A whole sequencing exome was performed. It reversed the Oshoa syndrome and revealed two other possible genetic etiologies of CAKUT: a Kabuki syndrome and a Sensenbrenner syndrome. It also revealed a mutation of TTN, the gene encoding the sarcomere protein titin, explaining the DCM.

Conclusions: Exome Sequencing have a dual role as a discovery and diagnostic Tool. It's clinical utility will be discussed especially in in countries with strong consanguinity and low-income as in North Africa

PUB142

Non-Compliance and Acute Dehydration Are Main Reasons for Acute Kidney Failure in Patients with Non-Infantile Primary Hyperoxaluria Type 1

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Background: Patients with primary hyperoxaluria type 1 (PH1) have an increased risk of acute or chronic kidney failure (AKF/CKF). There are two risk groups: infantile oxalosis patients with an unremarkable family history and adult patients with only an oligosymptomatic course (minor stone events), who get into end-stage renal disease (ESRD) due to oxalate-induced chronic inflammatory processes in the kidney. We were interested in the prevalence of acute kidney failure in patients with non-infantile PH1 seen in our Hyperoxaluria Center over the last 10 years.

Methods: We retrospectively analyzed the database of the German Hyperoxaluria Center for patients being seen in our outpatient clinic for AKF. AKF was defined as a sudden onset of kidney failure and the necessity of dialysis installment in patients, but a documented stable kidney function (no worse than stage 2-3 CKD) prior to onset of AKF.

Results: There were 117 PH1 patients in the center, of whom 6 had infantile oxalosis and thus early ESRD, 8 patients are currently on dialysis, and 6 patients have died. Transplantations were performed in 35 patients with PH1 (liver & kidney in 28 patients, liver-only in 4 patients, and kidney-only in 3 patients). Currently, we routinely follow up (3-4 times a year) 49 of 117 PH1 patients. Out of these 49 patients, AKF was diagnosed in 8 patients aged 11-56 years (1 pediatric patient, 3 patients 18-19 years old, and 4 patients 29-56 years old), which led to CKF and subsequently, maintenance hemodialysis in 7 patients and death in 1 patient. Non-compliance regarding medication or recommended fluid intake was the reason for AKF in 6 of the 8 patients. Acute massive diarrhea without adequate fluid substitution led to AKF in the other 2 patients.

Conclusions: AKF is not uncommon in patients with PH1. It is frequently related to either non-compliance or to situations of severe fluid losses with inadequate fluid substitution and not based on already extremely altered renal function. Therefore, interruption of medication or lack of fluid intake, even for short periods of time, can lead to severe clinical consequences in these patients.

PUB143

ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis: A Positively Rare Cause of RPGN

Anand Narayanan, Wafa Dawahir, Paru P. Kathpalia. *Mercy Hospital Medical Center, Chicago, IL*.

Introduction: Pauci-immune crescentic necrotizing glomerulonephritis (PICGN) is the most common subset of RPGN. Most cases of PICGN are antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; however, about 10-30% of patients are ANCA negative. Several studies have suggested that ANCA-negative PICGN has a lower incidence of extra-renal involvement, a poorer prognosis, and often dialysis dependent. Unfortunately given our limited understanding of the pathophysiology of ANCA-negative PICGN, current therapy is similar to ANCA-positive despite its worse prognosis.

Case Description: 60-year-old female presented for hypertension emergency. She had an elevated creatinine (Cr) of 1.48; baseline was 1.29 two weeks ago. Her Cr worsened to 2.05 and nephrology was consulted. Initial differential included acute drop in BP from restarting medications. UA showed 2+ protein, quantified 2 grams/gCr and RBC > 100. Findings of proteinuria and hematuria suggested RPGN however testing for ANCA, Anti-GBM, HIV, Hepatitis B and C, ANA, C3, C4 were negative. AKI due to ATN from infection was included in the differential for MDRO UTI. Despite treatment for infection and liberalized BP control, Cr continued to worsen and she became oliguric, acidotic and was started on dialysis. Given infiltrates seen on Chest CT, she had bronchoscopy with biopsy suggestive of bleeding that raised the possibility of pulmonary-renal syndrome. A renal biopsy was performed which showed pauci immune ANCA negative crescentic GN. Pathology showed almost 100% of glomeruli involved with global scarring and fibrinoid necrosis. She was started on steroids and Cytoxan. Six months later, she is off both medications but still on dialysis.

Discussion: Since patients with ANCA-negative PICGN have few extra-renal manifestations, are often dialysis dependent and have a worse prognosis, early recognition is crucial. The diagnosis primarily relies on performing a kidney biopsy rather than serological testing, otherwise the diagnosis may be missed. Early initiation of empiric therapy is appropriate to minimize the degree of irreversible injury and delay dialysis initiation. The degree of sclerotic fibrotic lesions in renal biopsy may predict treatment response. ANCA negative PICGN is a rare diagnosis; this case highlights why it is important to keep this diagnosis in the differential and why novel treatment options are needed.

PUB144

Collapsing Focal Segmental Glomerulosclerosis Associated with Parvovirus B19 Infection

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Introduction: Focal segmental glomerulosclerosis (FSGS) can be subdivided based upon its histologic classification. The collapsing subtype of FSGS is not only of the rarer forms of FSGS, but also carries the worst prognosis. We present a case of collapsing FSGS secondary to Parvovirus B19 infection in a patient with a relatively unremarkable past medical history.

Case Description: A 32-year-old female with prior history of gestational hypertension presented to emergency with a three-day history of bilateral lower extremity edema and periorbital swelling. On exam, profound periorbital edema and 2+ pitting edema up to the knees bilaterally was noted. Labs were consistent with a creatinine level of 5.0 mg/dL up from her baseline of 0.5 mg/dL three months prior. Urinalysis and random urine testing confirmed proteinuria of almost 19 grams per day. Renal ultrasound was obtained showing normal sized kidneys with increased echogenicity. Kidney biopsy was obtained and results were consistent with collapsing FSGS. Secondary workup for etiology of FSGS came back positive for Parvovirus B19 infection. Along with diuresis, decision was made to start IVIG and prednisone therapy. Initially, patient had improvement in kidney function post treatment and patient was followed up in clinic. However, required hemodialysis for one month.

Discussion: FSGS is commonly associated with nephrotic syndrome and stems from podocyte abnormalities. Podocyte detachment and death lead to segmental sclerosis, which is the hallmark pathophysiology of FSGS. Kidney biopsy is used to diagnose FSGS and characterized by the presence of sclerosis of at least one glomerulus on histologic examination. Histologically there are five classifications of FSGS with collapsing carrying the worst prognosis. Treatment is typically aimed at controlling proteinuria, edema, and cholesterol. In our patient with Parvovirus B19 induced FSGS, we used IVIG with prednisone therapy but no improvement. Further research is needed to find treatments for Parvovirus B19 induced FSGS for better outcome.

PUB145

A Whole Genome-Wide Arrayed CRISPR Screen in Primary Organ Fibroblasts to Identify Regulators of Kidney Fibrosis

Ina Sternberger. Evotec International GmbH *Evotec SE, Hamburg, Germany*.

Background: Robert J. Turner, Stefan Golz, Carina Wollnik, Nils Burkhardt, Ina Sternberger, Uwe Andag, Hauke Cornils Kidney fibrosis presents a hallmark of chronic kidney disease. With ever-increasing patient numbers and limited treatment options available, novel strategies for therapeutic intervention in kidney disease are warranted. Fibrosis commonly results from a wound healing response to repeated or chronic tissue damage, irrespective of the underlying etiology, and can occur in virtually any solid organ or tissue.

Methods: whole genome-wide arrayed CRISPR screening high content imaging

Results: In order to identify targets relevant for kidney fibrosis, we employed CRISPR screening in primary human kidney fibroblasts. Selected ht genes were validated.

Conclusions: We demonstrate that CRISPR technology can be applied in primary kidney fibroblasts and can furthermore be used to conduct arrayed CRISPR screening using a high-content imaging readout in a whole genome-wide manner. Hits coming out of this screen were validated using orthogonal approaches and present starting points for validation of novel targets relevant to kidney disease.

Funding: Commercial Support - Evotec, Bayer Pharma

PUB146

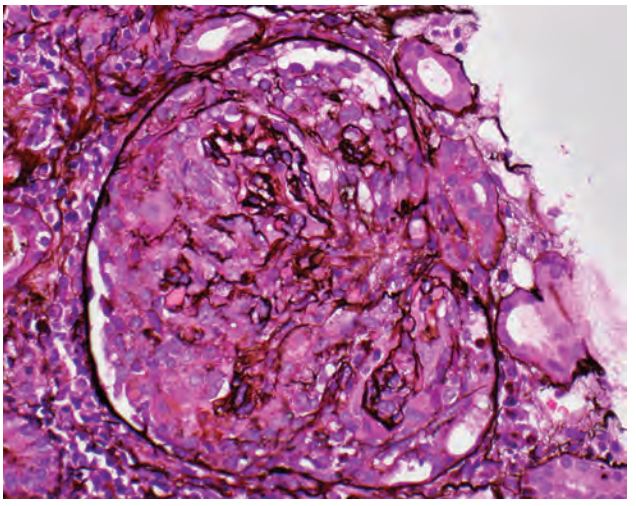
Dual Positive Anti-Glomerular Basement Membrane Disease and ANCA Disease: A Diagnostic Challenge

Niloufarsadat Yarandi,[1] Kevin Fu,[1] Avi Z. Rosenberg,[2] Renu Regunathan-Shenk.[1] *[1]Division of Kidney Disease and Hypertension, George Washington School of Medicine and Health Sciences, Washington, DC; [2]Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD.*

Introduction: Double-positive disease (DPD), defined as coexistence of anti-glomerular basement membrane (Anti-GBM) disease and an anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), is rare disease associated with variable outcomes. These patients often do not have typical presentation of either anti-GBM disease or AAV, making diagnosis a challenge.

Case Description: A 59-year-old male with history of hypertension presented with 1 week of fatigue and decreased urine output. Initial labs revealed a serum creatinine of 11.6 mg/dL and blood urea nitrogen of 133 mg/dL. Urinalysis showed specific gravity of 1.025, pH 5.0, 1+ protein, large blood, and 11-20 RBCs/hpf. Serological workup including anti-nuclear antibody, complement C3 and C4, HIV, hepatitis B and C were all unremarkable. The patient then developed hemoptysis and anuria. He was initiated on hemodialysis. Renal biopsy revealed extensive cellular and fibrocellular crescents, diffuse tubular injury with RBC casts, and 30% interstitial fibrosis and tubular atrophy. Immunofluorescence was negative. Further investigation revealed an elevated Anti-GBM titer, elevated anti-myeloperoxidase antibody and negative anti-proteinase 3 antibody. He was treated with methylprednisolone 1g intravenous for 3 days then daily prednisone 60mg and one dose of cyclophosphamide 1g intravenously. He was then transferred for initiation of plasmapheresis and received 8 sessions with normalization of Anti-GBM and ANCA titers. He also received another dose of cyclophosphamide 1g. He remained dialysis-dependent upon discharge.

Discussion: The varied presentation of DPD may cause a delay in diagnosis. DPD patients have a greater tendency to recover renal function but a higher risk of relapse. Early recognition and aggressive treatment is essential.



Crescent-GBM rupture

PUB147

Transcriptomic Profiling of Collagens in Proteinuric Kidney Disease

Prakash Narayan, Sony Dalapati, Ping Zhou, Natalia Prakash, Itzhak D. Goldberg. *Angion Biomedica Corp, Uniondale, NY.*

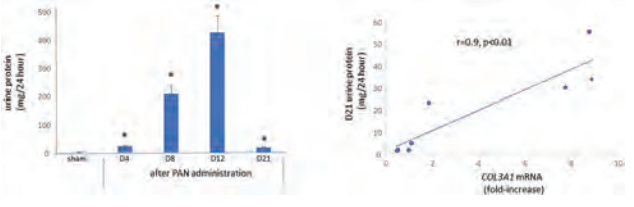
Background: The puromycin aminonucleoside nephropathy (PAN) model is associated with proteinuria and matrix accumulation. We tested the hypothesis that renal *COL1A1* and *COL3A1* are differentially expressed genes in PAN nephropathy.

Methods: Adult Wistar rats were administered water (sham) or PAN (~100 mg/kg, IP) and urine protein (24-hour) was measured on Days 4, 8, 12 and 21. Animals were sacrificed on Day 21, the left kidneys retrieved, and renal *COL1A1* and *COL3A1* mRNA levels measured using quantitative polymerase chain reaction.

Results: The rat PAN model was associated with increased proteinuria (*, $p<0.01$ vs. sham). Compared to the sham cohort, renal *COL1A1* and *COL3A1* mRNA expression levels were increased, 1.86-fold ($p<0.05$) and 8.4-fold ($p<0.01$), respectively, in the PAN cohort. Proteinuria correlated directly ($r=0.9$) and significantly ($p<0.01$) with renal *COL3A1* mRNA expression level.

Conclusions: Renal *COL1A1* and *COL3A1* mRNA expression levels are elevated in proteinuric kidney disease. Since *COL3A1* mRNA expression is associated with increasing proteinuria, targeting type III collagen might prove beneficial. Funded By: United States Department of Defense - PR180780/ W81XWH1910448

Funding: Other U.S. Government Support



PUB148

C3 Glomerulonephritis: Diagnostic Challenges and Overlap Syndromes

Krishna A. Agarwal, Esilida Sula Karreci, Larissa Kruger gomes, Ruth Schulman, Isaac E. Stillman, Stewart H. Lecker, Theodore I. Steinman, Bradley M. Denker. BIDMC *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: C3-glomerulonephritis (C3GN) is a rare complement-mediated GN, with an incidence of 1-3:1,000,000. Spectrum of presentation can range from asymptomatic hematuria and proteinuria to a full blown acute GN with hypertension, hematuria, and renal insufficiency. Serum C3 levels are typically low. Diagnosis is confirmed by renal biopsy. The underlying mechanism appears to be dysregulated alternate complement pathway, triggered by genetic, environmental or a combination of both factors. Medical management addresses blood pressure, proteinuria, and dyslipidemia. Immunosuppression with glucocorticoids, antimetabolites, and anti-complement agents is used alone or in combination. Here we present 2 cases of biopsy-proven C3GN, mimicking infection-associated GN (IAGN) and TTP/HUS.

Case Description: Case 1: A 49-year-old man presented with 4-5 days of fevers, chills, nausea, vomiting and diarrhea. Labs revealed mild thrombocytopenia, proteinuria, microscopic hematuria and a low C3 level. Blood cultures revealed Streptococcus pyogenes. His hospital course was marked by rapidly progressive pancytopenia and hemodialysis-requiring acute renal failure. He received a single dose of eculizumab empirically due to concern for atypical HUS, but platelet counts improved too rapidly

to be consistent with eculizumab benefit. Kidney biopsy revealed acute tubular injury with glomerular C3 deposition. EM did not reveal immune deposits. Subsequent renal recovery followed 4 hemodialysis sessions. One-month post-discharge, he had normal renal function and hematologic cell counts. Case 2: A 74-year-old man with CKD III was admitted with altered mental status, septic shock, and acute kidney injury. Extensive workup did not detect infection or altered autoimmune status. His course was complicated by worsening renal failure, proteinuria, and hematuria. Renal biopsy demonstrated acute tubular injury and glomerular C3 deposition without immune deposits on EM. Eculizumab was deferred due to normal C3 and C4 levels. A steroid pulse was associated with an improvement in creatinine beginning on day 4 and return to baseline kidney function by day 17.

Discussion: Our cases highlight the variable presentation and complexity associated with accurate diagnosis of C3GN, including considerable overlap with IAGN and TTP/HUS.

PUB149

To Treat or Not to Treat? The Dilemma of C3 Glomerulonephritis vs. Infection-Related Glomerulonephritis

Rehan Ansari, Miroslav Sekulic. *University Hospitals, Cleveland, OH.*

Introduction: With a paradigm shift of infection related glomerulonephritis (IRGN) from a post-streptococcal infection of the young in developing countries to a poly-microbial infection of the elderly in the western world, the differentials have broadened. This has coincided with an evolving phenomenon of C3 glomerulopathy [C3G- C3 glomerulonephritis (C3GN) & Dense Deposit Disease (DDD)]. In all these entities a common feature is C3 dominant staining. Although subtle differences have been described in the nature of these deposits, we present a case in which the clinical course & biopsy findings highlight the challenges of identifying C3GN vs. IRGN.

Case Description: A 62 y/o female with HTN, hypothyroidism, epidural abscess, & recent MSSA bacteremia presents with AKI & anemia. Her creatinine was 2.92mg/dL vs. 0.53mg/dL (three weeks ago). Labs: Total Protein/Creatinine 4.29 mg/mg, negative blood cultures, unremarkable ANA, ANCA, SPEP, UPEP, K/L, Antistreptolysin O (ASO) Antibodies 541 IU/mL (0-200) & C3 77mg/dL (87-200), C4 47 mg/dL (10-50). Kidney biopsy: C3 dominant glomerulonephritis, >50% crescents, 3+/4 staining for C3 in mesangium & capillary loops, EM revealed finely granular mesangial, intramembranous, & subepithelial electron-dense deposits. She was started on steroids & C3 improved to 95 mg/dL after three weeks. Creatinine plateaued ~4.1mg/dL prior to discharge. Full complement profile available after one month (C1 Inhibitor 84.6mg/mL (21-39), C3 Nephritic 0units/mL (0), C4Bp 136.3% (61- 116), Factor H AutoAB 30unit/mL (<=22), SC5b-9 313ng/mL (<= 244).

Discussion: Classically, neutrophilic infiltration, occasional crescents (<50%) & subepithelial humps with co-deposition of C3 & IgG or IgA are described with IRGN, while mesangial & diffuse endocapillary proliferation exclusively with C3 deposition is expected with C3G. However biopsy alone is not specific for identifying the underlying etiology. ASO titers are elevated in >50% cases of C3GN and 25% of IRGN cases present with only C3 staining. Based on a strong history of infection, & improvement of C3, we treated as IRGN. Although testing for complement pathway mutations is recommended, results are not readily available. The clinical significance of these mutations remain under scrutiny. Until issues of testing & treatment can be generalized a holistic approach with close follow up is needed in cases of C3 dominant glomerulonephritis.

PUB150

A Young Asian Man with Heavy Chain Deposition Disease

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Introduction: Heavy chain deposition disease (HCDD) is an exceedingly rare condition characterized by nonamyloid tissue deposition of monoclonal immunoglobulin heavy chain. It typically presents in patients above age 50. Here, we report a case of a young Asian male who presented with acute kidney injury (AKI) and nephrotic syndrome (NS).

Case Description: A 32-year-old Chinese man presented with anasarca. He has no significant past medical history and his family history was also unremarkable. On presentation, he was afebrile with an elevated blood pressure to 205/136. Exam showed peri-orbital and 2+ lower extremity edema. Laxed skin was noted in his neck and abdomen. Laboratory studies showed an initial serum creatinine of 1.5 mg/dl with unknown baseline, it quickly rose to 10.4 mg/dl over the next 4 weeks requiring dialysis support. His LFT was normal, serum albumin was 2.0 g/dl, total cholesterol was 224 mg/dl. 24-hour urine total protein was 10.9 gm with albumin 7.7 gm. Serologies showed negative ANA, dsDNA, hepatitis and HIV panel, SPEP and UPEP for m-spikes. His complement levels were also normal. Urine sediment revealed 360 RBC with acanthocytes and 10 WBC under high power field. His kidney ultrasound was unremarkable. Kidney biopsy revealed nodular mesangial sclerosis with membranoproliferative features. There were intense immunoglobulin G1 staining in the mesangium, glomerular and tubular basement membranes and vessel walls. Kappa, lambda, IgM and IgA immunofluorescence were undetectable. Thus, a diagnosis of γ-type HCDD was made. The patient was started on treatment with bortezomib and dexamethasone. Within 2 months, he came off dialysis, 24hr urine total protein improved to 5.9 gm. Four months after starting bortezomib therapy, serum creatinine improved to 1.4 mg/dl and 24hr urine protein was down to 1.6 gm.

Discussion: In summary, this is a unique HCDD case diagnosed in a young Asian gentleman. He did not have detectable monoclonal serum protein. Like other reported cases, he responded well to a bortezomib based regimen.

PUB151

A Challenging Case of Renal-Limited Vasculitis

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Introduction: Anti-neutrophil cytoplasmic autoantibody (ANCA)-Associated Vasculitis (AAV) is an autoimmune disease that causes inflammation of blood vessels and has a wide spectrum of clinical presentation. It can present as multisystem or renal-limited disease. The typical renal presentationis that of a rapidly progressive glomerulonephritis (RPGN). We present an interesting case of renal-limited vasculitis with atypical features.

Case Description: A 76 year old male with a past medical history of Hypertension (treated with hydralazine) and CKD Stage 3 presented with weakness and shortness of breath for about two weeks. Physical exam and vitals were unremarkable. Laboratory workup revealed AKI with creatinine of 6.5 mg/dl. Urinalysis revealed microscopic hematuria and proteinuria (urine protein/creatinine ratio of 0.9). Renal ultrasound was unremarkable. Serologic workup including ANA, C3, C4, anti-GBM Ab, HBsAg, HBsAb and HBcAb was unremarkable. However, p-ANCA titer was high (1:160). He was treated with IV fluids. Interestingly, he continued to have good urine output as well as improvement in serum creatinine to 4.8 mg/dl and was discharged from the hospital. Follow-up renal function panel in two weeks showed worsening serum creatinine of 6.8 mg/dl. The patient was readmitted to the hospital. Repeat serologic workup revealed p-ANCA titer of 1:320 and elevated MPO IgG of 78 U/ml. Renal biopsy revealed pauci-immune glomerulonephritis. Steroids and rituximab were initiated as treatment. Due to worsening kidney function, patient was started on hemodialysis. He remained dialysis dependent with no significant renal recovery. Given atypical features of disease presentation, hydralazine was considered to be an etiologic agent hence, and was discontinued.

Discussion: We present a case of renal-limited vasculitis with atypical features making the diagnosis very challenging. Firstly, the patient remained nonoliguric throught the first hospital course. Secondly, his serum creatinine improved with supportive treatment leading to his discharge with presumptive diagnosis of ATN. In summary, ANCA associated GN may present with nonoliguria as well as waxing and waning renal function. Atypical features of AAV should raise concern for drug-induced etiology.

PUB152

Collapsing Focal and Segmental Glomerulosclerosis with Thrombotic Microangiopathy Found on Renal Biopsy in a Patient Receiving Intravitreal Aflibercept for Age-Related Macular Degeneration

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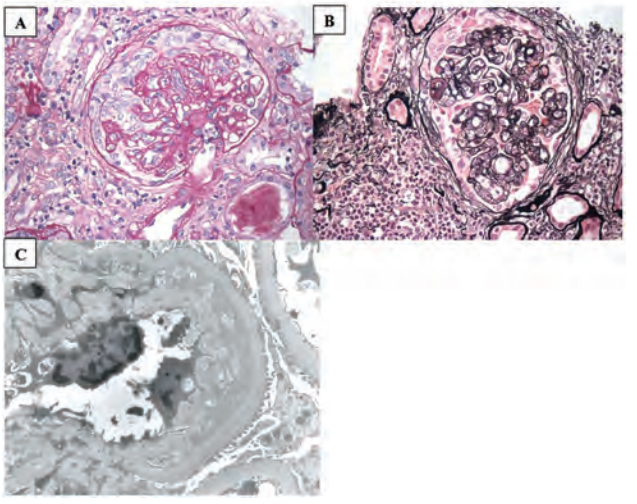
Introduction: Intravitreal Vascular Endothelial Growth Factor (VEGF) Receptor blockade is used for a variety of retinal pathologies. These include age related macular degeneration (AMD), diabetic macular edema (DME), and central retinal vein obstruction (CRVO). Reports of absorption of intravitreal agents into systemic circulation have increased in number, and confirmation of depletion of VEGF has been confirmed. Increasingly there are studies and case reports showing worsening hypertension, proteinuria, renal dysfunction, and glomerular disease. The pathognomonic findings of systemic VEGF blockade, thrombotic microangiopathies (TMAs) are also being increasingly reported. One variant of TMAs that has been described is collapsing focal and segmental glomerulosclerosis (cFSGS). CFSGS has been postulated to occur due to TMA induced chronic glomerular hypoxia. We present the third reported case of cFSGS in the setting of intravitreal VEGF blockade, a chronic TMA component was crucially found on biopsy.

Case Description: This patient is a 74-year-old non-diabetic male receiving aflibercept for AMD. Of the two prior cases of cFSGS in setting of VEGF blockade, one had AMD and the other had DME.

Discussion: This case solidifies the finding of cFSGS and its association with chronic TMA as a lesion that may be frequently encountered in patients receiving intravitreal VEGF inhibitors.

Figure 1



PUB153

A Case of IgA Vasculitis in Liver Cirrhosis

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Introduction: IgA vasculitis (previously termed Henoch-Schönlein purpura) is a systemic immune-complex mediated condition characterized by predominant IgA1 deposition in microvessels. We present a case of biopsy-proven IgA vasculitis involving skin and kidneys in a patient with known liver cirrhosis.

Case Description: A 71-year-old man with liver cirrhosis due to chronic ETOH use presented to ER with a one-month history of progressive rash and pedal edema. He denied arthralgias, melena, hematemesis, abdominal pain, or fever. Diffuse, erythematous, palpable, non-pruritic petechial lesions were noticed on bilateral thighs, arms, and anterior abdominal wall with few lesions coalescing to purpura. Laboratory evaluation revealed an elevated creatinine at 1.7 mg/dl. Urinalysis showed dysmorphic erythrocytes, leucocytes, and proteinuria. ANA was positive (1:320), C3 slightly low with normal C4. Cryoglobulin, RA factor, SPEP, ANCA, anti-dsDNA, HBsAg, antibodies to HIV, HCV, rickettsia, and syphilis were negative. Peritoneal fluid culture was sterile. Kidney biopsy revealed severe proliferative glomerulonephritis, cellular/fibrocellular crescents and mild interstitial fibrosis. Skin biopsy revealed dense perivascular neutrophilic infiltration with fibrin deposition and erythrocyte extravasation consistent with leukocytoclastic vasculitis. He was diagnosed with IgA vasculitis and treated with pulse IV steroids followed by oral taper along with monthly IV cyclophosphamide infusions. Petechial lesions improved markedly but renal function was unchanged at 4-month follow-up. Unfortunately, the patient died 5 months after initial presentation due to complications of underlying liver disease and secondary infection.

Discussion: IgA vasculitis, more commonly observed among children than adults, manifests clinically as palpable non-blanching purpura, arthritis, intussusception, and kidney injury. Adults commonly develop ESRD in one-third of cases. Similar to crescentic IgA nephropathy, a combination of IV followed by oral steroids and IV cyclophosphamide is recommended in patients with rapidly progressive renal failure with more than 50% crescents on renal histology. In our case, the patient had an underlying liver disease which is an independent risk factor associated with glomerular IgA deposition due to inadequate clearance. The degree of contribution to the pathogenesis of IgA vasculitis remains unknown.

PUB154

Poststreptococcal Glomerulonephritis in an Elderly Patient: A Rare but Often Overlooked Differential in AKI

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Introduction: Poststreptococcal glomerulonephritis (PSGN) is a complication of specific Streptococcal strains. Presentation ranges from asymptomatic microscopic hematuria to acute nephritic syndrome, with oliguria, edema, hypertension, and acute kidney injury (AKI). It mostly occurs in children of developing countries. Its incidence is not well characterized in elderly individuals but is thought to be extremely rare. We report a case of PSGN in an elderly female complicated by hypertensive urgency and heart failure.

Case Description: An 89-year-old female with history of COPD, HFpEF, CKD stage 3a presented with lethargy and weakness. She was treated for bronchitis 3 weeks prior and initially improved but then developed progressive dyspnea and swelling in her lower extremities. On presentation, BP was 252/120, CXR showed cardiomegaly and pulmonary edema. Labs revealed a creatinine of 2.72 (baseline 1.4). She was started on IV diuretics, BiPAP, and nitroglycerin drip with improved BP control. She remained oliguric. Nephrology was consulted due to no improvement in urine output despite bumetanide and thiazide diuretic challenge. Renal ultrasound was unremarkable. Autoimmune workup was negative. She required emergent hemodialysis (HD) as her kidney function failed to recover. A renal biopsy showed chronic tubular and arteriolar changes with noted glomerular endocapillary immune-complex glomerulonephritis, concerning for post-infectious GN. She ultimately required an arteriovenous fistula for longterm HD.

Discussion: PSGN primarily occurs after an upper respiratory infection or impetigo. It is less common in adults, however, is associated with a worse prognosis compared to children, with less than 25% achieving full recovery of renal function. Unlike children, the elderly tend to present with etiologies of lower respiratory infections (LRI) and UTIs. Studies show the time between infection and renal injury may be little to none, as infections in the elderly are often nonspecific and might go unrecognized. Our patient had an AKI after a LRI, resulting in significant oliguria and lack of renal recovery leading further work up with a biopsy. It is therefore imperative that providers consider PSGN as a differential diagnosis in elderly patients with severe AKI. Treatment is mainly supportive, and patients, like ours, might require HD.

PUB155

Staphylococcal-Associated Glomerulonephritis due to Necrotizing Panton Valentine Leukocidin-Positive Methicillin-Resistant *Staphylococcus aureus* Pneumonia: A Case Report

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Introduction: Post-infectious glomerulonephritis (GN) occurs due to cross-reactivity of host and pathogen antigens and antibodies, leading to immune complex deposition in the glomerulus and acute kidney injury after a bacterial infection. Staphylococcal-associated GN differs in its pathogenicity, occurring during an active infection. Staphylococcal-associated GN usually occurs due endocarditis, soft tissue or bone infections, while pneumonia is an uncommon cause. This is a case of GN in a 39-year-old man that resulted from Panton-Valentine Leukocidin (PVL) positive MRSA necrotizing pneumonia complicated by septic emboli, leading to GN requiring renal replacement therapy (RRT).

Case Description: A 39-year-old man with a past medical history of cocaine abuse, intravenous heroin abuse and hypertension presented initially with four days of nausea, vomiting, pleuritic chest pain and cough. His labs were notable for BUN of 80 mg/dL and a creatinine of 4.9 mg/dL and WNC of 14,900. Urinalysis > 500 mg/dL of protein, 50 >182 RBCs/hpf. HIV assay was nonreactive, as was his hepatitis panel. C3 was 101 mg/dL, C4 was 7 mg/dL. 24 hour urine protein was 4.8 g/day. A CT chest showed septic emboli and a right middle lobe consolidation consistent with pneumonia. Blood cultures were positive for MRSA. TEE did not reveal valvular vegetations. Renal biopsy showed C3 deposits by immunofluorescence and scattered subepithelial and intramembranous electron deposits by electron microscopy concerning for staphylococcal-associated GN. The patient was started on RRT and had persistent bacteremia for nearly 2 weeks despite being on vancomycin and cefepime. After a positive PVL assay, these were switched to linezolid and ceftaroline with clearance of bacteremia. Interdialytic creatinine decreased and RRT was stopped.

Discussion: Staphylococcal-associated GN differs from PSGN by occurring during active infection. This rarely occurs in pneumonia. PVL is an under-recognized virulence factor that contributes to the pathogenicity of MRSA especially in the case of necrotizing pneumonia. It can lead to higher virulence and prolonged antigen exposure, increasing the risk of immune complex formation and deposition.

PUB156

A Remission Case with Obsolescent IgA Nephropathy in Aspirin Plus Eicosapentaenoic Acid

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Introduction: In case of evacuating immunosuppression therapy to IgA nephropathy, ACEI, ARB, or both has statistically improved renal prognosis evaluated in urine protein(UP)[1)]. Eicosapentaenoic acid(EPA) on IgA nephropathy has documented alternative effects and side effects to steroids[2,3)].

Case Description: A 68-year-old woman was referred to nephrologist with complaint of bilateral leg edema accompanied with proteinemia and microscopic hematuria. She had been treated on diabetes, dyslipidemia, hypertension, and obesity in this clinic, then already pointed out that urine abnormality at 2 years ago. Her BP was 177/93mmHg, body weight 61 Kg, OB(3+), urine RBC 10-30/HPF, UP 2.2g/day, serum Cr 0.63mg/dl, HbA1c 7.6%, IgA 331mg/dl, and IgG 1,059mg/dl, on 20mg valsartan[1)]. Paraproteinemia was screened out. Percutaneous kidney biopsy show mild focal segmental proliferative glomerulonephritis with 2/19 segmental sclerosis and fibrous crescent, and 6/19 obsolescence glomeruli, IgA nephropathy, Oxford:M0,E1,S1,T1. In addition to this obsolescence glomeruli, her high BP and blood glucose led us add 100mg aspirin(ASA) plus 1,800mg EPA to reduce UP[4,5)]. Daily salt intake was restricted to 6g. After 4 years, TP/Cr,OB, urine RBC has normalized(**Table**).

Discussion: This case is diagnosed as chronic IgA nephropathy; this pathology might illustrate why her UP had not reduced with valsartan. On the other hand, acute lesion such as necrotized, or cellular or fibrocellular crescents was not detected. This finding gave us discussion on alternative medication which could evacuate from steroids and immunosuppressants. In addition to EPA 900-1,800mg per day on ARB[4)], ASA on EPA[5)] has reported to significantly reduce UP. Those authors speculated that ASA superimposed physiological effect on antiinflammatory lipids mediators[6,7)]. Taken together, this chronic IgA nephropathy has been normalizedurine dipstick findings by means of ASA plus

EPA. **References**:1)Coch Db Syst Rev 2011;**(3)**:CD003962.2)Lancet 1984;**1**:11017.3) NEJM 1994;**331**:1194.4)Intern Med 2013;**52**:193.5)Intern Med 2015;**54**:2377.6)Sci Rep 2014;**4**:e6406.7)J Clin Med 2017;**6**:70.8)J Hum Hypertens 2002;**16**:97.

	BP (mmHg)	BW (Kg)	HbA1c (%)	ESI* (g)	LDL (mg/dl)	HDL (mg/dl)	TG (mg/dl)	Alb/Cr (mg/gCr)	TP/Cr (mg/gCr)	Cr (mg/dl)	IgA (mg/dl)	OB	RBC (/HPF)
Nov 2014	177/93	61	7.6	11.7				1,359		0.63	418	(3+)	10-30
May 2015		59.5	7.2					3,050	4,352		379		
May 2016	155/94		6.3		89	42	132	1,321	1,258	0.73	331	(1+)	
Aug 2017	120/70	59.0	6.5	13.2				205	299	0.72	301	(1+)	1-5
Aug 2018	110/70	54.0	6.4	11.9	99**	45	125	63.0	91.2	0.83	275	(+/-)	1
Sep 2019	113/75	60.8	6.0	12.3	81**	45	84	54.8	97.6	0.75		(+/-)	1-4
Oct 2019	145/75	59.7	6.0	11.0	85**	49	72		124.2	0.74		(-)	1
May 2020	118/72	55.5	6.6	12.0	97**	54	70		137.2	0.79		(-)	1

*:estimated salt intake[5],**:by the Friedewald's equation.

PUB157

The Masquerading Diagnosis of Secondary Thrombotic Microangiopathy

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Introduction: Thrombotic microangiopathy (TMA) is an umbrella term defined by hemolytic anemia, thrombocytopenia and end organ damage secondary to microvascular thrombi. TMA is subclassified as either inherited or acquired (i.e lupus). We report a case of secondary TMA initially masquerading as atypical HUS.

Case Description: A 27 year old female with no significant medical history presented with shortness of breath for one month. She was noted to have acute kidney injury and new onset congestive heart failure. An echocardiogram revealed a dilated left ventricular and a severely reduced ejection fraction (10%). Her admission labs were notable for platelet count of 57, creatinine of 7.4 and schistocytes on peripheral smear. Given the concern for thrombotic thrombocytopenic purpura (TTP), an ADAMST13 level was drawn and plasmapheresis was initiated. Despite therapy, her kidney function worsened. As there were no overt causes of TMA, such as anti-phospholipid syndrome, infections, malignancy, or drugs, we strongly suspected aHUS and administered one dose of eculizumab. On hospital day 4, a kidney biopsy was performed which revealed an immune complex deposition driven glomerulonephritis with significant TMA as well as membranoproliferative changes consistent with class IV/V lupus nephritis. Eculizumab was discontinued and she was started on cyclophosphamide and pulse dose steroids. Her kidney function continued to decline and she eventually required hemodialysis. Serial echocardiograms revealed improvement in cardiac function and she was discharged from the hospital on dialysis.

Discussion: TMA can occur with autoimmune diseases. Although the mechanism remains unclear, there is evidence of complement activation leading to injury. For these cases, there is no evidence that treating TMA itself changes outcomes. It is important to distinguish between the causes of TMA as treatment differs between primary and secondary. There are current ongoing trials of the use of eculizumab in lupus nephritis, however current guidelines recommend induction treatment using cyclophosphamide and steroids. The cause of her heart failure remained unclear, thought was secondary to microvascular coronary damage from SLE.

PUB158

Membranous Nephropathy and Autoimmune Thyroid Disease

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Introduction: The relationship between thyroid dysfunction and nephrotic syndrome (NS) has been recognized since the 1970s, yet the mechanisms connecting them are poorly understood. Here we present a patient with profound hypothyroidism and idiopathic membranous nephropathy (iMN).

Case Description: 54-year-old Caucasian female with a 32-year history of hypothyroidism and BMI 54 kg/m^2, sought care for 3 months of dyspnea, bilateral leg edema and a 30 kg weight gain. She was admitted to her local hospital and had workup for anasarca. Physical exam: Vitals: BP 145/71 mmHg, pulse: 86 bpm and spO2 of 98%. Thyroid was normal size, morbid obesity and anasarca noted. Labs: creatinine 1.2 mg/dL, albumin 0.9 g/dL, and a thyroid stimulating hormone (TSH) 97.55 m[IU]/L. Urine protein/creatinine ratio of 12.6 g/g. A kidney biopsy demonstrated MN with phospholipase A2 receptor (PLA2R) positive antibody staining. Supportive treatment for iMN was initiated and she sought a second opinion at our institution. Additional testing revealed elevated anti-thyroid peroxidase antibodies (TPO), consistent with Hashimoto's Thyroiditis (HT). Treatment with the modified Ponticelli protocol and 200 mcg of levothyroxine daily was initiated.

Discussion: An association between HT and iMN has been described, but the underlying mechanism connecting these conditions remains poorly understood. Hypothyroidism is associated with increased serum creatinine, decreased glomerular filtration rate and higher risk of chronic kidney disease. Similarly, nephrotic patients with thyroid dysfunction have increased proteinuria and lower albumin levels compared to those without thyroid disease. In addition, loss of TSH and thyroid binding globulins due to NS can cause or exacerbate hypothyroidism. Interestingly, a recent study reports the presence of elevated anti-PLA2R antibodies in patients with isolated HT, raising the question of an autoimmune phenomenon affecting both organs. Although we cannot definitively determine that the same autoimmune process was affecting both organs in our patient, it is an intriguing question based on new evidence. Certainly, her underlying hypothyroidism was worsened by the development of NS. Nephrologists should consider screening for hypothyroidism when diagnosing NS, as treatment has the potential to significantly improve patient symptoms.

PUB159

Patient Journey, Perceptions, and Burden Associated with Immunoglobulin A Nephropathy (IgAN): A Qualitative Study

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Background: There is a lack of published evidence on patient perspectives in IgAN; a rare condition that can progress to end stage renal disease (ESRD). The objective of this study was to understand the patient journey, disease perceptions and burden of disease from the patients' perspective.

Methods: This qualitative study was conducted after review board approval through a moderated online bulletin board platform and by telephone interviews, to allow comprehensive answering of pre-defined questions. Participants were recruited via physician referral and were screened to ensure eligibility and willingness to participate. Analysis was conducted using a combination of various qualitative analytical tools.

Results: Eight participants with a confirmed diagnosis of IgAN from North America and Europe, aged 29–58 years participated. Diagnosis was often incidental as symptoms were underestimated or unnoticed. Participants were overwhelmed to learn they were diagnosed with a chronic disease and many did not understand the seriousness of the outcomes associated with the same. Post diagnosis, participants were referred to a nutritionist to discuss diet changes and received blood pressure medications. Some participants also received steroids and immunosuppressants. Frequency of monitoring visits varied and created anxiety if the disease progressed, based on new lab values. Speed of disease progression was different amongst patients. Besides symptoms like fatigue and lack of energy, some participants had to deal with emotional burden of feeling alone and fearful of the future with potential dialysis, transplantation and shortened life expectancy. According to the participants, the lack of standard procedures for early screening and diagnosis along with the absence of adequate information in patient friendly language and counselling were some of their needs. Additionally, participants expressed the need for a support mechanism with similar peers to learn to live with the disease and to counteract the feeling of being alone.

Conclusions: This study provides insights into how differently IgAN patients perceive and live with their disease. The insights obtained can be used to inform drug development and include what matters most to patients. Finally, this study highlights that a comprehensive education program for patients and caregivers is needed.

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PUB160

Retinal Drusen in Antibody-Mediated and Pauci-Immune Glomerulonephritis

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Background: Membranous and anti-glomerular basement membrane (GBM) glomerulonephritis are autoantibody-mediated diseases, where the antigens (PLA2R, THSD7A and collagen IV a3 respectively) are also expressed in the retina. Drusen are retinal deposits caused by complement activation and lipid debris in Bruch's membrane. Drusen have been described in one individual with membranous nephropathy and linear IgG deposits in Bruch's membrane of another with anti-GBM disease. In contrast, pauci-immune anti-neutrophil cytoplasm antibody (ANCA) vasculitis triggers complement but does not produce glomerular immune deposits. This study examined individuals with antibody-mediated or pauci-immune glomerulonephritis to determine how often drusen occurred in each group.

Methods: This was a cross-sectional observational case-series of individuals with antibody-mediated (n=15, membranous n=9, anti-GBM disease n=6) or pauci-immune (n=16, granulomatosis with polyangiitis n=7, microscopic polyangiitis n=7, eosinophilic granulomatosis with polyangiitis n=2) glomerulonephritis recruited from a general renal clinic in an Australian tertiary-care hospital. Two-field colour fundus images were obtained with a non-mydriatic camera (CANON, Japan). Images were coded and assessed for drusen count, location and size by two trained graders using the Wisconsin Age-Related Maculopathy Grading Grid. Central drusen counts ≥10 were considered abnormal.

Results: Four (27%) individuals with antibody-mediated disease (membranous n=2, anti-GBM disease n=2) but only one (6%) with a pauci-immune vasculitis had ≥10 central drusen. Gender, mean age and disease duration were not different between the two groups.

Conclusions: These results suggest that retinal disease occurs together with glomerular disease when the target antigen is found in both locations. Retinal drusen may be a useful biomarker for some forms of glomerulonephritis, and drusen pathogenesis may explain in part the pathogenesis of glomerular immune deposits. In addition, treatments that target retinal drusen may also be useful in antibody-mediated glomerulonephritis.

PUB161

Long-Term Therapeutic Plasma Exchange (TPE) in Management of Focal Segmental Glomerulosclerosis (FSGS) in Native Kidneys

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Introduction: Circulating permeability factors (CPF) may be involved in the pathogenesis of some forms of FSGS that are non-responsive to intensified immunosuppression and exhibit a rapidly progressive course. The role of CPF-mediated FSGS is indicated by the post-transplant recurrence of proteinuria and its response to TPE. Moreover, experimental animals injected with plasma from patients with FSGS can develop proteinuria. While TPE in patients with post-transplant recurrence can prevent graft failure, evidence to support its use in resistant FSGS in native kidneys is lacking.

Case Description: A 62-year-old Caucasian female presented with anasarca and nephrotic-range proteinuria (5.0 g/day) in March 2018. Kidney biopsy revealed minimal change disease. The first 14 months of her course were complicated by steroid resistance, side effects of high-dose steroids and calcineurin inhibitors (CNI), recurrent AKI, CNI/ARB-induced hyperkalemia, and worsening of proteinuria with CNI reduction. She received 4 doses of rituximab (375 mg/m2) during that period. Genetic testing for the steroid-resistant nephrotic syndrome was negative. In June 2019, a trial of 10 TPE sessions resulted in a significant improvement in proteinuria (UPCR= 1.8-2.0), which worsened over the following 4 months after discontinuation of TPE (UPCR= 4.0). Repeat kidney biopsy revealed FSGS. Given the previous response to TPE, a central-venous port was placed for long-term TPE in December 2019. The patient received TPE twice a week for the first 6 weeks. With improved proteinuria, TPE was tapered to twice a month with maintained partial remission (PR) (UPCR= 1.5) for the last 5 months. The patient is off ARB, on a minimal dose of CNI. The symptoms associated with nephrotic state and the side-effects of multiple drugs have resolved.

Discussion: This case highlights the dilemma of therapeutic decision-making in patients with resistant FSGS. Long-term TPE successfully maintained symptom-free sustained PR and stabilized renal function. TPE has become the preferred choice of our patient to avoid the toxic effects of long-term intensive immunosuppression. More studies are required to study the efficacy and safety of TPE in patients with native kidney FSGS resistant to therapy.

PUB162

Association Between Anti-GBM Titers and Kidney Inflammation with a New Activity Score

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Background: Anti-glomerular basement membrane (anti-GBM) disease is a rare glomerulopathy characterized by rapidly progressive loss of kidney function, leading to end stage kidney disease in a significant amount of cases. The main objective of our study is to determine whether anti-GBM titer correlate with rate of activity in renal biopsy and long-term kidney survival in patients with anti-GBM, hence identifying patients who would potentially benefit from more intensive treatments.

Methods: A retrospective analysis was performed on anti-GBM cases from 2007 to 2018 with both positive biopsy and serology. Anti-GBM levels and kidney function at admission and discharge, treatment, and kidney biopsy findings were collected. All biopsies were reevaluated by a single, blinded pathologist. Based on a recent study by Van Daalen et al, we developed an activity score. The score was divided in a glomerular and interstitial section. In the glomerular section, a sclerotic pattern (>50% of glomeruli) was given 0 pts in activity and 3 in chronicity, a mixed pattern was given 1 pt in activity and chronicity, and a crescentic pattern (>50% with cellular crescents) was given 3 pts in activity and 0 in chronicity. In the interstitial section, the presence of fibrosis and atrophy was given between 0 and 3 pts in chronicity and the presence of tubulitis or interstitial infiltrate with neutrophils were given points in activity (0 to 3 respectively). Spearman correlation was performed between anti-GBM levels, our biopsy score, and kidney survival at follow-up.

Results: Twelve cases were identified, 9 were males, mean age was 54. Anti-GBM at admission ranged from 40 to 1517 U/mL. Ten patients were treated with cyclophosphamide, 1 with rituximab plus cyclophosphamide and 1 with only rituximab. The median number of therapeutic plasma exchange sessions was 8 (range 6-12). High antibody titers correlated with greater activity on biopsy (r 0.6, p= 0.04) and lesser chronicity (r -0.7, p= 0.02). Kidney loss at follow-up (35 months) was 92%.

Conclusions: These results suggest that patients who present higher titers have more acute inflammation, and therefore could benefit from more intensive treatment. It would be interesting to study this score in larger cohorts in order to produce more definitive conclusions.

PUB163

Antisynthetase Syndrome and Nephrotic Syndrome

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Introduction: The presence of anti-synthase syndrome and IgA nephropathy is unusual. symptoms similar to other diseases that affect the connective tissue: Lupus, Rheumatoid arthritis or polyomyositis

Case Description: A healthy female 19-year-old patient starting with oligoarthritis on knees and wrists as well as low grade fever, viral pharyngitis was suspected and ibuprofen was started, without any improvement, ciprofloxacin, naproxen and acetaminophen because urinary tract infection was suspected. Edema of extremities is added as well as persistence fever, again revalued, finding the presence of proteinuria and rhabdomyolysis with CPK 33,000, reasons why it is referred to our center. Hepatomegaly was confirmed with transaminasemia, rhabdomyolysis and 4.2 g of proteinuria in 24-hour collection, hypoalbuminemia of 1.8gr/dL compatible with nephrotic syndrome, renal biopsy was performed. Because the persistence of fever, it starts an approach discarding infectious causes such as hepatotropic agents (HCV, HBV, HIV, EBV, CMV, HAV, Leptospira and Tuberculosis) as well as fever of unknown origin such as liver abscess, endocarditis, brucellosis, all these being negative. Collecting blood cultures and urine cultures, without bacterial growth. During the 4 day of in-hospital stay, muscle weakness with predominant involvement of the proximal arms (scapular and pelvic girdle), later it begins with dysphagia to solids then to liquids. The diagnostic approach for causes of rheumatological diseases is addressed, with negative ANA, positive ANCAs 1:10 (MPO (-) and PR3 (–), Low C3 complement and positive Anti JO1 and Anti Ro 52 +++. Electromyography was performed reporting normal sensory neuroconduction as well as motor conduction. Muscle biopsy shown the presence of perimissial infiltrate. Renal biopsy shown mesangial proliferation and immunofluorescence with IgA. Symptoms progress to type 2 respiratory insufficiency, severe hypercapnia, starting with methylprednisolone 3 doses with slight improvement, adding immunoglobulin at dose of 2 g / kg, recovering muscle strength, respiratory parameters and decreasing CPK.

Discussion: IgA nephropathy is an atypical manifestation in patients with antisintetase syndrome, only 3 cases have been reported, the pathophysiological origin is unknown, the most accepted hypothesis is humoral activation.

PUB164

Efficacy and Safety of Induction Treatment with Rituximab, Mycophenolate, and Low Doses of Corticoids in Patients with ANCA-Associated Vasculitis

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (VAA) increases considerably the risk of requiring chronic renal support therapy (CRST) and death. Induction treatment with cyclophosphamide and corticosteroids is not always effective and has adverse effects. The kidney biopsy (KB) is usually required prior to the start of treatment; however, the clinical presentation and the systemic nature may influence the time of its performance. We report the efficacy and safety of pre-KB initiation of induction therapy using Rituximab, low-dose steroids, and mycophenolate. We report the adverse effects during follow-up. Induction protocol methylprednisolone 250mg (x3), Rituximab 1gr (x2), mycophenolate 500mg / 12h. Maintenance therapy consisted in mycophenolate and prednisone.

Methods: Nineteen consecutive patients were included. Follow-up period: means (min-max): 28 (3-64) months. Average age 65 years. Patients treated pre-KB 17 (90%). It was also administered during induction: immunoglulins in 10 (53%) patients and plasmapheresis in 8 (42%). 2 patients (11%) required Eculizumab as rescue therapy. 15 (79%) patients were anti-MPO + [title: median: 281 (84-570) AU / ml]. Berden's classification selected the following patterns: sclerotic: 5 (26%), focal: 5 (26%), crescentic 2 (11%), 3 (16%) insufficient material, mixed: 1 (5%) and 3 (16%) patients were not biopsied.

Results: The current survival it was 100% and only 2 (11%) require CRST (one of them had a baseline GFR of 9ml / min / 1.73m2). The median (p25-p75) of eGFR at the momento of presentation was 17.9 (7.8–27.2) ml / min / 1.73m2. The average eGFR increased globally during follow-up in 9.9ml / min / 1.73m2 (P <0.01, eta2partial: 0.46); those with sclerotic histology 7.3ml / min / m2 (P = 0.26) and in those without available histology 10ml / min / 1.73m2 (P = 0.04, eta2parcial: 0.21). The regimen was tolerated satisfactorely, we registred 5 patients with infections issues (26%) [2 (11%) required hospital admission]. No patient developed steroid-induced DM.

Conclusions: The early use of this induction regimen was associated with excellent overall and renal survival. The safety profile and systemic nature of VAAs seems to justify the early use of immunosuppression even in those treated without available histology.

PUB165

A 39-YearOld Female with Acute Renal Failure of Unclear Etiology

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Introduction: Rapidly progressive glomerulonephritis, or RPGN, is a disorder of the kidney with accelerated loss of kidney function that manifests histologically by glomerular crescent formation. This rare entity may be caused by pauci-immune crescentic glomerulonephritis, which is strongly associated with antineutrophil cytoplasmic antibody (ANCA) vasculitis. Nevertheless, a small portion of patients lack ANCA. There is limited literature on the comparison of ANCA positive and ANCA negative patients. We present the case of a 39 year old female presenting with shortness of breath, hypoxemic respiratory failure, and acute renal failure. Her lack of ANCA rendered her disease entity mystifying and puzzled providers in terms of how to proceed with treatment.

Case Description: A 39-year-old Caucasian female was admitted to the hospital with a one day history of shortness of breath. Her admission was complicated by rapidly progressive hypoxemic respiratory failure, warranting intubation and subsequent placement on venovenous extracorporeal membrane oxygenation. Labs showed acute kidney injury (AKI) with a serum creatinine of 3.70 mg/dL. Urinalysis demonstrated

large blood, 4–10 red blood cells, and proteinuria > 1000 mg/dL. Urine protein creatinine ratio was 3,895 mg/g. She developed bloody endotracheal tube secretions, warranting performance of bronchoscopy that was consistent with diffuse alveolar hemorrhage. Given that serological work up, including ANCA, returned unremarkable, the etiology of her renal failure was unclear. Her AKI became oliguric and she was initiated on continuous venovenous hemodialysis (CVVHD). Given the uncertainty regarding the etiology of her renal failure, and therefore how to proceed with treatment, despite her hemodynamic instability, renal biopsy was performed. Findings were consistent with segmental sclerosing pauci-immune glomerulonephritis with small cellular crescents.

Discussion: Studies on the characteristics of patients with ANCA negative pauci-immune GN, as well as prognosis, are vital, as up to 30% of patients with pauci-immune glomerulonephritis lack ANCAs. Prompt recognition and appropriate treatment has proved essential to preservation of renal function. Additional literature regarding ANCA negative pauci-immune GN may ameliorate the need for renal biopsy in unstable patients, and may guide more timely treatment.

PUB166

Bloody Tubules: Is It the Warfarin?

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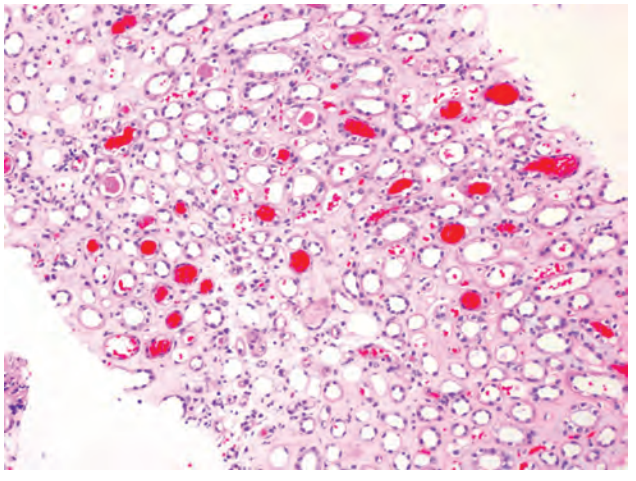
Introduction: Acute kidney injury(AKI) with gross hematuria can have a myriad of urological and glomerular etiologies. Anticoagulation related nephropathy is one of them and has been known to cause AKI in the setting of warfarin use. This is a case of a pateint with primary biliary cirrhosis(PBC) on warfarin that presented with persistent hematuria and AKI requiring hemodialysis. Her renal biopsy revealed warfarin nephrotoxicity with secondary IgA nephropathy from liver disease.

Case Description: 72 year old hispanic female with history of PBC and osteoarthritis underwent a right knee arthroplasty and was started on warfarin for DVT prophylaxis by orthopedics for a month. She subsequently developed persistent gross hematuria and underwent a cystoscopy that was unremarkable. Labs showed creatinine: 5.5mg/dl, UPCR: 5.81g/g and INR: 1.0 as the patient by then had stopped taking warfarin. Serologies were all negative and a renal biopsy was performed that revealed acute tubular necrosis with numerous intratubular red blood cell casts suggestive of warfarin nephropathy. The biopsy also showed mesangial, subendothelial and capillary wall IgA deposits likely secondary to her underlying liver disease(PBC).

Discussion: Previsouly known as warfarin induced nephropathy; this renal etiology is now recognized as anticoagulation related nephropathy as it is seen with other anticoagulants as well. Characteristic histology shows tubular injury and occlusive red blood cell casts that lead to ischemia and hemorrhage into the tubules and bowmans capsule. Risk factors include supratherapeutic INR and underlying chronic kidney disease. Our case report is unique as her undiagnosed secondary IgA nephropathy from primary biliary cirrhosis precipitated the warfarin nephrotoxicity. The pateint is currently stable on bi-weekly hemadialysis.



Intratublar casts-warfarin nephrotoxicity.

PUB167

Staphylococcal Infection-Associated Glomerulonephritis and Nephrotic Syndrome in an Intravenous Drug User with Hepatitis C: A Challenging Clinical Scenario

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Introduction: Renal disease in intravenous drug users, especially those with Hepatitis C, can present with challenging clinical scenario and biopsy picture. We describe a case of a 46-year-old male who presented with shortness of breath, chest pain and acute kidney injury.

Case Description: A 46-year-old male with a history of Intravenous (IV) drug use and untreated Hepatitis C presented with shortness of breath and chest pain. Patient was found to have Methicillin Resistant Staphylococcal bacteremia and tricuspid valve endocarditis. Physical examination was positive for bilateral leg edema and pan systolic murmur over left lateral sternal border. Initial serum creatinine was 1.54 mg/dl (baseline creatinine 0.94 mg/dl). Urine analysis revealed proteinuria 2+ and hematuria and the sediment was consistent with isomorphic WBCs and RBCs with many granular casts. Renal US revealed right kidney 11.6 cm and left kidney 13.5 cm in maximum dimension with no hydronephrosis. All serology tests were negative except for a low C3 and positive c-ANCA with negative MPO and PR3 levels. A percutaneous renal biopsy showed proliferative GN (diffuse proliferative GN) with focal MPGN pattern in few glomeruli and rare crescent (in one glomerulus), full house immunofluorescence (IF) with IgA co-dominance and both capillary wall and mesangial staining (IgA 3+, IgG1-2+, IgM 2+, C3 3+, C1q 1+, kappa 1-2+ and lambda 3+) and small subepithelial (hump-like) and both small and large subendothelial deposits on ultramicroscopy. Final biopsy diagnosis was given as IgA-codominant staphylococcal infection-associated glomerulonephritis (SAGN). Patient was treated with eight weeks of IV antibiotics and underwent supportive hemodialysis during hospitalization. He was discharged home off hemodialysis and followed up in outpatient clinic for Chronic Kidney Disease stage IV.

Discussion: The presence of nephrotic syndrome in this patient presents a challenging scenario and MPGN secondary to hepatitis C may be considered a differential here although SAGN is a stronger contender based on clinical and biopsy findings and nephrotic-range proteinuria, though not common, has been described in SAGN and endocarditis-associated GN cases in variable percentages, ranging from 6-48%.

PUB168

Unmasking of Pancreatobiliary Carcinoma in a Patient with Fibrillary Glomerulonephritis

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Introduction: Fibrillary Glomerulonephritis (FGN) is a rare disease with known malignancy correlation. Cancer can be discovered simultaneously with the diagnosis of FGN or later in the course of the disease. As per our knowledge, this case is a first description of rapidly progressing pancreatobiliary carcinoma (PBC) associated with FGN.

Case Description: 49 y/o white woman presented to the nephrology office with proteinuria of 1.3 g/day and hematuria. She had a past medical history of smoking (>20 years) and hysterectomy for endometriosis. Serologic workup and urology evaluation were unrevealing. Kidney biopsy reported FGN with minimal interstitial scarring. Oncology referral was made to rule out hidden malignancy. She had an unremarkable CT scan of the chest and abdomen, PAP smear, mammogram, colonoscopy as well as normal chemical evaluation and ultrasound of thyroid. Patient quit smoking and had conservative management for the first 11 months. Introduction of ACE-I led to reduction in proteinuria to 0.6 g/day. Unfortunately, she had decline in creatinine from 0.6 to 1.0 mg/dl, and worsening of proteinuria to 1.3 g/day associated with edema and weight gain. Therapy with Acthar® injections was initiated at the dose of 80 units thrice weekly. Patient had rapid improvement in proteinuria and swelling, and after 12 months of therapy, Acthar® dose was reduced to 40 units twice weekly. Creatinine remained stable. 24 months after the initial presentation and 13 months from Acthar® therapy initiation, she developed acute pancreatitis. Imaging studies showed pancreatic pseudocyst. Unfortunately, her pain did not resolve. During the second hospitalization, a month later, HIDA scan and EGD were performed with unrevealing results. She was managed with pain medications and Acthar® therapy was uninterrupted. Patient underwent MRCP 3 months after the initial presentation, which showed pancreatic mass and multiple liver lesions. Biopsy of the liver lesion demonstrated poorly differentiated PBC. Palliative chemotherapy was initiated but was not tolerated by the patient. Patient deceased 4 months after the development of pain symptoms.

Discussion: Consideration of a hidden malignancy is a part of FGN management. PBC is a devastating cancer with dismal survival. Conducting an aggressive and repetitive work up for malignancy in patients with a new diagnosis of FGN may improve outcomes.

PUB169

A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Following Influenza Infection

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is relatively a new entity. It is a form of monoclonal gammopathy with renal significance. Our patient is presented with this rare disease triggered by very common illness, influenza infection.

Case Description: A 61-year-old female with a past medical history of chronic kidney disease stage IIIB, and type 2 diabetes mellitus presented to the hospital with gross hematuria for 1 week and right-sided flank pain started within last 24 hours. The patient was diagnosed with influenza A infection 10-days before her hospital admission and treated with Oseltamivir. She was started on ciprofloxacin after 1 week due to concern for pneumonia. In the emergency room, she was hypertensive otherwise hemodynamically stable. Her physical exam was significant for right-sided costovertebral angle tenderness. BMP showed creatinine as 2.73 mg/dl which was 1.33 mg/dl at baseline. She was diagnosed with acute kidney injury and started on IV fluid resuscitation. Her urinalysis revealed 58/HPF red blood cells and 7/HPF white blood cells. The kidney ultrasound was unremarkable. CT abdomen and pelvis did not show any evidence of

urolithiasis or hydronephrosis. Urine albumin/creatinine ratio was 470.8 mg/g in a spot urine sample which was 104 mg/g before admission. Serum C3 level was normal at 134 mg/dl (reference: 88-201). Anti-streptolysin O antibody (ab), c-ANCA (antinuclear ab), p-ANCA, anti-glomerular basement membrane ab were negative. Her immunoglobulin G level elevated to 1,740 mg/dl (reference 649-1618), kappa level elevated to 1,470 mg/dl (reference 574-1276), and lambda level elevated to 774 mg/dl (reference 269-638). Serum electrophoresis did not show M-spike and serum immunofixation study was negative for monoclonal gammopathy. Kidney biopsy was recommended by nephrology which revealed endocapillary-proliferative glomerulonephritis with linear glomerular capillary wall staining for IgG1-kappa. She did not receive any immunosuppressive treatment as her kidney function returned to baseline without intervention.

Discussion: PGNMID is a rare form of glomerulonephritis which can mimic immune-complex glomerulonephritis especially in a patient with an infection. Therefore, considering renal biopsy with light-chain and IgG staining is crucial for proper diagnosis.

PUB170

Dual Positive Myeloperoxidase and Proteinase 3 Antibodies and Class V Lupus Nephritis in an Elderly Female with Cocaine Use

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Introduction: Cocaine contaminated with levamisole is a reported cause of dual positive ANCA vasculitis and rarely has been associated with lupus nephritis. We present a case of an elderly female who presented with unexplained acute kidney injury (AKI) and chronic cocaine use and was found to have dual positive ANCA and Class V lupus nephritis.

Case Description: A 70-year-old female with a history of hypertension, coronary artery disease, atrial fibrillation on warfarin, pre-diabetes, remote history of breast cancer status post lumpectomy, baseline serum creatinine (SCr) 0.8 mg/dL was sent to the emergency room after being found to have a SCr 6.0 mg/dL on outpatient labs. Urinalysis was significant for proteinuria and microscopic hematuria. Urine protein/creatinine ratio was 2.7 g/g. Workup revealed positive anti-nuclear antibody titer of >1:320, double-stranded DNA antibody titer 270 IU, myeloperoxidase (MPO) antibody of 5 AI and proteinase 3 (PR3) antibody of 1 AI. Serum complement 3 was 149 mg/dL and complement 4 was 31 mg/dL. She had no clinical symptoms of systemic erythematous lupus (SLE) or systemic vasculitis. Urine toxicology was positive for cocaine. She was pulsed with steroids due to concern for a rapidly progressive glomerulonephritis and then underwent kidney biopsy, which demonstrated full house immunofluorescence with IgG predominant subepithelial deposits, few mesangial deposits and mild acute tubular injury. No proliferative glomerular lesions or crescents were observed. She was initiated on mycophenolate mofetil with improvement in SCr to 3.8mg/dL and proteinuria to 1.2g/g.

Discussion: Dual positive (MPO and PR3) ANCAs have been reported in patients with lupus nephritis, but rarely in the setting of class V lupus nephritis. Although our patient's history of cocaine use may explain positive MPO and PR3 antibodies, she did not have the pauci-immune crescentic glomerulonephritis often seen with ANCA, but rather an immune complex, non-inflammatory glomerulopathy. Given her unusual manifestation of late-onset lupus nephritis, we hypothesized that chronic cocaine use may have led to an altered immune response and autoimmune disease, as rarely described for SLE in young men with chronic cocaine use.

PUB171

Collapsing Glomerulopathy due to Hemophagocytic Lymphohistiocytosis: A Case Report

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Introduction: Collapsing glomerulopathy (cFSGS) is most commonly seen in association with Human Immunodeficiency Virus infection (HIVAN) and can also occur in association with viral and non viral infections, autoimmune diseases, malignancy and drug exposure. Patients typically present with rapidly worsening renal function and nephrotic syndrome. We report a case of cFSGS due to Hemophagocytic lymphohistiocytosis (HLH)

Case Description: A 41-year-old man with acute myeloid leukemia and allogenic hematopoetic stem cell transplant with graft versus host disease on Ruxolitinib, was admitted for hypervolemia, respiratory failure, rapidly rising creatinine and nephrotic range proteinuria. He was noted to have anemia, thrombocytopenia, high LDH, low haptoglobin and abnormal liver function tests. He underwent renal biopsy that showed collapse of capillary loops and podocyte hyperplasia on light microscopy with marked foot process effacement on electron microscopy. Extensive work up was pursued to identify the etiology of cFSGS. Infectious work up including HIV, hepatitis B and C, parvo virus B19, BK virus, CMV, EBV, HSV, Human herpes virus 6, SARS-COV-2, Mycobacteria, fungal, and parasitic organisms was negative. He had marked elevation of ferritin at 35,000ng/ml and triglycerides at 1,529 mg/dL in the setting of severe pancytopenia and fever raising concern for HLH. He underwent bone marrow biopsy that showed hemophagocytosis of nucleated cells supporting diagnosis of HLH. Soluble interleukin 2 receptor levels (sCD25) were normal consistent with the use of Ruxolitinib. Despite receiving Anakinra, Rituximab, and Dexamathasone for HLH he deteriorated clinically and was transitioned to comfort care

Discussion: cFSGS has been associated lupus, IgA nephropathy, diabetic nephropathy, thrombotic microangiopathy/acute glomerular ischemia, bisphosphonate therapy, HLH, and infections like HIV, Parvo virus B19, pulmonary tuberculosis, CMV and more recently SARS-COV-2. Treatment of cFSGS is directed towards the underlying cause. cFSGS complicating HLH is rare. Excessive immune activation with release of pro inflammatory cytokines targeting the podocytes is hypothesized to cause cFSGS in HLH. Renal prognosis appears to be poor despite therapy and most patients remain dialysis dependent. HLH has been reported post stem cell transplant and should be considered in the differential diagnosis of cFSGS

PUB172

Epidemiology of Glomerular Diseases in Minia Governorate: A 5-Year Single-Center Experience

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Background: Studying the pattern of glomerular diseases gives an important insights about factors associated with its development or progression.

Methods: This is a retropective study includes 312 patients underwent kidney biopsy at Minia university hospital between 2014 to 2019. The aim of this study was to highlight the histopathological patterns of glomerular disease in Minia governorate.

Results: A total of 312 biopsy-proven glomerular diseases were reported. The mean age was 31.65±13.77 years, 61.5% were females Table (1). The most common clinical presentation was nephrotic Syndrome (39.4%). Lupus Nephritis contributed 27.9%, followed by Membranoproliferative glomerulonephritis (15.4%) Focal segmental glomerulosclerosis (13.5%), IgA nephropathy (11.5%), amyloidosis (7.7%), Crescentic glomerulonephritis (5.8%), Thrombotic microangiopathy (4.8%), Vascular nephropathies (3.8%), Minimal change disease (3.8%), Membranous nephropathy (2.9%), Postinfectious glomerulonephritis (1.9%) and Diabetic nephropathy (0.96%). Table (2). Eighteen patients (62.1%) of lupus nephritis belonged to ISN/RPS class IV, seven patients belonged to class III, and four patients belonged to class V.

Conclusions: Histopathological patterns of glomerular disease may indicate regional and ethnic variations that could point towards genetic or environmental influence. This might help in effectively managing this disease by identifying the predisposing factors.

Percentage of glomerular patterns: Table (2)

Renal Diseases	Number	Overall percentage
Minimal change disease (MCD)	12	3.8%
Focal segmental glomerulosclerosis (FSGS)	42	13.5%
Membranous nephropathy (MN)	9	2.9%
Lupus nephritis (LN)	87	27.9%
Membranoproliferative glomerulonephritis (MPGN)	48	15.4%
Postinfectious glomerulonephritis (PIGN)	6	1.9%
Crescentic glomerulonephritis (CresGN)	18	5.8%
Amyloid	24	7.7%
Diabetic nephropathy (DN)	3	0.96%
Vascular nephropathies (VN)	12	3.8%
IgA	36	11.5%
Thrombotic microangiopathy	15	4.8%

Demographic and clinical data: Table (1)

	Descriptive statistics (n=312)
Males	120(38.5%)
Females	192(61.5%)
Male to female	0.63
Mean age (years)	31.65 ± 13.77
Age range (years)	13-75
Hypertension	51(16.3%)

PUB173

A for Amyloidosis

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Introduction: We present a case of osteomyelitis related amyloidosis presenting as acute injury injury (AKI) with nephrotic range proteinuria.

Case Description: A 62 years old male with type 2 diabetes mellitus and hepatitis C (treated) was admitted with complaints of bilateral foot pain of 3 weeks duration leading to inability to ambulate. Work up revealed pedal wounds with drainage and imaging was consistent with osteomyelitis. Blood cultures were positive for methicillin sensitive staphylococcus aureus (MSSA) which was treated with IV antibiotics. Baseline serum creatinine (sCr) was 2.0 mg/dL and sCr on admission was 3.85 mg/dL, which was thought to be from acute tubular necrosis related to sepsis from osteomyelitis. Work up of AKI revealed nephrotic range proteinuria of 4.7g, hematuria without dysmorphic red blood cells and monoclonal kappa IgM spike on serum protein electrophoresis. Kappa/Lambda ratio was 1.86. Total protein was 8.5 g/dl with serum albumin of 1.9 g/dl. Hemoglobin A1c level was 4.6%.Left below knee amputation was performed and patient was transitioned to 4 weeks of oral cephalexin. sCr on discharge was 2.9 On clinic follow up, repeat labs showed non-resolution of AKI as well as nephrotic range proteinuria of 6.8g and a kidney biopsy was obtained. His wound was healing slowly and antibiotic duration was extended. Kidney biopsy showed no glomerular obsolescence or hypercellularity. Mesangial and glomerular capillary walls showed Congo Red Positive deposits. Thickening of glomeruli was noted with segmental duplication. Tubular atrophy and interstitial fibrosis was 20%. Staining was positive for serum amyloid A (AA) in glomeruli, arterioles, and tubular basement membranes. Immunofluorescent staining was negative. Electron microscopy showed mesangial expansion with randomly arrayed extracellular fibrils with solid cores and a mean diameter of 9.8 nanometer.

Discussion: Patient completed extended oral antibiotic therapy for osteomyelitis with resolution of M spike on SPEP and improvement of creatinine to baseline. Deposition of serum amyloid A (SAA) protein, an acute phase reactant is a potential complication of chronic inflammatory conditions. Most commonly involved organ is the kidney presenting as nephrotic syndrome. Clinical evaluation for secondary amyloid is important in the setting of infection. Unusual disease course should prompt evaluation for less common causes even in presence of comorbidities such as diabetes and hepatitis C.

PUB174

Factors Related to Clinical Efficacy of Corticosterone Combined with Tonsillectomy for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most frequent primary glomerulonephritis in Japan. Treatment combining tonsillectomy with intermittent intravenous methyl prednisolone (PSL) and alternate-day oral PSL (TSP therapy) may be sometimes chosen, and results from multiple prospective multicentered studies have been reported for its clinical usefulness. However, the treatment selection criterion has not been cleared. We retrospectively analyzed the patients who underwent TSP therapy in our facility and investigated the factors associated with efficacy of this therapy.

Methods: Subjects are 63 patients with IgAN who underwent TSP in our hospital from April 2012 to July 2019. Intravenous methyl PSL 500 mg/day was administered for 3 days in the first 2 weeks after tonsillectomy, followed by oral PSL 30 mg every other day. The protocol was repeated 3-times every 2 months, then PSL was tapered off. Treatment evaluation was performed 6 months after initiation of the therapy. When urinary protein was 0.5 g/gCr or less or decreased by 50% or more, and the urine red blood cell count was less than 20 per microscopic field, the treatment was considered to be effective.

Results: The mean age of enrolled patients was 36.2.±13.5 year, eGFR 75.2±23.6 mL/min, urine protein 0.92±0.81 g/gCr, and serum IgA 332. 9±141.2 mg/dL. Thirty-two patients were effective and 31 patients were non-effective at 6 months after the start of the therapy. Clinical parameters showing significant difference between the two groups were age (33.2±15.2 in responder vs 39.4±10.9 in non-responder, p=0.02), diastolic blood pressure (71.2±10.1 in responder vs 78.5±13.2 in non-responder, p=0.017) and serum IgA (368.3±174.3 in responder vs 296.2±84.0 in non-responder, p=0.024). Logistic-regression showed a significant association with respect to efficacy only for serum-IgA (OR=1.010, 95% CI 1.00-1.02, p=0.047). Cut-off level of serum IgA to the efficacy of TSP therapy by ROC-analysis was 291 mg/dL (AUC=0.675, sensitivity=0.842, selectivity=0.571).

Conclusions: Serum IgA levels may be a reference for predicting the efficacy of TSP therapy for IgAN.

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PUB175

An Elusive Case of Renal Failure in a Patient with Atypical Hemolytic Uremic Syndrome

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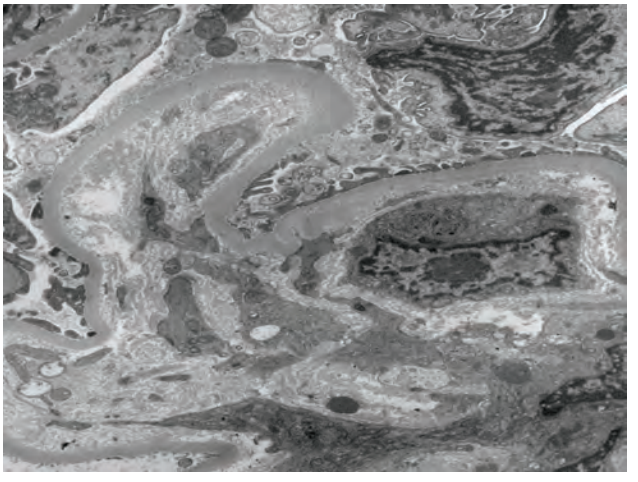
Introduction: AHUS is microangiopathic hemolysis, thrombocytopenia, and AKI with normal ADAMTS13 and absence of STEC. It involves activation of complement via alternative pathway causing TMA with end-organ involvement. Causes can be complement regulation deficits, infections, and drugs. Here is a rare case of AHUS after a *C.difficile* infection, requiring dialysis.

Case Description: 19-year-old man with OSA, ADHD, and obesity had a 3-week course of diarrhea and fever. Cr was 2.15, platelet 143, and tested + for C.diff and was on po vanco then flagyl. Given worsening symptoms, he went to the ER and Hb was 13.9, platelets 24, WBC 14.8, BUN 130 and Cr 8.4. He had low complements (C4 <7.9, C3 46.2), few schistocytes on peripheral smear, mildly elevated LDH and high-normal haptoglobin. He began dialysis, plasmapheresis and had a renal biopsy. Imaging showed splenomegaly (15-20 cm) and lymphadenopathy (negative BM and lymph node biopsy). ADAM13 level was 50 and plasmapheresis was stopped. Further infectious and autoimmune workup was negative. Renal biopsy showed a TMA process and C5b-9 staining was positive in the glomerulus and arteriolar vessels. Serum C5b-9 level was elevated (343). A genetics panel showed no variant associated with AHUS nor predisposition to poor response to eculizumab. He was discharged with eculizumab maintenance and dialysis. Recently, his labs improved with a Cr of 1.5 and platelets of 163.

Discussion: Here, typical features of hemolysis were missing, and diagnosis was made on renal biopsy with findings of TMA and + C5b-9 stain. Ongoing understanding of causes for AHUS include hereditary (complement and DGKE gene mutations) and acquired (infection, autoantibodies to complement, drug toxicity and autoimmune). Although genetic panel was negative, it cannot be ruled out as genetic mutations are only identified in 50-70% of cases. Shiga-toxin and pneumococcal-HUS are causes, but here we found rare *C.difficile*-induced cause. Patient was successfully treated with eculizumab. Thus, AHUS is elusive and clinically challenging in diagnosis.



PUB176

IgA Nephropathy in a Patient with Beta-Thalassemia Minor: A Case Report

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Introduction: IgA nephropathy (IgAN) is the most prevalent type of primary glomerulonephritis worldwide. There are few reports on IgAN development in thalassemia, especially among beta-thalassemia trait (minor) carriers.

Case Description: A 52-year-old male Mexican patient was evaluated for hypertension, hematuria, proteinuria, and rising serum creatinine levels. His history included an ischemic cerebrovascular accident and beta-thalassemia minor (trait). He was treated initially, by another provider, with hydrochlorothiazide/irbesartan and carvedilol for hypertensive nephropathy. Despite treatment, he continued with rising creatinine levels. Then, he was switched to irbesartan only. During this period, the patient developed metabolic acidosis treated with NaHCO3. When referred to our care, we began our approach by completing biochemical and immunodiagnostics assessments (IF), ultrasound imaging (USG), and pathology for glomerulonephritis. On biopsy, we observed IgA nephropathy with advanced nodular glomerulosclerosis and grade II interstitial fibrosis. On IF, IgA, C3, lambda, and kappa chains (mild) were positive. IgG, IgM, C1q were negative. On USG, we documented renal replacement lipomatosis. The patient had microcytic hypochromic anemia, but GBM, C3, C4, ANA antibodies were negative. We managed successfully with irbesartan, amlodipine, NaHCO3 then furosemide.

Discussion: To our knowledge, there are only three additional cases of IgA nephropathy among beta-thalassemia minor. All, including ours, shared as chief complaint rising serum creatinine, hypertension, and persistent microscopic hematuria. However, one report noted bilateral sensorineural hearing loss and prior psychosis under treatment, which may be a syndromic disease presentation. A common feature also is negative antinuclear, anti-DNA, anti-neutrophil cytoplasmic, anti-glomerular basement membrane antibody, HBV, HIV, serum complements antibodies. Significantly, at the time of biopsy, all cases had fibrosis in various degrees ranging from partial to global sclerosis with fibrous crescents. Notably, prior cases occurred in Asian ethnicities, were IgAN is prevalent; our case is the first Hispanic affected patient.

PUB177

Sudden Explosive Onset of Collapsing FSGS in the Setting of Influenza: An Unusual Presentation

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Introduction: Collapsing FSGS(Focal Segmental Glomerulosclerosis) is often seen in the setting of HIV, pamidronate use, parvovirus infections. Here we present a case that was explosive in onset and was associated with influenza.

Case Description: Elderly African American male in his 60s presents with flu-like symptoms. His influenza swab was positive. His past medical history was significant was occasional cocaine use, hypertension, parathyroid adenoma, hypercalcemia, prostate cancer. His vitals revealed BP 107/64 | Pulse 61 | Temp 97.2 °F (36.2 °C) | Resp 16 | SpO2 97%. Physical examination was benign. His creatinine was 6.9. His baseline creatinine was 1.8(for the past few years) and thought to be related to his hypertension. Other labs indicated corrected calcium of 11, potassium of 5.9, Co2 of 18, hemoglobin of 8 with normal platelets, and WBC. USG(Ultrasound) of kidneys revealed obstructing 3mm left UJV stone with hydroureteronephrosis. UA revealed 3 plus protein with moderate blood, 10-20 RBC per HPF, bacteria. He was started on antibiotics and a double JJ stent was placed. His stone disease is probably a manifestation of parathyroid adenoma. He was awaiting parathyroidectomy and was maintained on sensipar in the interim. His creatinine continued to increase and peaked at 7.5 mg/dl. However repeat urinalysis revealed significant proteinuria and on quantification, it was 17g with albumin of 2. He also had lower extremity edema indicative of nephrotic syndrome. Of note, he did not have proteinuria a week before his hospital admission. At this point, a renal biopsy was undertaken and was noted to have collapsing glomerulopathy with 80-90 percent effacement of foot processes. The patient continued to improve to creatinine of 2.4 with improvement in urine output at which point he was discharged on ACE-I.

Discussion: Collapsing FSGS in probably related to complex interplay of multiple factors like infection, acute kidney injury due to other etiologies, genetic risk factors such as APOL1. Recent cases of COVID-19 related AKI point towards the possibility of collapsing FSGS as the etiological mechanism, especially with APOL1 association. Though it is traditionally described in the setting of infections like parvovirus and HIV, there could underlying common mechanisms for infections that may not be exclusive to these and may expand to other infectious etiologies like influenza, COVID.

PUB178

Hypoalbuminemia Out of Proportion to Proteinuria in a Patient with Nephrotic Syndrome

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Introduction: Hypoalbuminemia is a fundamental characteristic of nephrotic syndrome, with most of the albumin loss resulting from urinary excretion. As such, the degree of proteinuria in a glomerular process often mirrors the serum albumin. The differential and work-up changes when there is discordance between the two.

Case Description: A 68-year-old African American male presented with three weeks of a worsening cough, diarrhea, and progressive swelling. His past medical history was notable for dysphagia secondary to esophageal rings with dilations in the past, acute myeloid leukemia s/p allogenic stem cell transplant and deep vein thrombosis. His stem cell transplant was a year prior to presentation, and he was tapered off MMF and to a lower dose of tacrolimus with prednisone. On physical exam, he had gross anasarca. His labs were notable for a serum creatinine of 1.5 mg/dL from a prior baseline of 1.3 mg/dL. His albumin was 1.2 g/dL with a spot urine protein to creatinine ratio of 3.12 and 24-hour urine protein of 3.5 gm/day. A lipid panel showed a cholesterol of 391 and a LDL of 292. Serologies for hepatitis and lupus were negative. Complement levels were normal and no monoclonal protein was seen on serum/urine electrophoresis. A serum PLA2-R was negative. He underwent a kidney biopsy that demonstrated subepithelial glomerular, mesangial, and tubular basement membrane deposits consistent with secondary membranous nephropathy. Staining for PLA-2R was positive. He was started on Rituximab and continued treatment as an outpatient.

Discussion: Here we describe a case of nephrotic syndrome in which the degree of hypoalbuminemia was not consistent with the amount of proteinuria. This discordance represents a defect in the homeostasis of albumin typically seen in nephrotic syndrome. At a steady state, albumin synthesis is balanced by albumin catabolism and urinary loss. In nephrotic syndrome, catabolism is decreased while synthesis and urinary loss increases. The patient's history of diarrhea and dysphagia suggested that he had either increased catabolism from non-renal GI losses or decreased synthesis due to poor intake. This case highlights alternative laboratory findings in membranous nephropathy and a framework for understanding the differences.

PUB179

Renal Response and Its Predictive Factors of Lupus Nephritis: A Two-Year Cohort of 77 Hospital-Based Patients

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Background: To evaluate the renal response rates of lupus nephritis (LN) patients undergoing standard treatment during a two-year follow-up and investigate its predictive factors.

Methods: A prospective cohort study enrolled 77 clinically diagnosed LN patients was carried out. All patients underwent standard treatment according to Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations or American College of Rheumatology (ACR) guidelines for the management of LN. Regular visits were performed every 6 months until 2 years. Data on renal response and clinical characteristics were collected and analyzed.

Results: Among 77 patients, 41(53.2%) and 15(19.5%) patients achieved complete response (CR) and partial response (PR) at 6 months after induction therapy, respectively. With every 6-months visits, 53(68.8%) patients completed the whole 2-year follow-up. 38(71.7%) and 5(9.4%) patients developed CR and PR at 2 years. During follow-up, serum creatinine (SCr) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score showed a significant decrease as compared to baseline data, while estimated glomerular filtration rate (eGFR) and C3 level gradually elevated. In multivariate regression model, immunological disorder (OR 4.73, 95%CI 1.00-22.40, p=0.05), eGFR (OR 1.04, 95%CI 1.02-1.07, p<0.001) and SLEDAI (OR 1.21, 95%CI 1.05-1.40, p=0.01) at baseline were found to be associated with CR/PR at 6 months as compared to non-responders.

Conclusions: Nearly 70% LN patients achieved renal response after 6-months standard induction therapy, and the renal response rates were higher after 2 years. Renal function and disease activity showed a significant improvement during follow-up. Besides, immunological disorder, higher baseline eGFR and SLEDAI were predictive factors for renal response.

Funding: Government Support - Non-U.S.

PUB180

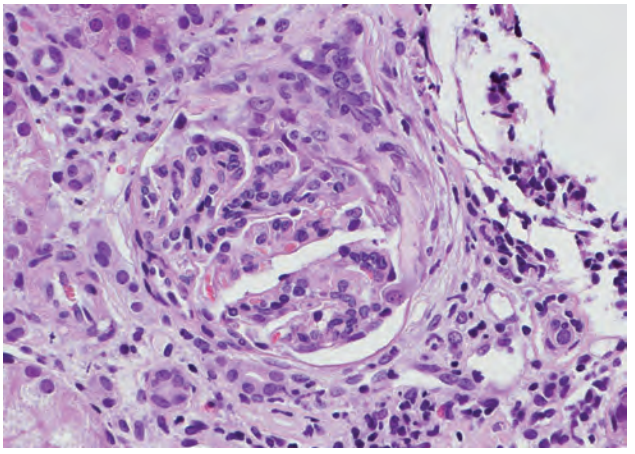
An A-Tip-ical Side Effect of Lithium

Casie James, Randall Craver, Isa Ashoor. *Louisiana State University Health Sciences Center, New Orleans, LA.*

Introduction: Lithium is a mood stabilizer approved for bipolar disorder treatment in children as young as 12 years. Though effective in the pediatric population, lithium requires close monitoring for toxicity and adverse effects.

Case Description: An 18 year old male with Hashimoto's thyroiditis, bipolar I disorder, and anxiety presented with 10 days of edema, weight gain, progressive abdominal pain, emesis, diarrhea, and decreased urine output with frothy urine. Medications included levothyroxine, Risperdal, and lithium. Creatinine was 1.2 mg/dl, up from baseline of 0.8 mg/dl. There was nephrotic-range proteinuria, with spot urine protein/creatinine ratio of 9. Serum lithium level was 2.5 mmol/L (therapeutic range 1-1.2 mmol/L). Renal biopsy showed tip variant focal segmental glomerulosclerosis (FSGS), with diffuse fusion of foot processes, but no tubular epithelial changes. Lithium was discontinued, and the patient underwent diuresis with Lasix/albumin infusions. Proteinuria resolved within two months, and he remains in remission. Bipolar disorder is now treated with Lamictal and Risperdal.

Discussion: Lithium has a wide side effect profile, requiring close monitoring. Lithium-induced nephrotic syndrome is a known, idiopathic side effect. Most renal biopsies show minimal change disease; however, FSGS has also been associated with lithium use. To our knowledge, this is the first documented case of tip variant FSGS in a teenager. While lithium may have induced nephrosis, the low effective circulating volume in nephrotic syndrome with subsequent decrease in glomerular filtration rate likely led to poor excretion of lithium, leading toxic levels and protracted recovery from adverse effects. Despite atypical histology, the patient followed a favorable course and remains in remission without immunosuppressive therapy.



Glomerulus with hilum toward left, slightly below center, and sclerotic segment at the apex adherent to the proximal tubule, at mid-upper right. Variable visceral cell hyperplasia. (Hematoxylin and eosin, 400X)

PUB181

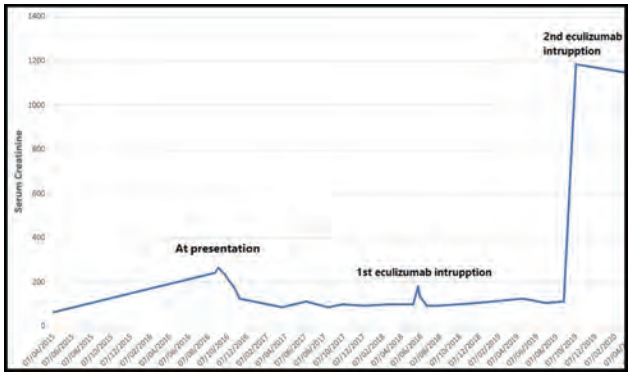
AKI After Eculizumab Interruption in a Case of C3 Glomerulopathy

Mostafa F. Elshirbeny, Mohammed E. Hussain, Essa Abuhelaiqa, Awais Nauman. *Hamad Medical Corporation, Doha, Qatar*.

Introduction: C3 glomerulopathy (C3G) is a newly recognized rare disease characterized by predominantly glomerular deposition of complement C3. Treatment with the C5 complement inhibitor eculizumab may be a therapeutic option but due to rarity of the disease, predicting tools of the outcomes remain largely unknown.

Case Description: Here we report 25-year old female patient who was referred to nephrology clinic with renal impairment, hematuria, and proteinuria. Kidney biopsy results revealed membranoproliferative changes with predominant C3 deposits, suggestive of C3 glomerulopathy. Genetic testing revealed two unrelated mutation in C3 gene, likely not related to C3G. Patient was responding well to oral steroid and MMF with remission of proteinuria and normalized serum creatinine. She was relapsed again, 1 year later with hematuria and nephrotic proteinuria. Steroids and MMF were resumed with no response then started on eculizumab, after which she achieved partial remission with reduction in serum creatinine and urine protein. During next 2 years, patient missed eculizumab in 2 occasions. The first, when she missed one dose followed by mild rise in serum creatinine which improved after eculizumab resuming and few months later she missed two doses then presented with severe AKI requiring dialysis. Was started on steroids and eculizumab was resumed with no improvement in kidney function and patient still dialysis dependent.

Discussion: Despite looks like safe and valuable therapeutic option in patients with C3G but the response to eculizumab is heterogeneous and when to discontinue the therapy still unsolved problem as transient interruption of the therapy sometimes complicated with AKI which may be severe enough to end with ESRD like this case.



Serum creatinine results during 40 months of follow up

PUB182

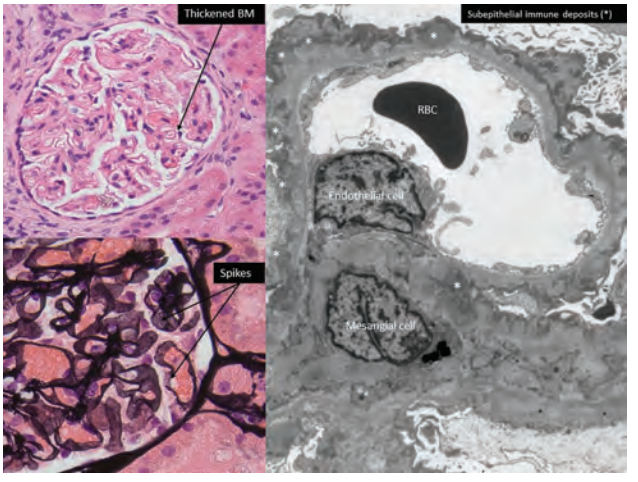
A Rare Case of Primary Membranous Glomerulonephritis in HIV Successfully Treated with Adrenocorticotropin Injection Gel (Acthar)

Mohammed Nazmul, Neil Alouch. *Creighton University, Omaha, NE*.

Introduction: HIV patients are immunocompromised and treatment with steroids or cytotoxic agents for glomerulonephritis (GN) is challenging, There is paucity of data regarding Adrenocorticotropin injection like Acthar gel as an alternative immunosuppressive agent for Primary membranous GN in HIV patients.

Case Description: Our patient is a 55 years old African American lady with PMH of HTN, HIV on remission with Emtricitabine, Tenofovir alafenamide, CKD with baseline creatinine 1.0-1.5 mg/dl. February 2018, patient's urine showed protein: creatinine ratio 6.1. Secondary work ups for proteinuria were negative. On renal biopsy, light /EM revealed membranous GN, minimal mesangial deposits favoring primary. Serum PLA2R antibody was 1:1120 (Normal <1.10), malignancy screening was negative. Patient started on Lisinopril then switched to Losartan to maxmum dose, proteinuria improved to 1.5 gram in February 2019 but increased again to 10.9 gram on November 2019, serum creatinine rose to 2.32 mg/dl. HIV specialist recommended against steroid, Acathr gel was started in April, 40 units s/q twice a week. Patient tolerated the medication well, HIV viral load undetectable, normal CD4 count and after 1 month proteinuria decreased to 4.9 gram, creatinine improved to 2.0 range and PLA2R antibody titer went down to 1:140. Acthar gel dose being uptitrated further accrding to patient's clinical response.

Discussion: This case study highlights the efficacy and tolerance of ACTH hormone therapy with RAAS blockade in HIV patient with primary membranous GN. Acthar gel may improve proteinuria due to its anti-inflammatory properties similar to steroid and can be considered as steroid sparing agents in difficult situations such as underlying HIV or other immunosuppressive diseases like HCV, HBV, malignancy. We conclude that, combination of RAAS blockade and Acthar gel can be a reasonable treatment regimen in complex case of primary membranous GN with coexistent HIV.



PUB183

Pathological Features and Clinical Course of IgA Nephropathy Patients with Isolated Hematuria

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Background: Microscopic hematuria is the most common manifestation of IgA nephropathy (IgAN). There are a few studies identifying the remission rate of microscopic hematuria as an important clinical predictor of deterioration of renal function. Microscopic hematuria caused by glomerular microvasculitis may have clinical significance. Renal biopsy was performed rarely in case with isolated hematuria. Renal pathological features and the renal prognosis of IgAN patients with isolated hematuria are unclear. Thus, there are no established treatments guides. In present study, we evaluated the pathological features and clinical course in IgAN patients with isolated hematuria in our cohort.

Methods: We retrospectively recruited 47 biopsy proven patients with IgA nephropathy who showed isolated hematuria at real biopsy from 2012 to 2017. We evaluated renal pathological findings in those patients. Moreover, we analyzed clinical course during 24 months from the diagnosis. Thirty of these patients were treated with steroid pulse therapy combined with tonsillectomy (TSP group) and the others were conservatively treated (CT group). In CT group, only three patients were treated with renin-angiotensin system inhibitor. We analyzed clinical parameters, such as, levels of urinary red blood cells, onset of proteinuria, eGFR and serum IgA.

Results: Although age, sex and degree of hematuria at the time of renal biopsy were not significantly different between the TSP and CT group, baseline eGFR was significantly lower in TSP group (88.7 versus 105.9mL/min/1.73 m2). Of note, 51% of patients showed crescent or endocapillary proliferation. At the end of observation period,

remission rate of hematuria in TSP group (100%) was much higher than that in CT group (71%). Moreover, immunosuppression therapy was effective to prevent significant decline in kidney function.

Conclusions: We clarified that more than half of patients with isolated hematuria showed crescent or endocapillary proliferation in present study. Immunosuppression therapy is effective for those lesions. Thus, even in the patients with isolated hematuria, conservative treatment can be a risk for deterioration of renal function.

PUB184

Indolent Pauci-Immune Crescentic Glomerulonephritis

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Introduction: Pauci-immune glomerulonephritis (PIGN) is most commonly associated with a rapidly progressive course towards renal failure, although rarely, an indolent course may be observed. PIGN has a frequent association with either MPO- or PR3-antibodies and is associated with extra-renal manifestations. We report a patient with slowly declining renal function over the course of two years that had a renal-limited MPO-antibody associated pauci-immune glomerulonephritis.

Case Description: A 61 year old Caucasian female with controlled hypertension, hypercholesterolemia, and prediabetes without complaints was noted by her PCP to have a slowly rising creatinine over two years. A nephrology referral was made with new onset 1+ pitting edema in the bilateral, distal lower extremities and a creatinine of 1.7mg/dL. Urinalysis at this point showed a sediment and 2g/g of creatinine to protein. A renal ultrasound showed structurally sound kidneys. Common infectious causes of renal disease to include hepatitis B, C, and HIV were ruled out. MPO, PR-3, ANA, C3, and C4 were sent to see if there was an autoimmune cause. A positive MPO prompted a renal biopsy which yielded a sample of 50 glomeruli with 15 completely sclerosed, 4 with crescent formation, and moderate to severe interstitial fibrosis and tubular atrophy. This confirmed the diagnosis of MPO associated PIGN. Immunosuppression was begun with a rituximab based therapy, but the second dose of rituximab was interrupted due to severe back pain combined with nausea and vomiting. Creatinine was elevated at 3.6mg/dL from 2.2mg/dL the day before. Methylprednisolone was tapered and further infusions were not pursued due to development of deranged liver function tests, hospitalization for diverticulitis, development of uncontrolled DM, and severe psychological symptoms. Over the following two months, the patient's creatinine has trended down to 1.5 mg/dL.

Discussion: Her consistently rising creatinine was the main driver to begin immunosuppressive therapy despite having moderate to severe interstitial fibrosis and tubular atrophy. Rituximab based therapy was shown in the RAVE trial to be non-inferior to cyclophosphamide for induction of remission in ANCA associated disease. This combination may also have superior relapse rates and a better safety profile in comparison with cyclophosphamide. Her improving creatinine suggests that even an incomplete regimen might have conferred some benefit.

PUB185

IgG4-Related Disease Presenting with Membranous Nephropathy

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Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a condition, affecting multiple organs. Retroperitoneal fibrosis with obstructive nephropathy and interstitial nephritis are most typical kidney damage. Rare cases of glomerular disease, including membranous nephropathy (MN), had been described. Search for IgG4-RD cases in the database of our nephrology unit found 11 patients, in three cases kidney biopsy showed MN, and we present one of them

Case Description: 73 years old Caucasian female with a history of arterial hypertension, diabetes, skin patchy hyperpigmentation, asthma and nasal polyposis manifested in 2016 with the weight loss and skin rush. 9 months later, at admission, she was undernourished, with multiple skin scratches, pedal edema, and otherwise unremarkable physical exam; her blood pressure was 150/90 mm Hg, vital signs were normal. Work up demonstrated nephrotic syndrome and marked eosinophilia (32.6% - 2.6*10^9/L). Her blood chemistry tests, serum and urine immunochemistry, p and c ANCA, anti Scl-70, anti-RNT and anti-CENP-B antibodies were within normal range. Kidney biopsy showed MN with IgG, C3, kappa and lambda fine granular deposits on the capillary loops periphery. Her anti-PLAR2 antibodies titer was <1:10; kidneys, abdomen, neck and pelvis ultrasound, chest CT, gastroscopy and colonoscopy were unremarkable. Tests for parasitic infections and myeloid hypereosinophilic syndrome markers (FIP1L1-PDGFRα and ETV6-PDGFRβ) were negative. IgG4 level was 1.9g/L (0.8-1.4) – 29.2% (4.0-5.0). We diagnosed IgG4-RD and started her on oral prednisone 40 mg daily. Her skin rush resolved immediately, in a month her eosinophil count became normal, two months later she achieved partial remission of nephrotic syndrome. We added cyclosporin A and slowly tapered prednisone. At the latest follow-up visit January 2020, she was doing well, with the complete remission of nephrotic syndrome, preserved kidney function and normal IgG4 level

Discussion: Clinical presentation was suggestive for ANCA-associated vasculitis or systemic sclerosis, not confirmed by serology and kidney pathology findings. The search for the hypereosinophilic syndrome causes was negative, and only IgG4 testing gave a clue to the diagnosis. Steroids allowed controlling hypereosinophilia symptoms, but not kidney disease, which responded to cyclosporin. We conclude that IgG4-RD should be considered in differential diagnostics of membranous nephropathy

PUB186

Role of Therapeutic Plasmapheresis in ANCA-Associated Vasculitis: A Single-Center Study

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Background: Recently Pexivas trial showed no benefit of plasmapheresis (PEX) in ANCA-associated vasculitis (AAV), even in patients with alveolar hemorrhage, but is this the end of PEX in AAV? The aim of this study is to describe the indications, method and complications of PEX, as well as whether PEX is associated with improvement in renal function and survival at 12 months.

Methods: Retrospective study of 28 patients with severe manifestations of AAV, who had received PEX adjunctive to conventional therapy for the first episode of AAV or in relapse.

Results: We recorded twelve patients receiving PEX. This group (n=12) had an average age at diagnosis 79years and was followed for a median period of 20 months. In 75% of the patients MPO-ANCA was positive, in 17% ANCA negative and in 8% double positive anti-GBM/ANCA. On admission, all patients had abnormal renal function with average creatinine 5mg/dl±2.12 and the majority of patients (9/12) were dialysis dependent. Indications for plasmapheresis were: alveolar hemorrhage in 33%, renal impairment in 25% and combination of the two above in 42%. Plasmapheresis was performed using filtration and fresh frozen plasma as replacement fluid. The mean number of plasmapheresis treatment was 8 (1-19 days) and the average internal time between admission and first plasmapheresis treatment was 3 days. No episodes of severe infection or death were recorded during plasmapheresis. All patients received concomitant therapy with Cyclophosphamide and corticosteroids while Rituximab was added in 3 patients. Alveolar hemorrhage was resolved in all patients (100%). After one year, 75% of the patients had renal recovery (cre=5mg/dl±2.12 vs cre=2.6mg/dl±1.6, p=0.06) and 67% of the patients who required hemodialysis at the time of diagnosis, during the first year became independent of dialysis (75% vs 33%, p=0.5). Finally, survival rate at the end of the first year was 83%.

Conclusions: Plasmapheresis is quite often used in daily clinical practice with remarkable results in dialysis independence and survival, without serious complications.

PUB187

Retrospective Analysis of Five Cases of Proliferative Glomerulonephritis with Monoclonal IgG Deposition Regarding Their Clinical Course and Responses to Therapy

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Introduction: Background At present, limited knowledge is obtained regarding pathophysiology and clinical course of proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID). It is rarely diagnosed by renal biopsy, and there is no established therapeutic strategy for this disease. We report clinical course and responses to the therapy of 5 cases diagnosed as PGNMID in our facility.

Case Description: Method Five cases (3 males and 2 females, median age 62 years) with renal biopsies and diagnosed as PGNMID between January 2016 and December 2019 were retrospectively analyzed regarding the transition of eGFR and urine protein level by the treatment. Three of 5 cases were treated by steroid alone in combination with intravenous methyl Prednisolone (PSL) 500 mg/day for 3 days and oral PSL 30 mg/day. Remaining 2 cases were treated with intravenous methyl PSL and oral PSL followed by Cyclophosphamide intravenously (750 mg/day, twice) or orally (100 mg/day, daily) administration and Rituximab (500 mg/body, twice) administration. **Results** Light microscopic findings were MPGN type in all cases, and immunofluorescent staining showed 4 cases were IgG3-kappa and only 1 case was IgG3-lambda. Three cases in the first month of the treatment had partial remission (KDIGO diagnostic criteria, defined as a urinary protein level of < 0.3-3.5 g/day and a reduction of ≧ 50% from baseline), and all had partial remission at 6 months. Hematuria was observed at the start of treatment in three cases and disappeared in only one case by the treatment. And, the remarkable deterioration of renal function was not observed during the clinical coourse. However, two cases showed the increase of urine protein after about one year from mPSL administration, and IVCY and RTX were administered, but urine protein and hematuria were not decreased, and mPSL was administered again. In one case, the improvement of the urinary finding was scarce even after the increase in the administered steroid.

Discussion: Conclusion Our results suggest that the treatment responsiveness to IVCY and RTX is poor, that steroids are more responsive to initial therapy, that disease activity increases with dose reduction (a steroid-dependent condition), and that treatment responsiveness to steroids may decrease after relapse.

PUB188

AA Amyloidosis and CKD in a Patient with Coexisting Hepatitis C Infection and Crohn Disease

Arteen Pirverdian, Monica E. Corral, Grace Mcnutt, Julio P. Zavala Georffino. *University of the Incarnate Word, San Antonio, TX*.

Introduction: AA amyloidosis is in the differential diagnosis of patients with proteinuria and may lead to chronic kidney disease (CKD). It is usually associated with chronic inflammatory conditions like rheumatoid arthritis which is implicated in 40% of cases. Crohn's disease (CD) is also recognized as an underlying etiology. We present a patient with chronic Hepatitis C infection (HCV) and CD who developed proteinuria and CKD in a relatively short period of time.

Case Description: 33-year-old man with a past medical history of CD, HCV, and cocaine/heroin abuse with frequent IV drug use presented to the ED with complaints of bilateral lower extremity swelling and tenderness. Initial laboratory studies were significant for a creatinine of 4.56 and nephrotic range proteinuria. On review, his creatinine had been trending up from 0.75 mg/dl to 4.09 mg/dl in the last year. Secondary work-up for proteinuria including: ANA, RPR, RF, ANCA, C3, C4, Cryoglobulin with reflex, ds DNA Ab, UPEP, and SPEP w/ immunofixation screenings all yielded negative results. S. cerevisiae Ab IgA was 51.5, a positive confirmation of patient's CD. HCV antibody test was positive with a positive HCV RNA. Renal biopsy was performed and revealed AA amyloidosis with severe interstitial fibrosis and tubular atrophy.

Discussion: AA amyloidosis is a disorder characterized by the overproduction of extracellular proteins that deposit and subsequently cause organ and tissue impairment. It is often attributed to chronic inflammatory/infectious diseases. Though literature about the incidence of AA amyloidosis in people afflicted with HCV is limited, incidence in individuals afflicted with CD has been reported to be between 0.5%-8%. AA amyloidosis has also been found to be a major cause of CKD in IV drug users. One UK study found that up to 35% of these patients have associated HCV. There are reports of increased CD "flares" in patients undergoing treatment for chronic HCV, which may suggest that the coexistence of both diseases may lead to worse morbidity. Our case is unique due to the coexistence of two chronic diseases that lead to inflammatory/infections processes known to be involved in the pathophysiology of AA amyloidosis. This co-existence may lead to a faster progression of CKD and overall worsening outcomes.

PUB189

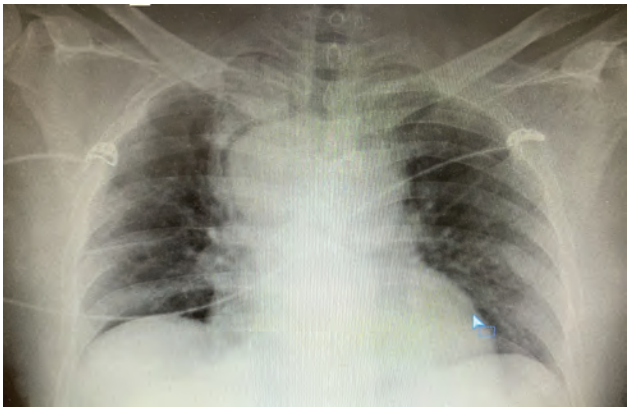
Awareness of Association of ANCA Vasculitis and Aortic Aneurysm Can Improve Survival

Sonalika Agarwal, Jitendra Kumar. *QRG Hospital, Faridabad, India*.

Introduction: ANCA vasculitis is a small-medium vessel vasculitis which is characterized by systemic necrotizing inflammation of blood vessels. Aortic aneurysm is a very rare complication of ANCA vasculitis. We describe a case of such association and highlight the need for guidelines for its screening in patients diagnosed with ANCA vasculitis.

Case Description: 40 year old man with no known medical history presented with renal failure and was started on dialysis. Kidney biopsy showed pauci immune crescentic glomerulonephritis. As per KDIGO guidelines, he was treated with steroids, cyclophosphamide and plasmapheresis after which he recovered from dialysis. 3 months later, he presented with hematemesis and shock. Due to worsening hematemesis and shock, upper endoscopy was done which revealed aorto-esophageal fistula and patient died of shock with no time for surgical intervention. On retrospective analysis, we found that unfolding of aorta seen on chest xray 3 months ago was likely aortic aneurysm which had increased in size and ruptured.

Discussion: To the best of our knowledge, this is the first case reported from India. The reason we think ANCA vasculitis is associated with aortic aneurysm is because it has been proven by biopsy in case reports in the past and in few of them, aneurysm had even decreased in size with chemotherapy. Also, it is surprising that such degenerative condition would occur without any risk factor like smoking, atherosclerosis, history of hypertension, or family history of connective tissue disorders in such a young patient. Since both ANCA vasculitis and aortic aneurysm are rare pathologies, it is reasonable to consider that they are related when occurring together. Again, Its rapid expansion and rupture within a span of 3 months favors an underlying association. This case highlights that nephrologists should be aware of such association, screen the patient on presentation and then at intervals likely earlier than recommended for aortic aneurysm of other etiologies.



PUB190

Atypical Presentation of Microscopic Polyangiitis

Alejandro Garcia Rivera, Luz Y. Villegas, Marcos Adrian E. Lopez, Ríos C. Katia yuritzi, Carlos A. Villavicencio López, Teresa Muñoz, Arantxa K. Aguilar, Jesús A. Rico sánchez, Jesús A. Vega López de Nava, Isela Márquez magaña, Ana M. Molgado castillo, Arisbeth Villanueva Perez. *Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Hospital General Regional No.46, Instituto Mexicano del Seguro Social, Guadalajara, Mexico.*

Introduction: MPA is an uncommon disease, more common in men, in white and Asian populations and whose incidence increases with age. We describe an atypical presentation of MPA

Case Description: 48-year-old female patient, no relevant past medical history, who came to the ER with a 2-week history of bradypsychia, gait disturbances, arthralgia, lower limb pain. On PE non-blanching red-purple papules were noted. A lab panel showed increased creatinine at 5.79 mg/dL (baseline Cr was 1.09), microscopic hematuria and sub-nephrotic proteinuria. Kidney ultrasound was normal, urinary sediment showed dysmorphic RBC with RBC casts She was placed an acute catheter for HD prior biopsy. Immunological panel showed positive ANCA, specificity for PR3 antigen; C3 and C4 levels were normal; the rest of the panel and HIV, HBB and HCV serologies were negative. CT showed maxillary sinusitis, lungs were normal Skin biopsy showed a leukocytoclastic vasculitis and kidney biopsy showed a pauci-immune necrotizing glomerulonephritis, with diffuse extra-capillary proliferative lesions, mild interstitial fibrosis; no granulomas. Patient was diagnosed with a MPA, and treatment was started with IV GC and RTX. Patient was discharged to continue treatment in the out-patient clinic and currently has received a second dose of rituximab, with no need for hemodialysis and a creatinine of 2.5 mg/dL (7 days after starting treatment)

Discussion: MPA is a rare disease with unknown frequency in Mexico. Our case was atypical since it presented in a Hispanic female younger patient, with a histopathological phenotype of MPA but positive to PR3, with no respiratory involvement and no upper airway destructive lesions

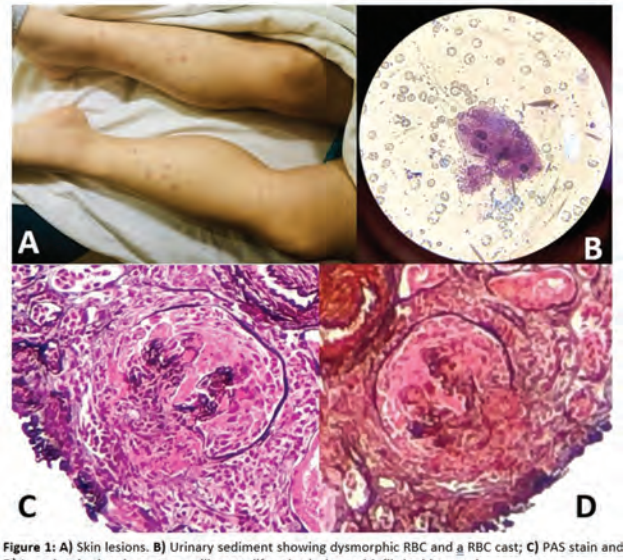


Figure 1: A) Skin lesions. **B)** Urinary sediment showing dysmorphic RBC and a RBC cast; **C)** PAS stain and **D)** Jones' stain showing extra-capillary proliferative lesions with fibrinoid necrosis.

PUB191

Kidney Crashes: Stop That Drug!

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Introduction: Drug associated antineutrophilic cytoplasmic antibody(ANCA) associated vasculitis(DAV) with rapidly progressive glomerulonephritis(RPGN) is rare. Historically linked to antithyroid drugs, new evidence implicates almost every pharmacologic class. Unrecognized, it is catastrophic. Prompt diagnosis & cessation of the offending agent is paramount. This is a case of DAV-RPGN secondary to diltiazem

Case Description: 76-year-old male with T2DM, cirrhosis, HTN & MM in remission, on diltiazem, propranolol, insulin, presented to an outside hospital with 10-days of weakness, reduced appetite & leg swelling. On exam BP 191/79,T97°F & anasarca was present. Labs showed Na128, K5.3, Cl100, HCO3 19, BUN79, creatinine(Cr) 2.8, increased to 4.18 by admission day 10, Ca 7.6, phos 4.7, WBC 8.8, Hb 9.4 & PLT 214. CT abdomen showed renal cysts, mild ascites & no hydronephrosis. Renal biopsy showed crescentic pauci-immune vasculitis & severe necrotizing arteritis with positive pANCA, MPO, ANA, DS-DNA, RhF & low C3. He received IV methylprednisolone for 3 days, followed by prednisone 60mg od, transferred to our hospital, then started on cyclophosphamide 15mg/kg q2 weeks with plasmapheresis. There was suspicion for DAV secondary to diltiazem. Antihistone Ab(AHa) was sent & diltiazem stopped. Electron microscopy showed subendothelial deposits & intracellular macrophages suggestive of SLE. AHa was positive with negative cryoglobulin. Diagnosis of drug induced SLE from diltiazem with p-ANCA positive RPGN was made. He was discharged on prednisone 60mg daily with slow taper & Rituximab. Cr at discharge was 3

Discussion: DAV is an elusive diagnosis due to limited epidemiological data & identical features to primary ANCA associated vasculitis (PAAV). Although there is no clear definition, CHCC2012 describes it as "Vasculitis associated with probable specific etiology".Pathophysiology of drug induced ANCA formation & DAV is poorly understood. Possible mechanisms include reversal of epigenetic silencing & increased MPO & PR3 autoantigen expression in neutrophils, as in hydralazine, or formation of reactive intermediate species by PTU that act as MPO substrates. Regardless DAV must be differentiated from PAAV. It may present with lower Cr, urinary protein & CRP levels, tends to be ANA+ & AHa can be present, as in this case. Treatment involves prompt cessation of the offending agent & immunosuppression, with improved prognosis compared to PAAV

PUB192

C3 Glomerulonephritis: Can Therapy Be Individualized?

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Introduction: C3GN is a rare form of glomerulonephritis with variable clinical course. Therapeutics traditionally include corticosteroids, MMF and plasma exchange. Complement directed therapies remain under investigation. We report a case ofC4Nef and C5Nef positive C3GN treated with eculizumab.

Case Description: A 31 year old female was diagnosed with membranoproliferative glomerulonephritis (MPGN) in 2006 at age 19. She was treated with high dose prednisone for six months with no response. Conservative therapy was instituted. She was referred for to our centre for evaluation in 2018. At this time she was nephrotic with proteinuria 12g/day, serum albumin 21 g/L, serum creatinine 101umol/L with low C3 was 0.15 (0.8-1.9) and normal C4 at 0.13 (0.13-0.4). Repeat kidney biopsy revealed C3GN, with MPGN pattern, 4/34 globally sclerotic glomeruli and moderate interstitial fibrosis. Immunofluorescence showed C3 3+; IgM 1+; C1Q negative. There were no dense deposits on electron microscopy. Complement function studies demonstrated elevated C5b-9 level, low C5, C5 nephritic factor (C5Nef) positive at 1+ and C4 nephritic factor (C4Nef) strongly positive at 4+. C3 nephritic factor was negative. The positive C5Nef and C4Nef prompted testing for C5b-9 deposition on endothelial cells. sC5b-9 was elevated at 160% (normal < 150%). As complement functional testing suggested targeted terminal complement pathway for treatment may benefit this patient. We commenced eculizumab was commenced. At 6 months follow up, proteinuria has decreased (urine ACR 427mg/mmol), creatinine improved at 84 umol/L, and albumin increased to 33 (versus 21). C3 remains low at 0.11.

Discussion: We have demonstrated a case of C3GN with positive C3 adn C5Nef with cell surface activation of complement, classical and terminal complement pathway involvement. This highlights the importance of complement function studies to help aid the localization of complement pathway defect, and to individualize therapy.

PUB193

A Rare Case of NSAID-Induced Minimal Change Disease

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Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause acute tubular necrosis (ATN) via inhibition of prostaglandin synthesis, and vasoconstriction. Drug-induced minimal change disease (MCD) is postulated to be due to a reduction in renal perfusion and glomerular filtration rate. We present a case of NSAID induced acute renal failure (ARF) due to ATN and MCD in a healthy 37-year-old adult.

Case Description: A 37-year-old male with no medical history came to the ED with 1 week of vomiting, abdominal pain, and reduced urine output. He attributed his symptoms to food poisoning but sought evaluation after no improvement. Over the last 2 weeks, he had an upper respiratory infection and dental pain for which he took 1g of ibuprofen daily. Labs yielded a BUN of 104mg/dl, creatinine (Cr) of 16.9mg/dl, and urine protein to creatinine ratio of 5.85. Renal ultrasound showed no hydronephrosis. Abdominal CT showed diffuse colitis. Dialysis was initiated for uremic colitis. Workup for ARF was negative for hepatitis, HIV, and autoimmune markers. Kidney biopsy revealed podocyte effacement and nonspecific minimal deposits with severe ATN. Immunofluorescence showed nonspecific mild granular tubular and glomerular IgG deposition. Electron microscopy noted widespread podocyte effacement consistent with MCD. Prednisone 60 mg daily was started. Within 48 hours oliguria resolved and dialysis was discontinued. Cr at discharge was 3.6. After a slow taper of steroids, he had a full recovery.

Discussion: Although NSAID-induced ATN is well understood, it is unusual to see ATN causing ARF with oliguria in a young patient with no comorbidities. Nephrotic syndrome induced ATN has been specifically documented in association with MCD. This is likely the mechanism of ATN development in our patient with drug-induced MCD. MCD is the most common cause of nephrotic syndrome in children but accounts for only 10-15% of adult cases. Data evaluating drug-induced MCD in adults is limited to a few case series and retrospective studies associating NSAIDs with acute interstitial nephritis, rather than ATN, as the cause of MCD. Contrary to our case, NSAIDs have shown to reduce proteinuria in idiopathic nephrotic syndrome. Corticosteroids are the first-line therapy, and adults with MCD require prolonged therapy with a slow taper. The majority of ARF induced by MCD is reversible, with complete recovery of renal function.

PUB194

Kidney Aging and Estimation Equations for GFR in Beijing

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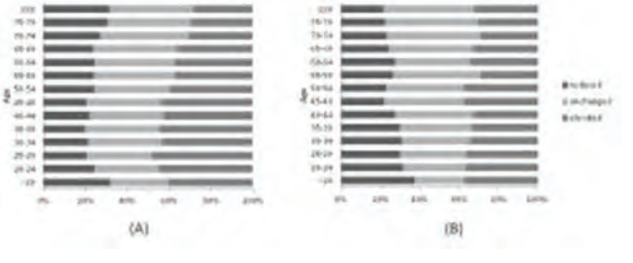
Background: When evaluating renal function, eGFR data show significant variation across different equations, particularly in elderly patients. Here, we investigated how age affected renal function in healthy subjects in Beijing and compared different eGFR equations for the evaluation of renal function.

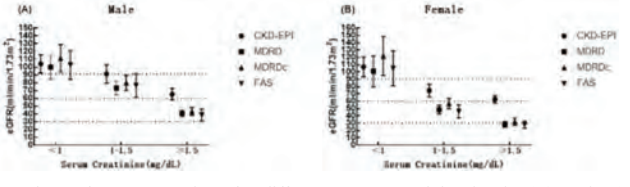
Methods: We recruited all patients undergoing routine assessment in our hospital between January 2012 and December 2014. For each patient, we recorded age, gender, and sCr. Kidney function was evaluated by five equations: CKD-EPI, MDRD, MDRDc, FAS and BIS.

Results: A total of 46,713 subjects were enrolled. Subjects were 16 - 100 years-of-age and were followed-up for 3 years. All subjects showed an increase in sCr and decrease in eGFR with increasing age. For males, there was a more obvious and significant reduction of eGFR in the elderly; butin older females, eGFR did not tend to change. Different equations showed good consistency[the intraclass correlation coefficients (ICC) was 0.849 for males, and 0.817 for females.];The CKD-EPI equation yielded scores that were indicative of more advanced CKD(according to sCr levels). There was no obvious trend for age-related change in the 3-year mean rate of eGFR change when compared across age groups. For subjects aged over 70 years, the MDRD and MDRDc equations yielded significantly higher eGFR data and the BIS produced the lowest eGFR values.

Conclusions: The annual rate of GFR change was not associated with age. Different eGFR equations yielded data that varied across different populations of patients and sCr levels. We were unable to identify a specific equation for use in the elderly Chinese population.



A comparison of different eGFR equations across all age groups. (A) Male. (B) Female.



Comparison of eGFR equations for different serum creatinine levels. (A) Male. (B) Female.

PUB195

A Workplace Wellness Program Results in Improvements in Physical Activity and Blood Pressure in the Staff of a Hemodialysis Clinic

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Background: Evidence indicates that health and wellness programs in the workplace provide numerous benefits with respect to altering indices of health. The purpose of this study was to assess the feasibility of a workplace wellness program (WOW) as a means of improving blood pressure by participation in habitual physical activity (PA) and improving dietary choices among the staff at a hemodialysis clinic.

Methods: 26-staff members (age:46.8±12.2;BMI: 28.7±5.6 kg/m2) from a hemodialysis clinic (nurses, technicians, social workers, dieticians, and administrative staff) participated in the 12-week WOW program that consisted of weekly counseling sessions, the provision of educational resources, PA incentive challenges, and healthy dietary choices challenges. Body weight(kg), height(cm), blood pressure, BMI, 24-hr dietary recalls, PA behaviors (IPAQ), and waist/hip circumference(cm) were collected at weeks 0(baseline), 6, and 12 following the conclusion of the intervention. Statistical analysis was performed using SPSSv.24. All primary and secondary outcomes were assessed by one-way Analysis of Variance (ANOVA) comparing values at the different testing time points, with significance at ($p<0.05$). Paired sample t-test was used to for the questionnaire (IPAQ) data that was collected at baseline and post intervention.

Results: The program also resulted in improvements in several health related metrics. This included reductions in body weight (1.07kg±21.4; $p<0.05$), body mass index ($p<0.05$), waist circumference cm (96.9±14.8; $p<0.05$), and hip circumference cm (111.7±13.6;$p<0.05$). Systolic blood pressure change was non-significant but trending toward significance ($p=0.08$), while diastolic blood pressure was reduced ($p<0.05$). There were significant changes in PA behavior, specifically walking behavior ($p<0.05$), as indicated by the IPAQ

Conclusions: The WOW program demonstrated increased measures in the staff's PA. As a result, this led to the improved health outcomes which included body weight reductions, BMI improvements, lowered hip and waist circumference, and improved diastolic blood pressures values. The study suggests that a workplace wellness program has the potential to improve health indices of the staff of hemodialysis clinics and may positively impact the health behaviors in the hemodialysis patients under their care.

PUB196

Frailty Changes in Patients on Hemodialysis After an 8-Week Exercise Intervention

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Background: The Fried frailty phenotype defines frailty as having at least 3 of the following: unintentional weight loss, decreased grip strength, slow gait speed, exhaustion, and decreased physical activity. The vulnerability inherent in frailty is exacerbated in people with end-stage renal disease, but frailty assessments are typically not used. Exercise during dialysis has been shown to have positive effects on functional outcome and physiologic measures, but are not standard clinical care. The purpose of this study was to investigate the effects of an 8-week, supervised resistance and cycling program on frailty and function measures of patients undergoing dialysis.

Methods: 11 patients from the Wise Health System Dialysis Center in Decatur, TX (6 in the experimental group, 5 in the control group). The experimental group received a supervised elastic band resistance and cycling ergometer program 3 days per week for 8 weeks during dialysis. The resistance component included: ankle dorsiflexion and plantarflexion, knee flexion and extension, and hip abduction. A repeated measures 2-way ANOVA was conducted on the dependent variables of: frailty scores, gait speed, grip strength, 2-Minute Step Test, exhaustion, Timed Up and Go, and 30-second Sit to Stand Test.

Results: There was a significant difference in pre- to post-test frailty scores [$F(1, 9)=6.14$, $p=.035$, $\eta^2=.41$]. Specifically, the exercise group's frailty score dropped from 3.67 to 2.67 while the control group's score did not change. This change in frailty score was influenced by the change in the exhaustion component of the frailty score from a mean of 1.00 to 0.17 [$F(1, 9)=16.05$, $p=.003$, $\eta^2=.64$)]. There were no significant differences found in the other dependent variables. There were no adverse reactions to the exercise intervention.

Conclusions: The results of this feasibility study support the hypothesis that an exercise program during dialysis can change frailty scores in people with ESRD, as the exercise group decreased their frailty classification from frail to pre-frail. It is not clear if the benefit would persist after this time or if results would change based on the length of the program, which provides support for additional longitudinal research designs. In conclusion, it appears that a resistance and cycling exercise intervention can mitigate frailty effects in persons with ESRD.

PUB197

Relation Between Anxiety, Depression, and Frailty in Maintenance Hemodialysis Patients

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Background: Both psychological disorders and frailty are prevalent and burdensome in MHD patient. However, the relationships between these entities are unclear. The aim of this study was to investigate the prevalence and associations between frailty and psychological disorders in Southern Chinese MHD patients.

Methods: This was a multicenter, cross-sectional and observational investigation conducted at 4 institutions. Frailty was evaluatd with the Tilburg Frailty Indicator (TFI) and it was used as the self-reported questionnaire. Anxiety symptoms was assessed by the Self-Rating Anxiety Scale(SAS, depressive symptoms was assessed by the Self-Rating Depressive Scale(SDS). We collect sociodemographic and clinical characteristics the patients who complete the scale. Statistical analysis was performed using SPSS20.0 for Windows.

Results: Of the 623 patients visiting each institution, 300 were enrolled in this study. The mean age was 61.95±13.64 years, with mean duration of HD 30.7 (43.39±2.36) months.116 patients (38.7%) were female and 133 (44.3%) had diabetic kidney disease. In total, there were 225 patients (75%) were evaluated as frailty. The prevalence of frailty increased steadily with age and was more prevalent in the diabetes mellitus patients. A multivariate logistic regression analysis revealed that the factors independently associated with frailty were the following: age, Charlson comorbidity index, DM,SAS, SDS. There was no relationship between the duration of HD and frailty status. Anxiety and depression symptoms by SAS and SDS were identified in 52.6% and 72.0% of MHD patients. MHD patients with both anxiety and depression generally had higher frailty score. The coexisting frailty and psychological disorder were present in 45.0% patients. There was an additive effect of psychological disorder and frailty on nutritional status. For the groups with frail and psychological conditions and no frail and no psychological conditions, both serum albumin and creatinine decreased.

Conclusions: This study demonstrated that anxiety and depressive symptoms are associated with prevalent frailty in Southern Chinese MHD patients. Older age, diabetes mellitus, CCI and lower serum albumin were associated with frailty among patients on MHD. Anxiety and depressive symptoms are independent risk factors of frailty.

Funding: Clinical Revenue Support

PUB198

Potassium Binders for Treatment of Hyperkalemia: Patient Survey Examining Side Effects, Tolerability, Palatability, and Interference with Daily Activity

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Background: Even mild hyperkalemia is associated with increased mortality. There are three FDA-approved oral potassium binders for outpatient treatment of non-life-threatening hyperkalemia: sodium polystyrene sulfonate (SPS), patiromer, and sodium zirconium cyclosilicate (ZS-9). Specific studies of patient experience, satisfaction, and adherence have not been conducted for any of the three agents. We surveyed outpatients regarding their experience with these medications, including taste, texture, tolerability, and interference with daily activity.

Methods: An online, anonymous survey of outpatients ≥18 years old who were dispensed SPS, patiromer, and/or ZS-9 from September 2017 to August 2019 at military treatment facilities in the National Capital Region was conducted over 8 weeks. Respondents were invited by letter including the survey url (with a reminder at 4 weeks). Survey questions included queries about demographics, medical diagnoses, medications associated with hyperkalemia, side effects, taste, palatability, and daily activity interference.

Results: 212 qualifying individuals were invited to participate. Response rate was 16% (34/212). All respondents were ≥51 years old. 36% were on RAASI. 28 respondents had used SPS, 6 had used patiromer, and 1 had used ZS-9. 18% of respondents treated with SPS vs. 0% treated with patiromer reported side effects. 1 reported discontinuing SPS without informing their physician due to side effects. 48% reported diarrhea with SPS. 50% reported constipation with patiromer. Respondents favored taste and texture of patiromer vs. SPS (72 vs. 56 for taste, and 70 vs. 50 for texture, with a scale rating of 100 being best), and reported more difficulty swallowing SPS vs. patiromer (3% vs. 0%). Side effect severity and interference with daily activity were the same (2 and 3 respectively for both SPS and patiromer; scale of 0-10, 10 being worst).

Conclusions: Respondents who used patiromer reported better palatability and fewer side effects than those who took SPS. However, side effect severity and daily activity interference were equivalent between SPS and patiromer. Disclaimer: The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army/Navy/Air Force, the Department of Defense, nor the US Government.

PUB199

Evaluation of the Establishment of a Nutrition Care Process in a Group of Spanish Haemodialysis Patients

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Background: Keeping a good nutritional status during hemodialysis must be a priority goal of the treatment to prevent complications and mortality, as well as, to improve patients quality of life. The main objective of this survey will be to evaluate if the establishment of a nutritional care process adapted to the chronic kidney disease, could improve anthropometrics and biochemical parameters in a hemodialysis hospital group of patients. We will also try to asses if the compiled results of the questionnaire about malnutrition and inflammation are correlated to the biochemical results obtained.

Methods: Information about sex, gender, dry weight, IMC, albumin status, PCR and Malnutrition Inflammation Score were collected during the months of July 2019 and March 2020. 38 haemodialysis patients participated in this study. A descriptive and frequency analysis has been carried out with all the parameters obtained. The T of Student for a related sample test was used due to the normality of the data and the participants condition of intervention - control.

Results: The results indicate that since the month of July 2019 until March 2020, 81,7% of the patients stayed on the hemodialysis program, 13,1% of the patients died, 2,6% changed hemodialysis to peritoneal dialysis, and 2,6% were transplanted. 42,1% of the total number of patients decreased their dry weight, 13,2% maintained it, and 26,3% increased it. The medium values obtained in July and March respectively were: dry weight (70.2±14.44 y 68.9±12.4kg), IMC (26.8±5.62 y 26.3±4.9kg/m^2), albumin (3.6±0.3 y 3.7±0.3mg/dL), PCR (1.5±2.6 y 1.4±1.8) and MIS (6±2.8 y 6.1±2.8). No statistical significance in any of the values has been found, being dry weight and IMC (p = 0.08) the closer parameters to get this condition.

Conclusions: The establishment of a nutritional care process seems to be a helpful and efficient method to improve anthropometrics and biochemical parameters in hemodialysis patients. Likewise, the use of malnutrition inflammation questionnaire as a tool to evaluate the nutrition status, seems to be effective when correlating with better biochemical nutritional parameters in hemodialysis patients.

PUB200

Scope and Consistency of Physical Fitness Outcome Measures in CKD: A Systematic Review

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Background: Impaired physical fitness is prevalent in people with chronic kidney disease (CKD), associating with an increased risk of mortality, falls and hospitalization. A plethora of physical fitness outcomes have been reported in randomized trials. This study aimed to assess the scope and consistency of physical fitness outcomes and outcome measures reported in trials in CKD.

Methods: A systematic review of randomized trials reporting physical fitness outcomes in adults with CKD (not requiring kidney replacement therapy), receiving hemodialysis or peritoneal dialysis, and kidney transplant recipients was conducted. Studies were identified from MEDLINE, Embase and the Cochrane Library from 2000 to 2019. The scope, frequency and characteristics of outcome measures were categorized and analyzed.

Results: From 112 trials and 6,047 participants, 87 tests/measurements were used to evaluate 30 outcomes measures that reported on 23 outcomes, categorized into five domains of physical fitness: neuromuscular fitness (reported in 76% of trials), exercise capacity (64%), physiological-metabolic (49%), body composition (36%) and cardiorespiratory fitness (30%). Neuromuscular fitness was examined by 37 tests/measurements including the physical function component of questionnaires (27%), 1-repetition maximum (9%) and hand-grip strength (9%). Outcome measures were assessed by lab-based (58% of all trials), field-based (31%) and patient-reported measures (11%), and commonly evaluated at 12 (30%), 26 (23%) and 52 weeks (10%).

Conclusions: There is large heterogeneity in the reporting of physical fitness outcomes, with inconsistencies in the use of validated and patient-important outcome measures. Standardization in the assessment of physical fitness is required to improve the comparability of trial outcomes and enhance clinical recommendations.

PUB201

Diet Composition and Understanding of Plant-Based Eating (PBE) in an Inner-City Population of CKD Compared with Family Medicine Patients

Kingsley Cruickshank, Ahmad Saleh, Takisha Morancy, Elizabeth G. Kasparov, Mariana Markell. *SUNY Downstate Health Sciences University, Brooklyn, NY.*

Background: Patients with CKD may benefit from PBE but dietary restrictions may create confusion regarding implementation. We compared attitudes toward plant-based eating and dietary components in an indigent, immigrant population of patients with CKD and those attending Family Medicine clinic (FM).

Methods: A face-to-face survey was conducted in a random convenience sample of pts in CKD (23) and FM (22) clinics. Patients chose answers from 5 Likert style questions about PBE assessing their beliefs regarding difficulty in finding foods in restaurants, affordability, ability to get proteins and vitamins, and ability to find good tasting recipes. A mean score was calculated with lower score indicating more difficulty (PBE-score). Diet analysis was based on 24hr recall and analyzed using ASA-24 software. Comparisons are by t-test unless noted.

Results: Mean age was 54.3±2.5 yrs. There were 16 (36%) males and 29 (64%) females with 40 black (89%). 36 (80%) had not completed college. 23 (51%) had an income < $20K. 16 (35%) were employed. 20 (44%) had diabetes. Mean BMI was 30.4±1.6 with 41% >30. There were no differences in these variables between clinics. CKD pts had a higher creatinine (2.01±0.39 vs 0.85±0.05) more positive attitude towards PBE (PBE-score 2.57±0.1 vs 2.21±0.13, p<0.05) and ate more cholesterol (411.6±65.2 vs 248.7±30.3, p=0.031), fatty seafood (1.41±0.54 vs 0.17±0.1, p=0.034) eggs (1.05±0.27 vs 0.42±0.16, p=0.048) and drank more fluid (2499.0±335.6 vs 1367.9±167.1, p=0.005) than FM pts, but fruit/veg intake was poor. PBE-score did not correlate with dietary intake of any nutrient in either group.

Conclusions: In our populations 1. Pts with CKD had a more positive attitude towards plant-based eating. 2. CKD pts ate more cholesterol with higher intake of eggs and fatty seafood. 3. Despite difference in attitude there was no difference in actual vegetable intake between groups. 4. The positive attitude of CKD pts towards PBE suggests that education will be successful in this group, especially as they appear to be following the recommendation to increase fluid intake. The poorer attitude in FM patients should be addressed as the population as a whole has a high prevalence of hypertension, obesity and diabetes and all patients could benefit from PBE.

PUB202

Low Influenza Vaccination Rates and Patient Misconceptions in Inner-City CKD and Kidney Transplant (KTR) Patients

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Background: Pts refuse vaccination for unclear reasons. Vaccination rates and attitudes towards vaccination were studied in an inner-City population of CKD pts and KTRs.

Methods: A face-to-face survey was conducted in a random convenience sample of pts with kidney disease attending CKD (30) and Transplant clinic (45). Pts were asked if they refused or accepted the influenza vaccine and assocations between beliefs about vaccines and cause of vaccine refusal examined.

Results: There were 37 (49.3%) women and 38 (50.7%) men with 60 black (80%). 40 (40%) did not attend any college. 17 (22.7%) were employed. Mean age was 56.8±1.4 yrs. 34/65 pts (45.3%) reported having had influenza with more TXP pts (63% vs 31%, p=0.009) and more men (62% vs 37%, p=0.035) in the group by Chi-square. 18/36 (50%) who answered did not take the flu vaccine the previous year, with no difference between CKD and KTRs. Reasons were believeing thet were not at risk (28%), experience with side effects (33%), fear related to 3rd party information (22%) and other. Pts who did not think illnesse prevented by vaccines were severe agreed they should question shots (r=0.58, p<0.0001), felt knowledgeable about vaccines (r=0.36, p=0.012), trusted information they received (r=0.55, p<0.0001) and felt they could discuss concerns with their doctor (r=0.58, p<0.0001). They were more likely to receive information from friends and family (r=0.58,p<0.0001). Pts who were concerned about side effects were concerned with vaccine safety (r=0.77, p<0.001) and felt they may be ineffective (r=0.76, p<0.0001) but they did not feel knowledgeable about how vaccines work (r=-0.372, p=0.01).

Conclusions: In our population 1. Influenza vaccination rates are low and prevalence of self-reported influenza high. 2. Patients who refuse vaccines believe they are low risk for the disease, and have concerns about vaccine safety and side effects. 3. Pts who believed preventable illnesses were not severe were more likely to receive information from friends and family, felt knowledgeable but did feel comfortable discussing concerns with their doctor. 4. Pts who were concerned with vaccine safety did admit to lack of knowledge. 5. Effective education regarding how vaccines work as well as efficacy and side effect profiles may help improve vaccination rates in this high risk population.

PUB203

Time to Revisit Contemporary Heart Failure Risk Prediction Models: Chloride, the Neglected Electrolyte

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Background: While the prognostic role of hyponatremia has been extensively studied in patients with heart failure (HF), more recent studies have identified chloride as an independent and possibly stronger predictor of outcomes in this setting. Since the clinical course of HF is known to be variable, several predictive models have been developed that simultaneously take into account multiple factors to refine their prognostication ability. We sought to explore the inclusion of serum chloride levels in contemporary risk prediction models of HF.

Methods: Articles cited in the PubMed database using keywords "heart failure", "prediction", and "model" were searched. Available data from clinical trials performed between January 1995 and December 2019 were included. The studies were selected if they prognosticated outcomes in the HF population through a predictive model that consisted of at least 2 factors. Pertinent data on clinical and laboratory parameters (e.g. hypochloremia and hyponatremia) were extracted and reviewed.

Results: A total of 15 studies with 82,706 participants were included, of which 5 were validated in a HF cohort different from the model derivation cohort. They consisted of

a variety of HF populations (e.g. acute, chronic, carrying mechanical circulatory device) and the median number of included parameters was 7. There was substantial variation across models in the reporting of the kidney related parameters as well as the studied outcomes. While no study included eGFR, serum creatinine and BUN were included in only 6 and 4 studies respectively. Interestingly, serum chloride level was included in none of the included models, while 4 did contain data on serum sodium level.

Conclusions: The emerging clinical evidence on the paramount prognostic value of hypochloremia for adverse outcomes in HF is in keeping with distinctive physiologic mechanisms relating it to renin secretion and modulation of renal tubular sodium transporters. However, we found that there is still a lag in its integration into contemporary predictive models of HF. This observation highlights the need for revisiting these models in backdrop of emerging data and explore whether incorporation of hypochloremia, or replacing hyponatremia by hypochloremia, would add to their predictive value.

PUB204

Long-Term Ambient PM2.5 Exposure Associated with Major Cardiovascular Risk Factors in a Large Chinese Population-Based Study

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Background: The association between long-term exposure to ambient air pollution and hyperlipidemia or overweight is still controversial. We aimed to investigate the relationship between long-term exposure of PM2.5 and cardiovascular risk factors in a large multi-provincial and multi-ethnical Chinese adult sample.

Methods: We recruited 19,236 adult participants from 2007 to 2010 in 6 provinces of China (Chinese Physiological Constant and Health Condition Study, CPCHC). A questionnaire, physical examination, and biochemical tests were performed. The PM2.5 data used were derived from aerosol optical depth with the GWR model and GEOSChem method.

Results: The average age of the participants 42.79±16.12 years and nearly half were male (47.0%). Annual average PM 2.5 exposure 1-year before the CPCHC study was 33.4 (14.8-53.4) $\mu g/m^3$. Multivariate linear regression showed that each 10$\mu g/m^3$ increment of PM2.5 was associated with 0.025% (95%CI: 0.011%, 0.040%) decrease of cholesterol and 0.098% (95%CI: 0.083%, 0.113%) decline of BMI. Adjusted by age, sex, education, ethnicity, physical activity, and smoking, logistic regression indicated that PM2.5 exposing still associated with the prevalence of hyperlipidemia (OR = 0.958, 95%CI: 0.942, 0.974) and overweight (OR = 0.925, 95%CI: 0.911, 0.939). PM2.5 exposure was also corresponded to elevated SBP (0.048%, 95%CI: 0.034%, 0.063%) and an increased prevalence of hypertension (OR=1.020, 95%CI: 1.001, 1.039).

Conclusions: Long-term PM2.5 exposure was associated with an increased prevalence of hypertension, decreased prevalence of hyperlipidemia and overweight.

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PUB205

Predictive Models for Prognosis of Cardiovascular Events (in 5 Years) in Asian Patients with CKD

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Background: Chronic kidney disease (CKD) is viewed as a major health problem worldwide. However, independent influencing factors related to the prognosis with CKD patients (especially in cardiovascular events) is still potential to be exploited, and few researches on predictive models for individualized prognosis in CKD patients were published, especially in Asian area. Therefore, we are willing to evaluate independent influencing factors in regard to prognosis of CKD patients and build predictive models for individualized prognosis in CKD patients.

Methods: 1246 participants were included in this cross-sectional study. All date were used In univariate Cox proportional hazards regression models and multiariable Cox regression analyses (P<0.05). Then, 1246 participant were divided into two cohort(development cohort and validation cohort). we will establish one best predictive model by the means of CINDEX, AIC, NRI, IDI.

Results: In the Cox regression analysis of cardiovascular events, we found that HGB, K, Pre-albumin, APOB, Heart failure, CKD progression are independent influencing factors of cardiovascular events, and lower HGB is independent protecting factor, and Higher K, Pre-albumin, APOB, Heart failure, CKD progression are independent risk factors. In the development cohorts, we found that the model 6(K, pre-albumin, HGB, HF, CKD)is the best prediction model of cardiovascular events(P=0.088e^(1.93584*APOB + 0.00356*pre-albumin + 0.00679*HGB + 1.11488*heart failure - 0.22131*K - 0.10215*CKD progression)is the best prediction model of cardiovascular events.

Conclusions: Lower HGB is independent protecting factor of cardiovascular events, and higher K, Pre-albumin, APOB, heart failure, CKD progression are independent risk factors of it. And we establish the best prediction model (P=0.088e^(1.93584*APOB + 0.00356*pre-albumin + 0.00679*HGB + 1.11488*heart failure - 0.22131*K - 0.10215*CKD progression) of cardiovascular events (in 5 years).

C-INDEX & AIC of 6 models

Model	C-INDEX & AIC	Development group	Validation group
APOB	C-INDEX	0.895	0.636
	AIC	1001.383	
APOB、K	C-INDEX	0.893	0.649
	AIC	1001.668	
APOB、K、PA	C-INDEX	0.889	0.652
	AIC	1000.47	
APOB、K、PA、HGB	C-INDEX	0.889	0.598
	AIC	991.264	
APOB、K、PA、HF、HGB	C-INDEX	0.897	0.661
	AIC	989.088	
APOB、K、PA、HGB、HF、CKD	C-INDEX	0.998	0.986
	AIC	310.117	

PUB206

Epidemiology of Cardiovascular Risk Factors in Hemodialysis Patients in a Tertiary Care Hospital

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Background: Cardiovascular events remains the leading cause of mortality in patients with end stage renal disease (ESRD) and the risk of cardiovascular events is 10 to 20 times higher in ESRD as compared to general population. The main objective of this study was to evaluate the prevalence of traditional cardiovascular risk factors in the population of ESRD outpatients on chronic hemodialysis in a tertiary care center in Kolhapur city of Western India.

Methods: All patients undergoing regular hemodialysis for ESRD in the tertiary care center of CPR Hospital were considered for inclusion in the retrospective study. Clinical and demographic data were obtained from the medical records, whereas laboratory data were obtained as the most recent result in the six preceding months. Adequate statistical tests were carried out and for all tests, a p-value <0.05 was considered statistically significant.

Results: A total of 1937 patients were included from the data of 2 years from May 2018 to April 2020 at our institute. Their average age was 61.3 years old, 69.3% were males. The prevalence of cardiovascular risk factors observed was 89.3% for hypertension, 83.9% for dyslipidemia, 75.3% for sedentary lifestyle, 49.7% for tobacco use, and 43.5% for diabetes. In a multivariate adjusted analysis, we found that sedentary lifestyle (p = 0.041, PR 1.15 – 95%CI: 1.09 - 1.17), dyslipidemia (p = 0.021, PR 1.05 – 95%CI: 1.01 - 1.11), and obesity (p < 0.0001, PR 1.88 – 95%CI: 1.59 - 2.95) were more frequent in women; and hypertension (p = 0.019, PR 1.03 – 95%CI: 1.01-1.17) and tobacco use (p = 0.009, PR 3.1 – 95%CI: 1.97 - 4.67) were more often found among patients under 65 years old. Sedentary lifestyle was independently associated with time in dialysis less than 12 months (p < 0.001, PR 1.33 – 95% CI: 1.19 - 1.43).

Conclusions: The population in chronic hemodialysis in the city of Kolhapur presents a high prevalence of cardiovascular risk factors. These findings confirm the high-risk cardiovascular profile of hemodialysis patients. Prospective studies and clinical trials are needed to further clarify interventions that can be transformed in public health strategies to prevent cardiovascular death in hemodialysis patients.

PUB207

Prevalence and Associated Risk Factors of Pre-Hypertension and Hypertension Among University Students in Bahrain

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Background: The increase of hypertension in the developing countries may be connected with the economic transition within those countries. This study aimed to assess the prevalence of prehypertension and hypertension among university students and their associated risk factors.

Methods: The study used a cross-sectional design. Data were collected from February 2019 to May 2019 at the Arabian Gulf University Campus in Bahrain. A total of 411, randomly selected students aged 17 to 24 years (196 males, 215 females) were included in the study. The data were obtained through a self-completed structured questionnaire, which included data about nutritional lifestyle, sleep, exercises, family history and smoking pattern. In addition, blood pressure and body mass index were measured. Systolic and diastolic blood pressure measurements were taken by trained personnel.

Results: The mean age was 19.4±1.9 years. Normotensives constituted 61.3% (n=252), prehypertensives formed 30.7% (n = 126), and hypertensive students comprised of 8% (n = 33). The overall proportions of hypertension and prehypertension were higher among male students (81.8 and 69.8%) than female students (18.2 and 30.2%), respectively.

Higher body mass index was associated with significantly higher prevalence of hypertension (normal weight 27.3%, overweight 33.3%, and obesity 39.4%) but not with pre-hypertension (normal weight 47.6%, overweight 32.5%, and obesity 17.5%). The Univariate analysis showed an association between hypertension and age, sex, body mass index (BMI), nutritional lifestyle, sleep duration, physical activity, smoking pattern and family history of hypertension ($p < .05$). Multivariate logistic regression analysis revealed a significant association between hypertension and the above stated factors.

Conclusions: The findings of the present study highlighted the prevalence of hypertension (8%) and prehypertension (30.7%) among university students in Bahrain. The blood pressure values increased with associated risk factors (age, sex, body mass index, smoking, sleep duration, physical activity and family history of hypertension). The results of this study recommended that periodic screening and monitoring of students for hypertension should be done to the university students.

PUB208

A Combined Effect of Sacubitril/Valsartan and Evolocumab on Chronic Heart Failure in an ESRD Patient

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Introduction: End-stage renal disease (ESRD) patients generally have underlying risk factors for coronary artery disease and heart failure (HF) such as hypertension and diabetes mellitus. In fact, chronic HF is highly prevalent and is one of the leading causes of death in these patients. We report a combined effect of sacubitril/valsartan and evolocumab on chronic HF in an ESRD patient.

Case Description: A 63-year-old man with a history of chronic HF for 3 years, along with hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease status post coronary artery bypass graft with multiple stents, and ESRD on hemodialysis, presented with worsening dyspnea over 2 months (NYHA Class IV). His medication list included enalapril, valsartan, carvedilol, clonidine, amlodipine, hydralazine, isosorbide mononitrate, ranolazine, aspirin, warfarin, amiodarone, erythropoietin, rosuvastatin, sevelamer, linagliptin, and insulin. An echocardiogram revealed an ejection fraction (EF) of 15%. He was placed on a cardiac transplant waiting list after receiving an implantable cardioverter defibrillator. Meanwhile, enalapril and valsartan were replaced by sacubitril/valsartan for chronic HF, and evolocumab was added to reduce the risk of myocardial infarction. During an initial follow-up for 10 months, his dyspneic symptoms improved significantly to NYHA Class I. An echocardiogram later revealed an EF of 60%. He was followed up for 4 years without any hospitalizations, worsening of HF, or side effects of the medications such as hypotension, hyperkalemia, and nasopharyngitis.

Discussion: Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, has multiple mechanisms of action and is known to reduce the risk of cardiovascular death and HF hospitalization in patients with chronic HF with reduced EF. Besides, evolocumab, a PCSK9-inhibitor antibody, is known to promote plaque regression and stabilization. The combined use of sacubitril/valsartan and evolocumab in our patient for 10 months resulted in an improvement of his EF from 15% to 60%, most likely due to a significant improvement of coronary blood flow with a recovery of hibernating ischemic myocardium. Therefore, additional studies are highly recommended to explore the beneficial effect of these medications used in combination.

PUB209

Fanconi Syndrome and Acute Interstitial Nephritis: A Toxic Combination Associated with Ifosfamide

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Introduction: Ifosfamide is an alkylating chemotherapeutic agent used in the treatment of various soft tissue tumors. Nephrotoxicity associated with ifosfamide is less frequently reported in adults. We describe a patient with Ewing sarcoma, who presented with AKI and Fanconi syndrome. Worsening renal function prompted renal biopsy which showed acute interstitial nephritis. AIN associated with ifosfamide may portend a bad prognosis due to lack of response to steroids.

Case Description: 33-year-old female with chest wall Ewing Sarcoma presented with neutropenic fever. She had received 5cycles of chemotherapy with VIDE (Vincristine/Ifosfamide/Doxorubicin/Etoposide), last two cycles included only ifosfamide(3000mg/m^2) and doxorubicin. On presentation, she had AKI, hypokalemia, hypophosphatemia, hypouricemia, without hyperglycemia. UA showed proteinuria and glycosuria. Urine electrolytes showed potassium and phosphorus renal loss. She was diagnosed with ifosfamide associated Fanconi syndrome. Spot urine protein to creatinine ratio was 2.13gm/gm proteinuria. Renal function continued to worsen. Kidney biopsy revealed acute tubular injury with cytomorphologic changes consistent with ifosfamide associated effect and AIN. She was started on prednisone 60mg/day. She received prednisone for about 11weeks with no improvement. After extensive discussion, steroids were tapered off and she is being prepared for dialysis.

Discussion: Ifosfamide frequently causes proximal tubular dysfunction. Risk of renal toxicity has been associated with higher doses of ifosfamide(>100g/m^2). We describe hypokalemia as the first manifestation of proximal tubular dysfunction which resulted in complete Fanconi syndrome. Renal function never returned to baseline, prompting renal biopsy. Biopsy evidence of AIN was treated with steroids with no recovery. This was consistent with ifosfamide associated renal toxicity which often results in irreversible damage. Our patient received a total of 15g/m^2 of ifosfamide, which is way below the cumulative dose associated with nephrotoxicity. Since ifosfamide associated AIN has been associated with high resistance to steroids, alternate agents for treatment should be explored. More studies are warranted to see if occurrence of Fanconi syndrome with acute interstitial nephritis is associated with worse prognosis.

PUB210

Case Report: Membranous Nephropathy and Tyrosine Kinase Inhibitor

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Introduction: Tyrosine kinase inhibitors (TKI) have been used as adjuvant therapy in the treatment of a number of malignancies including gastrointestinal stromal tumors (GIST). TKIs have been associated with a number adverse events including hypertension and proteinuria.

Case Description: A 70-year-old male with metastatic GIST on TKI therapy for 6 years (initially on imatinib for 2 years and switched to sunitinib due to serositis) was referred for difficult to manage hypertension. Two years into the use of sunitinib, he had worsening hypertension, edema and hypoalbuminemia with a rising creatinine leading to sunitinib being stopped (see Table 1). Further work up confirmed the presence of nephrotic syndrome (urine protein to creatinine ratio (UPCR) of 20.76 mg/mg of creatinine) and an elevated phospholipase A2 receptor (PLA2R) immunoglobulin G titer of 1:640. Renal biopsy showed findings consistent with membranous glomerulopathy with PLA2R positive immunofluorescence, interstitial fibrosis and arterial sclerosis. Given these findings, a diagnosis of PLA2R associated membranous nephropathy was made. Bumetanide was started for management of fluid overload with good effect. Given proteinuria improved significantly after stopping therapy, sunitinib may have contributed to worsening of the underlying nephrotic syndrome. Ultimately, a decision was made to restart sunitinib with a plan to treat the membranous nephropathy with rituximab.

Discussion: Our patient developed hypertension and nephrotic syndrome, ultimately found to be PLA2R associated membranous nephropathy, in the setting of sunitinib use. It is possible that in our patient, sunitinib contributed to worsening of the nephrotic syndrome, as evidenced by the fact that proteinuria improved with stopping the TKI. While TKIs have been implicated in the development of proteinuria and nephrotic syndrome, it is important to rule out other possible causes to allow for continuation of oncological therapy if deemed necessary.

Table 1. Trend of laboratory testing

	Cr (mg/dL)	Alb (g/dL)	PLA2R	UPCR
Day 0	1.34	2.2	–	20.76
Day 2	1.38	2	–	18.73
Stopped TKI				
Day 13	1.23	2.3	1:640	4.42
Day 20	1.7	2.9	1:1280	1.62
Day 27	1.42	2.5	1:1280	4.27
Day 36	1.37	2.6	1:320	5.44
Restarted TKI				
Day 63	1.38	2.5	1:640	8.63

PUB211

Biopsy-Proven Cast Nephropathy from Lambda Light Chain Measured at 3684 mg/dL in a Multiple Myeloma Patient

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Introduction: Kidney injury is a common presentation of underlying Multiple Myeloma. In a recently published study, considered the largest analysis to date between free light chain (FLC) and biopsy confirmed MCN (myeloma cast nephropathy), median lambda light chain at diagnosis was 426.7mg/dL. Here, we present a case of a patient presenting in stage III acute renal failure with Lamba light chains measured at a level almost 9 fold greater at 3684mg/dL.

Case Description: A 78 year old female with past medical history significant for breast cancer 20 years ago is electively admitted from her primary care doctor's appointment after having symptomatic anemia with a measured hemoglobin (hgb) of 6.3 g/dL. She was feeling weak, with weight loss of 30 pounds in 2 years as well as persistent watery diarrhea and decreased intake over the previous 2 months. She was transfused 2 units of packed red blood cells and labwork showed creatinine on 10.79mg/dL, BUN 94 mg/dL, bicarbonate 16mmol/L, potassium 5.9 mmol/L, phosphorous 10mg/dL calcium 7.5mg/dL, and urinalysis with <30 mg/dL albumin. She was volume resuscitated and nephrology consulted for acute kidney injury. Further workup significant for urinary protein of 404 mg/dL and 43mg/dL creatinine, with urine pro/cr ratio of 9.3. 24 hour urine collection showed total 24 hour protein of 4.4g. FLC assay showed Lambda load of 3,694 mg/dL, kappa 3.41 mg/dL. Kidney biopsy revealed interstitial fibrosis and tubular atrophy of 50-60% and glomerulosclerosis 30-40% with strong lambda staining casts present. Hematology consulted and performed bone marrow biopsy which revealed over 90% plasma cells, confirming MM. Patient was started on hemodialysis for metabolic complications, and started on treatment with CyBorD therapy.

Discussion: Our patient presented with an extremely high light chain burden, and was treated aggressively with hemodialysis and immediate chemotherapy. The fairly recent development of the free light chain assay provides a tool to screen for MM and measuring serum light chain quantitatively. Currently, there are conflicting results as to whether or not overall light chain burdens have direct correlation and impact on overall kidney survival and salvageability. Further testing and meta-analyses are needed to determine if this can be used a prognostic tool.

PUB212

AKI Associated with Immune-Checkpoint Inhibitors: Management Challenges and Dilemmas Without Renal Biopsy

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Introduction: There is much to be learnt about renal lesions seen in patients with acute kidney injury (AKI) associated with the use of immune-checkpoint inhibitors (ICI). Acute tubulointerstitial nephritis is the most common, with glomerulonephritis (GN) being increasingly recognised.

Case Description: A 61 Chinese male presented with generalised arthritis and AKI with nephritic-nephrotic syndrome on a background of Stage IV metastatic clear cell RCC and left radical nephrectomy. At presentation, he was on treatment with pembrolizumab (PD-1 inhibitor) and axitinib (VEGF receptor TKI). Investigations revealed 24hr TUP of 8.26g/day and peak serum creatinine (sCr) of 605 μmol/L (CTCAE G3; baseline sCr 117 μmol/L). Autoimmune markers and complements were negative. Patient was counselled for but refused a high-risk renal biopsy. Pembrolizumab was discontinued. High dose prednisolone was initiated for renal and rheumatological IRAE. SCr improved to 224 μmol/L at 3 months but his nephritic-nephrotic state persisted. Risks and benefits of empiric mycophenolate mofetil were discussed extensively and patient opted to continue with corticosteroid (CS) monotherapy. His subsequent clinical course was complicated by community acquired pneumonia and herpes simplex viral oral mucositis, before eventually succumbing to polymicrobial sepsis from acute cholecystitis despite optimal management.

Discussion: The clinical presentation of our patient is highly suggestive of an underlying GN. In view of concurrent rheumatological IRAE, we postulated that his AKI was related to ICI use. Empiric use of high-dose CS resulted in partial improvement in renal function but persistence of nephritic-nephrotic state, suggesting that CS monotherapy is suboptimal. Without histological data, directed therapy was not possible. However, given the rarity and heterogeneity of ICI associated GN, success of previously tried agents was limited to case reports and optimal treatment remains unknown. In view of this uncertainty, hesitancy with the empiric use of immunosuppressants beyond CS is understandable. While we await further research, in-depth discussion of treatment risk and benefits, especially infective complications, during shared decision making remains a key element in the optimal care of this unique population with advanced malignancies and often, limited life expectancy.

PUB213

Abiraterone-Induced Rhabdomyolysis as an Unusual Cause of AKI Requiring Hemodialysis

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Introduction: A 86-year-old male diagnosed with metastatic, castration-resistant prostate cancer (mCRPC) treated with abiraterone (Zitiga) for 3 months was admited to the emergency department due to hyporexia, worsening fatigue and lethargy.

Case Description: After being diagnosed with prostate cancer, the patient had been subject to a radical prostatectomy 10 years prior to admission; 12 months prior to admission he developed deep-vein thrombosis that required endovascular treatment. The patient was prescribed daily 10mg rivaroxaban and 5mg prednisone for 1 year. For over 4 years, the patient had an irregular consumption of esomeprazole, atorvastatin and risperidone. Upon admission to the emergency department laboratory analysis revealed a dialytic emergency: serum creatinine of 6.1mg/dL, urea 295 mg/dL, BUN 138mg/dL and potassium of 7.3mEq/L. The patient refused renal replacement therapy. Agressive hydration and treatment with calcium gluconate, IV insulin and beta-agonist micronebulizations were prescribed to treat hyperkalemia. 24 hours later the patient persisted with serum creatinine 5.8, urea 276, BUN 128 and potassium of 7.0 despite optimal hydration management and potassium-lowering measures. As the clinical status didn't improve wiwth the previously described measures, the patient agreed to hemodialysis. Neurological symptoms improved, but the patient persisted with localized muscle pain in both legs, and it was decided to measure myolisis enzymes, with the following results: CPK 425 CPK-MB 92 and Myoglobin of 500 ng/mL. (7 times over the reference value). The patient was subject to three additional hemodialysis sessions, until creatinine, urea, BUN, K, CPK, and myoglobin levels were at reference parameters. The patient was discharged and at the follow-up appointment one month later he had complete resolution of symptoms and laboratory values, with the following parameters: serum creatinine 1.6 mg/dL urea 47.9 mg/dL BUN 13 mg/DL, K 4.1 mEq/L, myoglobin 41 ng/mL, CPK 34 U/L.

Discussion: There are only a few case reports that describe an association betweent abiraterone and rhabdomyolysis requiring renal replacement therapy. In Mexico, this is the first reported case. It is an important lesson, particularly in an oncologic hospital, as this unusual cause of acute kidney injury may be under-recognized in patients with prostate cancer undergoing treatment with this medication.

PUB214

A Unique Case of CKD with Multiple Primary Genitourinary Tumors

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Introduction: Studies in pre and post dialysis chronic kidney disease (CKD) patients have shown a high risk for urinary system malignancy. There is a 44% higher risk of malignancy in patients with eGFRs less than 45 mL/min/1.73 m. Renal cell carcinoma (RCC) represents 3% of all adult cancers. Primary penile melanoma is rare with an incidence less than 0.2% of all melanomas. Multiple primary genitourinary tumors are uncommon. Here we highlight an unusual case of a CKD patient with bilateral RCC and penile melanoma.

Case Description: We present a 78-year-old man with history of gout, osteoarthritis, and hypertension who underwent radical left nephrectomy for an incidental RCC (Fuhrman grade 2, pT1A). He went on to develop a spindle cell penile melanoma (pT3b). He was treated with a glansectomy and received a neophallus. Moreover, he was diagnosed with stage 3 CKD. He subsequently developed RCC (Fuhrman grade 2-3, pT1A) in the right kidney and was treated with cryoablation. His serum creatinine ranged from 136-185 mM/L, GFR from 31-45 mL/min/1.73m^2, urea from 14.8-17.4 mmol/L, and potassium from 4.5-4.7 mmol/L. Unfortunately, his melanoma progressed with multiple recurrences and he subsequently passed away.

Discussion: Moderate CKD may be a risk factor for malignancies in the genitourinary tract, particularly in older men. As the prevalence of CKD in the aging population increases globally, the importance of the recognition of CKD as a risk factor for genitourinary cancers must also increase. Our case highlights the association of CKD with multiple genitourinary tumors. There is a need for assessing the impact of CKD on treatment and prognosis of genitourinary cancers.

PUB215

Bilateral Renal Burkitt Lymphoma Presenting with Persistent Lactic Acidosis in an HIV-Negative Patient

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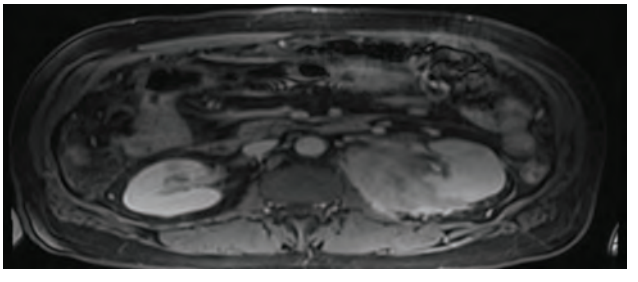
Introduction: Burkitt lymphoma is an uncommon and aggressive B-Cell lymphoma accounting for <1% of adult Non-Hodgkin Lymphomas. The ileocecal region is the most common affected area, but it can involve extra nodal sites including the kidney. Renal involvement is usually asymptomatic and requires a high degree of suspicion to prevent early complications

Case Description: 63 years old non-smoker, HIV negative male with a history of an incidentally found left medial upper pole exophytic perinephric hematoma on CT 2 months prior to presentation, presented to the ED complaining of acute on chronic lumbar back pain. Noted afebrile, BP 86/52 mmHg with orthostatic changes, HR 92bpm, RR 20rpm and SO2 96% on RA somnolent but arousable, pale, no abdominal, spinal or costovertebral tenderness. Laboratories showed Hb 8.2 (14.7 a month prior), WBC 17,000, Na 126, Sodium bicarbonate 16, Anion gap of 22, Lactic acid 5.0 and SCr 1.5 (baseline 0.8). UA unremarkable. CT-CAP w/o contrast with interval increase of perinephric hematoma and rectus abdominis hematoma. Urology recommended no surgical intervention. He was resuscitated with isotonic IV fluids, with resolution of shock. Subsequent MRA showed no evidence of enhancing left perinephric hematoma but multiple rounded hypo enhancing lesions in the renal parenchyma bilaterally. He remained with persistent anion gap metabolic acidosis with increasing lactic acid up to 14.5. A kidney biopsy was planned but aborted as patient became hypotensive and confused with a drop-in hemoglobin to 5.6. Patient endorsed dark stools so, when hemodynamically stable, EGD was performed and gastric biopsies showed aggressive Burkitt's lymphoma.

Discussion: Lactic acidosis (LA) can occur in the presence or absence of tissue hypoxia (type A and type-B LA respectively). Persistent LA without identifiable causes of tissue hypoxia should prompt clinicians to suspect non-hypoxic etiologies, including occult high-grade malignancies. Hematological malignancies constitute and uncommon cause of type-B LA, carrying a poor prognosis.



PUB216

Oxaliplatin-Induced Hypomagnesemia

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Introduction: Platinum based chemotherapy is used in the treatment of several malignancies including lung, colorectal, ovarian, breast, head/neck, bladder and testicular cancers. We present a case of profound electrolyte disturbances in the setting of oxaliplatin therapy.

Case Description: 78-year-old Caucasian male diagnosed with pancreatic cancer three months prior to admission, on oxaliplatin therapy, presented to emergency room with new onset atrial fibrillation. He was afebrile, hemodynamically stable, and without respiratory distress. He endorsed a history of chronic diarrhea since beginning chemotherapy, however he began to have weakness and dizziness three days prior to

admission. Laboratory analysis revealed hypokalemia: 2.9mmol/L, hypomagnesemia: 0.8mg/dL, hypocalcemia: 6.2mg/dL with ionized calcium of 0.8mmol/L. Urine magnesium (Mg) was 10.2mg/dL, and urinary fractional excretion of Mg was calculated to be 2.75%, consistent with renal Mg wasting. The atrial fibrillation resolved after adequate repletion of electrolytes, and he was transitioned from intravenous to oral supplements. He was discharged home on oral calcium carbonate, magnesium oxide, and potassium chloride supplements. Repeat labs one week post hospitalization showed stable potassium of 4.2 mmol/L and calcium 9.3mg/dl, however hypomagnesemia persisted to 1.3mg/dL, requiring an increase in Mg supplementation.

Discussion: Platinum based chemotherapy agents including cisplatin and to a lesser extent carboplatin have been known to cause electrolyte disturbances, in particular hypomagnesemia. However, case reports of oxaliplatin associated magnesium wasting are limited. This can be partially explained by the fact that oxaliplatin is protein bound and cannot readily accumulate in the kidney tubules to mediate nephrotoxicity, as is the case with carboplatin which is not protein bound. Magnesium deficiency is an under recognized entity, however it can precipitate potentially fatal cardiovascular dysfunction. Clinicians need to be aware of this potential adverse effect related to oxaliplatin therapy, as its prompt diagnosis and treatment can prevent the associated complications.

PUB217

Immune Checkpoint Inhibitor-Induced Renal and Cardiac Sarcoidosis

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Introduction: Immune related adverse events (irAEs) associated with immune checkpoint inhibitors (ICI) are increasingly recognized as a side effect in patients receiving this therapy. Sarcoid-like / granulomatous lesions from ICIs are reported to be as high as 5% based on case series and registries. In all reported cases, patients presented with lymph node, skin, or lung involvement. We present the first case of sarcoid lesions in the kidney and heart in a patient being treated with immune checkpoint therapy.

Case Description: A 62-year-old male with stage IV metastatic melanoma received two cycles of pembrolizumab in November 2019 followed by three cycles of with ipilimumab and nivolumab. In March 2020 he was admitted with acute kidney injury, creatinine peaked at 2.85 mg/dl (baseline 0.88-0.94 mg/dl). Urinalysis and serologies were unremarkable. A kidney biopsy was obtained and revealed granulomatosis tubulointerstitial nephritis with focal necrotizing granuloma. Acid-Fast Bacilli (AFB) and Grocott methenamine silver (GMS) stains were negative. Incidentally, the patient was noted to have increased shortness of breath. Echo revealed new-onset cardiomyopathy with ejection fraction (EF) of 22% and SVT. Cardiac catherization was negative for coronary artery disease, but endomyocardial biopsy revealed lymphohistiocytic infiltrate with granulomatous myocarditis consistent with cardiac sarcoidosis. He was initiated on pulse IV steroids with improvement of both his cardiac and renal function. EF improved to 46% and creatinine improved to 1.0 mg/dl. Follow-up PET/CT imaging showed small inguinal nodes that could be sarcoidosis otherwise no indication of melanoma.

Discussion: Use of ICI has dramatically improved patient survival; however, there is a growing appreciation for adverse events that can be associated with increased morbidity. To our knowledge, this is the first case of sarcoid involvement in both the kidney and heart. Our case highlights the need for aggressive approach to ICI toxicity when clinical work-up is unrevealing. The timely manner that both kidney and heart biopsies were performed, allowed for definitive diagnosis and guided treatment. Despite holding his ICI therapy to treat his irAEs, he continues to have cancer response from checkpoint therapy. Further follow-up is needed to determine long-term outcomes of both irAEs and cancer status.

PUB218

Drug-Induced AKI from Gemcitabine

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Introduction: The current decade has ushered in an incredible number of novel chemotherapeutics that has improved patient survival. These drugs cause various patterns of kidney injury, contributing to the burgeoning field of Onco-Nephrology. AKI in patients with cancer is linked with increased mortality. Since 1995, Gemcitabine has remained the first- or second- line treatment for patients with pancreatic cancer. We present a case of tubular injury and thrombotic microangiopathy in a patient on Gemcitabine and novel immunotherapy drug called LOKON.

Case Description: A 43 year old Caucasian male with history of stage 4 pancreatic cancer on active chemotherapy (Cycle 2 of LOKON clinical trial drug/ Gemcitabine/ Paclitaxel) was admitted to the hospital for Stage 3 AKI (Creatinine of 2.39 mg/dL), hemolytic anemia with schistocytes, thrombocytopenia, and leukopenia. The patient had received his second cycle of Gemcitabine one week prior to hospitalization. Patient reported generalized fatigue and fever after his treatment. Given his acute presentation and abnormalities, we suspected thrombotic microangiopathy. His ADAMTS13 was negative for Thrombotic Thrombocytopenic Purpura. Urine microscopy showed RBC casts and coarse granular casts. The haptoglobin was 187 mg/dL and LDH was 223 U/L. We performed a kidney biopsy to confirm the diagnosis of a drug-induced TMA and to guide further chemotherapy management because this patient is part of a trial. His biopsy revealed acute tubular injury with 10 % interstitial fibrosis with tubular atrophy. Proximal tubules lacked brush border which was consistent with ATN. Glomerulus contained segmental sclerosis with thick capillary basement membrane, double contouring, and smudgy mesangial tissue - consistent with chronic TMA. There were no vascular thrombi, RBC fragmentation, or crescent. Gemcitabine was discontinued and the patient was treated with supportive care. Four weeks after presentation, the creatinine remained elevated at 2.0 mg/dL.

Discussion: The nephrotoxicity associated with Gemcitabine can occur weeks to months after the drug is initiated. The mechanism of injury is driven by antibody formation to the drug and resulting endothelial injury and microvascular occlusion within the glomeruli. Treatment consists of discontinuation of this drug. Neither steroids nor plasma exchange have been reported as beneficial. AKI from this drug is reversible with supportive care.

PUB219

Gemcitabine-Induced Thrombotic Microangiopathy in Breast Cancer

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Introduction: Thrombotic microangiopathies (TMA) are potentially life-threatening conditions caused by small-vessel platelet microthrombi and are characterized by microangiopathic hemolytic anemia, kidney injury, and thrombocytopenia. TMA secondary to gemcitabine therapy (GiTMA) is extremely rare and is associated with a poor prognosis, with nearly 50% of cases progressing to end stage kidney disease. The mainstay of management is withdrawal of the offending drug and supportive care.

Case Description: A 65-year-old Black female with a history of metastatic invasive ductal breast cancer on gemcitabine therapy, well-controlled hypertension, well-controlled type 2 diabetes mellitus without proteinuria, and normal baseline kidney function presented with a 1 month history of poor oral intake, worsening hypertension, and progressive decline in kidney function. She was receiving 1250 mg/m^2/week of gemcitabine for 3 weeks/month for the preceding 1 year, with the last dose being 4 weeks prior to presentation. On admission, BP was 210/110 mm Hg, serum creatinine 2.7 mg/dl (baseline creatinine 0.9 mg/dl), serum albumin 2.6 g/dl (4 g/dl a month ago), new onset anemia (hemoglobin 6.9 g/dl) and thrombocytopenia (platelet count 51,000/mm^3), lactate dehydrogenase 928 IU/L, and had schistocytes on blood film. Urinalysis revealed numerous acanthocytes and RBC casts. 24 hour urine protein was 1.8 g. Testing for ANA, ANCA, and hepatitis B and C serologies were negative and complements within normal range. Renal ultrasound was unremarkable. A diagnosis of GiTMA was suspected. She was transfused 1 unit of blood, started on intravenous crystalloids and gemcitabine was held. BP normalized, serum creatinine improved to 2.4 mg/dl and platelet count 81,000/mm^3 within 3 days and she was subsequently discharged with discontinuation of gemcitabine.

Discussion: Gemcitabine, a deoxycytidine analog antimetabolite, is a commonly used chemotherapeutic agent for cancers of the pancreas, breast, lung, and ovaries. GiTMA is a very rare and highly fatal condition with mortality rates ranging from 50 to 70%. It is thought to be immune and non-immune mediated. Physicians should have a high index of suspicion to diagnose GiTMA early in the course of the disease. Mainstay of management is discontinuation of gemcitabine therapy, supportive care, and treatment of kidney injury with dialysis if necessary.

PUB220

Recurrent Mesenteric Cyst in an ESRD Patient on Maintenance Hemodialysis

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Introduction: Mesenteric cyst is a rare tumor reported with an incidence of 1:100,000 in normal population. Here we report a case of recurrent mesenteric cyst in hemodialysis (HD) patients.

Case Description: We chronicle a case of 47 years old male on hemodialysis for last 15 years with an unknown primary cause of end stage renal disease (ESRD). He never underwent peritoneal dialysis and had no prior history of abdominal surgery. He presented with gradual onset of abdominal pain and altered bowel habits. CT scan of abdomen and pelvis revealed encysted fluid in mesentery, measuring 10 x 5 cm, located behind the anterior abdominal wall. Patient refused enucleation procedure. Later, aspiration was done, which drained three liters transudative fluid. Cytology was negative for malignant cells, Histopathology demonstrated cuboidal epithelial cells of enteric origin and was not suggestive of cells of mesothelial origin. One month after first aspiration, patient presented with re- accumulation of cystic fluid and underwent second session of aspiration. Patient presented with worsening symptoms of abdominal distension and pain within two months of last aspiration. Repeat CT scan showed large intra-abdominal cystic lesion measuring 14 x 20 x 16 cm in mid- abdominal region, pushing all the adjacent abdominal viscera to the left side. At this time, cystic mass was surgically removed. Abdominal ultrasound and CT scan were negative for cirrhosis or Budd chiari malformation. Hepatobiliary system was also unremarkable. It re -demonstrated large mesenteric cyst 13 x 10.3 x 14.1 cm, located in the small bowel mesentery around the ligament of Teitz, extending down and exerting mass effects on the adjacent bowel loops. The extensive workup for causes of ascites, including liver disease, hepatitis panel, Tuberculosis, Brucellosis, Hydatid cyst and malignancy screening with markers namely CEA, CA 125, CA 19-9, CA 15-3, were all unremarkable. Erythrocyte Sedimentation Rate (ESR) was mildly elevated at 35 mm/ hour.

Discussion: This is the first reported case of recurrent mesenteric cyst in ESRD patient from KSA. Recurrent mesenteric cysts are extremely rare and are very difficult to manage. Enucleation and aspiration, both are ineffective modalities for such cysts.

PUB221

Urinothorax: A Rare Cause of Pleural Effusion

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Introduction: Urinothorax [UT], the accumulation of urine in the pleural space, is an uncommon cause of pleural effusions resulting from trauma, obstruction, or iatrogenic causes. Thoracentesis with pleural fluid analysis and evaluation of biochemical characteristics, such as pleural fluid creatinine (PCr) to serum creatinine (Scr) ratio, is necessary to diagnosis.

Case Description: A 93-year-old man with a history of chronic kidney disease, right kidney transitional cell carcinoma with hydronephrosis, adenocarcinoma of the prostate status post brachytherapy complicated by proctosis and urinary obstruction was hospitalized for worsening hematuria and suprapubic pain. CXR showed a large right pleural effusion. CT of the abdomen and pelvis illustrated severe right-sided hydronephrosis and hydroureter with a heterogeneous density in the right renal pelvis and diffuse mural thickening in the posterior and right lateral bladder walls. An ultrasound guided thoracentesis was performed with the removal of 2L clear yellow fluid and analysis resulted: pH 7.423, LDH 48 IU/L, glucose 164 mg/dL, and PCr 2.5 mg/dL. Cytology was negative for malignancy. Scr was 2.59 mg/dL and thus PCr to Scr ratio of 0.96. A repeat thoracentesis was performed removing 1.85L clear yellow fluid. PCr and SCr were 4.1 mg/dl and 3.94 mg/dL respectively. Again, this confirmed the diagnosis of UT with a PCr to SCr ratio of 1.04. Bilateral retrograde ureteropyelograms with right ureteral stent placement failed to correct and an indwelling pleural catheter was placed.

Discussion: UT is a rare cause of transudative pleural effusion due to the mismatch of the rate of accumulation of pleural fluid and rate of reabsorption via pleural lymphatics. The most common etiologies resulting in a UT include trauma and obstructive uropathy. Diagnosis requires pleural fluid analysis and is associated with a paucicellular, transudative effusion with an ammonia-like odor, acidotic pH less than 7.4, and a PCr to SCr ratio greater than 1.0. Management is dependent on correcting the underlying pathology, such as repairing traumatic GU injury or obstruction.

PUB222

An Interesting Case of Proximal Renal Tubular Acidosis and Fanconi Syndrome due to Ifosfamide Nephrotoxicity

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Introduction: Ifosfamide is an alkalyting agent that is used in treatment of lymphoma, sarcoma and germ cell tumors. Ifosfamide causes kidney injury as an important adverse effect- Proximal tubular injury, Fanconi syndrome and Nephrogenic diabetes insipidus.

Case Description: 50 year old male with past medical history of hypertension, kidney stones and peripheral T cell lymphoma since 1.5 years who was on multiple chemotherapy in past who was admitted for ICE chemotherapy. Patient reported fatigue and chills, sore throat and non-productive cough. Patient did not have any vomiting or diarrhea or fever or rash or leg swelling or shortness of breath. Had dizziness for 2 days. No lower urinary tract symptoms. No NSAID use. No IV contrast exposure. No hypotension. Patient got chemotherapy with ifosfamide, carboplatin, etoposide (carboplatin and etoposide -day 1 to day 3) with ifosfamide 5 g/m2 on day 2 along with mesna for 24 hrs. Patient's baseline creatinine was 0.9 to 1.2. Patient's creatinine went up to 1.48 (4 days after ifosfamide dose) and then progressively went up to 1.8 -> 2.4 (in 10-12 days after dose). Patient developed a non-anion gap hyperchloremic metabolic acidosis around that time. There was associated hypokalemia and hypophosphatemia. Urine pH was 8 and patient had 2+ proteinuria and 3+ glycosuria and protein creatinine ratio was 4.69 and on repeat, it was 10 g/mg creat. Urine sediment exam showed granular casts. He had proximal RTA and Fanconi syndrome due to ifosfamide nephrotoxicity. He was managed with supportive treatment with repletion of potassium and phosphate and bicarbonate drip. This was notable given lower cumulative dose (11.25g) resulting in nephrotoxicity. Case reports mention nephrotoxicity mostly in children with 60-120 g cumulative dose.

Discussion: Ifosfamide induced AKI is reversible but can be permanent. Biopsy shows tubular injury/necrosis with swollen mitochondria. Ifosfamide enters proximal tubule cells via OCT 2. Chloracetaldehyde is the toxic metabolite produced by ifosfamide that causes kidney injury. Usually, CKD, previous cisplatin exposure and cumulative dose >90 -120 g/m^2 are risk factors for AKI. Management is mainly supportive such as repletion of deficient electrolytes and renal replacement therapy if indicated. Possible long term complications include permanent proximal tubulopathy, renal phosphaturia, CKD and ESRD.

PUB223

PLA2R-Positive Membranous Nephropathy in a Patient with Rectal Cancer

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Introduction: Malignancy associated Membranous Nephropathy(MA-MN) is well-recognized as a common paraneoplastic glomerulopathy, especially in solid tumors. Prevalence is around 10% of all membranous nephropathy(MN) cases. Anti M-type Phospholipase A2 receptor antibodies(Anti PLA_2R) are seen in 70-80% of Primary MN but have been detected in up to 30% MA-MN cases. Case reports of thrombospondin type-1 domain-containing protein 7A(THSD7A) antibodies in MA-MN also exist. Pathological features of MA-MN usually resolve with successful medical or surgical treatment of the malignancy, or even undergo spontaneous remission. However, proteinuria may persist for months after remission of the cancer. We highlight a unique case of MA-MN that did not resolve despite successful treatment of the primary disease.

Case Description: A 48 year old male with no known co-morbidities presented for evaluation of nephrotic syndrome. He had a urine protein creatinine ratio(UPC) of 6.8 g/g and hypoalbuminemia(serum albumin 2.6 mg/dL). Anti PLA_2R levels were 198 RU/mL. Renal biopsy showed membranous nephropathy stage III/IV, 1+ PLA_2R staining. IF showed granular 4+ IgG4 subtype, 3+ Kappa, 3-4+ Lambda staining. Workup revealed adenocarcinoma of the rectum and was started on a 5-week combination chemoradiotherapy protocol, along with Losartan. Despite being in remission from malignancy for 12 months, he continued to be nephrotic with UPC of 4-6 g/g and albumin 2.9 mg/dL. Thus, he was treated with tacrolimus initially and then rituximab. Currently, he is in remission from malignancy and nephrotic syndrome with a UPC of 0.3 g/g and albumin 4.1 g/g. Last anti PLA_2R titre was negative.

Discussion: Our case highlights a rare clinical course different from the known natural progression of the disease and established therapeutic guidelines. Typically, MA-MN either resolves spontaneously or with management of the primary cancer without additional immunosuppressive therapy. If nephrotic syndrome persists despite cancer remission, as in our patient, it is reasonable to consider immunosuppression after 12-18 months. Recurrence of proteinuria after initial remission should also raise suspicion for possible recurrence of underlying cancer. Additionally, age-appropriate cancer screening for all newly diagnosed MN cases is essential. We hope this report shall serve as a means for further discussion and research in onco-nephrology.

PUB224

An Unusual Presentation of Atypical Hemolytic Uremic Syndrome in a Patient with Skin Ulcerations

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Introduction: Atypical hemolytic uremic syndrome (aHUS), characterized by microangiopathic anemia and acute kidney injury (AKI), is a rare and debilitating disease, but its diagnosis can be difficult because of potential overlap with several other autoimmune conditions. We present a case of aHUS-induced acute renal failure with skin ulcerations as initial presentation.

Case Description: A 61-year-old female presented with progressively worsening skin ulcerations on her hands after two cycles of rituximab and bendamustine for B-Cell chronic lymphocytic leukaemia. She also reported cocaine use. On presentation, her physical exam was notable for bilateral ulcers on her knuckles and ankles. She was treated empirically for osteomyelitis without improvement. Skin biopsy was non-diagnostic. She was noted to have anemia, thrombocytopenia and AKI with nephrotic-range proteinuria. Other remarkable labs included a low haptoglobin and a high LDH. Urinalysis revealed dysmorphic red blood cells, and peripheral smear showed schistocytes. An autoimmune process was suspected; thus, pulse steroids was initiated. A renal biopsy was suggestive of thrombotic microangiopathy (TMA). A full immunological work-up eventually returned unremarkable. Plasmapheresis was initiated before her ADAMTS13 activity resulted at > 10%. She was then started on eculizumab. After one session of plasmapheresis and four doses of weekly eculizumab 900 mg, her platelet counts improved. However, she required initiation of renal replacement therapy. TMA panel and genetic testing showed a low factor H level and dysregulated complement cascade consistent with aHUS despite negative CFH-CFHR5 mutation. She had some improvement in urine output but continued to require hemodialysis on discharge. Biweekly eculizumab 1200 mg was continued with plan to closely monitor for renal recovery.

Discussion: Although a rare disease with features that may overlap with other autoimmune processes, aHUS can cause rapid decline in renal function, thus requiring early recognition and treatment. CHF-CFHR5 mutation can be negative in ~40% of the patients. In the presence of the dysregulated complement cascade, microangiopathic process and renal failure, early treatment with eculizumab is crucial in renal recovery, but the renal response to treatment can be delayed compared to the hematologic response.

PUB225

Renal Medullary Carcinoma Causing Obstructive Uropathy

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Introduction: Hypertrophy of the prostate (BPH) is a common cause of obstructive uropathy in older men. Here we present the case of a 62-year-old Hispanic man with BPH who was found to have an additional rare cause of hydronephrosis, metastatic renal medullary carcinoma (RMC).

Case Description: A 62-year-old Cuban male with a history of hypertension and BPH presented for urodynamic testing for worsening lower urinary tract symptoms. Further questioning revealed fever, chills, and 20-pound weight loss over 2 months. Laboratory data were remarkable for serum creatinine of 2.7 mg/dl. Urinalysis showed pyuria and bacteriuria but no casts. After placement of an indwelling urinary catheter and drainage of 500 ml of urine, a renal ultrasound showed increased kidney size (right: 16.2 cm, left: 15.2 cm) and moderate left-sided hydronephrosis for which a percutaneous nephrostomy was placed. A computed tomography revealed multiple nodular lesions in the liver, bones, right adrenal gland, and lungs, and tissue retrieved by liver biopsy was suspicious for PAX8-positive carcinoma. MRI demonstrated findings concerning for urothelial malignancy in the left renal pelvis extending into the renal parenchyma. Percutaneous biopsy of the mass showed tissue positive for PAX8, Pan-K, and CA-IX (focal) and negative for INI-1, confirming the diagnosis of RMC.

Discussion: RMC is a very rare malignancy that accounts for less than 1% of all renal neoplasms. It was first described by Davis et al in 1995. It is known to be very aggressive and often metastatic at the time of diagnosis, with a median survival of about 4 months. It has been associated with sickle trait, rarely sickle cell disease and is most prevalent in patients with African heritage in the age group 10 - 40 years. Our patient did have sickle cell trait. Given his significant renal failure he was deemed not to be a candidate for platinum-based chemotherapy and was started on Paclitaxel.

PUB226

Effect of Gemfibrozil on Kynurenine Aminotransferases Activity and Kynurenic Acid Production in Rat Kidney

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Background: Hypertriglyceridemia is the most common lipid disorder in chronic kidney disease. A tryptophan metabolite, kynurenic acid (KYNA), is produced from L - kynurenine (L KYN) by kynurenine aminotransferases (KATs). KAT I and KAT II isoenzymes are the best analyzed KATs. KYNA acts predominantly as a nonselective antagonist of ionotropic glutamatergic receptors. Diet rich in fatty acids was reported to elevate central and peripheral KYNA level. The goal of presented study was to analyze the influence of gemfibrozil, on KYNA production and the activity of KAT I and KAT II, in rat kidney *in vitro*. Additionally, the molecular docking of gemfibrozil to KAT I and KAT II structures was performed. On the final step the microarray datamining was carried out to investigate if gemfibrozil affects the expression of KAT coding genes.

Methods: The effect of gemfibrozil on KYNA synthesis together with KAT I and KAT II activity was tested in rat kidney homogenates *in vitro* after 2 hours incubation in the presence of L KYN and gemfibrozil. The drug was examined at the concentration of 1 μM, 10 μM, 50 μM, 100 μM, 500 μM and 1 mM. Production of KYNA was analyzed using the high performance liquid chromatography (HPLC) with fluorometric detector.

Results: Gemfibrozil at 100 μM, 500 μM and 1 mM decreased KYNA production in kidney homogenates *in vitro* to 66% ($P < 0.05$), 58% ($P < 0.01$) and 41% ($P < 0.01$) of control value, respectively. At 100 μM, 500 μM and 1 mM concentration gemfibrozil lowered renal KAT I activity *in vitro* to 68% ($P < 0.05$), 56% ($P < 0.01$) and 52% ($P < 0.01$) of control value, respectively. Moreover, gemfibrozil at 500 μM and 1 mM concentration decreased kidney KAT II activity *in vitro* to 47% ($P < 0.001$) and 26% ($P < 0.001$) of control value, respectively. Results of the molecular docking suggested that gemfibrozil may affect the active site of both KAT I and KAT II. Publicly available microarray datasets suggested that the expression of KAT-coding genes does not change after gemfibrozil administration.

Conclusions: Gemfibrozil decreases KYNA production in rat kidney *in vitro* through inhibition of KAT I and KAT II isoenzymes. Presented results indicate a novel mechanism of gemfibrozil's action in the kidney. Its potential role in nephrotoxicity needs verification in upcoming studies.

PUB227

Lowest Reported Serum Creatinine in a Normal-Weight Adult Highlights the Limitations of Serum Creatinine in Estimating Glomerular Filtration Rate

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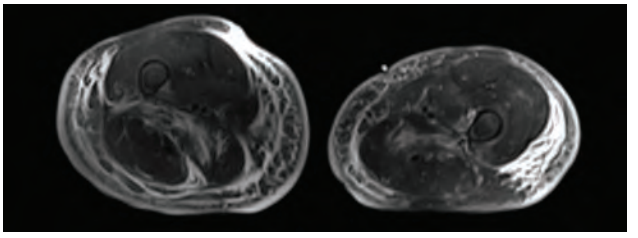
Introduction: Estimated glomerular filtration rate (eGFR) based on serum creatinine (SCr) is the most common way of measuring kidney function. Creatinine is a product of muscle breakdown that is filtered through the kidneys and is at a steady-state in people with normal kidney function.

Case Description: 31-year-old African American female with a history of systemic lupus erythematosus, polymyositis, chronic respiratory failure presented with sepsis & respiratory failure. Physical exam: weight 63 kg, height 62 inches. 3 days after admission she deteriorated with worsening septic shock, requiring multiple pressors. She became anuric secondary to acute kidney injury from septic shock, however, labs revealed a serum creatinine of 0.4 mg/dL and eGFR > 60 mL/min/1.73m^2. Prior to current admission, her SCr ranged from 0.06 to 0.08 mg/dL with an eGFR ≥ 60 mL/min/1.73m^2. Low baseline SCr is due to the patient's lack of muscle mass. Muscle biopsy was performed which showed "skeletal muscle was almost entirely replaced by fat and the few remaining fibers were mostly necrotic". Although the patient's SCr continued to rise compared to baseline, it was still well below or within normal limits with a peak of 0.54 mg/dL and eGFR remained ≥ 60 mL/min/1.73m^2 despite the patient being anuric and required renal replacement therapy for metabolic clearance and volume management

Discussion: As SCr is directly related to muscle mass and muscle breakdown, it is not surprising that our patient with little to no muscle mass maintained an unusually low SCr despite being in renal failure. SCr value of 0.06 mg/dL in a normal weight adult is one of the lowest reported values in the medical literature. eGFR based on SCr is the most common method of estimating kidney function it is important to recognize that the eGFR based on SCr may not be an accurate representation of the renal function, especially in persons with low muscle mass.



MRI lower extremity: Diffuse fatty replacement of all of the muscles of the bilateral thighs, with no loss of overall muscle bulk. This could be due to muscular dystrophy or end-stage myositis.

PUB228

Successful Treatment of the Pediatric Case with Anti-MDA5 Antibody-Positive Interstitial Lung Disease by Plasma Exchange Therapy

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Introduction: Anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are a type of myositis-specific autoantibodies. They are strongly related to rapid progressive lethal interstitial lung disease (ILD) with dermatomyositis. We experienced the 2 years old pediatric case with refractory anti-MDA5 antibody positive ILD and successfully treated with plasma exchange (PE).

Case Description: Two years old girl with normal development showed acute lower extremity weakness, dysphagia and face erythema three months before admission. She developed non-productive cough and fever. She visited nearby hospital one month before admission and was diagnosed as bilateral pneumonia with high KL-6 titer (2500 U/mL). Antibiotics had no effect and she admitted to another hospital. Additional examination revealed the high titer of anti-MDA5 antibody (1270 index) and normal creatinine kinase (48 IU/L) but high aldolase (10.1 IU/L). She also exhibited Heliotrope rash and Gottron's sign. She diagnosed as anti-MDA5 antibody positive juvenile dermatomyositis with ILD. Methylprednisolone pulse therapy (mPSL) and intravenous cyclophosphamide therapy were started but ILD was sustained. She transferred to our hospital for additional therapies. On the second hospital day, intravenous immunoglobulin was given and intravenous rituximab therapy was added on day 7 and 16. In spite of eradication of CD20-positive cells, her symptom was not improved. Therefore, we carried on PE with albumin-based replacement solution. After three courses of PE, the titer of anit-MDA5 antibody decreased to 83 index from 980 index on admission and her respiratory status was significantly improved.

Discussion: The mortality of anti-MDA5 antibody-positive ILD was reported as 20-30% regardless of intensive immunosuppressive therapy. Previous studies reported that anti-MDA5 antibody-positive ILD patients had high level of serum inflammatory cytokines and cytokine levels were related to the disease activity of ILD. Lowering them in addition to the titer of anti-MDA5 antibodies by PE may have a crucial therapeutic effect for anti-MDA5 antibody-positive ILD. Plasmapheresis therapy might be one of options to treat anti-MDA5 antibody positive patients with dermatomyositis complicated ILD.

PUB229

Use of Lisinopril in an Adolescent with "Extreme Dipper" Autonomic Hypertension Profile

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Introduction: The interaction between renin angiotensin aldosterone system and autonomic nervous system for blood pressure (BP) control is described. Angiotensin type-1 receptor activation in hypothalamus increases activity of paraventricular pre-sympathetic neurons as well as increases permeability of blood brain barrier to angiotensin. ADHD stimulant medication may be associated with cardiac autonomic dysfunction in children. Standard deviation (SD) of systolic BP (SBP) may be a better measure to study autonomic BP pattern particularly with nightime extreme dipper hypertensive profile.

Case Description: A 16-year-old non obese male presents with hypertensive urgency; BP of 168/102 mm Hg and symptoms of headache and vomiting. He was maintained on stimulant medication for ADHD that was stopped at initial presentation. The evaluation of secondary causes of hypertension was negative. He was started on Ca channel blocker. Four months after initial presentation, the 24-hour ambulatory BP monitoring (ABPM) study was done that showed hypertensive profile with extreme nighttime dipping. SD of SBP was high at 24.29 suggesting significant BP fluctuations (Figure-1). He was started on Lisinopril at the dose of 20 mg daily. ABPM study was repeated 3 months latter (Figure-2). There was marked improvement in daytime BP fluctuations (daytime SD of SBP-8.48) without worsening nightime BP dipping. Dizziness on changing posture was not reported.

Discussion: ACE inhibitors may be considered as an option for treatment of autonomic hypertension in adolescents with extreme nighttime dipping BP profile.

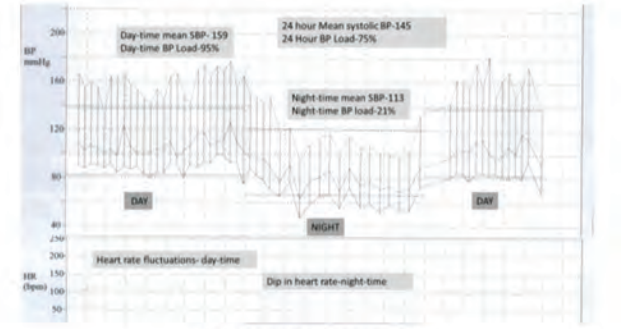

FIGURE 1 (without lisinopril)

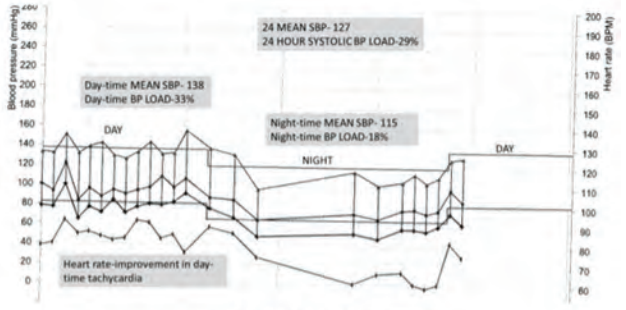

FIGURE 2 (with lisinopril)

PUB230

Influence of Biopsy Prognosis on Graft Survival

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Background: Renal transplantation is the best alternative renal replacement option for patients with advanced chronic kidney disease. However, the supply of young donors is limited, and does not cover the demand of patients on the renal transplant waiting list. For this reason, older donors are being used, and a high discard rate of those organs exists based on pathological results (*score*) of the preimplant renal biopsy. There are several methods to evaluate the quality of the kidneys and the Kidney Donor Profile Index (KDPI) has acquired special relevance to decide the performance of preimplant renal biopsy. Based on the score, a preimplant renal biopsy is performed, which is decisive in certain cases. However, there is poor evidence to support this decision, which can be described as "conservative," since there is not enough certainty that there is influence of the preimplant biopsy score influences graft survival.

Methods: 389 biopsies of kidney transplant donors of cadaver donors in brain death and asystole type III were included. Donors in asystole type II, combined and live, were excluded. Samples were examined by the same pathologist and in paraffin (no case by freezing). A graft survival analysis was performed based on the results of the renal biopsy (*score*). Likewise, a multivariate analysis of graft survival was carried out including, in addition to the results of the renal biopsy, results such as the age of the donor and recipient and the KDPI.

Results: Graft survival was compared between two transplant subpopulations in our hospital based on whether a preimplant biopsy was performed. According to the data used there are no significant differences in graft survival between transplants in which biopsy has been performed or not.

Conclusions: The preimplant biopsy score by itself and the evaluation of the different histological components in the biopsy have no infuence on graft survival. We believe that predictive indices that combine donor and recipient histological and clinical variables should be implented.

PUB231

De Novo Post Kidney Transplantation Thrombotic Microangiopathy

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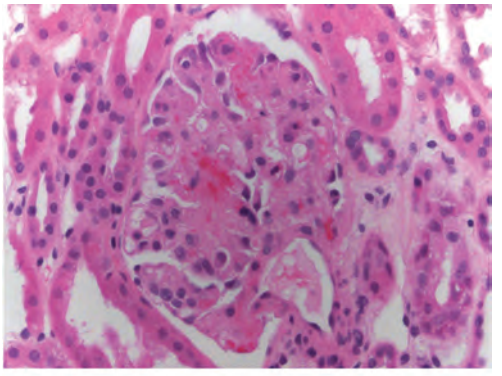
Introduction: De novo post kidney transplantation thrombotic microangiopathy (TMA) is rare. We present two cases of post kidney transplant TMA acquired from the donor kidney

Case Description: A 26 year old male with a significant past medical history of end-stage kidney disease secondary to hereditary focal segmental glomerulosclerosis (FSGS) requiring initially presented for deceased donor kidney transplantation. The kidney donation was from a brain death donor with no significant medical history. The preliminary kidney biopsy of the donor kidney revealed focal patchy acute tubular necrosis (ATN). Induction immunosuppression included a total dose of 5 mg/kg of thymoglobulin and followed by initiation of tacrolimus for goal trough of 8 - 10 mg, prednisone 40 mg, and mycophenolate 1000 mg twice daily. The patient had delayed graft function with a creatinine initially at 18 mg/dL which only reduced to 17 mg/dL over the next couple of days. On postoperative day 5, the patient was dialyzed due to symptomatic uremia. In addition, he was noted to have developed worsening anemia and thrombocytopenia with a platelet count dropping from 208 to 47 per microliter of blood. A renal biopsy was pursued and the pathology results revealed post-transplant thrombotic microangiopathy (TMA) due to hemolytic uremic syndrome. In addition, the final donor kidney biopsy had later revealed thrombotic microangiopathy within approximately 60% of the glomeruli. The patient who received the second kidney had a similar clinical course. Both recipients received one dose of eculizumab with improvement in allograft function. They were both discharged without hemodialysis with close follow up.

Discussion: TMA was acquired by the donor TMA which was likely caused by ATN. It wasn't until later in the course that the final biopsy report of the donor kidney revealed TMA which confused the diagnosis of allograft kidney injury.



thrombus and red blood cell fragments

PUB232

Hypercalcemia Secondary to Hyperthyroidism: A Unique Cause of Renal Failure in a Kidney Donor

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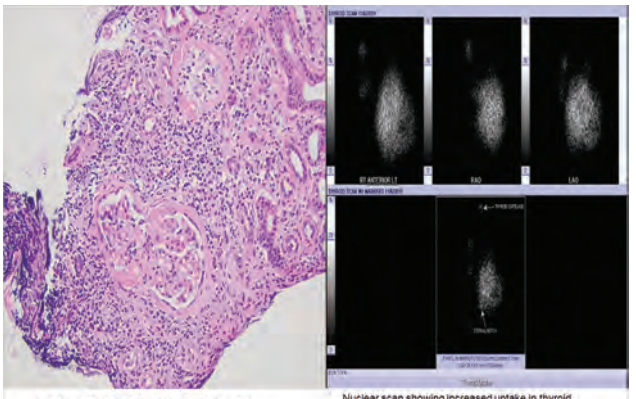
Introduction: Hyperthyroidism is associated with increased bone resorption resulting in hypercalcemia (HCa). Chronic HCa leads to defect in concentrating ability of kidneys by downregulation of aquaporin-2, calcium deposition in medulla, impairing osmotic gradient resulting in polyuria and persistent pre-renal state. HCa causes renal vasoconstriction leading to acute tubular injury (ATI) followed by atrophy and interstitial fibrosis (IFTA).

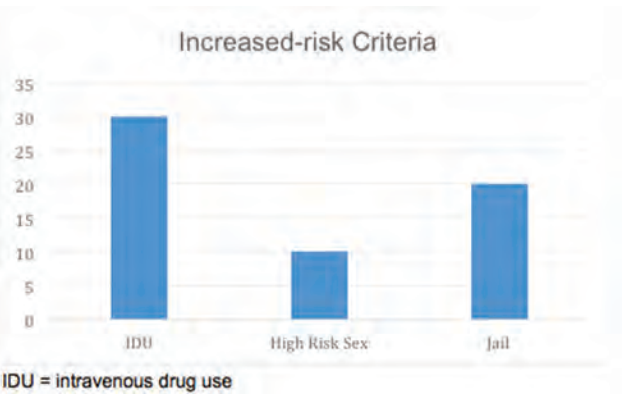
Case Description: We present a case of a 70 yr old female who donated a kidney 5 yrs ago with serum creatinine (Cr): 1.18mg/dL and Calcium (Ca): 10.2mg/dL at 2 yr f/u. At routine 3 yr f/u, Cr of 4.4mg/dL, BUN of 70 mg/dL, and Ca of 12.6mg/dl were noted. Kidney biopsy showed ATI, severe IFTA, negative for any immune deposits (Figure 1A). Work up of HCa revealed; PTH: 5 (18.5-88 pg/ml), 25(OH)VitD: 55 ng/ml, 1-25(OH) VitD: 70 ng/ml, angiotensin converting enzyme level: 42 (9-47U/L), serum/urine protein electrophoresis: negative, PTHrp: <2 pmol/L, Vit A: 76.6(22-69.5ug/dl) and detailed cancer work up was negative. CT scan revealed enlarged thyroid nodule (biopsy negative for cancer) and nuclear scan showed overactive thyroid nodule(Figure 1B). Thyroid studies [TSH: <0.005 (0.35-3.7 uIU/ml), FreeT4: 2.49 (0.76-1.46ng/dl)] were treated with radioactive iodine, methimazole and low dose steroids. After 9 months labs improved-TSH: 0.01 uIu/ml, FreeT4:0.93 ng/dL, Ca: 9 mg/dl and PTH: 42pg/ml. Unfortunately, Cr remained at 4.0mg/dL due to prolonged HCa leading to stage 5 CKD which eventually resulted in successful kidney transplant (KTx).

Discussion: To our knowledge we report the first case of irreversible renal failure in a kidney donor due to prolonged HCa from hyperthyroidism eventually requiring KTx. Progression of renal disease from prolonged HCa may be due to limited renal mass as a solitary kidney. Hence, prompt treatment and correction of hyperthyroidism and hypercalcemia may help in preventing progression of renal disease.



Interstitial Fibrosis, Tubular Atrophy, Glomerular sclerosis seen on Light Microscopy

Nuclear scan showing increased uptake in thyroid nodule



PUB233

Outcomes in Kidney Transplantation from Increased-Risk Donor Organs: A Single-Center Experience

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Background: Despite their lower Kidney Donor Profile Index (KDPI) score and demonstrated survival benefit of transplantation as compared with remain on dialysis, Public Health Service increased-risk donor (IRD) organs continue an underutilized source for transplantation.

Methods: This is a single-center retrospective cohort conducted at Boston Medical Center. Patients receiving IRD organs from 2016 and 2019 were evaluated. Baseline characteristics and outcomes one year after transplantation were described.

Results: We included 41 patients receiving IRD organs. Donors tended to be younger, with lower KDPI scores and good kidney function. Most common cause of death was anoxia from drug intoxication. Patients receiving IRD organs had stable kidney function at one year, with >70% having an estimated glomerular filtration rate (eGFR) of >60 mL/min (Table 1). None of the patients became positive for HBV, HCV or HIV.

Conclusions: Patients receiving IRD organs did not show a higher risk of infection or poor renal outcomes in this single-center population.

Table 1. Donor and recipient characteristics

Donor age (years)	33 (23-43)
KDPI (mean)	32 (sd 19)
Creatinine at death (mean)	0.99 (sd 0.44)
Donor gender	Male 73.1% Female 26.9%
Donor Race	White 80% Hispanic 15% African American 5%
Cause of death	Anoxia 82.9% Trauma 17.1%
Mechanism of death	Drug intoxication 59% Cardiovascular 20% Gunshot wound 10% Blunt injury 5% Asphyxia 4%
DCD criteria (%)	31
Use of pump (%)	26.8
Nucleic acid test (NAT)	HCV positive 7.3% HBV 0% HIV 0%
Recipient age (years)	50 (37-63)
Recipient race	African American 46% Hispanic 29% White 20% Unknown 5%
ESRD etiology	Hypertension 34.1% Glomerulopathy 21.9% Diabetes Mellitus 17% Other 17%
Induction therapy	Thymoglobulin 90.2%
Dialysis time (mean)	4.47 years (sd 2)
Cold ischemia (mean)	12 hrs (sd 4.95)
GFR >60 mL/min at one year (%)	70.7
Proteinuria at one year (mean)	0.27 (sd 0.41)

sd = standard deviation

DCD = donation after cardiac death

PUB234

Post-Transplant Lymphoproliferative Disorder (PTLD): A Single Institutional Experience

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Background: PTLD are a group of heterogeneous lymphoid proliferations in chronic immunosuppressed recipients of solid organ and hematopoietic stem cell transplantation. This study aimed to evaluate the clinical outcomes and to identify the predictors of mortality in adult renal transplant recipients who developed PTLD.

Methods: We have studied the incidence of PTLD in adult renal transplant recipients who were transplanted in our hospital from 1996 to 2019. Data was collected for demographics, transplant and immunosuppression history, EBV and CMV serostatus, diagnosis, treatment and outcomes. We performed uni and multivariate analysis to identify prognostic factors. PTLD was classified according to 2018 WHO lymphoma classification.

Results: Twenty-four patients (12 males and 12 females) were eligible for the analysis. Mean age at time of the transplant was 43.1 ± 16.9 years, with a time between grafting and PTLD of 66 months (IQR 36-98 months). Mean follow-up time was 87 months (IQR 61-117 months). 25% of patients received a living donor renal transplant. 5 cases were from Epstein-Barr virus (EBV) mismatched (D+/R-) transplants and there was seroconversion at time of PTLD diagnosis. 25% of patients have central nervous system involvement. 19 patients have monomorphic PTLD and the most common histological diagnosis was diffuse large B cell lymphoma. We identified that age >30 years at time of the transplant was predictor of mortality (HR 33.01; 95% CI: 3.24-336.14; p=0.003). Presence of B symptoms at time of PTLD diagnosis confer a better prognosis (HR 0,143; 95% CI: 0,035-0,579; p=0.006). All cases were managed with reduction in immunosuppression. 8 patients were treated with rituximab and there was no significant difference in the survival. 7 patients went into remission, 1 returned to chronic dialysis, and 16 patients died (15 of them due to the disease). Mean time between PTLD and death was 3 months (IQR 1-6 months).

Conclusions: PTLD is a infrequent disease with a poor prognosis. Some cases have a close relationship with EBV, but it can also develop in the absence of the classical risk factors. The factor affecting mortality in our population was age >30 years at time of the transplant. Presence of B symptoms at time of PTLD diagnosis seems to confer a better prognosis probably due to early investigation and diagnosis of the disease.

PUB235

Serum Phosphorus as a Predictor of Optimal Kidney Function in Immediate Kidney Transplantation

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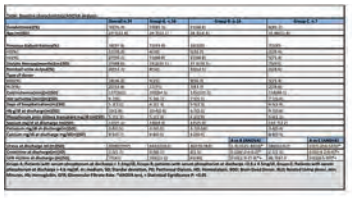
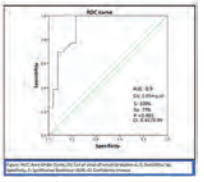
Background: In patients with CKD, there are alterations in serum phosphorus by widely known mechanisms, including in kidney transplant patients. The objective is to demonstrate that patients who decrease serum phosphorus in immediate kidney transplantation during hospitalization predict a GFR> 60 ml / min at discharge.

Methods: Prospective longitudinal study, 39 patients transplanted were analyzed, they were followed up daily until their discharge, they were divided into three groups according to their serum phosphorus**(p)** levels after transplantation; (Group **A**: p=<2.5, **B**: p=2.6 to 4.5, **C**: p=>4.6 mg/dl), the data were obtained on the days of hospitalization after his kidney transplant, obtaining this variables gender, age, type of donor, cold ischemia, days of hospitalization, uresis, creatinine and GFR dayle until discharge, data are shown in numbers, percentages, mean, ANOVA test and ROC curve.

Results: A total of 39 patients, 30(76.9%) patients were male, a mean age(29.5), 38(97.4%) had a history of dialysis, 21(53.8%) they were transplanted by a living donor, cold ischemia an average of 127min, days in hospital an avarage of 5.3, serum phosphorum prior kidney trasplant an average 5.7(2.3)mg/dl, in the ANOVA analysis a mean serum creatinine (Group A=0.9, B=2, C=2.1 mg/dl), a mean GFR (Group A=101, B=65, C=48.7 ml/min), a mean uresis (Group A=4423, B=3027, C=1865 ml/day) at discharge were compared; A vs B uresis P=0.3 IC=-1121/3913, creatinine at discharge P=0.1 IC=-2.6/0.2, GFR discharge P=0.03 IC=1.9/71, A vs C; uresis P=0.07 IC=-256/5372, creatinine at discharge P=0.01 IC=-4.2/0.4, GFR at discharge P=0.01 IC=8.5/97), AUC of 0.9, with a cutoff value of 3.05mg/dl have a TFG >60ml/min P=<0.001.

Conclusions: Patients who decrease serum phosphorus to normal or inclusive ranges of hypophosphatemia after immediate kidney transplantation, have better renal function than those who have hyperphosphatemia at discharge, serum phosphorus may be a predictor of optimal GFR in this patients.





Baseline characteristic, ANOVA test, ROC curve.

PUB236

Routine Monitoring of Donor-Specific Antibodies During the First Year of Kidney Transplant: Is It Underrated?

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Background: Kidney transplant (KT) recipients with *de novo* donor-specific antibodies (DSA) are at risk of graft loss. DSA could lead to a decline in kidney function due to antibody-mediated rejection (ABMR), or be asymptomatic. Efficacy and cost-effectiveness of routine DSA monitoring are not known. Confirmation of ABMR with kidney biopsy is advised. We aim to study the utility of routine DSA monitoring (RDM) in predicting rejection in asymptomatic pediatric KT recipients.

Methods: After IRB approval, a retrospective chart review of patients who had RDM was done. Patients with clinical suspicion of rejection were excluded from the study. Demographic data and clinical features were analyzed using descriptive statistics. Continuous and categorical variables were analyzed using the student's t-test and Fisher's exact test respectively. A p-value <0.05 was considered statistically significant.

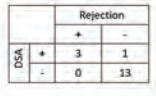
Results: Four out of 17 (24%) patients were tested positive for *de novo* DSA. There were no significant differences in age, gender, race, type of transplant, or serum creatinine between patients with positive and negative DSA. Three out of four (75%) patients had positive DSA at 4-6 months that persisted till the end of the year (1 had ABMR, 1 had T cell-mediated rejection and 1 had no rejection on biopsy), and one(25%) had positive DSA at 10-12 months with ABMR on biopsy. All patients with biopsy-proven rejection (BPR) received steroids, anti-thymocyte globulin, plasmapheresis, intravenous immunoglobulin, and/ or rituximab based on the type of rejection.

Conclusions: In our small cohort, we found that for every 5.7 asymptomatic patients who underwent routine DSA testing, one had *de novo* DSA with BPR. Larger, controlled studies are required to further evaluate the efficacy of RDM.

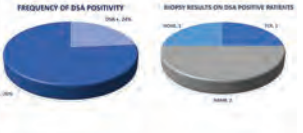
de novo DSA post transplant

Factor		DSA +	DSA -	p-value
N (%)		4 (24%)	13 (76%)	NS
Female		1 (25%)	9 (69%)	0.237
Race	Asian	0 (0%)	0 (0%)	1
	African American	2 (50%)	5 (39%)	
	Hispanic	1 (25%)	2 (15%)	
	Caucasian	1 (25%)	6 (46%)	
Type of Transplant	DDKT	4 (100%)	10 (77%)	1
	LRKT	0	2 (15%)	
	LUKT	0	1 (8%)	
Age, mean (SD)	at transplant	10.2 (6)	11.5 (4.5)	0.358
Serum Creatinine (mg/dL), median (IQR)		1.05 (0.62-1.34)	0.9 (0.56-0.94)	0.36
DSA + timing	At Transplant	0	n/a	n/a
	1-3 months	0	n/a	
	3-6 months	3 (75%)	n/a	
	7-9 months	1 (75%)	n/a	
	10-12 months	4 (100%)	n/a	
Biopsy results	ABMR	2 (50%)	n/a	n/a
	TCMR	1 (25%)	n/a	
	No rejection	1 (25%)	n/a	

DSA: Donor Specific Antibodies, DDKT: Deceased Donor Kidney Transplant, LRKT: Live Related Kidney Transplant, LUKT: Live Unrelated Kidney Transplant, ABMR: Antibody mediated rejection, TCMR: T cell mediated rejection



		Rejection	
		+	-
DSA	+	3	1
	-	0	13



PUB237

De Novo Thrombotic Microangiopathy Associated with Cytomegalovirus Infection and Alloreactivity: A Fork in the Road of Immunomodulation

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Introduction: De novo thrombotic microangiopathy (TMA) may yield cross-roads of diverging therapeutic approaches, not well delineated. We describe such a case in the setting of Cytomegalovirus (CMV) viremia and suspected rejection.

Case Description: A 52-year-old female with presumed hypertensive nephropathy received a deceased donor kidney transplant (KDPI 73%) complicated by progressive allograft dysfunction after 6 months. Anti-thymocyte globulin was used for induction, with tacrolimus (FK506), mycophenolate and prednisone for maintenance of immunosuppression. With step-wise rise in serum creatinine (baseline 1.7 mg/dL) to 2.5,3-4 and 5-7 mg/dL at 6, 8 and 9 months post-transplant respectively, three allograft biopsies were obtained. Secondary focal segmental glomerulosclerosis, moderate- severe interstitial fibrosis and tubular atrophy, and a mild tubulitis were seen in all biopsies;mild glomerulitis and peritubular capillaritis in the last two, and TMA in the last biopsy. C4d and HLA DSA were consistently negative. Despite methylprednisone given at month 8, creatinine continued to rise to 7 mg/dL by month 9. The course was complicated by leukopenia, brief thrombocytopenia (platelet count ~ 100 K/mm), progressive anemia (Hemoglobin 11.5 to 6.8 g/dl) and diarrhea in the setting of newly diagnosed CMV viremia (CMV DNA 1164 to 9177 IU/mL at months 8 and 9 respectively). Lactate dehydrogenase increased to 841 U/L with a normal haptoglobin and no reticulocytosis. Schistocytes were seen on a peripheral blood smear. ADAMTS-13, complement factors H, I, B, C3, C4, and stool pathogen panel were unremarkable. FK506 was switched to Cyclosporin (CYC) after diagnosing TMA. After clearance of CMV viremia and stopping valganciclovir, neutropenia resolved. Creatinine fell from 7 to averagely 5.8 mg/dL at month 10-11. Plasmapheresis (PP) and IVIG were initiated for suspected non-HLA antibody mediated rejection (AMR) with TMA.

Discussion: The constellation of TMA, CMV viremia, tubulitis, microvascular inflammation and myelosuppression, poses dilemmas in balancing management as FK506, CMV and AMR may all be contributory, in isolation or combination to TMA. We elected to maintain a calcineurin inhibitor and mycophenolate regimen in the face of TMA and CMV due to the risk of florid rejection, and initiated PP with IVIG.

PUB238

Hypofibrinogenemia as a Risk Factor of Bleeding After Plasmapheresis with Centrifuge in Renal Transplantations with Active Humoral Rejection

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Background: Humoral rejection represents an important cause of graft loss, multiple therapeutics have been implemented;therapeutic plasma exchange(TPE)is part of them, however one of its main complications as hypofibrinogenemia due to the risk of bleeding, which represents a challenge due to the risk of immunization in the event of a transfusion and even limiting the continuity of treatment due to the risk of bleeding imminent due to consecutive low figures during the passage of the sessions. Objective:to determine if hypofibrinogenemia(<100 mg/dl)after sessions of TPE with centrifuge is an absolute risk factor for bleeding that warrants the need for transfusion or cessation of therapy

Methods: In the period from June2017-May2019, 25 Mexican kidney transplant patients with diagnosis of active humoral rejection, without previous coagulation abnormalities, were submitted to TPE;a total of 5 sessions per patient were granted in an average of 10±2 days, with measurement of fibrinogen levels before and after each session;as well as daily clinical evaluation of active bleeding

Results: The age range was 21-35 years, 44% were female, the causes of ERCT up to 52% were not reported, cadaveric donor transplantation predominated in 52%.The initial average fibrinogen value was 397mg/dl, after the 1°session a reduction of 33% was observed, with an average value of 133mg/dl. The lowest level was 43mg/dl, the most important reduction after the 4°session. Only 1 major bleeding event was documented due to epistaxis that required transfusion. This event was after the 3°session, with fibrinogen of 79mg/dl. At the end of TPE treatment, fibrinogen levels normalized in all patients, with no further bleeding events

Conclusions: Despite the strong association of hypofibrinogenemia and bleeding, only one major bleeding event was reported in our population. There were no other events despite having level as low as<50mg/dl, therefore we consider close surveillance as the main measure during TPE;leaving the transfusion only in the context of active bleeding. The blood tissue is rich in immunoglobulins and therefore favors the host's immune response;It is paradoxical to remove antibodies and grant new ones with transfusions. Hypofibrinogenemia did not limit the continuity of treatment, concluding its treatment in a timely manner

PUB239

Kidney Transplant Recipients Suffer Fewer Complications After Adrenal Surgery

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Background: Chronic immunosuppression after kidney transplant (KT) is a known risk factor for developing a malignancy. While occurrences of other cancers have been well documented, there is a paucity of data regarding the incidence and effects of adrenal tumors after renal transplant. We aim to evaluate the differences in short-term outcomes between renal allograft recipients and the general population undergoing adrenal surgery.

Methods: A retrospective analysis was conducted using Nationwide Inpatient Sample (NIS) data between 2005 and 2014. The population of interest was adults with a kidney transplant undergoing adrenal surgery. ICD-9 codes were used to identify the procedures. Sample mean with standard deviations, and Student's t tests were calculated for categorical variables. Odds ratios were computed using weighted data. Multivariate linear regressions were utilized to compare outcomes at transplant and non-transplant centers.

Results: 54 patients met the inclusion criteria. KT recipients were older (p<0.001), more likely to be African American p<0.001), and had higher Elixhauser Comorbidity Index scores (p<0.001). We noted shorter length of stay (p=0.011), lower rates of any complications (p=0.001), and fewer packed RBC transfusion (p=0.039) compared to the non-transplant cohort. There was no mortality among transplant recipients. Weighted multivariate analyses highlight that total expenditures were lower for renal allograft recipients treated at transplant centers (p=0.021).

Conclusions: Previous publications have demonstrated that history of kidney transplant has deleterious effects on surgical outcomes. In the largest national cohort analysis of adrenal surgery after KT, we discovered that despite higher age and more comorbidities, renal transplant recipients benefitted from fewer post-operative adverse events. There was additional benefit from seeking treatment at transplant centers.

PUB240

Granulomatous Tubulointerstitial Nephritis in a Kidney Transplant Recipient

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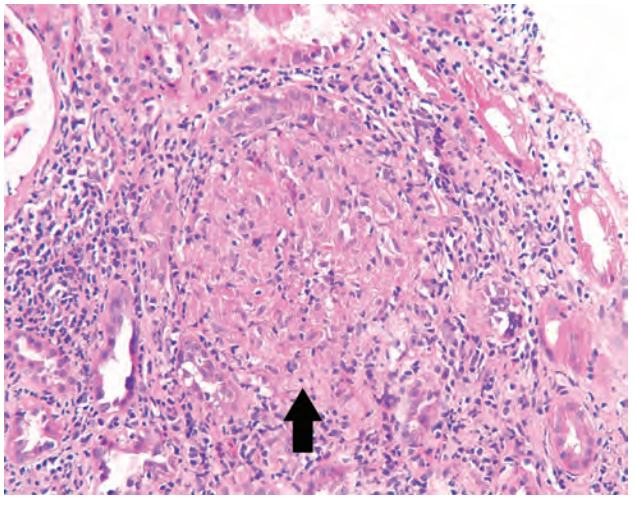
Introduction: Granulomatous tubulointerstitial nephritis (GTIN) is a rare pathological diagnosis accounting for 6% of all causes of tubulointerstitial nephritis (TIN). Causes of GTIN include fungal and tuberculous infections, sarcoidosis, and medications. We describe a case of GTIN in a kidney transplant recipient (KTR).

Case Description: A 65-year-old male with a history of diabetes mellitus, hypertension, active pulmonary and ocular tuberculosis (TB), and a deceased donor kidney transplant 8 years prior was admitted for acute kidney injury (AKI). Medications included isoniazid, rifampin, carvedilol, insulin, and tacrolimus. Serum labs showed: creatinine (Cr) 2.65 mg/dL (baseline Cr 1.3 mg/dL), corrected calcium 13.2 mg/dL, and tacrolimus trough level 7.6 ng/mL. Urine sediment examination and kidney ultrasound were unremarkable. Further workup for hypercalcemia revealed: parathormone (PTH) 7 pg/mL, 1-25 dihydroxy-vitamin D 54.3 pg/mL, PTH related peptide <2 pg/mL, and angiotensin-converting enzyme 47 U/L. Kidney biopsy showed TIN and non-caseating granulomas (figure A) with negative acid-fast bacilli (AFB) staining, bacterial, and fungal polymerase chain reaction. He was treated with prednisone taper over 6 weeks with complete resolution of AKI and hypercalcemia.

Discussion: GTIN in KTRs is rare, with an incidence of <1% in transplanted kidney biopsies. AKI and PTH-independent hypercalcemia with a negative workup for other causes of AKI should prompt a kidney biopsy. Granulomas with multinucleated giant cells can help differentiate GTIN from acute rejection – the most common cause of TIN in KTRs. Despite negative AFB staining of the biopsy tissue sample, it was impossible to exclude tuberculous GTIN in our patient who was on anti-tuberculous therapy. Cautious initiation of steroid therapy can be effective in these cases.



H&E stain showing a non-necrotizing granuloma (arrow) with tubulointerstitial inflammation.

PUB241

Kidney Transplants from Deceased Donor After 11 Days of Hemodialysis

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Introduction: There is little consensus on the use of organs from donors with acute kidney injury (AKI) for kidney transplant. Previously, the longest reported duration of dialysis before donation was 4 days. We detail the first successful kidney transplants from a donor after 11 days of hemodialysis.

Case Description: Donor was a healthy 41-year-old male with severe injuries from a car accident. He suffered severe AKI from rhabdomyolysis requiring 11 days of hemodialysis. Peak and terminal creatinine (Cr) were 4.55 and 3.23, creatine kinase was 10,582 U/L, and KDPI was 37%. Biopsy showed no vessel or interstitial injury, or global glomerulosclerosis. No casts were seen on urinalysis. Recipient 1 was a 60-year-old Asian male with ESRD from IgA nephropathy, on dialysis for 2 years with EPTS of 41%. Cold ischemia time (CIT) and pump time were 32 and 10.3 hours. Post-operative DGF required two dialysis sessions. Recipient 2 was a 61-year-old white male with ESRD from diabetes, on dialysis for 6 years with an EPTS of 90%. CIT and pump time were 26 and 17.5 hours. Profuse bleeding from graft biopsy site and pseudoaneurysm formation required treatment with transfusions, and dialysis for DGF. He was readmitted with hydronephrosis and carbapenem resistant enterobacteriae sepsis, requiring nephrostomy tube and antibiotics.

Discussion: Careful selection based on donor youth, good health without comorbidities, and injury by rhabdomyolysis were crucial in this case. Moreover, biopsies revealed excellent histology, with good flow and resistance on perfusion pump. These factors made the kidneys acceptable for transplant despite DCD donor with prolonged dialysis and CIT. Both patients received Tacrolimus, Mycophenolate and Prednisone. On follow up, recipients were dialysis independent and making urine. Complications in recipient 2 required prolonged hospitalizations, but none of the adverse events were due to donor AKI. Take Aways This case report is a novel opportunity to understand the extent of kidney transplantation after AKI. Despite 11 days of hemodialysis and DCD donor, procurement was possible because AKI due to rhabdomyolysis is transient and resolves within weeks. AKI donor-recipient matching is an individualized process. Clinician decision-making with rigorous donor and recipient selection is paramount in transplanting AKI organs. Post-operative DGF management is crucial in restoring graft function.

PUB242

Acute Rejection of Renal Allograft Caused by Drug-Induced Acute Interstitial Nephritis

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Introduction: We report a case of a 42-year-old man who had a living-unrelated kidney transplant in 2017 due to ESRD from post-infectious glomerulonephritis. He had an uncomplicated course with no episodes of rejection. He has been on a triple immunosuppressive regimen. Other past medical history was refractory autoimmune hemolytic anemia at age 20 that required splenectomy.

Case Description: In 2019, he developed fever and rash shortly after taking a 5 days course of azithromycin. This was associated with marked eosinophilia and an increase in his serum creatinine (sCr) from 1.0 mg/dl to 3.1 mg/dl. Donor Specific Antibody (DSA) was negative. Kidney biopsy showed active tubule interstitial nephritis with prominent eosinophils. He received pulse steroids followed by tapering oral steroids. His sCr improved to 2.7 mg/dl. A month later, he was admitted for hematuria and acute kidney injury. His sCr was 4.2 mg/dl. Urinalysis showed trace protein, RBC >50/HPF, and WBC 11-20/HPF. Tacrolimus level was within the therapeutic range. DSA was positive for class II; DQA1*05:01, DR17, DR52 with 18,000 MFI. Kidney biopsy showed mixed rejection; acute cellular rejection (ACR) Banff 1B and acute antibody-mediated rejection (ABMR)/ C4d positive. He was treated with high dose IV steroid, thymoglobulin, plasma exchange, and Rituximab. His sCr did not improve. Repeat biopsy showed improvement of ACR Banff 1A along with capillaritis and glomerulitis, suggesting ongoing ABMR but C4d staining became negative. On the last biopsy, there was diffuse interstitial fibrosis.

Discussion: We hypothesize that Acute Interstitial Nephritis (AIN) primed the T-cell lymphocytes to react against the allograft. His sCr improved after treatment of AIN but subsequently worsened reflecting mixed rejection. The treatment of rejection led to some improvement but did not resolve the ongoing damage that ultimately caused significant fibrosis with poor chances for recovery. To our knowledge, this is the first case where AIN is followed shortly by a mixed allograft rejection even in a patient with a previous splenectomy. In the past, splenectomy was the treatment for refractory ABMR. In conclusion, rejection should be considered as one of the differential diagnoses when renal function worsens after the treatment of AIN.

PUB243

Kaposi Sarcoma: A 30-year Experience of a Portuguese Kidney-Transplant Center

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Background: Kaposi sarcoma (KS) is a low-grade angioproliferative tumor associated with human herpesvirus 8 (HHV-8) infection, which incidence is higher in kidney-transplant recipients (KTR). This study aimed to review all cases of KS diagnosed in KTR, over the past 30 years, at our center. A total of 1476 transplants were performed during this period.

Methods: We reviewed all histologically diagnosed KS in KTR. Data were collected from electronic and paper medical records.

Results: Seven KTR were diagnosed with KS, of which 6 were men and 1 was HIV positive, all caucasian. The mean age at the time of KT was 51± 18y. Six cases occurred before 2010 and the last case in 2018, in an HIV positive patient and the only one to receive induction immunosuppression - IS (basiliximab). All but 1 patient were on maintenance IS with prednisolone (PDN), a calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF). The median time of transplant at KS diagnosis was 9 (2 – 99) months. Six patients had only cutaneous lesions, mainly in lower limbs and one had also abdominal lymph nodes involvement. HHV-8 viremia, evaluated in 2 patients, was positive. In 6 patients the CNI and MMF were replaced by an mTOR inhibitor. The other one was maintained with PDN and reduced dosage of CNI. All except one received antineoplastic

treatment: 3 were submitted to radiotherapy (RT), 1 to chemotherapy (CT) and 2 had both RT and CT. Pegylated liposomal doxorubicin was the drug of choice. At follow-up, 1 patient remains with normal kidney function, 1 with chronic graft dysfunction and 2 lost their KT (one by antibody-mediated rejection 3 months after KS diagnosis, and one by chronic graft dysfunction after 19y of KT, 14y after KS). Three patients have already died (with graft function), one directly to the KS.

Conclusions: Despite the scarcity of published series on KTR, the experience of KS in our center is in line with the literature, since it's more common in man, the incidence is higher in the first 2 years after transplant and cutaneous lesions were the main manifestation. In our series, a lower incidence of KS in the last decade has been reported. However, thorough surveillance in higher-risk groups, as HIV patients, should not be forgotten.

PUB244

Rapid Renal Allograft Failure Following Recurrence of Lupus Nephritis 12 Years After Renal Transplant

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Introduction: End stage kidney disease (ESRD) secondary to lupus nephritis (LN) is an important complication of systemic lupus erythematosus (SLE) for which the treatment of choice is to undergo a kidney transplant (KT). Following a KT, patients rarely develop recurrent lupus nephritis (RLN), but when they do, most events of recurrence occur within a few years after KT. We describe the case of a young Caucasian lady who underwent a living related KT for LN and maintained stable renal function for 12 years, and then developed severe RLN that was unresponsive to treatment.

Case Description: A 39-year-old developed ESRD from LN and her kidney biopsy (KB) demonstrated global sclerosis with immune complex glomerulonephritis with positive serum antinuclear (ANA) and anticardiolipin antibodies (ACA) in 2006. She received living related KT in 2/2007. Her post-transplant course was complicated with the development of Banff grade IIA acute cellular rejection 1-month later, which was treated with steroids. She responded to treatment and attained a baseline creatinine (Cr) measuring 1.2 to 1.3 mg/dL. She was maintained on tacrolimus, mycophenolate mofetil (MMF) and prednisone. Her MMF was replaced with azathioprine during an uneventful pregnancy in 2011. She had a slight increase in her baseline Cr over the years but maintained a stable Cr measuring 1.4- 1.6 mg/dl. In 7/2019, the Cr suddenly increased to 3.9 mg/dl with proteinuria and microscopic hematuria. Her platelet counts, complement, ANA, ANCA and double stranded DNA levels were normal. A KB demonstrated features of thrombotic microangiopathy, diffuse proliferative GN with focally crescentic LN and full house pattern on IF. Despite treatment with intravenous steroids and cyclophosphamide her renal allograft function deteriorated, she required dialysis by 11/2019.

Discussion: Even patients with stable renal function maintained on standard immunosuppressive medications many years after transplantation are at risk of RLN. Our case demonstrates that RLN can manifest suddenly, and with a lack of usual laboratory features characteristic of a lupus flare. Further studies are necessary to better identify reasons for lupus recurrence in patients with long standing stable renal function.

PUB245

Simultaneous Disseminated Adenovirus Infection and Rejection in a Kidney Transplant Patient

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Introduction: Adenovirus can lead to serious conditions in the immunocompromised transplant recipients. It infects urothelium and causes acute hemorrhagic cystitis and either nephritis or acute rejection causing functional deterioration of transplanted kidney.

Case Description: A 55-year-old male with history of ESRD on hemodialysis received a deceased donor renal transplant. After induction with steroids and Thymoglobulin, he was maintained on mycophenolate mofetil (MMF), tacrolimus and prednisone with stable creatinine of 1.1-1.3 mg/dL. After 6 months, he presented with right lower quadrant abdominal pain, hematuria, dysuria, productive cough, fever, conjunctivitis, sore throat and diarrhea. Labs showed mild elevation of creatinine (1.5 mg/dL). Urine microscopy showed non-deformed RBCs without glomerular casts. Chest x-ray and ultrasound of transplant kidney were normal. Patient was started on intravenous fluids and azithromycin for URTI along with home immunosuppressive regimen. Respiratory pathogen panel (RPP) was negative for any pathogen. Urine culture had no growth. Cystoscopy was unremarkable. Patient had worsening leukopenia and proteinuria of 3.3 grams. A repeat RPP was positive for adenovirus and serum Adenovirus PCR was 28,600 copies/ml. Biopsy of transplant kidney showed mild tubulo-interstitial rejection with transplant glomerulitis and negative for adenovirus nephritis. Due to simultaneous occurrence of infection and acute transplant rejection, MMF was reduced to 250mg BID and pulse steroids were started for 5 days. Serum adenovirus PCR was decreased to 1200 copies/ml in 7 days. On day 21, patient had increase in Adenovirus PCR to 1900 copies/ml. Decreasing immunosuppression was avoided given recent rejection episode. Patient's IgG level was low at 549 mg/dL and a dose of 300 mg/kg IVIG was administered. Repeat urinalysis showed resolution of hematuria and proteinuria. Serum Adenovirus PCR was undetectable at 2, 3 and 4 months follow up.

Discussion: Disseminated adenovirus infection after renal transplantation is becoming more prevalent. The treatment includes reducing the immunosuppressive therapy, IVIG infusions, anti-viral agents, or combination of these therapies. The approach to therapy is unclear due to no standard guidelines for selection, timing and efficacy of treatment modalities, which requires further investigation.

PUB246

A Case Report of Transplant Renal Artery Stenosis Presenting as Acute Encephalopathy and Cardiac Arrhythmia in a 28-Year-Old Man

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Introduction: Transplant renal artery stenosis (TRAS), defined as narrowing of the transplanted renal artery, is one of the most serious vascular complications post kidney transplantation. TRAS presents as hypertension and allograft dysfunction at 3 to 12 months after transplantation. Unique to this case is the early presentation with behavior changes and cardiac arrhythmia. No report of such has been published as of this writing, especially in a third world setting.

Case Description: This is a case of a 28-year-old filipino male patient with post kidney transplantation one month prior to admission. Donor and recipient matching revealed low immunologic risk for rejection with four HLA matched. Transplantation was unremarkable. He presented at the ER with behavioral changes, incoherence and SVT on ECG. Medical cardioversion with adenosine and verapamil was done. He was immediately dialyzed and noted resolution of symptoms. Course in the ward was unremarkable except for the persistence of hypertension and elevated creatinine. Doppler ultrasound is suggestive of TRAS on main renal artery allograft. Renal CT angiography confirmed 50 to 60% stenosis of right renal artery graft. He was given amlodipine 10mg/day and eventually underwent renal angioplasty as the definitive procedure to correct stenosis. Post angioplasty blood pressure was normal and remained on this level for the following days. Serum Creatinine lowered down to 110 umol/L. Repeat Doppler ultrasound showed an angioplasty stent in the proximal main renal artery of the graft. On his follow-up check up, his serum creatinine and BP rmained on normal levels.

Discussion: The case proves that although TRAS usually presents at 3 to 12 month post kidney transplant, it may occur earlier and unusually with encephalopathy and arrhythmia. Doppler ultrasound is essential in early detection, however, Renal CT angiogram is the imaging of choice for the confirmatory diagnosis. TRAS is catastrophic but early diagnosis and prompt medical-surgical intervention with amlodipine and renal angioplasty can lead to improved allograft survival and good prognosis for the patient.

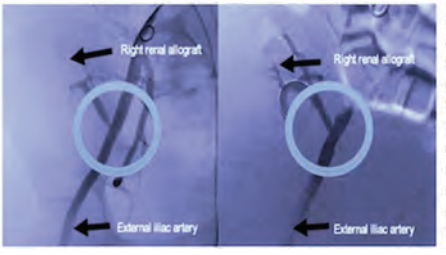

Figure 3. Renal CT angiography showing stenosis of right main renal artery graft at end to side anastomosis *(left-blue circle)*. Renal angioplasty with stent mounted across the stenotic site showing successful dilatation *(right-blue circle)*.

PUB247

Management of Kidney Transplant Waiting List in Belarus

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Background: The reasons for establishing an automated waiting list system were as follow: the main clinical information about patients was available only on paper, there was a problem of optimal choice from the list of compatible donor-recipient pairs based on a large number of factors, there were difficulties with information transfer rate, security and reliability.

Methods: The project was implemented as a web-application. The program's interface includes several parts: Unit "file-cabinet" that contains patients' passport data and contact information Unit "Clinical information" includes immunological and clinical data of recipients Units "Examination" and "Conclusion of the consilium" is based on examination results and determines the suitability waiting list Unit "Recipient selection" Unit "Calculator of graft function".

Results: Web application helps to allocate donor organs by medical and social principles of selection. The social principles are: priority of patients who waited kidney transplant longer considering of donor and recipient territorial compatibility increased chances for kidney transplant patients with "incomplete" phenotype (homozygotes) priority for highly sensitized patients priority for children priority for patients who needed multiple-organ transplantation Medical principles: balance between the potential kidney transplant and recipient survival stratified accounting of histocompatibility degree between donor and recipient reduction of kidney transplant cold preservation time creation of transplantation priority conditions for patients who needed urgent kidney transplantation initial kidney graft function prognosis accounting Scoring system is based on the fact that the main feature of social justice (maximum waiting period) is equated tomain medical principle of effectiveness (maximum compatibility degree). The allocation of organs accounts the risk of early graft dysfunction (automatic kidney graft functioncalculator based on multifactor analysis of donor - and recipient-dependent risk factors is integrated). The final result is a prioritized list of recipients with a score of each factor and to perform the final selection of the council of physicians.

Conclusions: The software application allows to keep records, make statistical data analysis of potential recipient, distribute the organs anytime, anywhere in the world where the Internet is available.

Funding: Commercial Support - EPAM systems

PUB248

Late-Onset Recurrent Granulomatous Interstitial Nephritis in Transplanted Kidney with Successful Treatment: A Case Report

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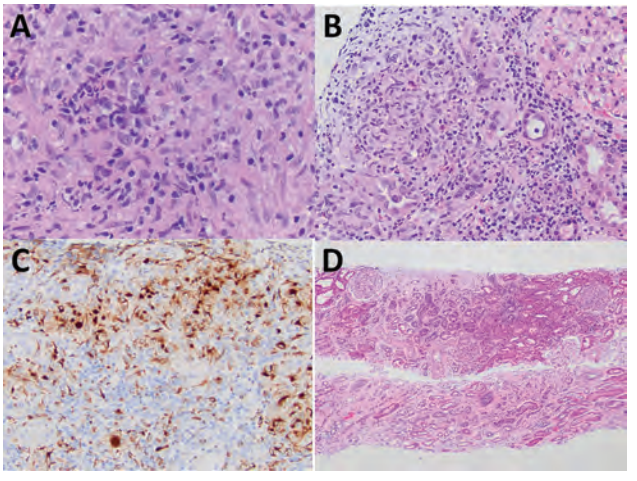
Introduction: End stage renal disease (ESRD) secondary renal sarcoidosis is rare and likely due to hypercalcemic nephropathy. There is limited data on recurrent renal sarcoidosis post kidney transplant. We report a case of unusually late onset, recurrent sarcoidosis in transplanted kidney with successful treatment.

Case Description: A 65 year-old female with history of pulmonary sarcoidosis and ESRD due to sarcoidosis related-granulomatous interstitial nephritis (GIN) received a renal transplant in 2008. She was maintained on tacrolimus, mycophenolate(MMF) and prednisone. Baseline serum creatinine (SCr) had been 1.5 mg/dL. In 2017, patient was diagnosed with recurrent metastatic colorectal cancer. In 2019, her SCr increased to 3 mg/dL. A transplant kidney biopsy showed non-necrotizing GIN. She was treated with prednisone 40 mg daily. SCr decreased to 2.3 mg/dL. 3 months later, a repeat transplant kidney biopsy showed resolution of GIN. Prednisone dosage was tapered.

Discussion: GIN related to sarcoidosis has an overall estimated occurrence at 0.18 % of native kidney biopsies. GIN in transplanted kidney due to recurrent sarcoidosis has been reported ~17%. Risk factors for recurrence include primary renal disease related to sarcoidosis and a shorter delay between the last sarcoidosis flare and renal transplantation. Recurrence typically occurred shortly after transplantation, averaging 13 months after transplantation. More studies on treatment of recurrent renal sarcoidosis are warranted. We report a case of late onset recurrent GIN, occurring 11 years after transplantation with successful treatment.



Native kidney biopsy showed prominent, non-necrotizing GIN (A). Transplant kidney biopsy showed non-necrotizing GIN, similar to that of the native kidney biopsy (B). Immunoperoxidase staining for CD68 highlighted the interstitial histiocytes (C). Repeat allograft kidney biopsy did not show previously identified non-necrotizing GIN (D)

PUB249

Elevated Donor-Derived Cell-Free DNA as an Indication for Kidney Transplant Biopsy

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Background: Donor derived cell-free DNA testing (dd cf-DNA) is increasingly employed for post-kidney transplant monitoring and may influence the decision to proceed with indication biopsy. The goal of this study was to identify those patients in whom the finding of an elevated dd cf-DNA was a key factor in the decision to obtain a kidney biopsy and to review 1) their biopsy findings and 2) any resulting treatment.

Methods: We reviewed the charts of 73 patients who underwent kidney transplant biopsy and had at least 1 dd cf-DNA (AlloSure) test performed. Ten patients underwent biopsy prompted primarily by an elevated dd cf-DNA level. Biopsy findings and resultant therapeutic interventions were abstracted.

Results: The median time from transplant to biopsy was 25.5 months. 2/10 patients had a normal biopsy. 5/10 had histological findings consistent with antibody mediated rejection (ABMR) with or without concurrent T-cell mediated rejection (TCMR). 2/10 had TCMR and 1/10 had recurrent glomerulonephritis. Of those with ABMR, 1/5 had a de novo HLA donor specific antibody (DSA) and 3/5 had positive non-HLA antibody (AT1 receptor antibody (AT1R)). 8/10 patients had a therapeutic intervention following biopsy. Dd cf-DNA decreased following treatment in 4/7 patients and did not change or worsened in 3/7 patients with available follow-up dd cf-DNA testing.

Conclusions: Kidney transplant biopsies in patients with an elevated dd cf-DNA frequently yield findings that warrant therapeutic intervention. Kidney transplant biopsy should be considered in patients with elevated dd cf-DNA, even if otherwise stable. Our observations warrant further examination on the uilitziation of long term dd cf-DNA monitoring, particularly in immunologically high risk kidney transplant recipients.

Funding: Commercial Support - CareDx

Patient	1	2	3	4	5	6	7	8	9	10
Sex	Female	Male	Female	Male	Male	Female	Female	Female	Female	Male
Time since transplant (months)	28	33	34	48	53	15	14	19	11	23
Dd cf-DNA (%)	1.3	0.7	1.2	3.0; 4.3	2.7	1.8	3.8	3.6	1.3	2.3
Time from dd cf-DNA to biopsy (days)	21	13	24	5	21	21	27	30	11	14
Creatinine (mg/dL)	0.93	1.14	1.32	1.12	1.35	1.02	0.97	1.14	1.79	1.87
Indication for biopsy	Missed immunosuppression	Missed immunosuppression	Transient creatinine increase	Monitoring	Transient creatinine increase	Monitoring	Monitoring	Monitoring	Monitoring	Transient creatinine increase
Biopsy findings	Borderline TCMR	TCMR (Banff IIA), ABMR	ABMR	ABMR	ABMR	Normal/mild calcineurin inhibitor toxicity	Borderline TCMR, ABMR	Normal	Borderline TCMR with peritubulitis capillaritis	Recurrent glomerulonephritis
Antibody screen	No antibody	De novo DSA	AT1R antibody	No antibody	AT1R antibody	No antibody	AT1R antibody	No antibody	No antibody	No antibody
Treatment	Steroid pulse	Steroids, ATG, rituximab	Increase in maintenance immunosuppression, ARB, eculizumab	Steroids, rituximab, IVIG, increase in maintenance immunosuppression	Steroids, ARB, increase in maintenance immunosuppression	None	Steroids, IVIG, rituximab, ARB	None	Steroid pulse	Rituximab
Follow up dd cf-DNA	↓	—	↓	↓	↓	↑	↑	↓	—	Non done
Follow up creatinine	—	↑	—	—	—	—	—	—	↓	↑

PUB250

Disseminated Nocardiosis in Renal Transplant Recipient

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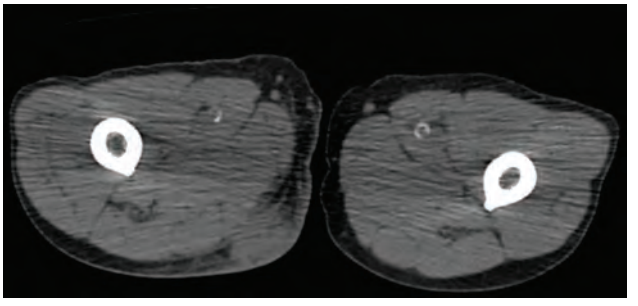
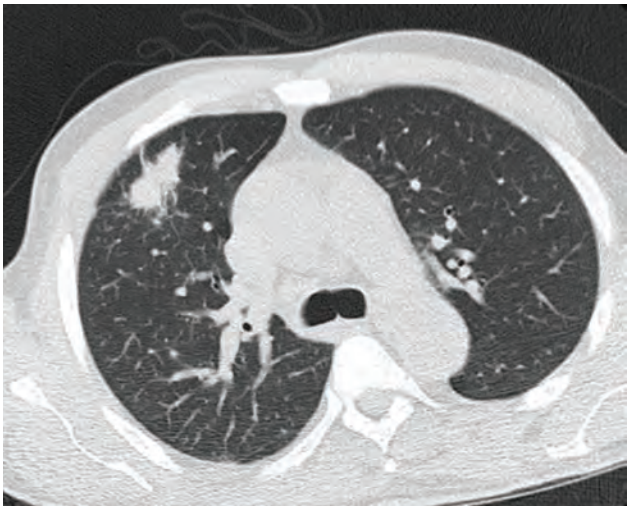
Introduction: Nocardiosis is an uncommon opportunistic Gram-positive bacterial infection caused by aerobic actinomycetes in the genus Nocardia. Nocardia can cause localized or systemic suppurative diseases involving eyes, kidneys, skin, lungs, bone, and Central nervous system. Disseminated Nocardia is a rare condition, seen among immunocompromised patients.

Case Description: We report the case of a 55-year-old African American kidney transplant recipient on maintenance immunosuppression, who was diagnosed with cutaneous and pulmonary Nocardiosis. Presenting symptoms were shortness of breath, bilateral lower extremities pain and swelling. Tissue culture grew gram-positive bacilli specified as Nocardia farcinica from thigh and gluteal abscesses (figure 1). CT thorax showed bilateral reticulonodular opacities (figure 2). Patient was managed with immunosuppression reduction and specific treatment with high dose Bactrim in conjunction with linezolid. Combination antibiotics were continued for four weeks, thereafter Bactrim alone was continued for twelve months, at which point all lesions had healed.

Discussion: Nocardiosis with systemic involvement carries a poor prognosis. The reported patient had disseminated Nocardiosis involving lungs and skin, though lungs were thought to be the primary source of infection. However, early diagnosis and appropriate antibiotic coverage, had a favorable outcome, in a renal transplant recipient. Recommended treatment duration is 6 to 12 months with frequent imaging.





PUB251

Native Kidney Cytomegalovirus Nephritis

Sandiya Bindroo, Paul D. Killen, Mona D. Doshi. *University of Michigan, Ann Arbor, MI.*

Introduction: Cytomegalovirus (CMV) is the most common opportunistic infection in solid organ transplant (SOT) recipients and is estimated to affect 15-30% of high-risk SOT recipients. Typical manifestations of CMV end-organ disease includes colitis, esophagitis, gastritis, and pneumonitis. However, native CMV nephritis is rare, reported in less than 1% of renal biopsies. We present a case of CMV nephritis in a high risk liver transplant recipient who completed six months of CMV prophylaxis four weeks prior to presentation.

Case Description: A 66-year old man with history of liver transplantation was hospitalized on post-transplant day 230 for worsening kidney function (serum creatinine 4.40 mg/dL, baseline 2.0 mg/dL) and fatigability. The patient's history was notable for cryptogenic cirrhosis and hepato-renal syndrome. Immunotherapy consisted of tacrolimus (target trough 6-10ng/mL), mycophenolate mofetil (MMF), and prednisone. The recipient was CMV seronegative and the donor was CMV seropositive. He received valganciclovir for CMV prophylaxis in first six months of transplantation, per protocol. The early post-transplant course was complicated by reactivation of muco-cutaneous herpes simplex virus-1, and *Clostridium difficile* colitis. On presentation, patient reported fatigue, loose stools, and nausea. He was afebrile and had a normal white blood cell count. Serum creatinine was 4.40 mg/dL (baseline 2.0 mg/dL). Urinalysis was positive for 3+ leucocyte esterase with a full field of leucocytes and 10-50 red blood cells per high power field. Urine culture grew > 10^5 cfu/mL of *Pseudomonas aeruginosa* species. A normal renal ultrasound was noted. He was treated with intravenous (IV) cefepime. To evaluate the cause of the persistent renal failure, a renal biopsy was performed, revealing acute tubular injury and focal severe interstitial nephritis. CMV intra-nuclear and cytoplasmic inclusions were visualized and confirmed by immunohistochemical staining. Plasma CMV DNA levels by quantitative PCR were 40862 IU/mL. Treatment consisted of IV ganciclovir at induction doses adjusted for renal clearance, followed by maintenance dose valganciclovir. His renal functions improved.

Discussion: We report a rare manifestation of CMV disease with evidence of CMV in native kidney. Clinicians should have a high suspicion for late onset CMV diseases as a diagnosis in at risk SOT recipients with signs and symptoms of genitourinary tract.

PUB252

Incidence and Risk Factors in Mexican Patients with Diarrhea After Kidney Transplantation

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Background: Diarrhea is one of the most frequent complications after kidney transplantation. Leads to dehydration, alteration of immunosuppressants serum levels, kidney function deterioration and graft loss. The prevalence of diarrhea varies from 20-50% globally. Focusing treatment on guidelines or recommendations, without considering local microbiology, may lead to mistakes in the management of this patients.

Methods: Cohort, analytical, retrospective study, were included kidney transplant patients from January 2014 to December 2018 in the Nephrology and Kidney Transplant Department at the Centro Medico Nacional 20 de Noviembre in Mexico City. Annual cumulative incidence calculation was performed. Binary logistic regression was used for the evaluation of risk factors. Survival analysis made by Kaplan-Meier curves.

Results: 92 patients were evaluated. Thirty two diarrhea episodes were recorded in 28 patients. 25% of the cases were in the first month after transplant, 40.6% of the episodes occurred in the 1-6 month period and 34.4% more than 6 months period. 71.9% of the cases were infectious etiology suspected, but only 45.8% had microbiological isolation. The most frequently isolated microorganism was Entamoeba histolytica in 45.5% of the cases. The cumulative incidence was 34%. There was no difference in graft survival in patients who developed diarrhea and those who did not ($p = 0.17$). Thymoglobulin induction increases up to 5 times the probability of developing post-transplant diarrhea (HR 5.98 p=0.01).

Conclusions: In our center, the cumulative incidence of diarrhea after transplantation is similar to reported in international series. The microbiology of diarrhea events, unlike that described in developed countries, is mainly associated with parasites. The impact of this complication on graft survival and accumulated survival is the same in patients who developed it versus in those who do not. Limited epidemiological data exist in our country and Latin America, for these reasons we must have better approach to research local epidemiological information and thereby improve therapeutics options for this patients.

PUB253

Unusual Presentation of Ramsay-Hunt Syndrome in a Kidney Transplant Recipient

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Introduction: Herpes-virus reactivation has long been recognized as occurring more frequently in immunocompromised individuals. There are only a few cases of Ramsay-Hunt Syndrome described after transplantation. We report a well-documented case of a kidney transplant recipient (KTR) with an atypical course due to multiple cranial nerve involvement.

Case Description: After treatment of esophageal candidiasis, a 50yo male KTR presented with persistent odynophagia, dysphagia, dysphonia, fever, hipoacusis, otalgia and vesicular lesions in the external left auditory canal, compatible with Herpes Zoster Oticus. He had underwent a deceased-donor kidney transplant ten years before, and maintained on mycophelonate mofetil (1.5 g/d), tacrolimus (2 mg/d) and prednisone (7.5 mg/d) immunosuppression. His past medical record included chickenpox in his childhood. A nasofibrolaringoscopy showed unilateral paralysis of the left vocal cord with saliva aspiration. Computed tomography scan of cranium, neck and thorax excluded expansive lesions. Blood polymerase chain reaction test detected Varicella-Zoster Virus (VZV). Only seven days later, he developed unilateral left facial and palatal paralysis. A cranium magnetic resonance image revealed linear enhancement of the left facial nerve. All these findings led to the diagnosis of Ramsay-Hunt Syndrome. Mycophenolate was withdrawn and the patient received intravenous acyclovir and prednisone 1mg/kg/day for 4 weeks. Due to severe dysphagia with significant weight loss, reaching 35 kg, he received enteral nutrition through a nasogastric feeding tube during 12 weeks. He gradually recovered motor function of the 7th and 10th cranial nerves. Six months after the onset of symptoms, the patient is under full immunosuppressive therapy and feeding through mouth with occasional choking to some solids.

Discussion: Reactivation of pre-existing VZV in craniospinal sensory ganglia causes Herpes Zoster, which is characterized by a painful erythematous rash in the affected dermatome. Ramsay-Hunt Syndrome occurs when VZV affects neurons of the geniculate ganglion. When it occurs unusually with multiple cranial neuropathies it leads to a potential missed diagnosis and delayed treatment.

PUB254

Tacrolimus: A Worth-Considering Culprit for Post-Transplant Anaemia Secondary to Parvovirus B19

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Introduction: Haematological side effects of tacrolimus seem to be rare and their aetiology is unclear. Parvovirus B19 is an uncommon yet clinically significant infection that manifests as refractory anaemia in post-transplant patient. The exact mechanism by which tacrolimus can aggravate pure red cell apasia (PRCA) is still unclear. Here we report a case of post-transplant anaemia where withdrawal of tacrolimus demonstrated significant improvement in chronic transfusion dependent anaemia.

Case Description: A 66-year-old male with end stage renal failure due to accelerated hypertension had a diseased donor transplantation in 2018. Before receiving his transplant, his peripheral blood counts were relatively normal. Patient was discharged nine days after operation with haemoglobin of 82 g/dl. Approximately five weeks following transplantation, the patient was found to have profound anaemia with haemoglobin level falling to 57 g/dl but white cell and platelet count remained normal. Following investigations, patient was found to have parvovirus B19 with positive DNA titre. Since then patient was transfusion dependent with two weekly red cell transfusion. Patient had two courses of IVIG, however, showed only transient improvement in viral DNA titre with no haematological improvement. Finally, tacrolimus was switched to cyclosporin A and showed rapid improvement within two weeks.

Discussion: Persistent parvovirus B19 infection can occur in immunocompromised host due to impairment of the neutralizing antibody response and/or cellular immunity thus failure to clear the virus. Tacrolimus, on the other hand, is believed to be an immunosuppressive agent without significant potential for myelosuppression. In this case, temporal relation of withdrawal of tacrolimus with improvement of anaemia suggests an etiological role of tacrolimus. The close inverse relationship between viral DNA PCR titre and erythropoietic activity reflected by the improvement of refractory anaemia showed that the direct cause of red cell aplasia was viral infection, rather than direct drug effect. Several authors postulated that parvovirus B19 infection in transplant patients is aggravated by the use of tacrolimus through impairment of its clearance by tacrolimus, which cannot be simply explained by a state of heightened immunosuppression.

PUB255

Use of Donor-Derived Cell-Free DNA to Identify Allograft at Risk by Late Surveillance

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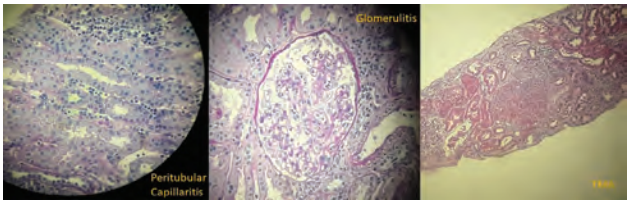
Introduction: Monitoring allograft function remains inadequate. Many allografts sustain subacute injury not detected in time resulting in poor long-term outcomes. Traditional tools utilized (creatinine, proteinuria and DSA) are insensitive and imprecise. The gold standard, allograft biopsy, is invasive and expensive. DD CF DNA has emerged as a sensitive and specific marker of allograft injury. This test is valuable in the early post-transplant period but also can be of great use for allograft surveillance late after transplant. We present a case where use of DD CF DNA helped identify simmering allograft dysfunction not picked up by traditional means, allowing active intervention and change in management.

Case Description: 36 YO WF with a H/O SLE leading to CKD, S/P LUKT in 2018. Induced with Campath, maintained steroid free on Tacrolimus and MMF. Nadir Cr 0.8 mg/dl. Current Cr 1.0 mg/dl. Urine Pr/Cr ratio 0.06 g/g. Seen for routine visit. Surveillance DD CF DNA (Allosure) done - 4.8%. Repeat after a few weeks - 5.4%. No DSA. ANA was at 1:40. ds DNA Ab negative. Normal complements. Biopsy was suggestive of acute active antibody mediated rejection with severe microvascular injury and renal limited TMA. C4d only focally positive. DSA repeated and negative. MICA Ab negative. AT1R

Ab positive by EIA with a level > 40 units/ml. Treated for Acute active ABMR due to AT1R Ab with plasmapheresis and IVIG for four sessions. Creatinine stable at 0.9 mg/dl. Allosure down to 1% after treatment.

Discussion: Monitoring allograft function, especially late after transplant, can be difficult given lack of sensitivity and precision of traditional markers. DD CF DNA is emerging as a sensitive and specific marker to detect allograft injury. In this case, significant allograft injury was detected on a biopsy performed solely because of abnormal surveillance DD CF DNA result. This led to aggressive intervention and management change. This test adds another tool available to monitor allograft health and may allow us to pick up allograft injury even when traditional markers remain silent.



Severe Microvascular Injury and TMA

PUB256

Infections in the Early Period After Kidney Transplantation

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Background: Infectious complications remain an important cause of morbidity and mortality in kidney transplant recipients, especially in the first year after kidney transplantation (KT). The aim of our study was to evaluate incidence, type of infectious complications and also, to identify risk factors and graft survival impact of these infections in the first 90 days after KT.

Methods: We performed a prospective cohort study, which included 67 adult patients (age ≥ 18 years), transplanted in our center between the 1st of October 2018 the 1st of October 2019. Demographics data, recipient, donor, transplant, treatment and infections parameters were analyzed.

Results: Among the 67 patients, the mean age was 41.3± 10.5 years, male was the predominant recipient gender (59.7%) and 65.7% received a graft from a cadaveric donor. During the first 90 days after KT, 26 infectious episodes occurred in 22 kidney recipients (32.8%). The majority of patients (68%) developed infection in the first 30 days after KT. The most common infectious site was the urinary tract (53.8%). The most frequent pathogens identified were Klebsiella pneumoniae (9 times) and Escherichia Coli (7 times). Median time of antibiotherapy was 10 days (7-15). Patients from the infection group received a graft from a significantly older donor (p=0.02), had a significantly higher cold ischemia time (p=0.02) and tended to received more frequent antithymocyte globulin (ATG) induction therapy (p= 0.09). No significant difference between patients with infectious and without infectious complications, in terms of delayed graft function (DGF) (p=0.14), acute rejection (p=0.13) and graft failure (p=0.17). Multivariate Cox regression analysis, showed that induction therapy with ATG (HR=3.02; CI 95%=1.08-8.42; p=0.03), DGF (HR= 3.61; CI 95%=1.09-11.91; p=0.03) and donor age (HR=1.04; CI 95%= 1.006-1.082; p=0.02) were independent risk factors for infection in the first 90 days after KT. Five out of 67 patients developed graft failure, and 3 of them (60%) lost their graft due to acute graft pyelonephritis (p<0.001).

Conclusions: We showed that infections in the early period after KT remain a common complication with negative impact on graft function, specially urinary tract infections. Likewise, induction therapy with ATG, DGF and donor age were independent risk factors for infectious complications.

PUB257

AKI in Kidney Transplant Patients: A Single-Center Experience

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Background: The incidence of acute kidney injury (AKI) after kidney transplantation varies depending on the centers but it is a significant risk factor for graft failure. Kidney transplantation recipients have various risk factors for AKI according to the time after transplantation, most commonly being infection, ischemic-perfusion injury, volume depletion, calcineurin induced nephropathy and acute rejection. We present the common causes of acute kidney injury in our center and the related outcomes.

Methods: A retrospective study was conducted and gathered the information from their first episode of acute kidney injury event starting from January 2011. Out of 180 patients, 65 patients were excluded due to the lack of detailed documentation. We looked up the causes of acute kidney injury from biopsy reports and serology data and the subsequent renal outcomes.

Results: Among 115 patients, 105 patients (88%) had non-oliguric AKI and 10 patients (8%) developed oliguric AKI. Biopsy results revealed the most common cause of AKI being the transplant glomerulopathy (chronic rejection) at 23% in non-oliguric groups and 60% in oliguric groups. Only a few patients (9.5%) recovered and most of them developed chronic kidney disease with 41% in non-oliguric group. Acute cellular mediated rejection was found in 18% patients in non-oliguric group. Dialysis was needed in 50% in oliguric patients.

Conclusions: Our data shows that non-oliguric AKI is the most common presentation in kidney transplant patients and had poor outcome. Surprisingly, the most common etiology of AKI is chronic rejection in our center. Close follow up and early detection with biopsy might help to prevent chronic kidney disease due to chronic rejection.

PUB258

Early Graft Dysfunction due to Banff 2A Rejection in a Non-Sensitized Cross-Match-Negative Recipient

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Introduction: With the introduction of potent immunosuppression, the incidence of acute rejection in the first year following transplant is 1-2% lower in living donor kidney transplants (LDKT) compared to deceased donor kidney transplants (DDKT). Ideally, immediate graft function should be expected after LDKT. We present a case report of early acute cellular rejection 26 hours after an ABO compatible, HLA crossmatch negative LDKT.

Case Description: A 65-year-old Caucasian male with ESRD due to anti-GBM disease presented for a LDKT from his 68-year-old wife. He was ABO compatible, HLA crossmatch negative, and 0% for both T-flow and B-flow PRA. Induction was with Basiliximab 20mg and Methylprednisilone 500mg and achieved immediate diuresis. He became anuric by 16 hours post-op, and a for-cause biopsy was done on POD 2 which showed Banff 2A acute cellular rejection with negative C4D. Patient was treated with rabbit anti-thymocyte globulin (rATG) with total dose 3mg/kg divided over 4 doses and pulse intravenous steroid at 250mg for 5 days. Immunosuppression was intensified and target tacrolimus levels were increased to achieve trough levels between 10-12 ng/mL. The patient has maintained excellent allograft function six months post-transplant with baseline serum creatinine baseline 1.8-2.0 and eGFR 34-38.

Discussion: Risk factors for acute rejection include multiple human leukocyte antigen (HLA) mismatches, a high panel reactive antibody (PRA), presence of donor specific antibodies (DSA), ABO blood group incompatibility, positive HLA crossmatch, prolonged cold ischemia time greater than 24 hours, African American ethnicity, and inadequate induction regimen. For patients with high risk factors for rejection, 2009 KDIGO guidelines recommend induction regimen with lymphocyte-depleting agents such as rATG rather than IL-2 receptor monoclonal antibody such as Basiliximab. This case report focuses specifically on the development of ACR in a low risk living donor transplant. We speculate that the development of ACR in this low risk patient was likely due to the HLA mismatches and possibly induction with Basiliximab. This case report poses the question of whether more intensive induction therapy should be considered in low risk patients with presence of HLA mismatches and the long-term allograft outcomes following acute rejection.

PUB259

Aspirin Prescribing Practices and Characteristics of Pregnant Women with CKD

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Background: Women with chronic kidney disease (CKD) are at a higher risk for preeclampsia compared to women without CKD. The U.S. Preventative Services Task Force has recommended use of low-dose aspirin in women with a high risk for development of preeclampsia, including women with renal disease since 2014. The authors sought assess the characteristics of pregnant women with CKD and aspirin prescribing practices at their institution.

Methods: The authors performed a retrospective chart review of data from pregnancies in women with CKD who delivered between January 1, 2015 and December 31, 2019. Potential pregnancies were identified with diagnostic codes for pregnancies and then included patients who had diagnostic codes for chronic kidney disease and proteinuria. We included pregnancies that had a formal diagnosis of CKD and those in whom baseline creatinine did not decrease at least 0.3 mg/dl during pregnancy. We excluded pregnancies that ended prior to 12 weeks. Means, standard deviations, medians, and interquartile ranges were used for continuous variables, and frequency and proportions were used for categorical variables, as appropriate.

Results: A total of 149 pregnancies were included. The mean age at due date was 30.8 (std. dev 5.6) with 27.5% of advanced maternal age. The majority (51.7%) were obese, with an overall mean BMI of 32.8 kg/m2 (std. dev 8.2). 15.4% had a history of prior pre-eclampsia. Just over half (57.5%) had been diagnosed with CKD prior to or during pregnancy with the most common underlying etiologies being type 2 diabetes mellitus. Of these, the mean baseline creatinine, obtained within 1 year of pregnancy, was 1.13 mg/dL (std. dev 0.64). Of 149 pregnancies included, 63 (42.3%) were prescribed aspirin prior to 28 weeks of gestation. Overall, 36.2% (54/149) were diagnosed with pre-eclampsia. Of those with a formal diagnosis of CKD prior to pregnancy, 52.9% were prescribed aspirin and 42.4% developed pre-eclampsia.

Conclusions: Chronic kidney disease is a well-recognized risk factor for pre-eclampsia with guidelines recommending the prescribing of aspirin to pregnant women with CKD. This study demonstrated low overall aspirin prescribing rates with relatively high rates of pre-eclampsia at a single institution.

PUB260

Magnesium Intake, Bone Mineral Density, and the Risks of Falls and Fractures in Post-Menopausal Women with Kidney Stone

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Background: Kidney stone formers are a unique patient population at high risk for fall and fractures due to dysregulated calcium homeostasis and early bone loss. Magnesium is an important component of bone, but its relation to falls and fractures among stone formers is unclear.

Methods: We performed regression analyses to determine the independent effect of dietary magnesium intake (DMI) on bone mineral density (BMD), and risks of fall and bone fracture among incident stone formers identified in the Women's Health Initiative (WHI), a prospective longitudinal multicenter study investiating the health of post-menopausal women.

Results: Out of a total of 145,942 WHI participants free of kidney stone history at baseline, 6024 developed kidney stone after 1,601,750 patient years of follow up. Among these incident stone formers, 82% were Caucasian, 23% were above age 70. Mean DMI was 304 mg/day, 30% had high DMI defined as >348 mg/day, 38% had medium DMI defined as 241-348 mg/day and 32% had low DMI defined as <241 mg/day. A total of 238 (4%), and 2581 (43%) incident stone formers had low BMD and new falls or fractures, respectively. Both low dietary calcium intake and active smoking associated with reduced BMD ($p<0.05$), but DMI did not affect BMD in the multivariate regression analysis, $\beta= 1.6$, $p=0.4$. Older age, black race, history of diabetes, history of either parent having broken bones after age 40 all associated strongly with risks of fall and bone fracture ($p<0.05$). However, DMI again did not have such significant association after adjustment for demographics and potential confounding factors, $\beta=1.7$, $p=0.4$.

Conclusions: DMI does not appear to affect BMD and the risk of fall or bone fracture among post-menopausal women.

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FR-OR51

Effect of Finerenone on CKD Outcomes in Type 2 Diabetes

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Background: Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) remain at risk of CKD progression despite guideline-directed therapies. Mineralocorticoid receptor (MR) overactivation may drive CKD progression through inflammatory and fibrotic processes. Finerenone, a novel, nonsteroidal MR antagonist, reduces albuminuria independent of hemodynamic effects. We assessed the long-term efficacy and safety of finerenone in slowing CKD progression in patients with CKD and T2D.

Methods: This global, phase 3, double-blind study randomized 5734 patients from 48 countries (1:1) to oral finerenone or placebo. Patients with T2D, urine albumin-to-creatinine ratio 30–5000 mg/g and estimated glomerular filtration rate (eGFR) 25–<75 mL/min/1.73 m^2, treated with optimized renin–angiotensin system blockade, were included. The primary outcome was time to kidney failure, sustained eGFR decline ≥40% from baseline or renal death. The key secondary outcome was time to cardiovascular (CV) death, non-fatal myocardial infarction, non-fatal stroke or heart failure hospitalization. (NCT02540993)

Results: Mean patient age was 65.6 years; 70.2% were male. At baseline, mean eGFR was 44.3 mL/min/1.73 m^2 and median UACR 852 mg/g. The primary outcome occurred in 504/2833 (17.8%) and 600/2841 (21.1%) patients treated with finerenone and placebo, respectively (hazard ratio [HR]=0.82; 95% confidence interval [CI] 0.73–0.93; *p*=0.0014). The prespecified secondary outcome was also reduced with finerenone (13.0%) vs placebo (14.8%; HR=0.86; 95% CI 0.75–0.99, *p*=0.0339). Overall treatment-emergent adverse events were balanced between groups. The incidence of hyperkalemia-related treatment discontinuation was higher with finerenone than placebo (2.3% and 0.9%, respectively).

Conclusions: Finerenone significantly reduced kidney and CV outcomes in patients with T2D and advanced CKD and was well tolerated. While the primary adverse event was hyperkalemia, it only necessitated treatment discontinuation in 2.3% of patients compared to 0.9% in placebo. These data support the use of finerenone to slow CKD progression and reduce CV risk in patients with CKD and T2D.

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FR-OR52

EMPEROR-Reduced: Empagliflozin and Outcomes in Heart Failure and CKD

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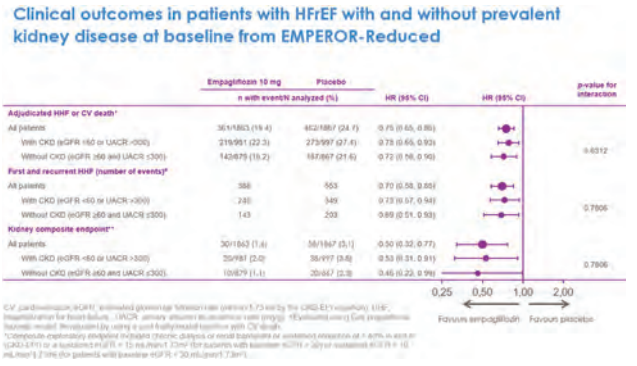
Background: In EMPEROR-Reduced, empagliflozin reduced cardiovascular death and heart failure hospitalizations and slowed the progressive decline in kidney function in heart failure and a reduced ejection fraction (HFrEF), with or without diabetes. We explored the effect of empagliflozin on cardiovascular and kidney outcomes, across the spectrum of kidney function.

Methods: 3730 patients were randomized, of whom 1978 (53%) had prevalent chronic kidney disease (CKD) (eGFR<60ml/min/1.73m^2 or an UACR>300mg/g). The key outcomes were (1) a composite of cardiovascular death or hospitalization for heart failure; (2) total hospitalizations for heart failure, and (3) eGFR slope; the last was supported by a prespecified composite renal outcome (defined as a profound sustained decline in eGFR, chronic dialysis or transplant). The median follow-up was 16 months.

Results: Patients with prevalent CKD had a higher rate of CV and kidney events. Empagliflozin reduced the risk of cardiovascular death and hospitalization for heart failure by 25% (P< 0.001), reduced total hospitalizations for heart failure by 30% (P<0.001) and reduced the composite of chronic dialysis, transplant and renal death by 50% (P<0.01). All three benefits were seen consistently in patients with and without CKD (figure) and were apparent even in patients with severe impairment (eGFR from 20 to 30ml/min/1.73m^2). Empagliflozin significantly slowed the yearly loss of eGFR and was well tolerated regardless of the level of baseline kidney function.

Conclusions: In patients with HFrEF, empagliflozin reduced serious heart failure and serious adverse kidney outcomes, and slowed the decline in kidney function, regardless of the presence or absence of CKD and across a broad spectrum of baseline kidney function.



FR-OR53

Sequential Treatment with Tacrolimus and Rituximab vs. Alternating Corticosteroids and Cyclophosphamide in Primary Membranous Nephropathy (PMN)

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Background: A cyclical corticosteroid-cyclophosphamide regimen is recommended for patients with PMN at high risk of progression. RTX monotherapy and calcineurin inhibitors have shown efficacy in inducing remission, but relapses are very common after discontinuation of calcineurin inhibitors.

Methods: In a randomized and open-label controlled trial, 86 patients (pts) with PMN and persistent nephrotic syndrome after a 6m observation period were assigned to receive a 6-m cyclical treatment with corticosteroid and cyclophosphamide (n=43) or sequential treatment with tacrolimus (full-dose for 6m and tapering for another 3m) and RTX (1 g at 6thm) (n=43). Primary outcome was complete or partial remission of nephrotic syndrome at 24m.

Results: The primary outcome occurred in 36 pts (84%) in the Ct-cyclophosphamide group and in 25 pts (58%) in the tacrolimus-RTX group (RR 1.44 95%CI 1.08-1.92). Complete remission at 24m occurred in 26pts (60%) in the corticosteroid-cyclophosphamide group and in 11pts (26%) in the tacrolimus-RTX group (RR 2.36 95%CI 1.34-4.16). Immunological response was faster in the corticosteroid-cyclophosphamide group and associated with remission at 24 m. Relapses occurred in 1 pt (2.7%) in the corticosteroid-cyclophosphamide group, and 3 pts (12%) in the tacrolimus-RTX group. The rate of serious adverse events was similar in both groups.

Conclusions: Treatment with corticosteroid-cyclophosphamide induced remission in a significantly greater number of patients with PMN than tacrolimus-rituximab. (NCT01955187).

Funding: Government Support - Non-U.S.

Underline represents presenting author/disclosure.

Table 1. Complete or Partial Remission at 3 to 24 months. Analysis per intention to treat

Composite of Complete or Partial Remission			
Time from randomization	Corticosteroid-Cyclophosphamide (n=43)	Tacrolimus - Rituximab (n=43)	Relative Risk (95% CI)
	No. of patients (%)		
3 mo	22 (51)	12 (28)	1.83 (1.04–3.22)
6 mo	32 (74)	19 (44)	1.68 (1.15–2.46)
12 mo	34 (79)	22 (51)	1.55 (1.11–2.15)
18 mo	36 (84)	23 (53)	1.57 (1.15–2.13)
24 mo	36 (84)	25 (58)	1.44 (1.08–1.92)
Complete Remission			
Time from randomization	Corticosteroid-Cyclophosphamide (n=43)	Tacrolimus - Rituximab (n=43)	Relative Risk (95% CI)
	No. of patients (%)		
3 mo	1 (2)	0 (0)	
6 mo	6 (14)	0 (0)	
12 mo	14 (33)	4 (9)	3.50 (1.25–9.78)
18 mo	19 (44)	7 (16)	2.71 (1.27–5.78)
24 mo	26 (60)	11 (26)	2.36 (1.34–4.16)

FR-OR54

Global Phase 3 Clinical Trials of Vadadustat vs. Darbepoetin Alfa for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD

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Background: Vadadustat (VADA) is an investigational, oral, hypoxia-inducible factor prolyl hydroxylase inhibitor which has completed patient enrollment in its phase 3 development for treatment of anemia of chronic kidney disease (CKD). In phase 2 trials, VADA safely raised and maintained hemoglobin (Hb) concentrations.

Methods: We conducted two randomized, phase 3, global, open-label, sponsor-blind, parallel-group, active-controlled noninferiority trials comparing oral daily VADA to parenteral darbepoetin alfa (DA) in patients with anemia of non-dialysis dependent (NDD)-CKD (PRO_2TECT program). The PRO_2TECT program included (1) Correction trial of patients previously not on erythropoiesis-stimulating agents (ESA) (ESA-untreated NDD-CKD trial, NCT02648347) and (2) Conversion trial of patients previously on an ESA (ESA-treated NDD-CKD trial, **NCT**02680574). The primary safety endpoint of PRO_2TECT program was time to first major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, nonfatal stroke), prespecified as a pooled event-driven analysis of both trials. Primary and key secondary efficacy endpoints, prespecified as separate analyses for each trial, were difference in mean change in Hb between baseline and weeks 24-36 and weeks 40-52, respectively, comparing VADA vs DA.

Results: In total, 4708 patients were screened for the ESA-untreated NDD-CKD trial, and 1751 were randomized. Most (N=1061) were from the United States; the remainder were from Europe or elsewhere. A total of 2961 patients were screened for the ESA-treated NDD-CKD trial, 1725 of whom were randomized. Most (N=1060) were from Europe or non-United States/non-European countries; the remainder were from the United States. The database was locked on July 31, 2020. Topline data and results of these global trials will be available in September 2020.

Conclusions: The trials will test if oral daily VADA is noninferior to parenteral DA, a common ESA, in patients with anemia of NDD-CKD, with respect to cardiovascular safety and hematologic efficacy.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceutical Co. Ltd.

FR-OR55

Oral Intradialytic Nutritional Supplements and Mortality in Hemodialysis Patients: A Cluster-Randomized, Pragmatic Clinical Trial

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Background: Dialysis is a catabolic state and observational studies suggest that administering oral nutritional supplements to hemodialysis patients with low serum albumin during the dialysis session may reduce mortality. Whether there are benefits in patients with normal serum albumin remains unstudied.

Methods: The Health Effects of oraL Protein Supplements in HD (HELPS-HD) Trial was an open-label cluster randomized pragmatic trial, comparing the effects of an intensive oral nutritional supplement protocol in which prevalent hemodialysis patients received supplements at every dialysis session regardless of serum albumin to standard care, in which supplements were administered to patients with albumin below 3.5 g/dL. As part of standard care, all incident patients received supplements for the first 90 days of dialysis. Following randomization of facilities to either the intensive or standard protocol, patients in facilities provided informed consent via waiver of consent documentation. The study intervention lasted from January 2017 to March 2020, and patients were enrolled through December 2019. The primary outcome, all-cause mortality, was assessed from medical records.

Results: Among 10,043 hemodialysis patients randomized from 105 participating DCI facilities, mean age was 63 years, 56% were men, 36% Black, and 46% had diabetes as primary cause of kidney failure; 32% were incident to dialysis. Supplement use was 2-fold higher in the 53 clinics randomized to the intensive protocol. Over median follow-up of 21 months, there were 3628 deaths, 35.8% in the intensive and 36.5% in the standard group, with an unadjusted rate of 20 deaths per 100-person years in both groups. In unadjusted Cox models, those randomized to the intensive protocol had similar outcomes to those randomized to the standard protocol (HR 1.02 [0.92, 1.14]); results were similar in models adjusted for age, sex and race and between incident and prevalent patients.

Conclusions: Discussion In a large, national population of hemodialysis patients, there was no difference in mortality between patients randomized to a standard oral nutritional supplement protocol, with receipt of supplements only when serum albumin was low, as compared to an intensive protocol, with receipt of supplements regardless of serum albumin.

Funding: Commercial Support - Dialysis Clinic, Inc

FR-OR56

Reducing the Burden of Dialysis Catheter Complications: A National Approach (REDUCCTION)

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Background: The major morbidity and cost from the use of central venous hemodialysis catheters is the increased risk of catheter-related blood stream infection (HD-CRBSI). Clinical practice remains variable and broad-scale, systematic interventions to reduce this burden have not been tested in randomized trials. The REDUCCTION trial aimed to systematically measure the rate of HD-CRBSI at a national level and test the effect of a multifaceted, evidence-based intervention upon the rate of HD-CRBSI in Australia.

Methods: This stepped wedge, randomized trial, clustered at the renal service level, included all patients receiving a central venous hemodialysis catheter in a participating renal service. After baseline data collection, services were randomly assigned to one of three time points (April 2018, Sept 2018, March 2019) for implementation of an intervention package based upon current evidence and guidelines. The primary outcome was the intervention's effect upon the study wide service-level rate of HD-CRBSI (per 1000 catheter days).

Results: A total of 37 renal services in all Australian states and territories participated in the trial between Dec 2016 and March 2020. Preliminary analysis shows that 5246 catheters (3506 patients) were inserted during the baseline phase and 4610 catheters (3144 patients) in the intervention phase, representing more than 1.1 million catheter days of exposure and over 300 adjudicated HD-CRBSI events. Final analysis is currently in progress with results presented at the Annual Meeting.

Conclusions: The REDUCCTION trial has systematically measured the use of HD CVCs in near real-time and demonstrated the feasibility of implementing a suite of evidence-based interventions in haemodialysis care. The study outcomes will have implications for future research and practice in dialysis access.

Funding: Government Support - Non-U.S.

Underline represents presenting author/disclosure.

FR-OR57

Regional Citrate vs. Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy Among Critically Ill Patients with AKI: A Randomized Clinical Trial

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Background: Although current guidelines suggest the use of regional citrate anticoagulation as first-line treatment for continuous kidney replacement therapy in critically ill patients, the evidence for this recommendation is based on few clinical trials and meta-analyses.

Methods: To determine the effect of anticoagulation strategies on filter lifespan and mortality, a parallel-group, randomized multicenter clinical trial was conducted in 26 centers across Germany between March 2016 and December 2018. Patients were randomized to receive either regional citrate (n=300) or systemic heparin anticoagulation (n=296) for continuous kidney replacement therapy. The two co-primary outcomes were filter lifespan and 90-day all-cause mortality. Secondary endpoints included bleeding complications and new infections.

Results: Among 638 patients randomized, 596 (93.4%) patients (mean age, 67.5 (±12.4) years, 183 (30.7%) women) completed the trial. Median filter lifespan was 47h [IQR, 19-70h] in the regional citrate and 26h [IQR, 2-51h] in the systemic heparin group; absolute difference (AD), 15h [95%CI, 11h to 20h]; *P*<0.001). 90-day all-cause mortality was 51.2% (150/300) in the regional citrate and 53.6% (156/296) in the systemic heparin anticoagulation group (adjusted AD, -6.1% [95%CI, -12.6% to 0.4%]; adjusted HR, 0.79 [95%CI, 0.63 to 1.004]; adjusted P=0.054; unadjusted AD, -2.4% [95%CI, -10.5% to 5.8%]; unadjusted HR, 0.91 [95%CI, 0.72 to 1.13]; unadjusted *P*=0.38). Compared with systemic heparin anticoagulation, the regional citrate anticoagulation group had significantly fewer bleeding complications (15/300 [5.1%] vs. 49/296 [16.9%]; AD, -11.8% [95% CI, -16.8% to 6.8%]; P<0.001) and significantly more new infections (204/300 [68.0%] vs. 164/296 [55.4%]; AD, 12.6% [95% CI, 4.9% to 20.3%]; P=0.002).

Conclusions: Among critically ill patients with acute kidney injury receiving continuous kidney replacement therapy, anticoagulation with regional citrate, compared with systemic heparin anticoagulation, resulted in significantly longer filter lifespan. The trial was terminated early and was therefore underpowered to reach conclusions about the effect of anticoagulation strategy on mortality.

Funding: Government Support - Non-U.S.

FR-OR58

Effects of Dapagliflozin on Kidney Function, Cardiovascular Events, and All-Cause Mortality According to Cause of Kidney Disease in the DAPA-CKD Trial

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Background: The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease trial (DAPA-CKD) assessed the sodium glucose co-transporter 2 inhibitor dapagliflozin in patients with chronic kidney disease (CKD) with and without type 2 diabetes. This pre-specified analysis explores outcomes according to underlying cause of kidney disease.

Methods: 4304 participants with eGFR 25–75 mL/min/1.73m^2 and UACR 200–5000 mg/g were randomized to receive dapagliflozin 10mg once daily or placebo. The effects of dapagliflozin versus placebo on the primary outcome (composite of sustained decline in eGFR ≥50%, end-stage kidney disease, or death from cardiovascular [CV] or kidney causes) and secondary outcomes (CV death or heart failure hospitalizations and all-cause mortality) were assessed in patients with diabetic nephropathy (n=2510), chronic glomerulonephritides (n=695), ischemic/hypertensive CKD (n=687) and CKD due to unknown/other causes (n=412).

Results: The effect of dapagliflozin on the primary outcome (hazard ratio [HR] 0.61, 95% Confidence Interval [CI] 0.51–0.72) was consistent in patients with diabetic nephropathy (HR 0.63, 95%CI 0.51–0.78), glomerulonephritides (HR 0.43, 95%CI 0.26–0.71), ischemic/hypertensive CKD (HR 0.75, 95%CI 0.44–1.26) and CKD of other/unknown cause (HR 0.58, 95%CI 0.29–1.19; p-interaction 0.53). The reduction in CV death or heart failure hospitalizations (HR 0.71, 95%CI 0.55–0.92) was also similar across kidney disease etiologies (p-interaction 0.24) as was reduction in all-cause mortality (HR 0.69, 95%CI 0.53-0.88; p-interaction 0.55). The proportion of patients who discontinued study drug due to adverse events or experienced serious adverse events was similar across kidney disease etiologies, with no clear evidence of difference (p-interaction 0.04 and 0.14).

Conclusions: In patients with CKD, dapagliflozin reduced the risks of kidney failure, death from CV causes or heart failure hospitalizations, and all-cause mortality, regardless of underlying etiology of kidney disease in this study.

Funding: Commercial Support - AstraZeneca

PO2622

Electronic Health Record Alerts for AKI: A MultiCenter Randomized Clinical Trial

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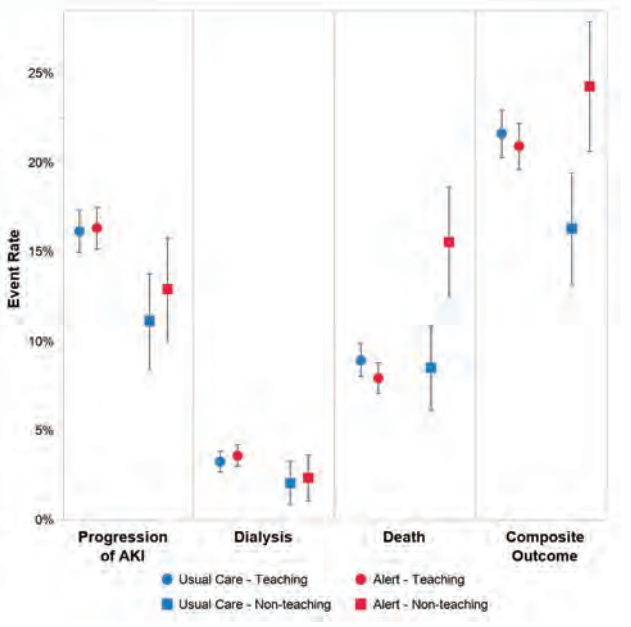
Background: Despite its strong association with adverse clinical outcomes, acute kidney injury (AKI) is often not recognized during clinical care. It is unclear whether automated alerts for AKI imrpove clinical outcomes.

Methods: Double-blinded, multicenter, parallel, randomized, controlled trial of an electronic AKI alert versus usual care (no alert). Adult participants across 6 hospitals were electronically identified and randomized via a best practice alert build in 1:1 fashion to the two study arms. The primary outcome was a composite of AKI progression, receipt of dialysis, or death at 14 days.

Results: 6,030 patients were randomized over 22 months. The primary outcome occurred in 653 (21.4%) patients in the alert group and 622 (20.9%) in the usual care group (relative risk 1.02, 95% confidence interval [CI] 0.93 to 1.13, p=0.67). Per-hospital analysis revealed worse outcomes in the two non-teaching hospitals (N=765, 13%), where alerts were associated with a higher risk of the primary outcome of 1.49 (95% CI, 1.12 to 1.98, p=0.006). More deaths occurred at these centers (15.6% in the alert group vs. 8.6% in the usual care group, p=0.003). Certain AKI care practices were increased in the alert group but did not appear to mediate these outcomes.

Conclusions: Alerts did not reduce the risk of our primary outcome among hospitalized patients with AKI. The heterogeneity of effect across clinical centers should lead to a re-evaluation of existing AKI alerting systems.

Funding: NIDDK Support



Underline represents presenting author/disclosure.

PO2623

Results from a Phase 3 Study Comparing the Efficacy and Safety of Molidustat vs. Darbepoetin Alfa in Patients Receiving Hemodialysis and Treated with Erythropoiesis-Stimulating Agents (ESAs)

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Background: Molidustat is a novel inhibitor of hypoxia-inducible factor-prolyl hydroxylase under investigation as an alternative to ESAs for the treatment of renal anemia.

Methods: This 52-week, phase 3 randomized, active-controlled, double-blinded, double-dummy, parallel-group, multi-center study (NCT03543657) compared the efficacy and safety of molidustat with darbepoetin alfa in Japanese patients with end-stage kidney disease receiving hemodialysis and ESA treatment. The dose of oral molidustat (5–200 mg/day) or intravenous darbepoetin alfa (10–180 μg every 1 or 2 weeks) was adjusted to maintain hemoglobin (Hb) concentrations within the target range 10.0–12.0 g/dL. The primary variables were mean Hb level during evaluation period (Weeks 33–36) and its change from baseline.

Results: Of 229 patients randomized to molidustat (n=153) or darbepoetin alfa (n=76), 180 completed 52 weeks of treatment (n=115 and 65). Median treatment duration was 364 days with molidustat and 364 days with darbepoetin alfa. Baseline characteristics were generally well balanced between groups: patients' mean age was 65.7, mean BMI was 22.5 and 61% were male. Mean baseline central Hb levels were 10.77 g/dL for molidustat and 10.84 g/dL for darbepoetin alfa. The mean (95% CI) for mean Hb level during the evaluation period were within the target range for both groups: 10.63 (10.42–10.84) g/dL with molidustat and 10.77 (10.59–10.95) g/dL with darbepoetin alfa. Noninferiority of molidustat to darbepoetin alfa for the change in mean Hb level from baseline to the evaluation period was established, with a margin of 1.0 g/dL (least square mean difference [95% CI] for molidustat vs darbepoetin alfa: -0.13 (-0.46–0.19] g/dL). There were no apparent between-group differences in incidence of treatment-emergent adverse events (TEAEs) (molidustat, 95.4%; darbepoetin alfa, 94.7%), serious TEAEs (24.2%; 18.4%), TEAEs with an outcome of death (1.3%; 2.6%) or AEs of special interest (4.6%; 3.9%).

Conclusions: In Japanese patients receiving hemodialysis and previously treated with ESAs, molidustat was noninferior to darbepoetin alfa for maintaining Hb levels, and no new safety concerns were observed.

Funding: Commercial Support - Bayer Yakuhin Ltd

PO2624

Continuous Low-Dose Iron Sucrose or Periodic High-Dose Ferric Carboxymaltose Therapy in Hemodialysis Patients (COPEFER): A Randomized Controlled Noninferiority Trial

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Background: Intravenous iron therapy is a cornerstone in the treatment of anemia in chronic hemodialysis patients. However, optimal dosing and frequency of administration is unknown and varies widely between centers. We compared the impact of equal cumulative doses of ferric carboxymaltose (FCM), which is not yet approved for use in hemodialysis patients, and iron sucrose (IS) administered as either a high dose bolus or low dose maintenance iron dosing strategy on hemoglobin concentration, iron balance, use of erythropoiesis stimulating agents (ESA), and adverse events in prevalent chronic hemodialysis patients.

Methods: We performed an open-label randomized controlled non-inferiority trial in two centers over 40 weeks (n=142). A total cumulative dose of two grams of iron was administered. The IS arm received 100 mg every two weeks, the FCM arm 500 mg every 10 weeks. Hemoglobin, iron markers, ESA use, C-reactive protein (CRP), phosphate, and liver enzymes were assessed. Primary end-point was the difference in hemoglobin at week 40 from baseline. A non-inferiority margin of -0.8 g/dl between both groups was pre-specified. Secondary end-points were differences in ferritin, transferrin saturation (TSAT), and ESA use.

Results: 108 patients completed the study. By 40 weeks non-inferiority criterion was not met as hemoglobin differed by -0.47 g/dl (95% CI: -0.95 to 0.01) in the FCM compared to the IS arm. In intention-to-treat analysis hemoglobin was significantly lower in the FCM arm compared to the IS arm (-0.46 g/dl (95% CI -0.92 to -0.01). At week 40, ferritin was 29.7% (95% CI 6.6 to 46.1) and TSAT was 27.7% (95% CI 16.3 to 36.6) lower in the FCM compared to the IS arm. ESA dosing, CRP, phosphate, and liver function parameters did not differ between groups. Adverse events that caused intermittent drug discontinuations and infections occurred more often in the IS arm.

Conclusions: IS administered more frequently at lower doses maintained hemoglobin and iron stores more effectively than FCM administered less frequently but at higher doses. However, FCM appeared safe in dialysis patients where we observed less infections compared to the IS group.

Funding: Commercial Support - Vifor

PO2625

Associations Between Achieved Hemoglobin and Cardiovascular Outcomes in the Pooled Phase 3 Roxadustat Studies of Non-Dialysis-Dependent Patients with Anemia of CKD

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, promotes erythropoiesis and increases bioavailability of iron. In phase 3 studies, roxadustat-treated patients achieved and maintained hemoglobin (Hb) values of 11±1 g/dL. We examined the associations between achieved Hb levels and cardiovascular outcomes in non-dialysis-dependent (NDD) patients with anemia of chronic kidney disease (CKD).

Methods: We analyzed pooled data from 3 pivotal, phase 3 studies of patients with anemia of NDD-CKD who received roxadustat. Incidence rates of adjudicated MACE (all-cause mortality, MI, and stroke) and MACE+ (MACE plus heart failure and unstable angina requiring hospitalization) were evaluated based on 1) Hb level immediately before the event and 2) maximum Hb level in the first 12 treatment weeks.

Results: Overall, 2391 patients were randomized to roxadustat. The mean (SD) baseline Hb of 9.1 (0.74) g/dL increased to 10.95 (0.76) g/dL over weeks 28-52. The MACE and MACE+ rates were highest when Hb was < 8 g/dl decreasing as Hb increased to 11-12 g/dL and ≥12 g/dL (Table).

Conclusions: In the NDD-CKD population, roxadustat corrected anemia and maintained Hb to 11±1 g/dL during weeks 28-52. MACE and MACE+ incidence rates were lowest when achieved Hb levels were ≥11g/dL.

Funding: Commercial Support - Fibrogen, Inc.

MACE and MACE+ rates in roxadustat-treated patients with anemia of NDD-CKD by Hb achieved

Parameter		Maximum Hemoglobin				
Overall PEY		59.1	179.9	1691.2	1417.4	690.0
		< 8 g/dL	8–< 9 g/dL	9–< 11 g/dL	11–< 12 g/dL	≥ 12 g/dL
Outcome	Time point	Event rate/100 PEY (95% CI)				
MACE	Immediately before event	60.9 (43.9–84.4)	25.6 (19.2–34.1)	9.6 (8.3–11.2)	4.9 (3.9–6.2)	6.7 (5.0–8.9)
MACE+	Immediately before event	82.9 (62.6–109.6)	35.0 (27.4–44.8)	13.0 (11.4–14.8)	6.8 (5.6–8.4)	9.7 (7.6–12.3)
MACE	Weeks 1–12	97.9 (52.7–181.9)	19.8 (9.9–39.6)	11.3 (9.2–14.0)	7.9 (6.5–9.6)	7.1 (6.0–8.4)
MACE+	Weeks 1–12	97.9 (52.7–181.9)	34.6 (20.5–58.4)	14.8 (12.3–17.8)	10.6 (9.0–12.5)	9.0 (7.8–10.5)

PEY: patient-exposure years

PO2626

Associations Between Achieved Hemoglobin and Cardiovascular Outcomes in the Pooled Phase 3 Trials of Roxadustat in Dialysis-Dependent Patients with Anemia of CKD

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, promotes erythropoiesis and increases bioavailability of iron. In phase 3 studies, roxadustat-treated patients achieved and maintained hemoglobin (Hb) values of 11±1 g/dL. We examined associations between achieved Hb levels and cardiovascular outcomes in patients with anemia of dialysis-dependent (DD) chronic kidney disease (CKD).

Methods: We analyzed pooled data from 3 pivotal, phase 3 studies of roxadustat-treated patients with anemia of DD-CKD. Incidence rates of adjudicated MACE (all-cause mortality, MI, and stroke) and MACE+ (MACE plus heart failure or unstable angina requiring hospitalization) were evaluated based on 1) Hb level immediately before the event and 2) maximum Hb level in the first 12 treatment weeks.

Results: Overall, 1943 patients were randomized to roxadustat. The mean (SD) baseline Hb was 9.63 (1.3) g/dL; from weeks 28-52, it was 10.85 (0.82) g/dL. The MACE and MACE+ rates were highest when Hb was < 8 g/dL decreasing as Hb increased to 11-12 g/dL and ≥12 g/dL (Table).

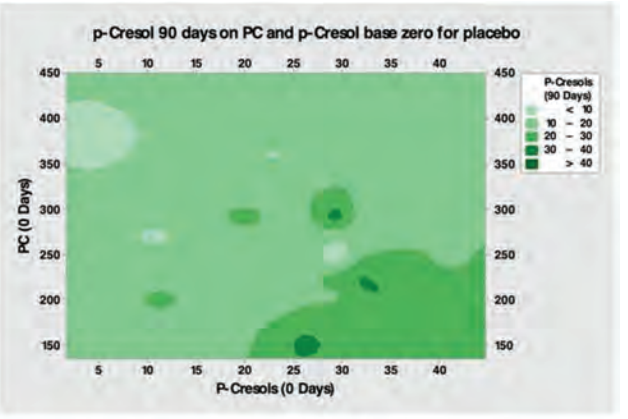
Underline represents presenting author/disclosure.

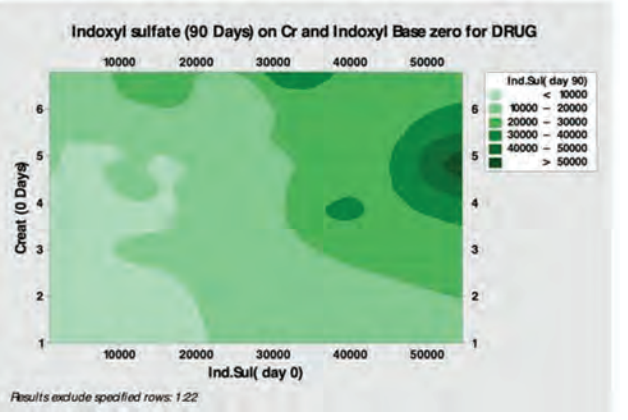
Conclusions: In the DD-CKD population, roxadustat corrected anemia and maintained Hb to 11±1 g/dL during weeks 28-52. MACE and MACE+ incidence rates were lowest when achieved Hb levels were ≥11g/dL.

Table: MACE and MACE+ rates in roxadustat-treated patients with anemia of DD-CKD by Hb achieved

Parameter		Maximum Hemoglobin				
Overall PEY		63.9	173.8	1519.7	1149.8	339.4
		< 8 g/dL	8–< 9 g/dL	9–< 11 g/dL	11–< 12 g/dL	≥ 12 g/dL
Outcome	Time point	Event rate/100 PEY (95% CI)				
MACE	Immediately before event	59.4 (43.3–81.7)	23.0 (16.9–31.4)	12.2 (10.5–14.1)	9.4 (7.8–11.3)	7.2 (5.3–9.9)
MACE+	Immediately before event	65.7 (48.6–88.9)	29.9 (22.8–39.3)	15.6 (13.7–17.7)	11.5 (9.7–13.6)	9.8 (7.5–12.9)
MACE	Weeks 1–12	73.4 (33.0–163.5)	13.0 (6.5–26.0)	12.1 (9.8–15.0)	10.2 (8.4–12.3)	10.1 (8.7–11.8)
MACE+	Weeks 1–12	85.7 (40.8–179.7)	13.0 (6.5–26.0)	14.9 (12.3–18.1)	11.9 (10.0–14.2)	11.9 (10.3–13.7)

PEY: patient-exposure years





PO2627

Abstract Withdrawn

PO2628

A Prospective, Double-Blind, Randomized, Placebo-Controlled Interventional Study to Evaluate the Safety and Efficacy of Enzobiotics in Pre-Dialysis CKD Patients

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Background: Synbiotics and proteolytic enzymes supplemented in CKD prevent formation of uremic toxins (UT) generated by undigested protein. Aim : Affect of Enzobiotics in reducing generation of P-Cresols and Indoxylsulfhate and quality of life in pre dialysis patients.

Methods: Double blind, randomized, placebo controlled multicentric clinical trial **CTRI/2019/01/017070** conducted over 90 Days. Eighty CKD stages 3-5 ND subjects from 5 centers divided into two groups of 40 each: group A received 1 Enzobiotic capsule TID, Group B 1 placebo capsules TID, for three months 5 minutes before food. Blood samples taken on visits 1 and 4 to measure *serum creatinine,* p- cresols, indoxyl sulphate (IS), **platelet count (PC) hsCRP** etc.

Results: Placebo increased p-cresol by 21% while drug reduced by 23%. Enzobiotic reduced indoxyl sulfate by 500 µg/ml (from 17200 to below 16700) with reductiion in creatinine. The potential patients above p-cresol level of 20 mg/lt between drug and placebo after 90 days were found to be 53% for placebo against 33% for drug. If testing is not available, Indoxyl sulfate and p-Cresol can be predicted by 2 equations (applied for patency) SF36 standard questionnaire revealed improvement in quality of life of treatment group. A**dversity ratio reduced significantly from 0.3362 to 0.1736 P-Value 0.000 over 90 days. Daily activity limitation, emotional problems and general health reduced adversity from** 60% to 47% (5.6%) **50% to 30%, 49% to 19% respectively.**

Conclusions: Enzobiotics improve make gut microbiome favourable, can delay dialysis in CKD patients by reducing uremic toxins, CRP, thrombocytopenia and improve cardiac performance, lipid profile, and quality of life.

Funding: Commercial Support - Mylin Biotech India Private Limited

PO2629

Effect of Ertugliflozin on Initial eGFR Decline and Chronic Slope: Analyses from the VERTIS CV Trial

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Background: SGLT2 inhibitors induce an initial reversible eGFR dip, based on natriuresis-induced reductions in glomerular pressure, with a return toward baseline over time in adults with T2DM. Preservation of the chronic eGFR slope by ≥0.75 mL/min/1.73m^2/year with treatment predicts protection against CKD progression. We aimed to assess the impact of initial eGFR dip and chronic eGFR slope in the VERTIS CV trial (NCT01986881).

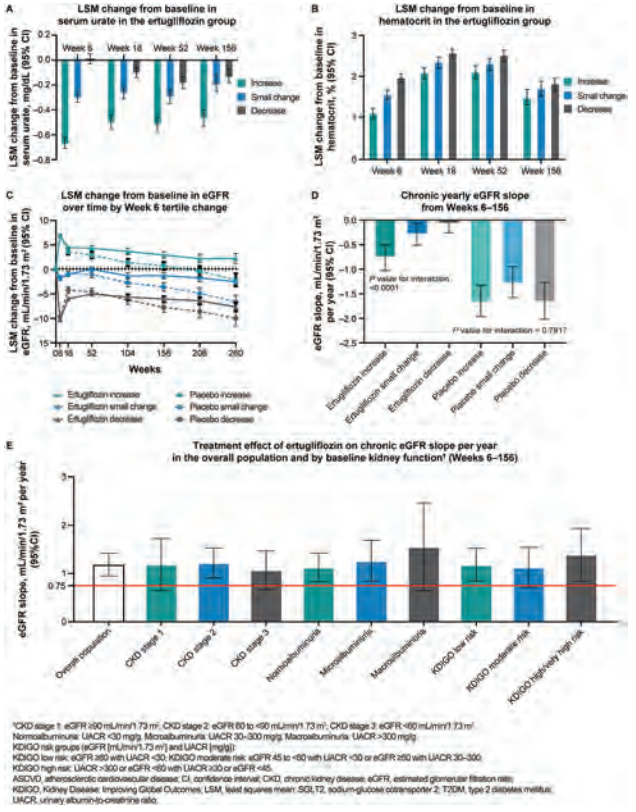
Methods: Patients with T2DM and ASCVD were randomized (1:1:1) to ertugliflozin 5 mg, 15 mg or placebo. Analyses assessed pooled ertugliflozin (n=5499) and placebo (n=2747). Patients were divided into 3 tertiles based on initial eGFR change at Week 6 (increase, small change or decrease). Changes in eGFR, hematocrit and uric acid were assessed at Weeks 6, 18, 52 and 156. Chronic eGFR slope/year by random coefficient models was also assessed.

Results: Glucosuria-associated effects (ie, uric acid) were larger in the eGFR increase tertile; natriuresis-associated effects (ie, hematocrit) were larger in the eGFR decrease tertile (Fig A, B). The ertugliflozin eGFR decrease tertile had the smallest decline in chronic eGFR slope (Fig C, D). Chronic slopes were similar across the placebo group tertiles and the rate of decline uniformly more rapid (Fig D). Mean placebo-adjusted effect of ertugliflozin on chronic eGFR slope (Weeks 6–156 [95% CI]) was 1.19 (0.95, 1.42) mL/min/1.73 m^2/year (Fig E) and >0.75 mL/min/1.73 m^2/year in all subgroups.

Conclusions: The initial eGFR dip may influence several clinical effects of ertugliflozin. Ertugliflozin has favorable effects on eGFR slope in patients with T2DM and ASCVD.

Funding: Commercial Support - Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA in collaboration with Pfizer Inc.

Underline represents presenting author/disclosure.



†CKD stage 1: eGFR ≥90 mL/min/1.73 m²; CKD stage 2: eGFR 60 to <90 mL/min/1.73 m²; CKD stage 3: eGFR <60 mL/min/1.73 m²
Normoalbuminuria: UACR <30 mg/g; Microalbuminuria: UACR 30–300 mg/g; Macroalbuminuria: UACR >300 mg/g
KDIGO risk groups (eGFR [mL/min/1.73 m²] and UACR [mg/g]):
KDIGO low risk: eGFR ≥60 with UACR <30; KDIGO moderate risk: eGFR 45 to <60 with UACR <30 or eGFR ≥60 with UACR 30–300;
KDIGO high risk: UACR >300 or eGFR <60 with UACR ≥30 or eGFR <45.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; LSM, least squares mean; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

PO2630

Canagliflozin Across the Spectrum of Kidney Function and Albuminuria: Integrated Data from CANVAS and CREDENCE

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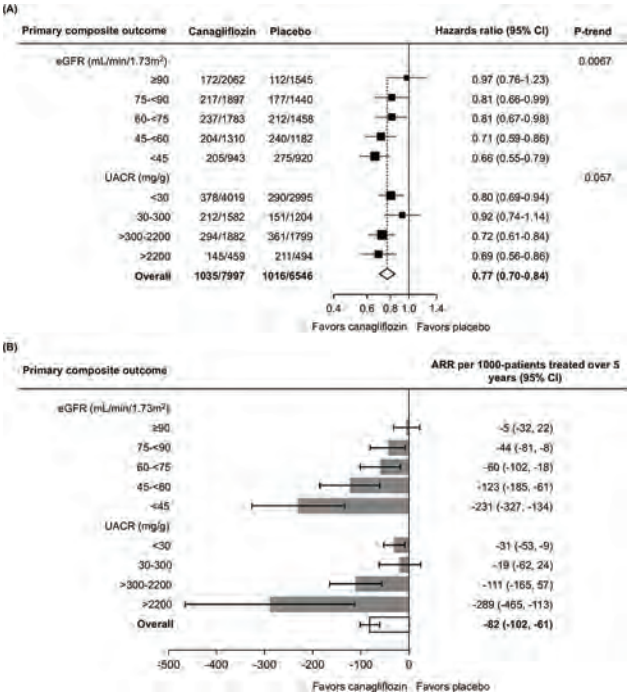
Background: People with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) are at very high risk of cardiovascular events and kidney failure. While canagliflozin reduces the risk of these outcomes, the consistency of this effect across all levels of estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR) remains uncertain.

Methods: We pooled individual participant data from the CANVAS Program (n=10,142) and CREDENCE trial (n=4,401) to assess the effect of canagliflozin on a primary composite outcome of myocardial infarction, stroke, heart failure, doubling of serum creatinine, kidney failure, cardiovascular or kidney death. The effect of canagliflozin was assessed using Cox regression models with treatment by subgroup interaction terms stratified by trial.

Results: 2,051/14,543 (14%) participants experienced the primary outcome over a median follow-up of 2.5 years. Overall, canagliflozin reduced the risk of the primary outcome (HR 0.77, 95% 0.70-0.84; Figure). The magnitude of relative benefit increased as eGFR declined (P-trend=0.0067; Figure) with some evidence of greater relative benefit at higher UACR (P-trend=0.057; Figure). Lower eGFR and higher UACR levels were independently associated with cardio-renal risk. Consequently, absolute risk reductions increased more than 5-fold across lower eGFR categories and more than 9-fold across higher UACR categories (Figure).

Conclusions: Canagliflozin reduces the risk of cardio-renal outcomes in people with T2DM; the magnitude of relative and absolute protection varies by severity of CKD.

Funding: Commercial Support - Janssen funded the CANVAS and CREDENCE trials. This analysis was not specifically funded and conducted independent of the trial sponsors.



PO2631

Ferric Pyrophosphate Citrate Injection: No Clinical Drug Interaction with Unfractionated Heparin in Hemodialysis Patients

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Background: Ferric pyrophosphate citrate (FPC) is a unique iron (Fe) replacement product indicated to maintain Fe balance and hemoglobin (Hgb) concentration in adult hemodialysis patients (HD). FPC can be administered via the dialysate (D) or as an intravenous (IV) preparation (Triferic® AVNU injection 6.75 mg Fe/4.5 mL for IV administration). A clinical study of the effects of unfractionated heparin (UFH) mixed with FPC was conducted.

Methods: An open-label, randomized 3-period, crossover trial, investigated the effects of FPC mixed with UFH compared with delivery of UFH and FPC by separate routes in 12 HD patients. The primary endpoint was the Anti Xa activity of UFH + FPC compared to UFH alone and UFH and FPC administered IV separately. Secondary endpoints were the activated prothrombin time (aPTT), thrombin time (TT) and serum iron profile (sFe). Effects were analyzed using the bioequivalence parameter of area under the concentration-time curve (AUC_{0-t}). Safety was assessed by recording adverse events (AE) and a visual dialyzer clotting scale (VCS).

Results: Coadministration of FPC+UFH pre dialyzer, met bioequivalence criteria for anti Xa activity of UFH compared to UFH alone or UFH and FPC separately. [Figure 1]. The FPC +UFH mixture had no impact on the AUC_{0-t} values of PTT or TT. The concentration-time profiles for sFe and TSAT were comparable. FPC was well tolerated with no reported adverse events. The VCS showed no detectable clotting of the dialyzer with any combination of UFH and FPC.

Conclusions: The results of this study demonstrates no clinically significant drug-drug interaction between FPC and UFH on the anticoagulation effect as assessed by anti Xa activity, aPTT, and TT or on the ability of FPC to deliver iron when these agents are co-administered as a single admixture. All treatments were well tolerated. These results support coadministration of IV FPC and UFH as an admixture to HD patients.

Funding: Commercial Support - Rockwell Medical Inc.

Underline represents presenting author/disclosure.

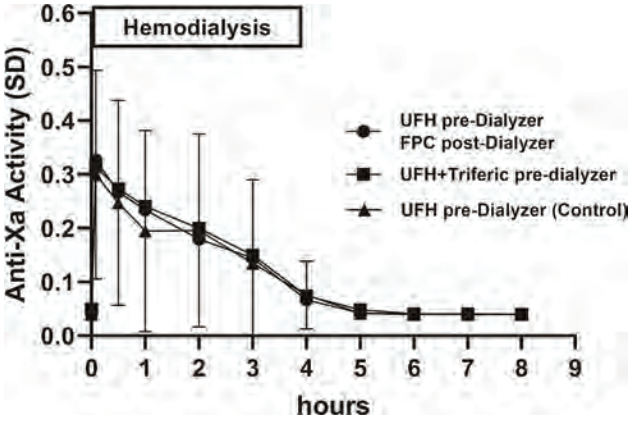

Figure 1.: Anti Xa Activity

PO2632

A Pilot Trial of Fistula vs. Graft Access Strategy in Older Adults on Hemodialysis

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Background: It is unclear whether surgical placement of an AVF confers significant clinical benefits over an AVG in older adults with ESKD.

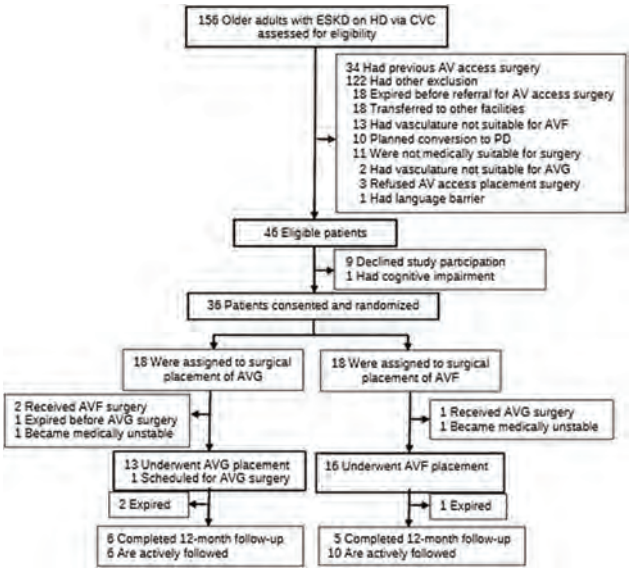
Methods: In this pilot randomized, parallel-group, open-label trial, patients ≥65 years old with ESKD, no prior AV access, on HD via a tunneled central venous catheter (CVC), referred for AV access placement by their nephrologist, were randomly assigned (1:1) to surgical placement of AVG or AVF.

Results: Of 122 older adults on HD with no prior AV access, 24% expired before or were too sick for surgery referral. Of 46 eligible patients, 36 consented and randomized to AVG (n=18) and AVF (n=18) placement; 13 (72%) and 16 (89%) underwent index AV access placement, respectively (Figure 1). At median follow-up of 321.0 days, primary AV access failure was noted in 31% in each group. Successful cannulation occurred in 8 (62%) in AVG and 8 (50%) in AVF group; median time to successful cannulation was 75.0 and 113.5 days, respectively. Endovascular procedures were recorded in 38% and 44%, and surgical re-interventions in 23% and 25% (Table 1). AV access infection was seen in 23% and 13% patients, respectively.

Conclusions: Based on these limited results, there is little reason to favor either AVF or AVG in this population until results from a larger randomized clinical trial become available.

Funding: Other NIH Support - National Institute of Health \ National Institute on Aging grant 1R03 AG060178-01

Table 1. Vascular Access Outcomes in Patients who Underwent the Assigned AV Access Placement Surgery Outcome	All (n= 29)	AVG-first (n= 13)	AVF-first (n= 16)
Primary, early AV access failure, n (%)	6 (21)	4 (31)	1 (6)
Time to early AV access failure, median (range), days	57.0 (22.0-85.0)	47.5 (22.0-79.0)	85.0 (-)
Primary, late AV access failure, n (%)	3 (10)	0	4 (25)
Time to late AV access failure, median (range), days	128.0 (120.0-244.0)	—	128.0 (120.0-244.0)
First AV access cannulation, n (%)	21 (72)	10 (77)	11 (69)
Time to first AV access cannulation, median (1st, 3rd Quartile), days	51.5 (36.0, 66.0)	39.5 (35.0, 55.0)	63.5 (45.8, 75.0)
Successful AV access cannulation, n (%)	16 (55)	8 (62)	8 (50)
Time to successful AV access cannulation, median (1st, 3rd Quartile), days	95.0 (66.5, 151.0)	75.0 (53.3, 108.0)	113.5 (89.0, 181.5)
Endovascular procedures on index AV access, n (%); #	11 (38); 16	5 (38); 7	7 (44); 9
Surgical re-intervention on index AV access, n (%); #	7 (24); 9	3 (23); 3	4 (25); 5
Follow-up from index AV access placement, median (1st, 3rd Quartile), days	321.0 (181.0, 365.0)	327.0 (202.0, 365.0)	321.0 (168.5, 365.0)



PO2633

Health Economic Evaluation of the Theranova 400 Dialyzer Among Hemodialysis Patients in the United States: Results from a Randomized-Controlled Trial

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Background: In a 24-week, open-label RCT, expanded hemodialysis (HDx) via the Theranova 400 medium cut-off dialyzer had superior reduction ratios of large middle molecule uremic toxins such as κ and λ free light chains, complement factor D, TNF-α, and β2-microglobulin, compared to a high-flux dialyzer (Elisio-17H) in the US (Weiner et al. 2020). The purpose of this study is to perform a cost-consequence analysis for comparison of healthcare costs between HDx and conventional high-flux hemodialysis (HD).

Methods: Hemodialysis patients were randomized to receive treatment with either Theranova 400 or Elisio-17H over 24 weeks in the US. Hospitalization rate and average length of stay were calculated directly from trial data. Frequency of erythropoiesis stimulating agent (ESA) and iron use were calculated at baseline and carried forward over a 1-year time horizon. ESA and iron doses were calculated as the average of median total monthly doses. Unit costs of medication were obtained from the Centers for Medicare and Medicaid Service (CMS) and hospital costs from the Kaiser Family Foundation. Both deterministic (±20%) and probabilistic (95% confidence intervals) sensitivity analyses were conducted to account for variability in model inputs.

Results: There were 86 patients (389 patient-months) in the Theranova group and 85 patients (366 patient-months) in the Elisio group. All-cause hospitalization rate was 43% lower with Theranova compared to Elisio (RR=0.57; p=0.069). Frequency of ESA use was 46.5% in the Theranova group compared to 55.8% in the Elisio group, but doses were similar between the two groups. Both frequency and dose of iron were similar between the two groups. Average annual cost of hospitalization was $3,925 lower with Theranova compared to Elisio. Annual cost of ESAs and iron were similar between the two groups, although the cost of ESAs was $400 lower in the Theranova group. Compared to Elisio, the average annual cost of Theranova was $4,340 lower per patient. Hospitalization rate and length of stay were the main drivers of cost in the model.

Conclusions: This study provides evidence that, in addition to Theranova's superior removal of large middle molecules, Theranova may also be a cost-saving therapy driven largely by reduction in patient hospitalization events.

PO2634

Intermittent Pneumatic Compression Promotes Presurgery Cephalic Vein Dilation: Preliminary FACT Trial Results

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Background: Arteriovenous fistulas (AVF) are the preferred for hemodialysis access with suitable (2.0-2.5 mm) veins. AVF maturation has been poor globally and often leads to increased catheter contact time and costs. Intermittent compression of upper arm veins may aid in forearm vein dilation pre-surgery to assist in AVF placement and maturation with size expectations and effectiveness.

Methods: This is was a prospective, IRB approved trial. A novel intermittent pneumatic compression device [Fist Assist® (FA)] was applied to upper arms below the shoulder to allow cyclic compression of 60 mm Hg four hours daily for 90 days. Sixteen (n=16) Stage 4 chronic renal failure (CRF) patients were in the study arm to test arm cephalic vein dilation. Vein size was measured and recorded at baseline and after 90 days by duplex measurement of the cephalic vein with a tourniquet. Clinical results: vein dilation at particular locations was recorded and tested for significance using a paired-difference t-test.

Underline represents presenting author/disclosure.

Results: Sixteen (n=16) mostly African American patients were involved in the first interim evaluation of the device in a USA FACT trial. All patients were in compliance with the study and followed the study protocol. No major complications or adverse effects were noted in any patient except one non-device related rash. Differences were noted with the measurements done with a cuff in the vein sizes in the forearm (FA) and upper arm (UA). Both were significant. **FA3M : 3-Month- Vein diameter (AP), with cuff, at 5 cm from radial bone UA3M : 3-Month- Vein diameter (AP), with cuff, at 1 cm above elbow UA : Enrollment-Vein diameter (AP), with cuff, at 1 cm above elbow FA : Enrollment-Vein diameter (AP), with cuff, at 5 cm from radial bone Difference between mean of (UA3M-UA) : t = 1.74, p-value = 0.05 Difference between mean of (FA3m-FA) : t = 1.72, p-value = 0.04 For Clinical Effectiveness:** FA: 18% ≥ 2.5 mm and 33% reached 2.0 mm or greater UA: 44% ≥2.5mm and 20% reached 3.0 mm or greater

Conclusions: Early application of a novel, intermittent pneumatic compression device may be successful in preparing forearm veins in Stage 4 CRF patients. The early study results of the FACT trial show statistical significance in vein size improvement, distensibility, and clinical effectiveness to reach predetermined size goals.

PO2635

A Randomized Controlled Trial of Dialysate Sodium in Hospitalized Hemodialysis Patients

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Background: Several large dialysis organizations have lowered the dialysate sodium concentration (DNa) in an effort to ameliorate hypervolemia. The implications of lower DNa on intra-dialytic hypotension (IDH) during hospitalizations of hemodialysis (HD) patients is unclear.

Methods: In this double-blind single center randomized controlled trial, hospitalized maintenance HD patients were randomized to receive higher (142 mmol/L) or lower (138 mmol/L) DNa for up to six sessions. Blood pressure (BP) was measured in a standardized fashion pre-HD, post-HD and every 15 minutes during HD. The primary endpoints were: 1) the average decline in systolic BP; and 2) the proportion of total sessions complicated by IDH (defined as a drop of ≥20 mmHg from the pre-HD SBP).

Results: A total of 139 patients completed the trial, contributing 311 study visits (Table 1). There were no significant differences in the average SBP decline between the higher and lower DNa groups (23 ±16 vs. 26 ±16 mmHg; P=0.31). The proportion of total sessions complicated by IDH was similar in the higher DNa group compared with the lower DNa group (54% vs. 59%; OR 0.72; 95%CI 0.36 to 1.44; P=0.35). In post-hoc analyses adjusting for imbalances in baseline characteristics, higher DNa was associated with an 8 mmHg (95%CI 2 to 14 mmHg) lesser decline in SBP, compared with lower DNa.

Conclusions: In this RCT for hospitalized maintenance HD patients, we found no difference in the absolute SBP decline between those who received higher versus lower DNa. Larger multi-center studies to confirm these findings are warranted.

Funding: NIDDK Support

Table 1

Characteristic	Lower DNa 138 mmol/L (n=69)	Higher DNa 142 mmol/L (n=70)
Age (yrs)	61 ± 14	58 ± 15
Male (n, %)	43 (62%)	36 (51%)
Black (n, %)	21 (30%)	25 (36%)
Diabetes (n, %)	36 (52%)	39 (56%)
Heart Failure (n, %)	28 (43%)	21 (32%)
Catheter Access (n, %)	16 (23%)	14 (20%)
Pre-HD SBP (mmHg)	135 ± 24	139 ± 24
Pre-HD Weight (kg)	80.4 ± 23.2	73.3 ± 21.6
Serum Sodium (mmol/L)	137 ± 4	137 ± 3
Blood Urea Nitrogen (mg/dL)	49 ± 19	48 ± 17
Hemoglobin (g/dL)	9.6 ± 1.5	9.5 ± 1.5

PO2636

Efficacy and Safety of Rapid Intermittent Correction vs. Slow Continuous Correction with Hypertonic Saline in Patients with Symptomatic Hyponatremia: A Randomized Clinical Trial (SALSA Trial)

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Background: Few high-quality evidences have clarified whether hypertonic saline is best administered as slow continuous infusion therapy (SCI) or rapid intermittent bolus therapy (RIB) for symptomatic severe hyponatremia.

Methods: Objective To compare the efficacy and safety of RIB and SCI with hypertonic saline in patients with symptomatic severe hyponatremia. **Design** Prospective, investigator-initiated, multi center, open-label, randomized controlled study from 24 August 2016 until 21 August 2019 **Setting** Emergency rooms and wards of three general hospitals in South Korea **Participants** 178 patients aged >18 years with symptoms and glucose-corrected serum sodium (sNa) ≤125 mmol/L were included. **Interventions** Either RIB or SCI of 3% hypertonic saline for 24-48 hours stratified by the severity of clinical symptoms. **Main outcome and Measures** The primary outcome was overcorrection at any given period, defined as follows: increase in the sNa level by >12/18 mmol/L within 24/48 hours. Secondary outcomes included efficacy and safety of the treatment approaches. SNa concentrations were measured at every 6 hours for 2 days.

Results: Patients (mean age 73.1 years, 45% male, mean sNa concentrations 118.2 ± 5.0 mmol/L) were randomly assigned to RIB group (n=87) or SCI group (n=91). Overcorrection occurred in 17.2% and 24.2% in RIB and SCI groups, respectively (absolute risk difference, -6.9% [95% CI -18.8% to 4.9%]). RIB group showed lower incidence of re-lowering treatment than SCI group (41.4% vs 57.1%; absolute risk difference, -15.8% [95% CI -30.3% to -1.3%]; number needed to treat [NNT]=6.3). Groups did not differ in terms of efficacy in increasing sNa concentrations or improving symptoms but RIB showed better efficacy in achieving target correction rate within 1 hour (32.2% vs 17.6%, absolute risk difference 14.6% [95% CI 2% to 27.2%]; NNT=6.8).

Conclusions: Both RIB and SIC therapies of hypertonic saline for treating hyponatremic encephalopathy were effective and safe, with no difference in the overcorrection risk. However, RIB had a lower incidence of therapeutic re-lowering treatment and tended to have a better efficacy in achieving sNa within 1 hour than SCI. RIB could be suggested as the preferred treatment of symptomatic hyponatremia, consistent with the current consensus guidelines.

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PO2637

12-Month Analysis of ILLUMINATE-A, a Phase 3 Study of Lumasiran: Sustained Oxalate Lowering and Kidney Stone Event Rates in Primary Hyperoxaluria Type 1

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Background: ILLUMINATE-A is a Phase 3 trial of lumasiran, an investigational RNAi therapeutic that reduces hepatic oxalate production.

Methods: The trial enrolled 39 patients ≥6 years with primary hyperoxaluria type 1 (PH1) and eGFR≥30 mL/min/1.73m^2. The trial had a 6-month (M) double-blind, placebo-controlled period (DBP) and an extension period (EP).

Results: During the DBP, the least square mean treatment difference in 24hr urinary oxalate (UOx) excretion for lumasiran compared to placebo was –53.5% ($p=1.7\times10^{-14}$), and 84% of lumasiran-treated patients achieved near-normalization or normalization of 24hr UOx excretion at M6 (vs 0% placebo-treated patients). In the EP, the 13 patients initially randomized to placebo crossed over to lumasiran (P/L), demonstrating a similar time course and magnitude of UOx reduction. After 6M of treatment, their 24hr UOx mean percent reduction was 57.3% and a comparable proportion (77%) achieved near-normalization or normalization of 24hr UOx excretion. In patients initially randomized to lumasiran (L/L), the reduction in 24hr UOx was sustained through M12. The calculated rate (per 100 person-days) of renal stone events (RSE) in the L/L group decreased from a reported rate of 0.87 (95% CI: 0.70, 1.08) over the 12M prior to consent, to observed rates of 0.30 (95% CI: 0.17, 0.51) for the 6M DBP, to 0.23 (95% CI: 0.13, 0.43) with an additional 6M of lumasiran. In the P/L group, RSE rates remained stable from a reported rate of 0.15 (95% CI: 0.07, 0.31) over the 12M prior to consent, to 0.18 (95% CI: 0.07, 0.48) during the 6M DBP, followed by a decrease to 0.05 (95% CI: 0.01, 0.32) during the first 6M of lumasiran treatment. Consistent with the DBP, the most common adverse events related to lumasiran in the EP were mild, transient injection site reactions.

Conclusions: The UOx reduction observed in the DBP was replicated by placebo crossover patients, confirming the robustness of the result. Lower RSE rates after 6-12M of treatment with lumasiran are encouraging.

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PO2638

Rituximab vs. Cyclophosphamide in the Treatment of Membranous Nephropathy: The RI-CYCLO Trial

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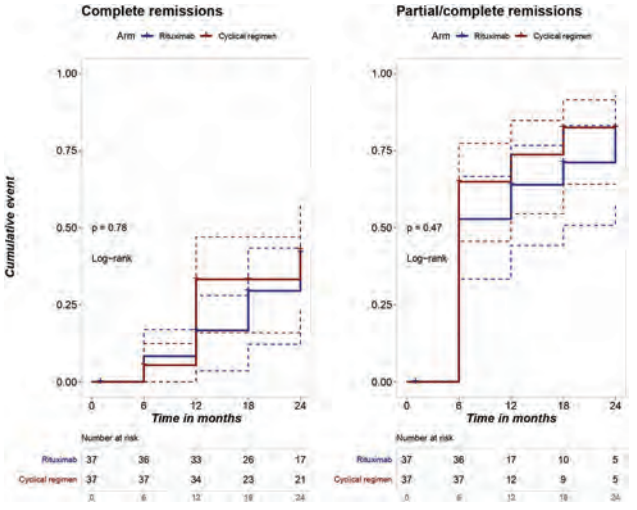
Background: Guidelines for membranous nephropathy (MN) management recommend cyclical corticosteroid-cyclophosphamide regimen (CYC) in patients with heavy proteinuria. Rituximab (RTX) may be a viable alternative, but head-to-head comparison is lacking.

Methods: Aim of this pilot RCT was to estimate the effects of RTX vs CYC regimen in MN, while assessing the feasibility of a larger trial. After a run-in of at least 3 months, patients with nephrotic syndrome were randomized to receive RTX (1g two weeks apart) or CYC. Complete remission (CR) was defined as proteinuria ≤0.3 g/day, partial remission (PR) as a reduction of proteinuria >50% and an absolute value of 0.3-3.5 g/day. Primary outcome was CR at 12 months; secondary outcomes included CR+PR at 12 and 24 months.

Results: 116 pts were screened, 74 randomized. Baseline median serum albumin was 2 g/dL and proteinuria 6 g/day in both arms. At 12 months, 6/37 pts (16%) in the RTX arm and 12/37 (32%) in the CYC arm had CR (OR according to "intention to treat_ ITT" analysis 0.4, 95% CI, 0.13-1.23, OR "according to per protocol_PP"0.28, 95% CI, 0.08-0.95), 23/37 (62%) in the RTX arm and 27/37 (73%) in the cyclical regimen arm had a CR+PR (OR ITT analysis 0.61, 95% CI 0.23-1.63, OR PP 1.11, 95% CI 0.42-2.98). Probabilities of CR and CR+PR at 24 months were 0.42 (CI 0.26-0.62) and 0.83 (CI 0.65-0.95) in the RTX arm and 0.43 (0.28-0.61) and 0.82 (0.68-0.93) in the CYC arm. Serious adverse events occurred in 7 and 5 pts, in the RTX and CYC arm, respectively.

Conclusions: Although the probability of CR was lower in the RTX arm at 12 months, the probability of CR at 24 months and of CR+PR at 12 and 24 months was similar in the two groups. No difference in side effects was found. While the efficacy of RTX and CYC in MN appears to be similar, a larger trial adequately powered would be difficult to perform.



PO2639

The Immunoglobulin G Degrading Enzyme Imlifidase for the Treatment of Anti-GBM Disease: The GOOD-IDES 01 Trial

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Background: Anti-GBM disease is an ultra-rare small vessel vasculitis with a yearly incidence below 2 per million. Most cases present with rapidly progressive glomerulonephritis and despite aggressive treatment with plasma exchange and cyclophosphamide renal survival is poor, at least for those presenting with advanced kidney injury. Imlifidase has been shown to cause depletion of circulating and kidney bound anti-GBM within a few hours, but it is not known if this leads to an improved outcome.

Methods: We conducted an international multi-center one-arm open-label study giving a single dose of 0.25mg/kg of imlifidase (non-proprietary name for IdeS = Immunoglobulin G Degrading Enzyme of *Streptococcus pyogenes*) on top of standard of care (ClinicalTrials.gov: NCT03157037). Main inclusion criteria were eGFR <15 ml/min/1.73m^2 and circulating anti-GBM antibodies. Main exclusion criteria were moderate or severe lung hemorrhage, dialysis dependency > 5 days and/or oliguria >48 hours. The primary outcome was dialysis free survival at 6 months.

Results: At 17 tertiary referral hospitals in 5 European countries 15 patients (6 women) were recruited between June 2017 and January 2020. Their median age was 60 years (range 19-77) and 5 were double positive for anti-GBM and ANCA. At inclusion 10 patients were dialysis dependent including 5 that were oliguric/anuric; the remaining 5 patients had eGFR of 7-14 ml/min. 6h hours after imflidase no patient had anti-GBM above the reference range. Return of antibodies prompting plasma exchange was seen in 10 patient 4 to 22 days after imlifidase (median 7 days), and they received a median of 8 session (range 2-17). At six months 10 patients were dialysis independent (median eGFR 27 ml/min, range 16-67), one was dead and 4 had developed ESRD. A favorable response was seen also in some patients that were anuric on inclusion and in some with 100% crescents. The safety profile was good; there were 7 serious adverse events (SAEs) reported but no serious unexpected suspected adverse reaction (SUSAR).

Conclusions: Imflidase leads to rapid clearance of anti-GBM which seems to widen the window of opportunity for treatment thereby increasing the chance of renal survival in difficult to treat patients with anti-GBM disease.

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PO2640

Phase 2 Study of N-Acetylmannosamine (ManNAc) for Glomerular Diseases

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Background: Sialic acid residues provide anionic charges to proteins, including those of the glomerular filtration barrier. Lectin analysis of kidney biopsies showed glomerular hyposialylation in nephrotic diseases, this may contribute to podocyte dysfunction and proteinuria. We showed in nephrotic mouse models that oral ManNAc, an uncharged precursor of sialic acid, normalized glomerular sialylation and markedly decreased proteinuria. ManNAc is also being studied to treat the rare hyposialylation disorder *GNE* myopathy (NCT04231266); it could be repurposed for patients with glomerular hyposialylation.

Methods: Phase 1 Results: A phase 1 study (NCT02639260; IND 125,192) of ManNAc in 7 nephrotic subjects showed that oral ManNAc was safe and well-tolerated. Plasma free sialic acid levels peaked ~10h after ManNAc dosing, remained elevated beyond 48h, and continued to increase during twice daily dosing, particularly in subjects with low eGFR. No adverse events occurred with increased plasma free sialic acid levels. Most subjects receiving ManNAc twice daily showed a 26-54% reduction in urine protein/creatinine ratio (UPCR), which appeared to correlate with the degree of glomerular hyposialylation.

Results: Phase 2 Design: An open-label phase 2 study will include assessment of longer-term pharmacokinetics, safety and efficacy. We will enroll 12 adults with focal segmental glomerulosclerosis, minimal change disease or membranous nephropathy, UPCR >2g/g, eGFR >45 ml/min/1.73m2 and glomerular hyposialylation. Glomerular sialylation will be assessed by lectin analysis of previous diagnostic biopsies. Subjects will receive oral ManNAc twice daily for 12 weeks, with clinical evaluations at baseline, interim and at the end of the study. Study outcomes will include safety and reduction of UPCR. Exploratory outcomes will include quality of life, patient-reported outcomes and improvement in eGFR.

Conclusions: Oral ManNAc therapy might benefit subjects with glomerular hyposialylation. ManNAc has minimal toxicity, is well tolerated, is easily administered, shows a trend to reduction of proteinuria, and could replace or augment existing therapies. The results of the planned phase 2 trial might offer a new therapeutic approach for primary and perhaps secondary glomerular diseases. Such results may change medical practice by including assessment of glomerular sialylation in the analysis of renal biopsies.

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